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REVIEW ARTICLE

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World Federation of Societies of Biological Psychiatry (WFSBP) guidelines update 2023 on the pharmacological treatment of eating disorders

Hubertus Himmerich[a,b], Yael Doreen Lewis[c,d], Chiara Conti[e], Hiba Mutwalli[a,f], Andreas Karwautz[g], Jan Magnus Sjögren[h], María Mercedes Uribe Isaza[i], Marta Tyszkiewicz-Nwafor[j], Martin Aigner[k], Susan L. McElroy[l,m], Janet Treasure[a,b] and Siegfried Kasper[n]; The WFSBP Task Force on Eating Disorders*

[a]Department of Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; [b]South London and Maudsley NHS Foundation Trust, Bethlem Royal Hospital, Beckenham, UK; [c]Hadarim Eating Disorders Unit, Shalvata Mental Health Center, Hod HaSharon, Israel; [d]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [e]Department of Psychological, Health, and Territorial Sciences, University "G. d'Annunzio" of Chieti-Pescara, Chieti, Italy; [f]Department of Clinical Nutrition, College of Applied Medical Sciences, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia; [g]Eating Disorders Care & Research Unit, Department of Child and Adolescent Psychiatry, Medical University of Vienna, Vienna, Austria; [h]Institute for Clinical Science, Umeå University, Umeå, Sweden; [i]Universidad Nacional de Colombia, Bogotá, Colombia; [j]Department of Child and Adolescent Psychiatry, Poznan University of Medical Sciences, Poznań, Poland; [k]Universitätsklinikum Tulln, Tulln an der Donau, Austria; [l]Lindner Center of HOPE, Mason, OH, USA; [m]University of Cincinnati College of Medicine, Cincinnati, OH, USA; [n]Center for Brain Research, Medical University of Vienna, Vienna, Austria

ABSTRACT

Objectives: This 2023 update of the WFSBP guidelines for the pharmacological treatment of eating disorders (EDs) reflects the latest diagnostic and psychopharmacological progress and the improved WFSBP recommendations for the assessment of the level of evidence (LoE) and the grade of recommendation (GoR).

Methods: The WFSBP Task Force EDs reviewed the relevant literature and provided a timely grading of the LoE and the GoR.

Results: In anorexia nervosa (AN), only a limited recommendation (LoE: A; GoR: 2) for olanzapine can be given, because the available evidence is restricted to weight gain, and its effect on psychopathology is less clear. In bulimia nervosa (BN), the current literature prompts a recommendation for fluoxetine (LoE: A; GoR: 1) or topiramate (LoE: A; GoR: 1). In binge-eating disorder (BED), lisdexamfetamine (LDX; LoE: A; GoR: 1) or topiramate (LoE: A; GoR: 1) can be recommended. There is only sparse evidence for the drug treatment of avoidant restrictive food intake disorder (ARFID), pica, and rumination disorder (RD).

Conclusion: In BN, fluoxetine, and topiramate, and in BED, LDX and topiramate can be recommended. Despite the published evidence, olanzapine and topiramate have not received marketing authorisation for use in EDs from any medicine regulatory agency.

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Guidelines; pharmacological treatment; anorexia nervosa; bulimia nervosa; binge-eating disorder

Introduction

Eating disorders (EDs) are characterised by persistently disturbed eating behaviours, which lead to changes in food intake, impaired physical health, and psychosocial problems. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and DSM-5 TR, the diagnostic group of feeding and EDs comprises anorexia nervosa (AN), bulimia nervosa (BN), binge-eating disorder (BED), avoidant restrictive food intake disorder (ARFID), pica and rumination disorder (RD) (American Psychiatric Association 2013, 2022). Over the last two decades, the worldwide prevalence of EDs has increased from ~4 to

CONTACT Hubertus Himmerich hubertus.himmerich@kcl.ac.uk Department of Psychological Medicine, King's College London, 103 Denmark Hill, London, SE5 8AF, UK

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*Ursula Bailer (Austria), Cynthia M. Bulik (USA), Chiara Conti (Italy), Martina De Zwaan (Germany), Angela Favaro (Italy), Fernando Fernandez-Aranda (Spain), Serguei Fetissov (France), Anja Hilbert (Germany), Hubertus Himmerich (UK/Germany), Hans Wijbrand Hoek (Netherlands), Carol Kan (Hong Kong/UK), Olga Karpenko (Russia), Andreas Karwautz (Austria), Siegfried Kasper (Austria), Walter H. Kaye (USA), Yael D. Lewis (Israel), Susan L. McElroy (USA), James Mitchell (USA), Palmiero Monteleone (Italy), Sabrina Mörkl (Austria), Daniel J. Müller (Canada/Germany), Hiba Mutwalli (Saudi Arabia), Bruno P. Nazar (Brazil), Hana Papežová (Czech Republic), Jan Magnus Sjögren (Sweden), Howard Steiger (Canada), Daniel Stein (Israel), Christopher P. Szabo (South Africa), Marta Tyszkiewicz-Nwafor (Poland), Ulrich Voderholzer (Germany), María Mercedes Uribe Isaza (Colombia), Tracey Wade (Australia), Wiesława D. Wranik (Canada), Kazuhiro Yoshiuchi (Japan)

~8% (Galmiche et al. 2019; Silén et al. 2020) and more and more affected people are seeking professional help (Schmidt et al. 2016). Therefore, there is a growing demand for the application of the most effective therapies currently available. Given remission rates after treatment are only at best around 50% (e.g. Linardon and Wade 2018), there is also a need for substantial amendments to current therapies or new treatment approaches (Monteleone et al. 2022; Treasure et al. 2022). Our understanding of the neurobiological basis of EDs is evolving thanks to global cooperation on genome-wide association studies, neuroimaging, and animal models (Bulik et al. 2022; Monteleone et al. 2022) which renders pharmacological treatment approaches plausible.

According to current national and international guidelines, for example, the guidelines of the National Institute for Health and Care Excellence of the United Kingdom (NICE 2017), the main therapeutic approach to EDs consists of (guided) self-help, psychotherapy, diet counselling, and physical health monitoring. However, our knowledge of biological therapy options and specifically psychopharmacological treatment is increasing. Since the first WFSBP guidelines for the pharmacological treatment of EDs were published in 2011 (Aigner et al. 2011), novel drug targets have been identified, new drugs have been suggested to be beneficial in EDs, and a significant number of randomised controlled trials (RCTs) have been performed. Whereas in 2011, only fluoxetine was approved for its use in BN (Aigner et al. 2011), lisdexamfetamine (LDX) has recently been approved for the treatment of BED in the USA, Canada, Brazil, and Australia (Himmerich et al. 2021). Additionally, our knowledge of side effects, pharmacokinetics including pharmacological interactions and therapeutic drug monitoring, and pharmacogenetics have rapidly increased. Therefore, the WFSBP Task Force on Eating Disorders decided to develop an update on the 2011 guidelines for the pharmacological treatment of EDs.

In 2019, the World Federation of Societies of Biological Psychiatry (WFSBP) proposed a new evidence and recommendation grading system for the development of WFSBP treatment guidelines to provide recommendations of the best possible treatment modalities for each patient (Hasan et al. 2019). This system provides guidance on how to grade the levels of evidence (LoE) and the grades of recommendation (GoR) for a specific treatment. It accepts clinical trials, meta-analyses as well as cohort studies from national or international registers for grading. However, it prioritises clinical trials taking into account internal and external validity, the control group and the similarity of conditions for the active and the control group, the randomisation, the blinding, the sample sizes, the applied statistics, the endpoints, and potential sponsor and allegiance effects (Hasan et al. 2019).

We have gathered an international task force of clinical and scientific experts from Africa, North and South America, Asia, Australia, and Europe, who have reviewed the literature systematically, assessed, documented, and graded the available evidence, and developed up-to-date recommendations for the pharmacological treatment of eating disorders in accordance with the new WFSBP grading system (Hasan et al. 2019).

Methods

Literature review

We performed a systematic review using the medical database PubMed. The search was performed from 1 January 2011, the year of the publication of the previous WFSBP guidelines (Aigner et al. 2011) until 1 January 2022 individually for each ED and was supplemented by internet searches, hand-searches of reference lists of included papers and potentially relevant reviews. All titles and abstracts were reviewed by at least two reviewers. The eligible articles were further reviewed in full text.

Search terms were extracted from the chapter on Feeding and Eating Disorders of DSM-5 (American Psychiatric Association 2013), the previous WFSBP guidelines for the pharmacological treatment of EDs (Aigner et al. 2011), from the latest specific systematic reviews or meta-analyses for the three main EDs (Blanchet et al. 2019; Hilbert et al. 2019; McElroy et al. 2019) and a comprehensive review on the psychopharmacological advances in all EDs (Himmerich and Treasure 2018).

Inclusion and exclusion criteria

For any treatment which has been investigated in AN, BN, BED, ARFID, pica, and RD we included all RCTs and meta-analyses. If there were no RCTs we included lower-level evidence, such as open trials or case series, case reports, and other types of available data.

We considered children and adolescents a special population and if there were no RCTs available for that population, observational reports referring specifically to the paediatric population were included.

Articles were included if:

- They described studies (RCTs, open studies, phase 2 or 3 studies, case series, case reports, meta-analyses)

testing a pharmacological treatment in the respective ED targeting core ED symptoms, e.g. weight, restriction, binge-eating episodes, meal anxiety, etc.
- Pharmacological treatment was part of the RCT study design or meta-analysis of RCT trials; or if pharmacological treatment was part of the non-RCT experimental design or of observational study design and there are no existing RCTs of this treatment or the study refers specifically to the paediatric population.
- Measurable results or outcomes were reported.

Articles were excluded if:

- Pharmacological treatment was not applied.
- Measurable outcomes or effects were not reported.
- Reported outcomes did not include core ED symptoms but more remotely ED related outcomes, such as medical complications including osteoporosis or growth restriction, or solely psychiatric outcomes, such as emotional dysregulation.
- There had been RCTs reported for the pharmacological treatment and the study is of lower level of evidence, i.e. observational study.
- The study dealt mainly with treatments other than pharmacological treatment.
- The article was not an original publication (e.g. review, case report, meeting abstract, book review).
- The article reported animal studies.
- The article was not written in English.

Tables 1, 3, 5, 7, 9, and 11 summarise the data extraction from the relevant studies and articles resulting from the literature review. The tables inform about the authors, the publication year, the study design, the favourable and unfavourable outcomes as well as the comparison with or the additional use of psychotherapy. The results section also includes a narrative data synthesis for each medical indication and medication.

SIGN evaluation of quality

The Scottish Intercollegiate Guidelines Network (SIGN) assessment tool for RCTs was used to evaluate the studies' design, risk of bias, and overall quality of RCTs and studies with a double-blind crossover design (SIGN 2019). The evaluation for each study was done by at least two members of the taskforce independently. If disagreements arose, they were resolved by a senior member of the task force. All RCT and crossover studies were evaluated regarding their quality; open-label trials, case reports, case series, retrospective case-control, and single session experiment studies were not. Rejected studies were those with an unacceptable quality as an RCT which means they scored '0' in the SIGN rating.

For study-specific SIGN evaluation, see Supplementary Material (SM) table SM1 for AN, SM2 for BN, SM3 for BED, and SM4 for RD. However, the results of studies that did not meet the RCT criteria could still inform the level of evidence (LoE) and grade of recommendation (GoR) as open studies or case series.

Assessing the level of evidence and the grade of recommendation

The Level of Evidence (LoE) and Grade of Recommendation (GoR) of study drugs were graded according to Hasan et al. (2019) in the following way:

> **LoE:** A: Strong evidence that the intervention is effective; B Limited evidence that the intervention is effective; C(1–3): Low evidence that the intervention is effective; D: No evidence; −A: Strong evidence that the intervention is NOT effective; −B: Limited evidence that the intervention is NOT effective; −C(1–3): Low evidence that the intervention is NOT effective.
>
> **GoR:** 1: Strong recommendation for using the intervention; 2: Limited recommendation for using the intervention; 3: Weak recommendation for using the intervention; 4: No recommendation possible; −1: Strong recommendation AGAINST using the intervention; −2: Limited recommendation AGAINST using the intervention; −3: Weak recommendation AGAINST using the intervention.

Results and recommendations

Anorexia nervosa

For AN, 70 articles were included in the final update (see Table 1), of which 32 studies had been reported in the previous guidelines (Aigner et al. 2011), 38 new studies, and four meta-analyses were additionally included in the 2023 update.

Antidepressants

Tricyclic antidepressants

Amitriptyline. Biederman et al. (1985) randomised 25 patients with AN to amitriptyline or placebo, and no drug benefit was shown for weight or other clinical measures including affective and ED symptoms or general clinical severity. Additionally, significant side effects were reported with amitriptyline. In a double-blind placebo-controlled trial by Halmi et al. (1986), 72

Table 1. Depicts the results of the literature review of pharmacological studies in AN.

Author	Year	Mean age (age range)	N	Agent	Treatment setting	Study design	Rando misation	Placebo-controlled	Double-blind	Treatment duration	Weight gain	Favourable outcomes/ superiority to placebo	Unfavourable or non-significant outcomes	Psychotherapy
Antidepressants														
Tricyclic antidepressants														
Biederman et al.	1985	16.9 (11–27)	43	Amitriptyline up to 175 mg/day, mean 115 mg/day	Mixed	RCT	Yes	Yes	Yes	5 weeks	No	NR	No significant weight change, SADS-C, HSCL, EAT, GSS, GIS	Yes, mix of individualised, CBT and FBT
Halmi et al.*	1986	20.6 (13–36)	72	Amitriptyline max 160 mg/ placebo/ cyproheptadine max 32 mg	Inpatients	RCT	Yes	Yes	Yes	Up to 90 days	No	Cyproheptadine increased treatment efficiency (time to target weight) in AN-R and decreased treatment efficiency in AN-B/P	No significant weight change, BDI, HDRS, HSCL, AAS, ABS	No
Crisp et al.	1987	21.2 (NR)	16	Clomipramine 50 mg/day	Inpatients	RCT	Yes	Yes	NR	11 weeks	No	Initially, higher hunger and appetite	No significant weight change, sensation and emotions VASs	Yes, intensive individualised and FBT
Selective serotonin reuptake inhibitors (SSRIs)														
Attia et al.	1998	26.2 (16–45)	33	Fluoxetine up to 60 mg/day if tolerated	Inpatients	RCT	Yes	Yes	Yes	Until goal weight maintained for 1 week or total of 7 weeks	No	NR	No significant weight change, HSCL-90, CGI, ABS, BDI, BSQ, EAT, YBC-EDS	Yes, individual psychotherapy including CBT
Kaye et al.	2001	22.5 (NR)	39	Fluoxetine 10-60 mg/day	Inpatients	RCT	Yes	Yes	Yes	Up to 12 months	Yes, for drug completers	Adherence to medication, at 1 year only; drug completers showed increases weight and reduced symptoms (HDRS, HARS, YBOCS, YBC-EDS)	NR	Yes, for inpatient phase and some of outpatient phase
Walsh et al.	2006	23.3 (16–45)	93	Fluoxetine up to 80 mg/day, usually 60 mg/day	Mixed	RCT	Yes	Yes	Yes	Up to 12 months	No	BAI	No significant weight change, time to relapse, EDI, BDI, RSE, YBC-EDS, QIesQ	Yes, manualized CBT for AN
Fassino et al.	2002	24.8 (16–35)	52	Citalopram 20 mg/day	Outpatients	RCT	Yes	No	No	12 weeks	No	BDI, HSCL-90 depression, obsessive-compulsive and somatisation subscales, EDI-2 ineffectiveness and impulsiveness subscales, STAXI tenemental anger	No significant weight change.	No
Luzier et al.	2019	13.5 (13–14)	2	Sertraline	Outpatients	Case report	No	No	No	NR	NA	Halt of relapse and reinduced remission	NR	No
Santonastaso et al.	2001	19.3 (14–34)	22	Sertraline 50–100 mg/day	Outpatients	Open trial	No	No	No	14 weeks	No	HSCL-58 depression, EDI interoceptive awareness, EDI ineffectiveness, EDI perfectionism	No significant weight change, other EDI subscales, HSCL-58 obsessive compulsive and anxiety symptoms	Yes, CBT

(*continued*)

Table 1. Continued.

Author	Year	Mean age (age range)	N	Agent	Treatment setting	Study design	Rando misation	Placebo-controlled	Double-blind	Treatment duration	Weight gain	Favourable outcomes/ superiority to placebo	Unfavourable or non-significant outcomes	Psychotherapy
Other antidepressants														
Naguy and Al-Mutairi	2018	16	1	Mirtazapine 30 mg/day	Outpatients	Case report	No	No	No	16 weeks	Yes	Weight gain, social and academic functioning	NR	Yes, CBT
Safer et al.	2011	50	1	Mirtazapine 30 mg/day	Outpatients	Case report	No	No	No	11 months	Yes	Weight gain and depression	NR	Yes, manualized CBT for AN and CBT for depression
Antipsychotics														
Typical antipsychotics														
Cassano et al.	2003	22.8 (NR)	13	Haloperidol 0.5–2 mg/day	Day program	Open trial	No	No	No	6 months	Yes	Weight gain, EDI (drive for thinness, bulimia and interoceptive awareness), EAT, CGI	NR	No
Mauri et al.	2013	25.8 (18–51)	9	Haloperidol 0.5–3.5 mg/day	Inpatients	Case series	No	No	No	During hospitalisation, up to 4 months	Yes	Weight gain, subjective clinical improvement in body image disturbance and drive for thinness	NR	No
Vandereycken	1984	23.5 (NR)	18	Sulpiride 300/400 mg/day	Inpatients	Double blind cross-over trial	Yes	Yes	Yes	3 weeks	No	NR	No significant weight change, EAT, BAT, ABSIO	Unclear, therapy given in later stage of admission
Vandereycken and Pierloot	1982	21.5 (15–36)	20	Pimozide 4–6 mg/day	Inpatients	Double blind cross-over trial	Yes	Yes	Yes	3 weeks	No	NR	Weight gain (trend only), ABSIO	Unclear, therapy given in later stage of admission
Atypical antipsychotics: olanzapine														
Attia et al.	2011	27.7, >16	23	Olanzapine 2.5–10 mg/day	Outpatients	RCT	Yes	Yes	Yes	8 weeks	Yes	Weight gain	BAI, BDI, BSQ, EDI, YBC-EDS, PANSS	No
Attia et al.	2019	28 (18–65)	152	Olanzapine 2.5–10 mg/day	Outpatients	RCT	Yes	Yes	Yes	16 weeks	Yes	Weight gain	YBOCS, EDE, CES-D, Zung Anxiety Inventory, CGI	Possible, some patients may have been engaged and continued non-specific outpatient psychotherapy if they had not gained weight 4 weeks prior to recruitment
Ayyilduz et al.	2016	17	1	Olanzapine 5 mg/day	Inpatients	Case report	No	No	No	2 days	NA	NR	NMS developed after 2 days of treatment	Unclear
Bissada et al.	2008	26.8	34	Olanzapine 2.5–10 mg/day	Day program	RCT	Yes	Yes	Yes	10 weeks	Yes	Weight gain rate, target BMI reached, YBOCS obsessions	YBOCS compulsions, PAI	Unclear if psychotherapy is part of day program
Brambilla et al.	2007	25, >18	35	Olanzapine 2.5–5 mg/day	Outpatients	RCT	Yes	Yes	Yes	3 months	Yes, for AN-B/P	Weight gain for AN-B/P, YBC-EDS rituals, direct aggressiveness in BDRS and greater in AN-B/P, TCI persistence and greater in AN-R	EDI, YBC-EDS, HVA, HDRS, BDRS	Yes—CBT for AN
Haruta et al.	2014	36	1	Olanzapine 2.5 mg/day	Inpatients	Case report	No	No	No	22 days	NA	NR	Hypoglycaemia developed and was detected on day 22, blood glucose level 23	Yes, Unspecified

(*continued*)

Table 1. Continued.

Author	Year	Mean age (age range)	N	Agent	Treatment setting	Study design	Rando misation	Placebo-controlled	Double-blind	Treatment duration	Weight gain	Favourable outcomes/ superiority to placebo	Unfavourable or non-significant outcomes	Psychotherapy
Kafantaris et al.	2011	17.1 (12.3–21.8)	20	Olanzapine 2.5–10 mg/day	Mixed	RCT	Yes	Yes	Yes	10 weeks	No	NR	No significant weight change, REE, RQ, EDE, YBC-EDS, HDRS, BPRS	Yes, individualised, FBT and multifamily group therapy
Leggero et al.	2010	13.7 (9.6-16.3)	13	Olanzapine 1.25–12.5 mg/day	NR	Open trial	No	No	No	6 months	Yes	Weight gain, CGAS, EAT-26, CGI-S, EDI interceptive awareness and impulsivity, CBCL, SIAB hyperactivity	EDI subscales	Yes, Unspecified
Marzola et al.*	2015	25.43 (NR)	75	Olanzapine and SSRI/aripiprazole and SSRI/SSRI	Inpatients	Retrospective case-control	No	No	No	NR	No	Greater reduction in YBC-EDS total and subscales in aripiprazole group compared to olanzapine and SSRI only. Decrease in purging in aripiprazole group *vs.* olanzapine group. Pre- and post-improvement in weight, HAM-A, HDRS	No significant weight change, No group effect for HAM-A, HDRS.	Yes, daily individual motivational and psychotherapy sessions, and weekly psycho-educational groups
Pruccoli et al.	2022	15.4	118	Olanzapine 3.4–4.4 mg/day	Inpatient and day care	Case control	No	No	No	NR	No	Low-dose olanzapine well tolerated. Improvement of BUT-GSI, BDI-II, and SAFA-D for all groups.	Full-dose olanzapine treated group experienced lower improvement in depressive measures: BDI-II and SAFA-D, than groups.	No
Spettigue et al.	2018	15.48 (11–17)	38	Olanzapine 2.5–15 mg/day	Mixed	Open trial	No	No	No	12 weeks trial, drug given until TGW achieved	Yes	Weight gain	Depression (CDI), Anxiety (MASC), EDI-3, EDEQ-A	Yes, individualised and FBT
Atypical antipsychotics: others														
Frank	2016	13.25 (12–17)	4	Aripiprazole 1–5 mg/day	Mixed	Case series	No	No	No	1 month – 1 year	Yes	Weight gain, weight and shape concern, anxiety	NR	Yes, individualised, FBT and multifamily groups
Frank et al.	2017	14.52 (NR)	22	Aripiprazole 1–5 mg/day	Mixed	Retrospective case-control	No	Yes	No	NR	Yes	Weight gain	NR	No
Marzola et al.*	2015	25.43 (NR)	75	Aripiprazole and SSRI/SSRI/Olanzapine and SSRI	Inpatients	Retrospective case-control	No	No	No	NR	No	Greater reduction in YBC-EDS total and subscales in aripiprazole group compared to olanzapine and SSRI only. Decrease in purging in aripiprazole group *vs.* olanzapine group. Pre- and post-improvement in weight, HAM-A, HDRS	No significant weight change, No group effect for HAM-A, HDRS.	Yes, daily individual motivational and psychotherapy sessions, and weekly psycho-educational groups
Tahıllıoğlu et al.	2020	14.3 (11–17)	11	Aripiprazole 2.5–15 mg/day	Outpatients	Case series	No	No	No	18-28 months	Yes	weight, ED behaviours, BDI, CGI. Intervention effective: weight, ED behaviours, BDI, CGI.	One patient reported elevated appetite, one patient reported sedation	Yes, unspecified

(*continued*)

Table 1. Continued.

Author	Year	Mean age (age range)	N	Agent	Treatment setting	Study design	Rando misation	Placebo-controlled	Double-blind	Treatment duration	Weight gain	Favourable outcomes/ superiority to placebo	Unfavourable or non-significant outcomes	Psychotherapy
Trunko et al.	2011	32 (15–55)	5	Aripiprazole 5–10 mg/day	NR	Case series	No	No	No	3 months and up	Yes	Weight gain, mood, anxiety, ED symptoms and rigidity	NR	Yes, Unspecified
Hagman et al.	2011	15.98 (12–21)	41	Risperidone 0.5–4 mg/day	Mixed	RCT	Yes	Yes	Yes	9 weeks	No	EDI interpersonal distrust subscale	No significant weight change, REE, EDI-2, MASC, BIS, CAPT, ADJ	No
Umehara et al.	2014	10	1	Risperidone 1mg/day, 12.5/2 weeks	Inpatients	Case report	No	No	No	1 month for oral admission, then 5 months for LA	Yes	Meal agitation and body image distortion decrease	NR	No
Powers et al.	2012	36 (18–65)	15	Quetiapine 177.7 mg/day (mean dose)	Outpatients	RCT	Yes	Yes	Yes	8 weeks	No	NR	No significant weight change, EDI, YBC-EDS, STAI, HDRS, PANSS	No
Ruggiero et al.	2001	24.11, >17	35	Amisulpride/ clomipramine/ fluoxetine	Inpatients	Head-to-head	Yes	No	No, single-blind	3 months		Yes, for amisulpride and fluoxetine, no between group difference	EDI	No
Antiepileptics and mood stabilisers														
Gross et al.	1981	19.8 (12–32)	16	Lithium titrated to blood level of 0.9 mmol/liter	Inpatients	RCT	Yes	Yes	Yes	4 weeks	Only for week 3 and 4	Weight in weeks 3 and 4, denial score on GAAQ, selective appetite on PRS	Weight in weeks 1 and 2, GAAQ, HSCL, PRS	Yes, including behaviour modification treatment
Pruccoli and Parmeggiani	2022	15.9 (14–19)	14	Valproate 100–1000 mg/day	Inpatients	Case series	No	No	No	9 weeks	Yes	Weight gain	Somnolence	Yes, unspecified
Appetite modulators														
Appetite stimulants														
Andries et al.	2014	33 (>18)	25	Dronabinol (delta-9-tetrahydrocannabinol) 5 mg/day	Mixed	Double blind cross-over trial	Yes	Yes	Yes	4 weeks each	Yes	Weight gain, 20% increase in intensity of physical activity	EDI, duration of physical activity	Yes, unspecified
Gross et al.	1983	23.6 (NK)	11	Dronabinol (delta-9-tetrahydrocannabinol) 7.5–30 mg/day/ diazepam 3–15 mg/day	Inpatients	Double blind cross-over trial	Yes	No—diazepam	Yes	4 weeks total, 2 weeks each drug	No	HSCL—somatisation, sleep disturbance and interpersonal sensitivity	No significant weight change, calorie intake	Yes, including individualised, group and CBT
Golberg et al.	1979	NR	81	Cyproheptadine 12–32 mg/day	Inpatients	RCT	Yes	Yes	Yes	NR		Only for severe AN: history of birth complications, significant weight loss or previous treatment failure	NR	Yes, drug given with or without CBT
Halmi et al.*	1986	20.6 (13–36)	72	Cyproheptadine max 32 mg/amitriptyline max 160 mg/placebo	Inpatients	RCT	Yes	Yes	Yes	Up to 90 days	No	Cyproheptadine increased treatment efficiency (time to target weight) in AN-R and decreased treatment efficiency in AN-B/P	No significant weight change, BDI, HDRS, HSCL, AAS, ABS	No
Opioid antagonists														
Marrazzi et al.	1995	25.5 (20–36)	6	Naltrexone 200 mg/day	Outpatients	Double blind cross-over trial	Yes	Yes	Yes	6 weeks	No	Reduction in B/P symptoms	No significant weight change	Yes, unspecified
Hormonal and endocrine treatments														
Gradl-Dietsch et al.	2022	15	1	Metreleptin 3–5.8 mg/d subcutaneously	4 days inpatients, then 5 days outpatients	Case report	No	No	No	9 days	Yes	Self-reported increments of appetite and hunger, improvement of eating disorder cognitions and depression	NR	No
Antel et al.	2022	16	1	Metreleptin 3–9 mg/d subcutaneously	Inpatients	Case report	No	No	No	10 days	Yes, after treatment period	Improvement of mood, eating disorder-related cognitions and hyperactivity	NR	No

(*continued*)

Table 1. Continued.

Author	Year	Mean age (age range)	N	Agent	Treatment setting	Study design	Rando misation	Placebo-controlled	Double-blind	Treatment duration	Weight gain	Favourable outcomes/ superiority to placebo	Unfavourable or non-significant outcomes	Psychotherapy
Milos et al.	2022	17, 19, and 26	3	Metreleptin 2–11.3 mg/d	Inpatients	Case series	No	No	No	6–14 days	Yes, in 2 of 3 patients	Improvement of overactivity, repetitive thoughts of food, inner restlessness, weight phobia and depression	NR	No
Hill et al.	2000	14.8 (12–18)	15	rhGH 0.05 mg/kg/day	Inpatients	RCT	Yes	Yes	Yes	4 weeks or until discharge	No	Time to medical stability	No weight change, duration of hospitalisation	No
Fazeli et al.	2010	28 (18–45)	21	rhGH 15–36.6 μg/kg/day titrated by IGF-I level	Outpatients	RCT	Yes	Yes	Yes	12 weeks	No	NR	No significant weight change	No
Fazeli et al.	2018	28.9 (NR)	22	Relamorelin 100 μg/day	Outpatients	RCT	Yes	Yes	Yes	4 weeks	No (trend)	Decreased gastric emptying time	Weight change (trend only), VAS hunger scores, BDI-2	No
Haruta et al.	2015	38	1	GHRP-2	Inpatients	Case report	No	No	No	1 year	Yes	Weight, appetite, muscle strength, fatigue, GI functions, hypoglycaemia.	NR	Yes—CBT
Russell at al.	2018	23.2 (16–57)	41	Oxytocin 36 IU	Inpatients	RCT	Yes	Yes	Yes	4–6 weeks (2 studies)	No	Lower EDE eating concern for OT, lower perseverative errors in WCST for OT, lower salivary response in wait for afternoon snack	No significant weight change, EDE-global, AQ, Leibowitz, REMT	No
Kim et al.	2015	22.5, >17	115 (AN, BN, healthy)	Oxytocin 35.2 mg	Mixed	Double-blind crossover study single session	Yes	Yes	Yes	24 h		EDE-Q, BDI, STAI, Wechsler Adult Intelligence Scale	No effect on food consumption in AN group	No
Kimball et al.	2019	(18–45)	90	Transdermal testosterone, 300 μg daily	Research centre	RCT	Yes	Yes	Yes	24 weeks	No	Week 4 trend towards a greater decrease in HAM-D score. Testosterone is safe and well tolerated.	Mean BMI increased by 0.0 ± 1.0 kg/m^2. No significant differences in eating disorder scores.	No
Léger et al.	2021	13.7	14	GH injection 0.050 mg/kg/day	Outpatients	RCT	Yes	Yes	Yes	12 months	No	A median (25th–75th percentile) HV increase of 1.0 cm/year. The effect of GH treatment increase after 6 months with height gain of 9.65 cm after 12 months.	Treatment adverse effects including increased fasting insulinemia and HOMA-IR, increase in IGF-1 SDS in one patient and glucose intolerance at 12 months in one patient and one suicidal attempt.	No
Gastroprokinetic agents														
Stacher et al.	1987	23.7 (18–35)	12	Cisapride 8 mg IV once	Inpatients	Double blind cross-over trial	Yes	Yes	Yes	Once	NR	Decreased gastric emptying time, increased antral contractile amplitude and decreased contraction frequency.	NR	No

(*continued*)

Table 1. Continued.

Author	Year	Mean age (age range)	N	Agent	Treatment setting	Study design	Rando misation	Placebo-controlled	Double-blind	Treatment duration	Weight gain	Favourable outcomes/ superiority to placebo	Unfavourable or non-significant outcomes	Psychotherapy
Stacher et al.	1993 (19–34)	22.5 (NR)	12	Cisapride 30 mg/day	Outpatients	Double blind cross-over trial	Yes	Yes	Yes	6 weeks	No	Decreased gastric emptying time	No significant weight change, EDI, BDI, STAI	yes, individualised and group psychotherapy
Szmukler et al.	1995	21.9 (18–40)	29	Cisapride 30 mg/day	Inpatients	RCT	Yes	Yes	Yes	8 weeks	No	Subjective hunger and general improvement	Gastric emptying, weight, BDI	Yes, unspecified
Saleh and Lebwohl	1980	28.7 (18–49)	7	Metoclopramide 40 mg/day	NR	Open trial	No	No	No	1 month	No	Pre and post weight gain, decreased GI symptoms, increased gastric emptying, and decreased gastric retention	NR	NK
McCallum et al.	1985	20 (14–40)	16	Metoclopramide	Inpatients	Single session	No	No	No	Once	NA	Accelerated gastric emptying	NR	Yes, including behavioural modification
Russel at al.	1983	17	1	Domperidone 30 mg/day	Inpatients	Case report	No	No	No	14 days	No	Improved subjective satiety and accelerated gastric emptying	No significant weight change,	No
Nutritional supplements														
Katz et al.	1987	16.42 (14–18)	15	Elemental zinc 50 mg/day	Mixed	RCT	Yes	Yes	Yes	6 months	No	STAI state anxiety, Zung depression scale	Weight, taste function, sexual maturation, skin abnormalities resolution	yes, including behavioural modification
Birmingham et al.	1994	22.3 (12–25)	35	Elemental zinc 14 mg/day	Inpatients	RCT	Yes	Yes	Yes	Until target weights reached (10% above baseline weight)	Yes	Increased weight gain	NR	Yes, including individualised and group psychotherapy and behavioural modification
Manos et al.	2018	14.7, <21	24	Omega-3 polyunsaturated fatty acid (PUFA)	Day program	RCT	Yes	Yes	Yes	12 weeks	No	NR	No significant weight change, EAT-26, CES-D, higher anxiety (BAIT) in PUFA group	No
Hart et al.	2021	13.5 (12–15)	2	Tyrosine (Amino Acid) 5 gr/day	Inpatients	Case report	No	No	No	12 weeks	Yes for 1 of the 2 participants	NA	No	No
Other medications														
Steinglass et al.	2014	25.6 (18–60)	20	Alprazolam 0.75 mg pre-meal	Inpatients	Double blind cross-over trial	Yes	Yes	Yes	NR	NA	NR	Caloric intake, anxiety	No
Casper et al.	1987	NR (19–28)	4	Clonidine 150–500–700/micrograms/day	Inpatients	Cross-over study	Yes	Yes	NR	4 weeks each intervention	No	NR	No significant weight change, hunger or satiety sensations, MHPG levels, depression or anxiety	Yes, unspecified

(*continued*)

Table 1. Continued.

Author	Year	Mean age (age range)	N	Agent	Treatment setting	Study design	Rando misation	Placebo-controlled	Double-blind	Treatment duration	Weight gain	Favourable outcomes/ superiority to placebo	Unfavourable or non-significant outcomes	Psychotherapy
Steinglass et al.	2007	27 (18–45)	14	d-cycloserin 50 mg before meal	Inpatients	RCT	Yes	Yes	Yes	4 sessions over 2 weeks, baseline assessment on admission, and FU 1 week after last training meal	No	NR	Caloric intake, BAI, sensations VASs, BDI (trend)	Yes, exposure therapy
Levinson et al.	2015	25.4 (14–49)	36	d-cycloserin 250 mg/day	Day program	RCT	Yes	Yes	Yes	4 sessions over 2 weeks, and another 1-month FU	Yes	Weight	Mealtime anxiety	Yes, exposure therapy
Okita et al.	2013	22.5 (NR)	2	Tandospirone 60 mg/day	Outpatients	Case series	No	No	No	6 months	Yes	Weight, EDE-Q	NR	No
Solmi et al.	2013	26	1	Adalimumab	Outpatient	Case report	No	No	No	9 months	Yes	Weight gain, resumption of menses at 9 months, decrease in weight and shape concern	NR	No
Scolnick et al.	2020	29	1	Ketamine 4 ketamine infusions over 4 days	Outpatient	Case report	No	No placebo controlled	No double blind, no multicentre	14 days	Yes	weight, mood, ED obsessions and behaviours	NR	No
Dechant et al.	2020	29	1	Ketamine 0.5 mg/kg IV	Outpatient	Case report	NA	NA	NA	5 weeks	NK	Suicidality and symptoms improvement. Treatment is more effective after weight restoration phase.	NR	No
Schwartz et al.	2021	49 and 30	4 (2 AN)	Ketamine 0.4 mg/kg IM, 0.5 mg/kg IM	Outpatients	Case series	NA	NA	NA	NR	Yes	Depression, ED symptoms, mood, energy, general wellbeing, BDI, anxiety, suicidality, BMI, hopelessness, food variety, anxiety related to eating certain foods, motivation and drive, STAI, regular menstrual periods	NR	Clinical management only
Mills et al.	1998	23–42	15	Ketamine, 20 mg/h for 10 h until patients appeared sedated	NK	Case series	NA	NA	NA	NK	Yes	Compulsion scores, sustained clinical response seen in improved eating behaviour and acceptance of increased weight.	Hallucinations in two patients In 80% of patients, treatment caused initially headache 30% had nausea but not severe	NK
Meta-analyses														
Dold et al.	2015	24.1	201	Olanzapine (4) Quetiapine (2) Risperidone (1)	NR	Random effect model meta-analysis of 7 RCTs for SGAs and individual agents	NA	NA	NA	NA	No	NR	No significant between group difference when pooling the all SGAs or for individual SGAs—for BMI change or secondary outcomes	NA

(*continued*)

Table 1. Continued.

Author	Year	Mean age (age range)	N	Agent	Treatment setting	Study design	Rando misation	Placebo-controlled	Double-blind	Treatment duration	Weight gain	Favourable outcomes/ superiority to placebo	Unfavourable or non-significant outcomes	Psychotherapy
Lebow et al.	2013	24.5	200	Olanzapine (5), Amisulpride (1), Risperidone (1)	NR	Random effect model meta-analysis of 7 RCTs	NA	NA	NA	NA	No	Beneficial effect for drugs over placebo for depression (2 studies included)	Nonsignificant increase in BMI with minimal inconsistency across studies and no effect of ED symptoms and cognitions.	NA
Kishi et al.	2012	NR	221	Olanzapine (4), quetiapine (1), risperidone (1), pimozide (1), sulpiride (1)	NR	Random effect model meta-analysis	NA	NA	NA	NA	No	Quetiapine better for eating attitudes and anxiety.	No significant difference in weight or questionnaire for depression, AN, body shape	NA
de Vos et al.	2014	>12	869	Antidepressants, Antipsychotics	In- and/or out-patients and/or others not reported	Meta-analysis	Yes	NA	NA	NR	Yes	Pharmacotherapy better than placebo pooled together ES 0.33 hormonal ES 0.42 significant but high heterogeneity	Antidepressant ES 0.26 non-significant, antipsychotic 0.25 non-significant	NA

NA: not applicable; NR: not reported; NK: not known; AAS: Anorectic Attitude Scale; ABS: Anorectic Behaviour Scale; ABSIO: Anorectic Behaviour Scale for Inpatient Observation; ADJ: adjustment; AN-B/P: anorexia nervosa binge-eating/purging type; AN-R: anorexia nervosa-restricting type; BAI: Beck Anxiety Inventory; BAT: burnout assessment tool; BDI: Beck's Depression Inventory; BDI-II: Beck's Depression Inventory-II; BDRS: Bipolar Depression Rating Scale; BIS: Barratt Impulsiveness Scale; BMI: Body Mass Index; BPRS: Brief Psychiatric Rating Scale; BSQ: Body Shape Questionnaire; BUT-GSI: Body Uneasiness Test, Global Severity Index; CAPT: Color-A-Person Test; CBCL: Child Behaviour Checklist; CDI: Children's Depression Inventory; CES-D: Centre for Epidemiologic Studies Depression Scale; CGAS: Children Global Assessment Scale; CGI: Clinical Global Impression; CGI-S: Clinical Global Impressions-Severity of Illness Scale; EAT: Eating Attitude Test; EAT-26: Eating Attitude Test 26 items; EDE: Eating Disorder Examination; EDE-Q: Eating Disorder Examination-Questionnaire; EDEQ-A: Eating Disorders Examination Questionnaire-Adolescents; EDI: Eating Disorder Inventory; EDI-2: Eating Disorder Inventory version 2; EDI-3: Eating Disorder Inventory version 3; GIS: Global Improvement Scale; GSS: Gudjonosson Suggestibility Scale; HARS: Hamilton Anxiety Rating Scale; HDRS: Hamilton Depression Rating Scale; HSCL: Hopkins Symptom CheckList; HSCL-90: Hopkins Symptom Checklist 90 items; HSCL-58: Hopkins Symptom Checklist 58 items; HVA: Hazard and Vulnerability Assessment; LA: Long-Acting; MASC: Multidimensional Anxiety Scale for Children; NMS: Neuroleptic Malignant Syndrome; PAI: Personality Assessment Inventory; PANSS: Positive and Negative Syndrome Scale; QlesQ: Quality of Life, Enjoyment, and Satisfaction Questionnaire; RCT: Randomised Controlled Trial; REE: Resting Energy Expenditure; RQ: Respiratory Quotient; RSE: Rosenberg Self-Esteem scale; SADS-C: Schedule of Affective Disorders and Schizophrenia-Change in symptomology; SAFA-D: Self-Administered Psychiatric Scales for Children and Adolescents, Depression subtest; SIAB: Structure Interview for Anorexic and Bulimic disorders; STAXI: State-Trait Anger eXpression Inventory; TGW: Treatment Goal Weight; VAS: Visual Analogue Scale; YBC-EDS: Yale-Brown-Cornell Eating Disorder Scale; YBOCS: Yale-Brown Obsessive Compulsive Scale; CBT: cognitive behavioural therapy; FBT: family-based therapy.

Lightly shaded rows indicate the inclusion of children and adolescents. Mean and range of age were reported where available.

*Study mentioned twice in the table.

patients received amitriptyline, cyproheptadine or placebo, with no effect of either agent on final weight.

Given that there were two RCTs with negative results, we conclude there is strong evidence against the use of amitriptyline (LoE: −A). Considering this along with the potential anticholinergic side effects there is a strong recommendation against its use (GoR: −1).

Clomipramine. Crisp et al. (1987) conducted a randomised clinical trial examining consumption of 50 mg clomipramine or placebo in 16 inpatients admitted for a weight restoration behavioural program including psychotherapy. Clomipramine was associated with increased appetite, hunger and calorie consumption only during the early stages of treatment with no impact on weight. With a single negative RCT with a moderate risk of bias there is limited evidence on the effectiveness of clomipramine (LoE: −B), and the recommendation against its use is limited (GoR: −2). A summary of the gradings for the LoE and the GoR can is depicted in Table 2.

Serotonin reuptake inhibitors

Fluoxetine. In a randomised double-blind placebo-controlled trial conducted by Attia et al. (1998) the augmentation of an inpatient AN program with fluoxetine was investigated in 33 participants. No impact was shown on weight, eating behaviour or psychological state.

A randomised double-blind placebo-controlled trial by Kaye et al. (2001) compared the adherence of 39 patients with AN to fluoxetine or placebo over one year. Adherence to fluoxetine was significantly higher, with 10 of 16 patients remaining on fluoxetine as opposed to only three of 19 on placebo. Only drug completers showed lower relapse and significant pre-post improvement in weight, symptoms of depression, anxiety, OCD and EDs.

Walsh et al. (2006) conducted another randomised double-blind placebo-controlled trial examining the effect of fluoxetine for relapse prevention. Ninety-three patients were randomised and 53 completed the 1-year study, with a similar proportion of completers in both groups. No difference was found in time-to relapse between the groups, and a drug effect was found only for anxiety symptoms.

With these contradictory results including two negative RCTs and one positive RCT, strong evidence against the use of fluoxetine emerges (LoE: −A), with a strong recommendation against its use (GoR: −1). Nota bene, the evidence against the use of fluoxetine refers to the main AN outcome of the studies (weight gain and AN psychopathology), not depressive or anxious symptoms.

Citalopram. Fassino et al. (2002) randomised 52 outpatients with AN to either receive citalopram or remain on the waiting list as a control group. In the citalopram arm, there were improvements in depression, obsessive-compulsive symptoms, impulsiveness and trait-anger with no effect on weight. This single RCT with a moderate risk of bias points to limited evidence that citalopram is not effective (LoE: −B), and a limited recommendation against using it in AN (GoR: −2).

Sertraline. An open, controlled 14-week trial with patients with AN-Restricting type (AN-R) revealed a reduction of depressive symptoms, perfectionist attitudes, ineffectiveness, and lack of interoceptive awareness, while no effect on weight was observed (Santonastaso et al. 2001).

Luzier et al. (2019) described two adolescents who had achieved remission from AN during treatment and experienced symptomatic relapse with the tapering of the sertraline. Once the dose was increased the decline in symptoms was halted and patients were stabilised.

As conflicting results show low evidence that the intervention is effective or not effective (LoE: D), no recommendation can be made for sertraline (GoR: 4).

Other antidepressants

Mirtazapine. Safer et al. (2011) described a case of a 50-year-old female patient with 7-year refractory AN and depression symptoms. Both improved with mirtazapine, and improvement was stable for the 9-month follow-up.

Naguy and Al-Mutairi (2018) described an adolescent case of a 16-year-old male with AN who had not responded to an SSRI trial, who improved in weight, functioning, and therapy engagement.

With two positive case reports, there is low evidence for the effectiveness of mirtazapine (LoE: C2), with a weak recommendation (LoR: 3).

Antipsychotics

Typical antipsychotics

Haloperidol. An open trial by Cassano et al. (2003) examined the effect of haloperidol as an adjunctive treatment to a day-care program and SSRI or TCA medication in 11 patients with treatment-resistant AN

Table 2. Anorexia nervosa: level of evidence (LoE) and grade of recommendation (GoR).

	LoE			GoR		
Medication	Evidence that the intervention is effective	No sufficient evidence	Evidence that the intervention is NOT effective	Recommendation for using the intervention	No recommendation possible	Recommendation AGAINST using the intervention
Antidepressants						
Tricyclic antidepressants						
Amitriptyline			−A			−1
Clomipramine			−B			−2
Selective serotonin reuptake inhibitors						
Fluoxetine			−A			−1
Citalopram			−B			−2
Sertraline		D			4	
Other antidepressants						
Mirtazapine	C2			3		
Antipsychotics						
Typical antipsychotics						
Haloperidol	C2			3		
Sulpiride			−B			−2
Pimozide			−B			−2
Atypical antipsychotics						
Olanzapine	A[a]			2		
Aripiprazole	C1			3		
Risperidone			−B			−2
Quetiapine			−B			−2
Amisulpride		D			4	
Antiepileptics and mood stabilisers						
Lithium	B			3		
Valproate	C2			3		
Appetite modulators						
Appetite stimulants						
Delta-9-tetrahydrocannabinol/dronabinol	B			2		
Cyproheptadine	B			3		
Opioid antagonists						
Naltrexone		D			4	
Hormones and endocrine medication						
Metreleptin	C1			3		
rhGH			−A			−1
Relamorelin	C1				4	−2
GHRP-2	C2			3		
Oxytocin		D			4	−2
Testosterone			−B			−2
Gastroprokinetic agents						
Cisapride			−A			−1
Metoclopramide	C2[b]			3[b]		
Domperidone	C2[b]			3[b]		
Nutritional supplements						
Zinc		D			4	
Polyunsaturated fatty acids			−B			−2
Tyrosine	C2			3		
Other medications						
Alprazolam		D			4	
Clonidine			−C2			−3
D-cycloserin		D			4	
Tandospirone	C2			3		
Adalimumab	C2[c]			3[c]		
Ketamine	C2			3		

The row for olanzapine is shaded green, because this is the best possible recommendation for AN. Olanzapine has the highest evidence for the treatment of AN among the tested medications. Due to its limited acceptability and adherence, the recommendation is, however, limited.

LoE: A: Strong evidence that the intervention is effective; B: Limited evidence that the intervention is effective; C(1–3): Low evidence that the intervention is effective; D: No evidence; −A: Strong evidence that the intervention is NOT effective; −B: Limited evidence that the intervention is NOT effective; −C(1–3): Low evidence that the intervention is NOT effective.

GoR: 1: Strong recommendation for using the intervention; 2: Limited recommendation for using the intervention; 3: Weak recommendation for using the intervention; 4: No recommendation possible; −1: Strong recommendation AGAINST using the intervention; −2: Limited recommendation AGAINST using the intervention; −3: Weak recommendation AGAINST using the intervention.

Please note: For details regarding the grading of LoE and GoR see text. The grading was performed according to Hasan et al. (2019).

[a]Evidence is restricted to adult patients and refers to weight gain only, not to psychopathological improvement.

[b]Evidence and recommendation refer to treatment of fullness and delayed gastric emptying in AN, not weight gain or other DSM-5 symptoms of AN.

[c]Evidence and recommendation limited to patients with AN and Crohn's disease. Green shading: Best possible recommendation for AN.

(mean BMI 15.6). Positive effects were observed including weight gain, reduction in ED symptoms and clinical severity.

A case series from the same group reviewed the charts of nine patients with severe restrictive AN (BMI $<$ 13, mean BMI 12.2) treated with haloperidol, four as monotherapy, and the others with other psychopharmacological agents (Mauri et al. 2013). They found a significant weight increase and described a subjective improvement in the desire for thinness and body image disturbance described as delusional.

These non-analytical studies give low evidence (LoE: C2), with weak recommendations for the use of haloperidol (GoR: 3).

Sulpiride. Vandereycken (1984) conducted a double-blind placebo-controlled cross over trial on sulpiride (300–400 mg) in 18 females with AN. No effect was shown for weight or psychological symptoms.

Pimozide. Vandereycken and Pierloot (1982) report a double-blind placebo-controlled cross over trial in 10 patients with AN treated with pimozide (4 or 6 mg) or placebo. A trend for pimozide to induce weight gain was observed but no further studies were reported on this drug.

Thus, limited evidence (LoE: −B) and limited recommendation (GoR: −2) can be made against the use of sulpiride or pimozide.

Atypical antipsychotics

Olanzapine. A double-blind randomised placebo-controlled trial by Attia et al. (2011) involving two centres tested the effect of olanzapine given in a dose of 2.5–10 mg/day, if tolerated, to outpatients with AN aged 16 or over, with BMI 14–19 for 8 weeks. The researchers had been in contact with 603 patients with AN, of whom 87 were eligible and agreed to a telephone screening interview. However, about half of the patients did not attend the in-person evaluation, others were not interested in the study or were lost due to other reasons. Therefore, only 23 were randomised of which 17 patients (74%) completed the study revealing a significant drug effect on weight gain but not on psychological symptoms including depression, anxiety and ED symptoms.

These findings were replicated in a larger multicentre double-blind randomised placebo-controlled trial of adult outpatients with AN (Attia et al. 2019). One hundred fifty-two participants from five centres were randomised to receive placebo or 2.5–10 mg/day of olanzapine. The completion rate of the study was 55% ($n = 83$), and intention-to-treat analysis showed a significantly greater BMI increase in the olanzapine group. No group differences were observed for the psychological symptoms.

Brambilla et al. (2007) conducted a double-blind randomised placebo-controlled trial with olanzapine given at 2.5 mg/day for one month and 5 mg/day for two months in 30 AN adult outpatients. There was no significant difference in weight gain between olanzapine and placebo in the whole group, but when AN subgroups were analysed a greater increase in weight gain was found in the AN-Binge-eating/-purging type (AN-B/P) group. Some drug benefits were also seen in several psychological measures, such as improvement in ED rituals and aggressiveness, with further inconsistent differences between AN-R and AN-B/P.

In a double-blind, placebo-controlled trial Bissada et al. (2008) randomised 34 patients with AN (mean age: 26.8 years) to receive 2.5–10 mg/day of olanzapine or placebo over 10 weeks in a day-care treatment program. The olanzapine group was significantly superior over the control group concerning rate of weight gain, earlier achievement of the target BMI and reduction of obsessive (but not compulsive) symptoms as measured by the Y-BOCS. No effect was observed for depression or anxiety symptoms.

Kafantaris et al. (2011) conducted a double-blind randomised placebo-controlled trial in 20 adolescents with AN-R up to the age of 21, with 2.5–10 mg/day of olanzapine or placebo. Both groups had similar weight gain and resting energy expenditure and no differences in psychological symptoms. A trend for increasing fasting glucose and insulin levels was found only in the olanzapine group at week 10.

In a naturalistic case-control study by Pruccoli et al. (2022) found that individuals treated with full-dose olanzapine experienced a significantly lower improvement in depressive measures compared to patients on low-dose olanzapine and patients not treated with olanzapine.

We would also like to mention one particular case report by Haruta et al. (2014) of a 36-year-old chronic AN-R patient (BMI = 12) who developed hypoglycaemia. While treated with olanzapine 2.5 mg/day food consumption increased, but she suffered nausea and general fatigue after meals and at night. On day 22 of treatment, she experienced disturbance of consciousness and a low blood glucose level was 23 mg/dl which warranted intravenous treatment with glucose. Hypoglycaemic symptoms resolved five days after olanzapine discontinuation.

Considering the evidence from five RCTs, four of which showed a significant effect on weight gain (Brambilla et al. 2007; Bissada et al. 2008; Attia et al. 2011, 2019), we conclude a strong level of evidence for olanzapine in AN (LoE: A). However, the reluctance of patients to take olanzapine (Attia et al. 2011), low adherence rates (Attia et al. 2019), moderate acceptably and reports of either hyper- or hypoglycaemia lead to a limited recommendation for olanzapine (GoE: 2) in adult patients.

Regarding adolescents, a protocol for a randomised double-blind placebo-controlled trial for the evaluation of efficacy and safety of olanzapine as an adjunctive treatment for AN in adolescent females was published in 2008 (Spettigue et al. 2008). The study protocol was modified, and the study was reported as an open-label study (Spettigue et al. 2018) which examined the effectiveness and safety of olanzapine in 32 adolescents with AN: 14 in the intervention group and 18 in the comparison group of whom eight switched from no adjunctive medication to olanzapine (Spettigue et al. 2018). A higher rate of weight gain was demonstrated in the olanzapine group, with no advantage in psychological symptoms. There were more abnormal chemistry results in the intervention group including elevated liver enzymes, cholesterol and asymptomatic prolactin levels. However, no elevated glucose levels or HBA1C were recorded.

Ayyıldız et al. (2016) reported a case of a 17-year old male inpatient with AN-B/P and BMI 11.9, who developed neuroleptic malignant syndrome after two days of treatment with olanzapine 5 mg/day. The illness presented with fever, muscle rigidity, and autonomic instability, including a second episode after the discontinuation of the medication.

An open trial by Leggero et al. (2010) evaluated the effect of olanzapine (mean dose 4.13 mg/day) on 13 girls with AN-R aged 9–16 years. Improvements were found in BMI, ED symptoms, anxiety, depression, and hyperactivity. Authors noted the improvement in hyperactivity distinguished responders from non-responders.

Aripiprazole. Trunko et al. (2011) reported five cases of AN treated with aripiprazole 5–10 mg/day, and described weight increase, mood elevation, and a reduction in eating-specific anxiety, and decreased rigidity.

Frank (2016) reported four adolescent AN cases treated with aripiprazole: three 12 year-olds and one 17 years-old, achieving weight gain and stabilisation as well as general psychosocial improvement. In one case drug-induced neutropenia was observed but the drug was maintained under monitoring due to the beneficial effect on eating-anxiety and to the patient's request.

Tahıllıoğlu et al. (2020) reported on a case series of eleven adolescents who received aripiprazole (2.5–15 mg/day) for up to 28 months with improved weight, ED behaviours, depressive symptoms, and general clinical condition.

Frank et al. (2017) performed a retrospective case-controlled study comparing 22 AN adolescents treated with aripiprazole (1–5 mg/day), with 84 AN adolescents who were not treated with the medication. Groups were matched for age, length of inpatients stay, BMI, and food avoidance behaviours on admission. In the aripiprazole group, there was a statistically significant greater increase in weight gain.

Another retrospective case-controlled study was conducted by Marzola et al. (2015) comparing three groups of adults patient treated with: (1) SSRI only, (2) SSRI and olanzapine, or (3) SSRI and aripiprazole. All groups improved in depressive, anxiety, and ED symptoms as well as weight gain. A greater reduction in ED rituals and pre-occupations was found in the aripiprazole group compared to olanzapine augmentation and SSRI only. An additional finding was a decrease in purging in the aripiprazole group *vs.* the olanzapine group.

Overall, the evidence for aripiprazole (in adolescents and adults) comprises two retrospective case-control study and three case series, thus limited evidence (LoE: C1 and weak recommendation for its use (GoR: 3).

Risperidone. Hagman et al. (2011) conducted an RCT to evaluate the safety and efficacy of risperidone in adolescents and young adults (12–21 years-old, mean age 16 years) with AN. Forty participants received 0.5–4 mg/day risperidone (mean dose 2.5 in drug group) or placebo for nine weeks. No drug benefits were demonstrated for weight, body image, or psychological symptoms.

The results of this RCT lead to limited evidence against (LoE: −B) and a limited recommendation against the use of risperidone (GoR: −2).

A case report from Japan describes a 10-year-old boy with restrictive AN who was re-introduced to meals after enteral meals (Umehara et al. 2014). Initial treatment with olanzapine was discontinued because of over-sedation. He was treated with risperidone 1 mg/day with a reduction in agitation during enteral feeding and body image distortion, and after one

month he resumed meals. Because he refused to continue oral risperidone therapy was switched to long-acting injections which were given for a year. His symptomatic remission was maintained at 1-year follow-up after the medication was stopped.

Quetiapine. A double-blind randomised placebo-controlled trial by Powers et al. (2012) studied the effect of quetiapine (mean dose 177.7 mg/day) in adult outpatients with AN. The investigators described difficulties in recruitment to the study with the most common reason being fear of weight gain. Of over 200 candidates contacted, only 15 were randomised and 10 completed the trial. There were no group differences in weight or psychological measures. Small effect sizes were observed for the outcome measures suggesting that a higher number of participants would not uncover a significant drug effect. Thus, there is limited evidence (LoE: −B) and a limited recommendation against the use of quetiapine (GoR: −2).

Amisulpride. Ruggiero et al. (2001) studied 35 inpatients with AN given one of three medications at the beginning of the re-feeding phase: amisulpride, clomipramine, and fluoxetine. After the 3-month study phase, the authors revealed a significant increase in the mean weight for amisulpride and fluoxetine but not clomipramine. However, no between group differences were detected. As this study did not have a placebo group and the results are inconclusive, it is not appropriate to make a recommendation based on the results (LoE: D; GoR: 4).

Antiepileptics and mood stabilisers

Lithium. A single placebo-controlled double-blind trial with Lithium was conducted by Gross et al. (1981) on 16 patients with AN aged 12–32. There was increased weight gain in weeks 3–4 of the trial but not in weeks 1–2. Denial of illness and selective appetite were the only psychological assessments that significantly differed between groups with no differences in depression, anxiety, or obsessive symptoms. This study suggests limited evidence for Lithium (LoE: B), and weak recommendation, because of considering significant side effects and required monitoring, and no further evidence accumulated since this study (GoR: 3).

Valproate. A recent case series by Pruccoli and Parmeggiani (2022) described 14 children and adolescent inpatients treated with valproate during their admission. Although treatment with valproate was intended for unstable mood, aggressive behaviour, or insufficient compliance with psychological, and nutritional program, weight gain and a rise in BMI were observed. This single report gives low evidence (LoE: C2) and a weak recommendation for the role of valproate in AN (GoR: 3).

Appetite modulators

Appetite stimulants

Cannabinoids. Gross et al. (1983) performed a 4-week, double-blind cross-over trial of delta-9-terahydrocannabiol (delta-9-THC, 7.5–30 mg/day) compared to diazepam (3–15 mg/day) in 11 patients with AN. Three patients experienced severe dysphoric reactions during 9-THC, and there was no difference in weight between the drugs.

Andries et al. (2014, 2015) conducted a double-blind placebo-controlled crossover study of dronabinol (delta-9-THC) 2.5 mg twice daily in 25 adult patients who had AN for at least 5 years. During the four weeks of drug therapy, there was a significant increase in weight gain compared with placebo, but no difference was reported in EDI scores.

The two RCTs show contradictory results but as the more recent study by Andries included more patients and had a placebo group, we concluded limited evidence (LoE: B) and limited recommendation for the use of dronabinol (GoR: 2).

Cyproheptadine. Goldberg et al. (1979) conducted a double-blind randomised controlled-trial investigating cyproheptadine with or without behavioural therapy in 81 inpatients with AN. No pre-post effect for the drug was found. Post-hoc analysis revealed increased weight gain with cyproheptadine in severe patient groups: those with birth complications, history of significant weight loss (41–51% of norm weight) or a previous outpatient treatment.

Cyproheptadine was also examined as one of three interventions in a randomised-controlled trial comparing amitriptyline, cyproheptadine and placebo (Halmi et al. 1986). Treatment efficacy, i.e. the rate of weight gain increased in the cyproheptadine group only for restrictive patients and decreased for patients with binge-purge AN.

With this insufficient data there is limited evidence to support the use of cyproheptadine (LoE: B). Its low use in the decades following these studies suggest low applicability and practicability, leading to a weak recommendation for its use (GoR:3).

Opioid antagonists

Naltrexone. Marrazzi et al. (1995) reported a double-blind placebo-controlled crossover study of naltrexone in adults outpatients with BN or pinge-purge type AN. In the six patients with binge-purge type AN, there was a reduction in binge-purge symptoms but also in weight. This study reports conflicting outcomes, with a decrease in binge-purge symptoms but also weight loss. Therefore, there is not sufficient evidence (LoE:D) to advise or recommend this medication (GoR: 4).

Hormonal and endocrine treatments

Metreleptin. Gradl-Dietsch et al. (2023) described the treatment of a 15-year-old female patient with AN with metreleptin, a human recombinant leptin, for nine days. The treatment was associated with self-reported increase in appetite resulting in rapid weight gain, and a substantial improvement of eating disorder cognitions and depressive symptoms.

Antel et al. (2022) reported the case of a 15-year-old adolescent male patient with severe AN with marked hyperactivity who was treated with metreleptin over 9 days. Substantial improvements in mood and ED-related cognitions and hyperactivity started after two days of treatment, sub-physiological testosterone and triiodothyronine levels normalised, and weight increased in the follow-up period.

Milos et al. (2020) published a case series of two adults and one adolescent patient with AN. Two of three patients gained weight in the treatment period. They also experienced an improvement in overactivity, repetitive thoughts of food, inner restlessness, fear of weight gain, and depression.

These case reports represent low evidence (LoE: C1); a weak recommendation can made for the use of metreleptin (GoR: 3).

Growth hormone. Hill et al. (2000) conducted a randomised placebo-controlled double bling study in 15 adolescent inpatients who received recombinant human growth hormone or placebo. The rhGH group reached medical stability, i.e. no orthostatic hypotension, more rapidly, but there was no effect on weight or duration of admission. Another randomised placebo-controlled double-blind trial in 21 outpatients was conducted by Fazeli et al. (2010) investigating the effect of 12-week administration of rhGH on weight and metabolic markers. While no difference was between the groups with regards to weight, the rhGH group had decreased fat mass. However, in a small RCT (Léger et al. 2021) in children with AN and low high velocity, eight patients were assigned to the growth hormone group and six to the placebo group. After 12 months, the percentage of patients with a high velocity of more than 5 cm per year during the study period was higher in the growth hormone group than in the placebo group. Therefore, children with AN and prolonged severe growth failure might benefit from growth hormone treatment in this particular indication.

However, the lack of effectiveness in two RCTs concludes strong evidence (LoE: −A) and a strong recommendation against the use of growth hormone (GoR: −1).

Relamorelin. Fazeli et al. (2018) performed a small RCT to study the ghrelin agonist relamorelin (100 μg/d subcutaneously) in 22 adult women with AN. After four weeks there was a trend towards increased weight in the drug group compared with the placebo group ($p = 0.07$). Three drug patients stopped medication use after reporting increased hunger. Gastric emptying time was significantly decreased with relamorelin. The task force decided that this study result counts as low evidence for (LoE: C1). However, as this was a very small study with an unclear statistical result and potentially low acceptability, this evidence did not translate into any recommendations (GoR: 4).

Growth hormone releasing peptide-2. Haruta et al. (2015) reported a case of a severely emaciated 38-year-old woman with refractory AN who was given growth hormone releasing peptide-2 (GHRP-2) 100–200 μg before meals for one year. Improvement in weight, appetite, muscle strength, fatigue, and GI functions were observed, leading to low evidence (LoE: C3) and a weak recommendation for use (GoR: 3).

Oxytocin. A study by Kim et al. (2015) found no effect of oxytocin on food consumption in people with AN. However, the study duration was only 24 h. Therefore, conclusions cannot be drawn from it. Russell et al. (2018) studied the effect of intra-nasal oxytocin (OT) 36 IU/day in two pilot studies of inpatients with AN during 4–6 weeks of admission. In the OT group, the EDE-eating concern score was lower, but no effect on weight was noted. There was a lower rate of perseverative errors in the Wisconsin test. The OT group also had a lower salivary response of cortisol in anticipation of the afternoon snack. Other psychological measures were similar between OT and placebo group. As the study showed reducing eating concerns and

reduced cognitive rigidity after oxytocin but no effect on weight, we have no sufficient evidence to advise for or against the use of oxytocin (LoE: D; GoR: 4).

Testosterone. Kimball et al. (2019) reported an RCT in 90 female patients with AN testing 300 μg transdermal testosterone daily or a placebo patch for 24 weeks. Testosterone was associated with less weight gain and did not lead to improvements in depression, anxiety, or disordered eating symptoms-compared with placebo in women with AN. Thus, there is limited evidence (LoE: −B) and a limited recommendation against the use of transdermal testosterone (GoR: −2).

Gastroprokinetic agents

As patients with AN often experience a feeling of fullness and satiety even after minimal food intake, gastroprokinetic agents like cisapride and metoclopramide were investigated to test whether they could help emptying the stomach of patients quicker and thus help with the feeling of fullness.

Cisapride. Stacher et al. (1987) reported quicker gastric emptying with a single dose of eight mg intravenous cisapride in 12 patients with primary AN. In a double-blind placebo-controlled crossover trial, cisapride 10 mg was given before meals three times a day for 6 weeks (Stacher et al. 1993). Again, decreased gastric emptying time was found but no effect on weight gain or psychological symptoms. A double-blind placebo-controlled trial by Szmukler et al. (1995) in 29 patients found no difference between cisapride group and placebo group in weight gain or in gastric emptying time. These two negative crossover RCTs give strong evidence (LoE: −A) and strong recommendation against the use of cisapride (GoR: −1).

Metoclopramide. An open trial by Saleh and Lebwohl (1980) studied seven patients with AN treated with metoclopramide 40 mg daily given before meals. Results included weight gain, decreased gastrointestinal symptoms, and accelerated gastric emptying. McCallum et al. (1985) reported a similar effect when 11 patients with AN were given a single dose of intramuscular metoclopramide 10 mg before a meal. Both studies found decreased gastric emptying time.

Domperidone. Russell et al. (1983) reported a case of a 27 year-old female with bloating and delayed gastric emptying. The patient improved both in satiety feeling and accelerated gastric emptying after treatment with domperidone 30 mg daily given before meals for 2 weeks.

These case reports represent low evidence (LoE: C2) and weak recommendations can be drawn for metoclopramide and domperidone (GoR: 3). However, it should be noted that this is not a recommendation to treat DSM-5 symptoms of AN, but to treat the problem of delayed gastric emptying.

Nutritional supplements

Zinc. Two randomised double-blind placebo-controlled trials were conducted to investigate the effect of zinc supplantation in patients with AN. Katz et al. (1987) studied 15 adolescents and while no effect on weight gain was demonstrated, depression and anxiety symptoms improved in the zinc group. Birmingham et al. (1994) studied a mixed population ($N = 35$) with an age-range of 12–25 years, with a significant increase in weight gain for the zinc group. These conflicting results from limited studies which were not further pursued represent insufficient evidence (LoE: D) to draw a recommendation (GoR:4).

Polyunsaturated fatty acids (PUFA). A pilot study by Manos et al. (2018) compared the outcomes with four daily doses of omega-3 PUFA supplementation or placebo in a double-blind, placebo-controlled randomised trial of adolescent females with AN ($N = 24$). No benefit was shown for weight or psychological symptoms. In conclusion, this study provides limited evidence against PUFA (LoE: −B), and a limited recommendation against its use (GoR: −2).

Tyrosine. Hart et al. (2021) reported two cases in which amino-acid tyrosine was given for 12 weeks. One of the two gained weight and improves depressive and OC symptoms. This is a non-analytic report with low evidence (LoE: C2), and a weak recommendation (GoR: 3).

Other medications

Alprazolam. Steinglass et al. (2014) performed a double-blind placebo-controlled crossover study to examine the effect of benzodiazepine treatment (alprazolam 0.75 mg) on meal anxiety and caloric intake at meal. No differences emerged between the drug and placebo condition, although alprazolam resulted in greater fatigue. As this is a single meal study, there is not sufficient data (LoE: D) on this intervention (GoR: 4).

Clonidine. Casper et al. (1987) reported a placebo-controlled crossover trial on the effects of clonidine in four patients with AN. Clonidine did not influence the rate of weight gain, nor did it affect hunger or satiety. This small study shows no efficacy of clonidine (LoE: −C2), which leads to a weak recommendation (GoR: −3) against the use of clonidine in AN.

D-cycloserine. Steinglass et al. (2007) conducted an RCT in 14 patients to compare the adjunctive administration of d-cycloserin before four meal-exposure sessions. Caloric intake was not different across interventions. A similar trial by Levinson et al. (2015) where c-cycloserine or placebo were given to 36 patients before three exposure sessions over 2 weeks and with 1-month follow-up, and resulted in an increase in BMI compared to the placebo group, although mealtime anxiety was unaffected. These limited data are insufficient (LoE: D) for any further recommendation (LoR: 4).

Tandospirone. Okita et al. (2013) describe two cases of patients with AN who improved in weight and EDE-Q after treatment with tandospirone, a 5HT1A partial agonist. These cases provide limited evidence (LoE: C2) and weak recommendations for tandospirone (GoR: 3).

Adalimumab. Solmi et al. (2013) reported a case of a 26-year-old who had been affected with AN since 14, continuously refusing treatment for 10 years while her BMI was between 14.5 and 16. At age 24 she developed Crohn's disease. After no response to prednisone or cyclosporin, treatment with infliximab was commenced. After six months of treatment, an allergic reaction appeared, and the medication was switched to the anti-tumor necrosis factor (TNF)-alpha medication adalimumab. During treatment, weight and shape concerns were gradually attenuated in parallel to weight increase up to BMI 17.6 kg/m^2. This case shows limited evidence (LoE: C2) and weak recommendation for adalimumab (GoR: 3) in people with AN and Crohn's disease.

Ketamine. Scolnick et al. (2020) reported a case of a 29 year old female with chronic AN who attained a 6-month stable remission from symptoms and weight restoration with ketogenic diet and ketamine. Several case studies have been reported in patients with depression and AN. Dechant et al. (2020) reported on patient with AN and depression who experienced a reduction in depression and suicidality. In a case series published by Mills et al. (1998), nine of 15 responded to treatment, with reductions in depression. And improvement in AN behaviour and psychopathology. Four cases published by (Schwartz et al. 2021) showed improvements in depression, anxiety, and eating disorder psychopathology. These case reports show limited evidence (LoE: C2) and weak recommendation for ketamine in combination with a ketogenic diet (GoR: 3).

Combination of pharmacotherapy with psychotherapy

Even though two independent open label trials reported that the combination of olanzapine and psychotherapy led to weight gain in patients with AN (Leggero et al. 2010; Spettigue et al. 2018), there is not sufficient evidence from RCTs (Brambilla et al. 2007; Kafantaris et al. 2011) to recommend olanzapine as an adjunct to psychotherapy.

Studies on the combination of antidepressants, such as fluoxetine (e.g. Kaye et al. 2001; Walsh et al. 2006) and psychotherapy are scarce. Therefore, specific recommendations for combinations of psychopharmacological substances with psychotherapy cannot be made.

Bulimia nervosa

After the literature search, we included 70 articles relevant to the guidelines (see Table 3). Fifty-seven articles had already been identified in the first version of the WFSBP guidelines on the pharmacological treatment of eating disorders (Aigner et al. 2011).

Antidepressants

Tri- and tetracyclic antidepressants

Imipramine. Five small RCTs (Pope et al. 1983; Agras et al. 1987; Mitchell et al. 1990; Alger et al. 1991; Rothschild et al. 1994) investigated the effect of imipramine in patients with BN. Pope et al. (1983) reported that imipramine treatment was associated with a significant decrease in the intensity of binge-eating episodes, decreased preoccupation with food, and greater subjective global improvement when compared to placebo. Agras et al. (1987) found a significantly greater reduction in purging (frequency of self-induced vomiting plus the use of laxatives) during imipramine treatment compared to placebo. Mitchell et al. (1990) performed a 4-armed study: (1) imipramine, (2) placebo, (3) imipramine plus intensive group psychotherapy, and (4) placebo combined with intensive group psychotherapy. Compared to placebo,

Table 3. Depicts the results of the literature review of pharmacological studies in BN.

Author	Year	Age (mean, range)	*N*	Agent	Treatment setting	Study design	Randomisation	Placebo-controlled	Double-blind	Treatment duration	Favourable outcome/superiority to placebo	Unfavourable or non-significant outcomes	Psychotherapy
Antidepressants													
Tri- and tetracyclic antidepressants													
Agras et al.	1987	30.9 (21–48)	22	Imipramine 300 mg/day	Mixed	RCT	Yes	Yes	Yes	16 weeks	Reduction in purging at 6 weeks and 16 weeks. BDI reduction at 6 weeks only	BDI: no significant difference at 16 weeks	No
Alger et al.*	1991	32.5 (NR)	69 (33 obese bingers, 22 BN)	Imipramine 200 mg/day, Naltrexone 100–150 mg/day	Mixed	RCT	Yes	Yes	Yes	8 weeks	Naltrexone reduced binge duration in BN; imipramine significantly reduced binge duration in obese bingers	No significant difference between treatment groups and placebo.	No
Mitchell et al.	1990	23.9 (18–40)	171	Imipramine 300 mg/day	Outpatients	RCT	Yes	Yes	Yes	12 weeks	Imipramine alone, imipramine with group therapy and placebo with group therapy all led to improvements in eating behaviours, HAM-D, HAM-A and global severity/improvement. Greater effects in all measures observed in group therapy alone compared to drug alone. Imipramine added to group therapy increased improvement of HAM-D, HAM-A and global severity/improvement.	NR	Yes, Intensive group treatment program, CBT, given with drug or placebo
Pope et al.	1983	27.7 (17–43)	22	Imipramine 200 mg/day	Outpatients	RCT	Yes	Yes	Yes	6 weeks	Binge frequency, binge intensity, preoccupation with food), subjective global improvement HAM-D	Self-control with food	No
Rothschild et al.	1994	32.8 (NR)	24	Imipramine 275 mg/day, Phenelzine 75 mg/day	Mixed	RCT	Yes	Yes	Yes	6 weeks	Phenelzine superior to imipramine and placebo in HAM-D and SCL-90-R overeating item. Phenelzine superior to imipramine and placebo (trend only) in binge/purge frequency		No
Agras et al.	1992	29.6 (18–65)	71	Desipramine 300-350 mg/day	Outpatients	Open trial	Yes	No	No	32 weeks	At 32 weeks, the combined (medication and CBT) 24-week treatment was superior to medication only given for 16 weeks, in reducing binges and purges. The combined treatment was superior to medication in reducing dietary preoccupation (16 weeks) and hunger inhibition (24 weeks).	No significant weight change	Yes, drug given with or without CBT
Agras et al.	1994	NR	61	Desipramine	NR	Open trial	Yes	No	No	24 weeks	At 16 weeks CBT or CBT with medication were superior to medication in binge frequency and purging.		Yes, CBT
Barlow et al.	1988	27.2 (NR)	47	Desipramine 150 mg/day	Outpatients	Double-blind crossover study	Yes	Yes	Yes	6 weeks	Binge frequency, vomiting frequency fatigue scale of the POMS	EDI, SCL-90	No

(*continued*)

Table 3. Continued.

Author	Year	Age (mean, range)	*N*	Agent	Treatment setting	Study design	Rando misation	Placebo-controlled	Double-blind	Treatment duration	Favourable outcome/superiority to placebo	Unfavourable or non-significant outcomes	Psychotherapy
Blouin et al.*	1988	25.5 (20–30)	36	Desipramine 150 mg/day, Fenfluramine 60 mg/day	Volunteers	Double-blind crossover study	Yes	Yes	Yes	15 weeks	Both fenfluramine and desipramine were effective for binge frequency, vomiting frequency and psychological symptoms. Greater response rate to fenfluramine	NR	No
Hughes et al.	1986	25.4 (18–40)	22	Desipramine 200 mg/day	Outpatients	RCT	Yes	Yes	Yes	6 weeks	Binge frequency, Global clinical status, ZSRDS, BSS		No
Walsh et al.	1991	25.2 (18–45)	80	Desipramine 200–300 mg/day	Volunteers	RCT	Yes	Yes	Yes	8 weeks (acute treatment), 34 weeks (maintenance), 14 months (discontinuation)	Reduced binge frequency, improved EAT, BSQ, SCL-90 and trait STRAI at 8 weeks. Binge frequency	29% of participants in 16-week maintenance phase relapsed. Not enough participants in 6-month discontinuation phase.	No
Brambilla et al.*	1995	22 (17–29)	15	Amineptine 300 mg/day, Fluvoxamine 300 mg/day	Outpatients	Open trial	Yes	No	No	4 months	BITE symptoms, BITE gravity for both drugs	Global EDI scores, HAM-D, HAM-A, BMI	Yes, CBT
Mitchell and Groat	1984	25 (20–37)	32	Amitriptyline 150 mg	Outpatients	RCT	Yes	Yes	Yes	4 weeks	Depressive symptoms	Eating behaviour	YES, Minimal behavioural treatment program
Sabine et al.	1983	23.7 (16–65)	50	Mianserin 60 mg/day	Outpatients	RCT	Yes	Yes	Yes	8 weeks	NR	No significant differences between groups in HAM-D, HAM-A, EAT, BRS, weight	No
Selective serotonin reuptake inhibitors													
Brambilla et al.*	1995	22 (17–29)	15	Fluvoxamine 300 mg/day, Amineptine 300 mg/day	Outpatients	Open trial	Yes	No	No	4 months	BITE symptoms, BITE gravity for both drugs	Global EDI scores, HAM-D, HAM-A, BMI	Yes, CBT
Fichter et al.	1996	Fluvoxamine: 25.3, placebo: 23.7 (18–50)	72	Fluvoxamine	NR	RCT	Yes	Yes	Yes	15 weeks	Binges in previous week, urges to binge, EDI-bulimia, SIAB total, fasting and vomiting subscales. scores.	EDI-total and SIAB bulimia subscale significant only in completer analysis and not in intention-to-treat	No
Schmidt et al.	2004	NR 18–50	267	Fluvoxamine 300 mg/day	Outpatients	RCT	Yes	Yes	Yes	8 weeks, 1 year	After 1 year, greater proportion of remission without additional psychotherapy for drug group.	No effects in bulimic or other symptoms at 8 or 1 year	Yes, CBT
Fichter et al.	1991	25.5 (NR)	40	Fluoxetine 60 mg/day	Inpatients	RCT	Yes	Yes	Yes	5 weeks	Weight reduction	No differences in eating behaviour and general psychopathology	Yes, intensive broad-spectrum behavioural treatment program
Fluoxetine Bulimia Nervosa Collaborative Study Group	1992	27.1 (>18)	270	Fluoxetine 60/20 mg/d	Outpatients	RCT	Yes	Yes	Yes	8 weeks	Binge frequency and vomiting frequency reduced with 60mg dose. Depression, carbohydrate craving, and pathologic eating attitudes and behaviours also improved with dose effect.	More adverse effects with fluoxetine: insomnia, nausea, asthenia, and tremor, without discontinuation	No

(*continued*)

Table 3. Continued.

Author	Year	Age (mean, range)	*N*	Agent	Treatment setting	Study design	Rando misation	Placebo-controlled	Double-blind	Treatment duration	Favourable outcome/superiority to placebo	Unfavourable or non-significant outcomes	Psychotherapy
Goldbloom et al.	1997	25.8 (18–45)	76	Fluoxetine 60 mg/day	Outpatients	Open trial	Yes	No	No	14 weeks	Binge episodes, vomiting episodes and combined fluoxetine and CBT was superior to fluoxetine alone.	Binge-eating, vomiting, dietary restraint, mood and self-esteem similar among groups. No superiority for combined treatment over CBT.	Yes, CBT with or without medication
Goldstein et al.	1995	26.5 (>18)	398	Fluoxetine 60 mg/day	Outpatients	RCT	Yes	Yes	Yes	16 weeks	Binge-eating, vomiting, EDI, CGI, PGI	HAM-D	No
Jacobi et al.	2002	26 (18–65)	53	Fluoxetine 60 mg/day	Outpatients	Open trial	Yes	No	No	4 months	Binge-eating and vomiting improved in all groups. Similar improvement in psychopathology.		Yes, CBT with or without medication
Kotler et al.	2003	16.2 (12–18)	10	Fluoxetine 60 mg/day	Outpatients	Open trial	No	No	No	8 weeks	Weekly binge-eating episodes, weekly purge episodes, CGI-I scale.	NR	Yes, Supportive psychosocial treatment
Mitchell et al.	2001	26.6 (18–46)	91	Fluoxetine 60 mg/day	Outpatients	Open trial	Yes	Yes	No	4 weeks, 16 weeks	Both drug effect and self-manual effective in reducing binge-eating episodes at vomiting at 4 and 16 weeks. Additive effect for combined treatment. CGI and PGI improved only with fluoxetine, not with manual.	EDI, HAM-D, laxative abuse, diuretic abuse, and days fasting	Self-help manual with or without drug/placebo
Romano et al.	2002	29.7 (>18)	232	Fluoxetine 60 mg/day	Outpatients	RCT	Yes	Yes	Yes	8 + 52 weeks	Longer time to relapse with drug than placebo. Binging and vomiting episodes, CGI, YBC-ED	NR	No
Sysko et al.	2010	26.9 (17–63)	785	Fluoxetine 20/60 mg/day	Outpatients	Open trial	Yes	Yes	No	8 weeks	NR	Patients with BN who did not report a ≥60% decrease in the frequency of binge-eating or vomiting at week 3 were unlikely to respond to fluoxetine	No
Walsh et al.	2000	29.9 (NR)	22	Fluoxetine 60 mg/day	Mixed	RCT	Yes	Yes	Yes	8 weeks	Frequency of objective binge-eating episodes, frequency of purging, global EDE, TFEQ disinhibition score.		No
Leombruni, Amianto, et al.	2006	27.5 (NR)	37	Fluoxetine 20–60 mg/day *vs.* Citalopram 20–40 mg/day	Outpatients	Open trial	Yes	No	No	12 weeks	Vomiting, CGI and BSQ improved in both groups. BDI improved only with citalopram and anger introjection improved only with fluoxetine.	NR	No
Sundblad et al.	2005	27 (21–45)	46	Citalopram 40 mg/day, Flutamide 500 mg/day	Volunteers	RCT	Yes	Yes	Yes	12 weeks	Reduction in binge-eating with flutamide alone or combined flutamide and citalopram	No binge reduction with citalopram only or placebo	No
Milano et al.	2004	NR 24–36	20	Sertraline 100 mg/day	Outpatients	Open trial	Yes	Yes	No	12 weeks	Decrease in binge-eating episodes and purging episodes		No

(*continued*)

Table 3. Continued.

Author	Year	Age (mean, range)	*N*	Agent	Treatment setting	Study design	Rando misation	Placebo-controlled	Double-blind	Treatment duration	Favourable outcome/superiority to placebo	Unfavourable or non-significant outcomes	Psychotherapy
Other selective monoamine reuptake inhibitors													
Christensen and Averbuch	2009	35	1	Duloxetine 60 mg/day (12 weeks), then 30 mg/day (4 months)	Outpatient	Case report	No	No	No	12 weeks + 4 months	Single reported binge/purge episode over an entire month. No symptoms over 3 months period.		Yes, CBT
Hazen and Fava.	2006	33	1	Duloxetine 120 mg/day	Outpatient	Case report	No	No	No	16 weeks	Complete remission of the patient's binge/purge symptoms and improvement in mood		No
El-Giamal et al.	2000	27.9 (19–53)	7	Reboxetine 8 mg/day	Outpatients	Case series	No	No	No	12 weeks	Binge-eating frequency, vomiting frequency, HAM-	Significant constipation in 2 patients leading to laxative use and dropout	No
Fassino et al.	2004	27.1 (NR)	28	Reboxetine 4 mg/day	Outpatients	Open trial	Yes	No	No	3 months	EDI-2 subscales, BSQ total, HAM-D, GAF	NR	No
Horne et al.	1988	NK	81	Bupropion	NR	RCT	Yes	Yes	Yes	8 weeks	Reduced binge-eating and purging episodes	Four subjects experienced grand mal seizures	No
Monoamine oxidase inhibitors													
Carruba et al.	2001	25.4 (18–40)	78	Moclobemide 600 mg/day	Outpatients	RCT	Yes	Yes	Yes	6 weeks	NR	Binge-eating and vomiting episodes, HAM-D, BITE Symptoms, BITE Severity Scale.	No
Kennedy et al.	1988	26.4 (18–40)	18	Isocarboxazid 60 mg/day	Outpatients	Double-blind crossover study	Yes	Yes	Yes	13 weeks	Binge-eating and vomiting	Over 50% of patients decided to discontinue isocarboxazid 1 year after the study	No
Kennedy et al.	1993	26.7 (18–40)	36	Brofaromine 200 mg/day	Outpatients	RCT	Yes	Yes	Yes	8 weeks	Vomiting episodes, weight	binge-eating episodes, eating and shape attitudes, depression and anxiety	Yes, CBT
Rothschild et al.*	1994	32.8 (NR)	24	Phenelzine 75 mg/day, Imipramine 275 mg/day	Volunteers	RCT	Yes	Yes	Yes	6 weeks	Phenelzine superior to imipramine and placebo in HAM-D and SCL-90-R overeating item Phenelzine superior to imipramine and placebo (trend only) in binge/purge frequency		No
Walsh et al.	1984	26.5 (21–36)	35	Phenelzine 60–90 mg/day	Volunteers	RCT	Yes	Yes	Yes	10 weeks	Binge-eating episodes	NR	No
Walsh et al.	1988	27 (18–45)	62	Phenelzine 60–90 mg/day	Volunteers	RCT	Yes	Yes	Yes	8 weeks	Binge-eating frequency, EAT	HAM-D, BDI, SCL-90,	No
Other serotonergic antidepressants													
Pope et al.	1989	26 (19–38)	46	Trazodone 400 mg/day	Volunteers	RCT	Yes	Yes	Yes	6 weeks	Frequency of binge-eating and vomiting patients' subjective assessments of improvement	NR	No
Antipsychotics													
Atypical antipsychotics													
Trunko et al.	2011	33.6 (15–55)	8 (5 AN, 3 BN)	Aripiprazole 5–15 mg/day	Outpatients	Case series	No	No	No	>4 months	Improved eating disordered, behaviour, depression, anxiety, and cognitive flexibility	NR	No

(*continued*)

Table 3. Continued.

Author	Year	Age (mean, range)	*N*	Agent	Treatment setting	Study design	Rando misation	Placebo-controlled	Double-blind	Treatment duration	Favourable outcome/superiority to placebo	Unfavourable or non-significant outcomes	Psychotherapy
Antiepileptics and mood stabilisers													
Guerdjikova, Blom, Martens, et al.	2013	32.6 (21–39)	12	Zonisamide 100–600 mg/day	Volunteers	Open trial	No	No	No	12 weeks	Frequency of binge/purge episodes. CGI-S, YBOCS-BE (total, obsession, and compulsion), TFEQ (disinhibition and hunger), HAM-D.	Weight was unchanged	No
Hedges et al.	2003	29.0 (16–50)	69	Topiramate	NR	RCT	Yes	Yes	Yes	10 weeks	EDI, EAT, HAM-A, PGI	HAM-D	No
Hoopes et al.	2003	29.0 (16–50)	35	Topiramate	NR	RCT	Yes	Yes	Yes	10 weeks	Binge and purge frequency	NR	No
Nickel et al.	2005	21.3, >18	60	Topiramate 250 mg/day	Volunteers	RCT	Yes	Yes	Yes	10 weeks	Binge/purge episodes, weight, SF-36	NR	No
Hsu et al.	1991	25.4 (NR)	68	Lithium carbonate 600–1200 mg/day	Outpatients	RCT	Yes	Yes	Yes	8 weeks	NR	No significant effect on BN compared to placebo	No
Kaplan et al.	1983	24.7 (20–34)	6	Carbamazepine serum levels 6–10 mg/ml	Outpatients	Double-blind crossover trial	No	Yes	Yes	6 weeks	Only one patient with comorbid bipolar disorder improved	Five patients had either no response or an equivocal response	No
Trunko et al.	2014	17.8 (15–21)	2	Lamotrigine 75–400 mg/day	Mixed	Case series	No	No	No	5-48 months	Reduced binge/purge frequency, improved mood and functioning	NR	No
Trunko et al.	2017	30.1 (18–42)	14 (AN, BN)	Lamotrigine 100–300 mg/day	Mixed	Open trial	No	No	No	60 or more days	BEST, ZAN-BPD	EDE-Q, STAI, BDI-II	Yes, DBT
Anti-ADHD medication and stimulants													
Guerdjikova and McElroy	2013	32 (NK)	1 BN	Methylphenidate 54–72 mg/day	Inpatient	Case report	No	No	No	1 year	Remission in binge/purge symptoms and improvement in ADHD after bipolar, substance use, and panic disorders were successfully treated with hospitalisation, intensive psychotherapy, quetiapine, and lamotrigine	NR	Yes, Psychosocial
Sokol et al.	1999	29 (20–38)	2	Methylphenidate 15/20 mg/day	Outpatients	Case report	No	No	No	4 days + 10 months	Decreased binging and purging	NR	No
Keshen et al.	2021	(18–55)	18	Lisdexamfetamine	Volunteers and outpatients	Open trial	No	No	No	8 weeks	Weight reduction, reduction in objective binge episodes and compensatory behaviours.	Increase in heart rate. 1 participant withdrawn for clinically significant weight loss.	NK
Appetite modulators													
Appetite suppressants													
Blouin et al.*	1988	25.4 (18–41)	36	Fenfluramine 60 mg/day, Desipramine 150 mg/day	Volunteers	Double-blind crossover study	Yes	Yes	Yes	15 weeks	Both fenfluramine and desipramine were also effective for binge frequency, vomiting frequency and psychological symptoms. Greater response rate to fenfluramine	NR	No
Fahy et al.	1993	24 (18–45)	43	d- Fenfluramine 45 mg/day	Outpatients	RCT	Yes	Yes	Yes	8 weeks	Binges, BITE symptom	'Weight, vomiting,, MADRAS, EAT, BITE severity	Yes, CBT
Ferreira et al.	2018	51	1	Sibutramine 180 mg/day	Outpatient	Case report	No	No	No	NR	NR	Recurrent psychotic symptoms following misuse of high dose sibutramine	No

(*continued*)

Table 3. Continued.

Author	Year	Age (mean, range)	*N*	Agent	Treatment setting	Study design	Rando misation	Placebo-controlled	Double-blind	Treatment duration	Favourable outcome/superiority to placebo	Unfavourable or non-significant outcomes	Psychotherapy
Opioid antagonists													
Alger et al.*	1991	32.5 (NR)	69 (33 obese bingers, 22 BN)	Naltrexone 100–150 mg/day, Imipramine 200 mg/day	Mixed	RCT	Yes	Yes	Yes	8 weeks	Naltrexone reduced binge duration in BNs	Binge frequency in BN and obese bingers	No
Huseman et al.	1990	NK	8	Naltrexone	NK	RCT	Yes	Yes	Yes	10 weeks	NR	No effect on frequency of binge/vomiting	No
Jonas and Gold	1988	NR	16	Naltrexone 100–300 mg/day	Outpatients	Open trial	Yes	No	No	6 weeks	Reduction of binge-eating and purging frequency in high-dose group only	HAM-D	No
Mitchell et al.	1989	23.7	19	Naltrexone 50 mg/day	Mixed	Double-blind crossover study	Yes	Yes	Yes	6 weeks	NR	No reduction in binge-eating and vomiting episodes	No
Hormonal and endocrine treatments													
Kim et al.	2015	22.5, >17	115 (AN, BN, healthy)	Oxytocin 35.2 mg	Mixed	Double-blind crossover study single session	Yes	Yes	Yes	24 h	Decrease in calorie consumption over 24 h in patients with BN.	No effect on food consumption in AN group	No
Other serotonergic agents													
Faris et al.	2000	29.1 (21–46)	26	Ondansetron 24 mg/day	Volunteers	RCT	Yes	Yes	Yes	6 weeks	Decreased binge and vomiting frequency, decreased time engaged in BN symptoms, increased normal meals and snacks consumption.	NR	No
Other medications													
Broft et al.	2007	34.6 (25–43)	7 (4 BED, 3 BN)	Baclofen 60 mg/day	Outpatients	Open trial	No	No	No	10 weeks	Reduction in binge-eating frequency in patients with BED and BN	BDI	No
Guerdjikova, Blom, Mori, et al.	2013	32 (20–58)	8	N-acetylcysteine 600–2400 mg/day	Outpatients	Open trial	No	No	No	12 weeks	NR	Binge-purge episodes frequency, eating pathology, mood or clinical impression	No
Combinations													
Sundblad et al.	2005	27 (21–45)	46	Citalopram 40 mg/day, Flutamide 500 mg/day	Volunteers	RCT	Yes	Yes	Yes	12 weeks	Reduction in binge-eating with flutamide alone or combined flutamide and citalopram	No changes in the groups given binge reduction with citalopram only or placebo	No
Meta-analyses													
Bacaltchuk and Hay	2003	>18	NA	TCA's, SSRIs, MAOI, and other ADs	NA	Systematic review and meta-analysis	NA	NA	NA	NA	Pooled relative risk for binge remission with drugs 0.87 similar efficacy among drug groups, fluoxetine had better patient acceptability	Ads (TCAs) treated patients has higher drop rate, more adverse drug effects in treated arm (antidepressants) causing treatment discontinuation.	No

NR: not reported; NA: not applicable; NK: not known; TCAs: tricyclic antidepressants; SSRIs: selective serotonin reuptake inhibitors; BDI: Beck Depression Inventory; BEST: Borderline Evaluation of Severity over Time; BITE: BN Investigation Test; BMI: Body Mass Index; BSQ: Body Shape Questionnaire; BSS: Bulimia Symptom Scale; BULIT: Bulimia Test; CGI: Clinical Global Impression Scale; CGI-I: Clinical Global Impressions-Improvement; EAT: Eating Attitudes Test; EDE: Eating Disorder Examination; EDI: Eating Disorder Inventory; EDI-2: Eating Disorder Inventory-2; FCI-II: Food Craving Inventory-II; GAF: Goldman's Global Assessment of Functioning Scale; HAM-A: Hamilton Rating Scale for Anxiety; HAM-D: Hamilton Rating Scale for Depression; MADRS: Montgomery-Åsberg Depression Rating Scale; PGI: Patient's Global Impression; POMS: Profile of Mood States; SCL-90: Symptom Checklist-90; SCL-90-R: Revised Form of the Hopkins Symptom Check List; SF-36: The Short Form Health Survey; SIAB: Structured Interview for Anorexia and Bulimia Nervosa; STAI: State-Trait Anxiety Inventory; STAXI: State-Trait Anger Expression Inventory; TFEQ: Three Factor Eating Questionnaire; VAS: Visual Analogue Scale; YBCEDS: Yale-Brown-Cornell Eating Disorder Scale; YBOCS: Young-Brown Obsessive-Compulsive Symptoms; YMRS: Young Mania Rating Scale; ZAN-BPD: Zanarini Rating Scale for Borderline Personality Disorder; ZSRDS: Zung Self-rated Depression Scale; CBT: cognitive behavioural therapy; DBT: dialectical behavioural therapy.
Lightly shaded rows indicate the inclusion of children and adolescent. Mean and range of age were reported where available.
*Study mentioned twice in the table.

imipramine led to a statistically significant improvement in the eating disorders inventory and a greater global improvement.

However, the addition of antidepressant treatment to the intensive group psychotherapy component did not significantly improve outcome over intensive group psychotherapy combined with placebo treatment. In their trial, 36 patients who received imipramine discontinued the study early. Whereas only 10 subjects who received placebo dropped out early. This difference was statistically significant.

In a 3-armed study by Alger et al. (1991) testing naltrexone, imipramine, and placebo, imipramine treatment did not result in a significant reduction in either binge frequency or binge duration in the normal weight patients with BN compared with the placebo control patients. In their trial, imipramine significantly reduced the binge duration in the subgroup of obese patients with binge-eating, but the reduction was not significantly different from the placebo arm. In a 3-armed study by Rothschild et al. (1994) investigating imipramine, phenelzine, and placebo, the imipramine and placebo groups showed minimal change in bulimic symptoms with no statistical difference between the two groups.

In summary, there are two small RCTs that did not find any statistical superiority over placebo for imipramine in BN, and three RCTs that did. However, one of the positive RCTs showed low acceptance for imipramine and no superiority of imipramine plus psychotherapy compared to psychotherapy only (Mitchell et al. 1990). Thus, the contradicting results lead to no sufficient evidence to advise for or against the use of the intervention (LoE: D) which means insufficient evidence to make any recommendations (GoR: 4).

Desipramine. There are four RCTs that tested desipramine 150–300 mg/day *vs.* placebo (Hughes et al. 1986; Barlow et al. 1988; Blouin et al. 1988; Walsh et al. 1991) in people with BN and several open trials. All four RCTs found statistical superiority in reducing binging and vomiting in patients with BN. However, some patients in the desipramine groups experienced intolerable side effects and left the trial (Hughes et al. 1986; Barlow et al. 1988; Walsh et al. 1991) which was not the case in the placebo groups. Blouin et al. (1988) reported the side effect of a dry mouth significantly more frequent in the desipramine group than in the placebo group. Thus, there is evidence from more than two RCTs that desipramine is effective (LoE: A). However, its poor acceptability leads to a grade 3 recommendation to use in BN.

Amineptine. An open study that included only five patients in the amineptine arm did not find any statistically significant reduction in the Eating Disorder Inventory (EDI) score (Brambilla et al. 1995). This result of a very small study which shows no efficacy (LoE: −C2), leads to a weak recommendation (GoR: −3) against the use of amineptine in BN.

Amitriptyline. There is one RCT with 32 female outpatients with BN who received either amitriptyline or placebo. Both groups improved significantly. However, the differences between drug and placebo treatment did not reach statistical significance regarding the eating behaviour. Thus, the intervention with amitriptyline is not more effective than placebo. This result yields limited negative evidence (LoE: −2) against amitriptyline and leads to a limited recommendation against the use of amitriptyline for the treatment of BN.

Mianserin. Sabine et al. (1983) tested mianserin in an RCT against placebo and found no significant difference between groups regarding BN symptoms or general psychopathology. Thus, we have found one RCT showing no superiority of mianserin to placebo. Therefore, there is grade -B evidence that mianserin is not effective. This leads to a grade −2 recommendation against using mianserin in BN.

Selective serotonin reuptake inhibitors

Fluvoxamine. Two RCTs tested fluvoxamine in BN. One RCT showed a significantly positive effect on relapse prevention in the fluvoxamine group compared to placebo (Fichter et al. 1996). The second RCT, however, found no superiority of fluoxetine compared to placebo regarding response to treatment in the short- or long term, but a potential benefit regarding relapse prevention (Schmidt et al. 2004). The latter RCT (Schmidt et al. 2004) reported 19 serious adverse events 17 of which were in the fluvoxamine group. These included three patients with grand mal fits. In summary, there some indication of fluvoxamine's effectiveness to prevent relapse, but also indication that it leads to serious adverse events, we have conflicting to advise for or against the use of fluoxetine in the treatment of BN (LoE: D) which makes no recommendation possible (GoR: 4).

Fluoxetine. Four large RCTs (Fluoxetine Bulimia Nervosa Collaborative Study Group 1992; Goldstein et al. 1995; Walsh et al. 2000; Romano et al. 2002) with a 'high quality' SIGN rating found a statistically

significant superiority of fluoxetine regarding binge-eating and vomiting, whereas only one small RCT did not detect a significant difference between fluoxetine and placebo when added to intensive inpatient therapy (Fichter et al. 1991). One RCT found that some adverse events (insomnia, nausea, asthenia, and tremor) occurred significantly more frequently with fluoxetine (60 or 20 mg/d) than with placebo. However, no statistically significant difference among treatment groups in the proportion of patients discontinuing the study because of adverse events was found. Thus, the higher frequency of side effects did not affect the acceptability of fluoxetine. A Cochrane Database Systematic Review found that fluoxetine had a similar acceptability to placebo in people with BN (Bacaltchuk and Hay 2003). Therefore, there is grade A LoE that fluoxetine is effective and a grade 1 recommendation for using it as an intervention for BN.

Citalopram. One RCT investigated the effect of citalopram *vs.* placebo in people with BN (Sundblad et al. 2005). The research team performed a four-armed study where patients received the androgen receptor antagonist flutamide, the serotonin reuptake inhibitor citalopram, flutamide plus citalopram, or placebo for 3 months using a double-blind design. The reduction in binge-eating compared with baseline was statistically significant in both groups given flutamide but not in the groups given citalopram only or placebo. Leombruni, Amianto, et al. (2006) investigated the effects of citalopram *vs.* fluoxetine in a single-blind RCT in which participants but not psychiatrists were open to the study agent. They found that citalopram did not significantly reduce bulimic symptoms in the Eating Disorder Inventory-2 but has a significant effect on depressive symptoms. Thus, we have grade − B evidence that citalopram is not effective regarding BN symptoms which translates into a grade −2 recommendation against using citalopram in BN to treat bulimic symptoms.

Sertraline. One open study with 20 participants was performed by Milano et al. (2004). After 12 weeks of treatment, the group treated with sertraline had a statistically significant reduction in binge-eating and purging compared with the group who received placebo. Thus, we have only low (LoE: C1) evidence that this treatment is effective which leads to a weak recommendation (GoR: 3) for the use of sertraline in BN.

Other selective monoamine reuptake inhibitors

Duloxetine. Two case reports are available for the treatment of BN with the serotonin-norepinephrine reuptake inhibitor (SNRI) duloxetine (Hazen and Fava 2006; Christensen and Averbuch 2009). Thus, the evidence for the effectiveness of duloxetine in BN is low (LoE: C2), and only a weak recommendation can be made (GoR: 3).

Reboxetine. An open trial (Fassino et al. 2004) and a case series with seven outpatients with BN (El-Giamal et al. 2000) found an improvement of BN and depressive symptoms under the treatment with the noradrenaline reuptake inhibitor reboxetine which equals low evidence (LoE: C1) for its benefits in patients with BN. As it showed good acceptability with little side effects, a low-grade recommendation (GoR: 3) was made.

Bupropion. A multicentre RCT by Horne et al. (1988) tested the noradrenalin-dopamine reuptake inhibitor (NDRI) bupropion in people with BN and found a superiority in reducing episodes of binge-eating and purging. However, four of 55 subjects treated with bupropion experienced grand mal seizures. The risks of seizures in people with BN who take bupropion is documented further in a case report by Dagan and Yager (2018). Thus, despite its positive effect on binge-eating and purging (LoE: B), we advise against its use (GoR: −2) due to the associated high risk for seizures.

Monoamine oxidase inhibitors

Moclobemide. Carruba et al. (2001) tested moclobemide in an RCT in 52 female patients with BN but found no superiority of moclobemide compared to placebo in reducing the weekly number of binge-eating episodes or BN psychopathology. Therefore, there is limited evidence against moclobemide (LoE: −B) and a limited grade of recommendation against its use (GoR: −2).

Isocarboxazid. Kennedy et al. (1988) investigated the effects of the non-selective, irreversible monoamine oxidase inhibitor isocarboxazid in the treatment of BN in a small RCT with a crossover design and found a significant reduction in binge-eating and vomiting during isocarboxazid treatment. Thus, there is limited evidence (LoE: B) and limited recommendation (GoR: 2) for isocarboxazid in BN.

Brofaromine. Kennedy et al. (1993) tested the selective and reversible monoamine oxidase-A inhibitor brofaromine in an RCT involving 36 female outpatients with BN but found no advantages of brofaromine on psychopathology or BN-specific symptoms. The level of evidence against brofaromine is limited (LoE: −B) as is the grade of recommendation against its use (GoR: −2).

Phenelzine. Three RCTs have been published on the use of the monoamine oxidase inhibitor phenelzine in BN (Walsh et al. 1984, 1988; Rothschild et al. 1994). The RCT with the highest quality according to the SIGN rating is Walsh et al. (1988). Eighty women with BN entered this RCT, 50 women completed it. Phenelzine was significantly superior to placebo in the reduction of binge frequency. This result was comparable with an earlier smaller study published by Walsh et al. (1984). One RCT, however, compared phenelzine with imipramine and found a superiority of phenelzine (Rothschild et al. 1994). Therefore, the available evidence (LoE: B) and the grade of recommendation (GoR: 2) are limited.

Other serotonergic antidepressants

Trazodone. Pope et al. (1989) investigated the use of trazodone in patients with BN in an RCT. Trazodone proved significantly superior to placebo in decreasing the frequency of binge-eating and vomiting while producing few adverse effects. Thus, there is limited evidence (LoE: B) and a limited (GoR: 2) recommendation for its use.

Antipsychotics

Atypical antipsychotics

Aripiprazole. A case series on the treatment of eight patients, five with AN and three with BN, with aripiprazole was reported by Trunko et al. (2011). Thus, the evidence for the effectiveness of aripiprazole in BN is low (LoE: C2), and only a weak recommendation can be made (GoR: 3).

Antiepileptics and mood stabilisers

Oxcarbazepine. Cordás et al. (2006) reported the use of oxcarbazepine in two self-mutilating bulimic patients. One benefitted regarding her BN symptoms, the other did not. These cases do therefore not provide sufficient evidence (LoE: D) to advise for or against the use of the intervention or to make any treatment recommendation (GoR: 4).

Zonisamide. An open-label, 12-week study of the antiepileptic drug zonisamide in 12 patients with BN found significant reductions in the frequency of binge-purge episodes, binge-purge days, ED psychopathology, obsessive-compulsive features, and depressive symptoms (Guerdjikova, Blom, Martens, et al. 2013). As only six patients completed the study, this open-label study provides level C2 evidence for the effectiveness of zonisamide in BN, and a weak grade of recommendation in BN (GoR: 3).

Topiramate. One RCT compared topiramate ($N = 35$) and placebo ($N = 34$) over 10 weeks (Hedges et al. 2003; Hoopes et al. 2003) in people with BN and found that topiramate was associated with significant improvements in both binge and purge symptoms. Another RCT of a similar size ($N = 30$ in each of the topiramate and the control group) reported a significant improvement in binge/purge frequency during topiramate treatment compared to placebo, too (Nickel et al. 2005). No cognitive or memory problems were encountered. The most frequent side effects were sedation, dizziness, paraesthesia, and headache which presented in similar frequencies in the topiramate and the control group. Acceptability was also comparable. Topiramate treatment was started at 25 mg/day and increased to a maximum dose between 250 (Nickel et al. 2005) and 400 mg/d. (Hedges et al. 2003; Hoopes et al. 2003). Thus, the evidence that topiramate is effective is strong (LoE: A) as is the grade of recommendation (GoR: 1). However, topiramate is contraindicated in pregnancy and in women of childbearing potential if not using a highly effective method of contraception.

Lithium. An RCT by Hsu et al. (1991) comparing lithium carbonate and placebo, found no differential effect. This finding translates into limited evidence against lithium (LoE: −B) and a limited grade of recommendation against its use (GoR: −2).

Carbamazepine. A double-blind crossover trial with six patients with BN testing carbamazepine was published by Kaplan et al. (1983). Five of these six patients had either no response or an equivocal response to carbamazepine; only one patient with a history suggestive of bipolar disorder responded dramatically with cessation of binge-eating. This provides low evidence against the use of carbamazepine (LoE: −C2) and a low grade of recommendation (GoR: −3) against its use.

Lamotrigine. One case series and one open trial (Trunko et al. 2014, 2017) tested lamotrigine in people

with BN. Both studies included 2 patients with BN each, and lamotrigine treatment was associated with reductions in ED symptoms. Thus, the evidence for its benefits is low (LoE: C2), and only a low-grade recommendation (GoR: 3) can be made.

Anti-ADHD medication and stimulants

Methylphenidate. Two publications (Sokol et al. 1999; Guerdjikova and McElroy 2013) reported successful treatment of three patients with BN in total with methylphenidate which translates to low evidence (LoE: C2) and a low grade of recommendation (GoR: 3) for methylphenidate.

Lisdexamfetamine. Keshen et al. (2021) performed an open-label feasibility study to test lisdexamfetamine (LDX) in 23 patients with BN, of which 18 completed the study. LDX was well tolerated. LDX led to a mean weight reduction of 2.1 kg, and one participant was withdrawn for clinically significant weight loss. Reductions in objective binge episodes and compensatory behaviours were reported. The authors state that this feasibility study should not lead to any recommendations for the use of LDX in BN. However, it generates a low level of evidence (LoE: C1). As weight loss is an unwanted side effect, we agree with Keshen et al. (2021) that no recommendation is possible (GoR: 4).

Appetite modulators

Appetite suppressants

Sibutramine. One case report by Ferreira et al. (2018) describes the misuse of sibutramine, an appetite suppressing sSNRI in a patient with BN for weight loss who developed psychotic symptoms. Due to its various psychiatric side effects, it has meanwhile been withdrawn from the market in most countries. Therefore, due to side effects and its potential for misuse (Ferreira et al. 2018) the task force sees negative evidence (LoE: −C2) against sibutramine in patients with BN, and we strongly recommend against its use (GoR: −1).

Fenfluramine. A small RCT with 22 patients (Blouin et al. 1988) used a crossover study design where the sympathomimetic stimulant fenfluramine, and desipramine, were each tested against placebo. Fenfluramine reduced the frequencies of binging and vomiting and BN psychopathology. This can be considered as limited evidence (LoE: B). Fenfluramine and d-fenfluramine (see below) were removed from the market because of an association with valvular heart disease leading to changes in the valvular morphology and regurgitation that could be seen in echocardiography (Connolly et al. 1997; Graham and Green 1997). Therefore, we recommend against its use (GoR: −1).

d-Fenfluramine. Fahy et al. (1993) conducted an RCT with 43 patients with BN and used fenfluramine enantiomer d-fenfluramine. They did not find any advantage over placebo when both fenfluramine and placebo were given in addition to psychotherapy. Therefore, there is limited evidence against d-fenfluramine (LoE: −B) and a recommendation against its use (GoR: −1) in BN because of valvular heart disease (see above).

Opioid antagonists

Naltrexone. One small RCT in 10 patients with BN with a crossover design (Huseman et al. 1990) tested the opiate antagonist naltrexone but did not find any statistically significant effect on BN psychopathology or on the frequency of binge/vomiting. Another small RCT was performed by Alger et al. (1991). This trial included 22 patients with BN and 33 'obese bingers' which would presumably fulfill the criteria for BED according to DSM-5 (American Psychiatric Association 2013) which was issued in 2013. In the 22 patients with BN, naltrexone caused a significant reduction in binge duration compared with placebo, but it did not significantly reduce binge frequency when compared with placebo. Changes in psychopathology were not reported in the publication (Alger et al. 1991). Two patients with BED and one patient with BN developed liver enzyme elevation. Thus, there is limited evidence (LoE: −B) that naltrexone is not effective and a limited recommendation against its use in BN (GoR: −2).

Hormonal and endocrine treatments

Oxytocin. Three brief experimental studies with a randomised-controlled crossover design have been published (Kim et al. 2015, 2018; Leslie et al. 2019). However, only two of these experimental studies reported outcomes regarding BN psychopathology and eating behaviour (Kim et al. 2015; Leslie et al. 2019) but found no differences between the oxytocin and the placebo group. Thus, there is a limited level of evidence against oxytocin (LoE: −B), and a limited

grade of recommendation against its use in patients with BN (GoR: −2).

Other serotonergic agents

Ondansetron. One double-blind RCT was performed testing the serotonin receptor antagonist ondansetron against placebo in 26 patients (Faris et al. 2000). Mean binge and vomit frequencies were significantly lower in the ondansetron group at four weeks and there were significant improvements in secondary indicators of disease severity. Thus, the level of evidence (LoE: B) and the grade of recommendation (GoR: 2) are limited.

GABAergic medications

Baclofen. One open-label study tested baclofen (Broft et al. 2007). In this trial, three of seven female patients suffered from BN. Two patients with BN experienced a significant decrease in binge-eating frequency, and one patient was free of binge-eating after 10 weeks. Thus, this study counts as low evidence (LoE: C2) and leads to a weak (GoR: 3) recommendation of baclofen for BN.

Other medications

N-*acetylcysteine.* Guerdjikova, Blom, Mori, et al. (2013) performed a 12-week open-label flexible-dose study in eight patients with BN to test the amino acid and cysteine pro-drug N-acetylcysteine (NAC) which reduces the synaptic release of glutamate in BN. Only two patients completed the study. NAC was not associated with significant reductions in the frequency of binge-purge episodes or measures of clinical severity, eating, or mood pathology. Thus, there is low level evidence of a lack of effectiveness (LoE: −C2) and poor acceptability (GoR: −3).

Combinations

Flutamide and citalopram. Sundblad et al. (2005) tested the effects of the androgen antagonist flutamide and the SSRI citalopram in a four-armed placebo-controlled pilot study in which patients received flutamide ($n = 9$), citalopram ($n = 15$), flutamide plus citalopram ($n = 10$), or placebo ($n = 12$). A reduction in binge-eating compared with baseline was statistically significant in both groups given flutamide but not in the groups given citalopram only or placebo. A moderate and reversible increase in serum transaminase levels led to discontinuation in two subjects in the flutamide group. Binge-eating was significantly reduced in the arm with flutamide plus citalopram compared to placebo. This single and small RCT can only lead to a limited level of evidence (LoE: B) for the combination of flutamide and citalopram. As hepatic toxicity and teratogenicity are known side effects of flutamide (Sundblad et al. 2005; Katsambas and Dessinioti 2010), there is limited recommendation (GoR: −2) against its use.

Combination of pharmacotherapy with psychotherapy

In two independent open trials, the combination of desipramine with cognitive behaviour therapy (CBT) showed a reduction in binge eating, purging, diet preoccupation, hunger and a demonstrated effectiveness in preventing relapse (Agras et al. 1992, 1994). Thus, we have limited (LoE: C1) for the combination of desipramine and CBT in the treatment of BN. In combination with desipramine's poor acceptability, there is only a weak recommendation (GoR: 3) for the combination of desipramine and CBT in BN.

Studies testing the combination of psychotherapy with fluoxetine showed controversial results (Fichter et al. 1991; Goldbloom et al. 1997; Jacobi et al. 2002; Kotler et al. 2003). Thus, there is no clear evidence to recommend the addition of fluoxetine to psychotherapy in patients with BN (LoE: D; GoR: 4). Table 4 summarises LoE and the GoR of studies on BN.

Binge-eating disorder

From the literature search, we included 68 articles relevant to the guidelines (see Table 5). Forty-four articles had been identified in the first version of the WFSBP guidelines on the pharmacological treatment of eating disorders (Aigner et al. 2011).

Antidepressants

Tricyclic antidepressants

Imipramine. Alger et al. (1991) performed an 8-week RCT investigating the effect of naltrexone and imipramine on 33 patients with obesity and binge-eating behaviour and 22 patients with bulimic symptoms. Imipramine significantly reduced the binge duration in the former group of patients, but the reduction in binge frequency was not statistically significant. Two patients in the imipramine group had liver enzyme elevation, and one had a drug rash. In another, a small RCT with 31 obese people with binge-eating, a significant reduction in binge frequency in the imipramine

Table 4. Bulimia nervosa: level of evidence and grade of recommendation.

	LoE			GoR		
Medication	Evidence that the intervention is effective	No sufficient evidence	Evidence that the intervention is NOT effective	Recommendation for using the intervention	No recommendation possible	Recommendation AGAINST using the intervention
Antidepressants						
Tri- and tetracyclic antidepressants						
Imipramine		D			4	
Desipramine	A			3		
Amineptine		D			4	
Amitriptyline			−B			−2
Mianserin			−B			−2
Selective serotonin reuptake inhibitors						
Fluvoxamine		D			4	
Fluoxetine	A			1		
Citalopram			−B			−2
Sertraline	C1			3		
Other selective monoamine reuptake inhibitors						
Duloxetine	C2			3		
Reboxetine	C1			3		
Bupropion	B					−2
Monoamine oxidase inhibitors						
Moclobemide			−B			−2
Isocarboxazid	B			2		
Brofaromine			−B			−2
Phenelzine	B			2		
Other serotonergic antidepressants						
Trazodone	B			2		
Antipsychotics						
Atypical antipsychotics						
Aripiprazole	C2			3		
Antiepileptics and mood stabilisers						
Oxcarbazepine		D			4	
Zonisamide	C2			3		
Topiramate	A			1[a]		
Lithium			−B			−2
Carbamazepine			−C2			−3
Lamotrigine	C2			3		
Anti-ADHD medication and stimulants						
Methyl-Phenidate	C2			3		
Lisdexamfetamine	C1				4	
Appetite modulators						
Appetite suppressants						
Sibutramine			−C2			−1
Fenfluramine	B					−1
d-Fenfluramine			−B			−1
Opioid antagonists						
Naltrexone			−B			−2
Hormones and endocrine treatments						
Oxytocin			−B			−2
Other serotonergic agents						
Ondansetron	B			2		
GABAergic medications						
Baclofen	C2			3		
Other medications						
N-acetylcysteine			−C2			−3
Combinations						
Flutamide and citalopram	B			−2		
Combination of pharmacotherapy with psychotherapy						
Desipramine and CBT	C1			3		

LoE: A: Strong evidence that the intervention is effective; B: Limited evidence that the intervention is effective; C(1–3): Low evidence that the intervention is effective; D: No evidence; −A: Strong evidence that the intervention is NOT effective; −B: Limited evidence that the intervention is NOT effective; −C(1–3): Low evidence that the intervention is NOT effective.

GoR: 1: Strong recommendation for using the intervention; 2: Limited recommendation for using the intervention; 3: Weak recommendation for using the intervention; 4: No recommendation possible; −1: Strong recommendation AGAINST using the intervention; −2: Limited recommendation AGAINST using the intervention; −3: Weak recommendation AGAINST using the intervention.

Please note: For details regarding the grading of the Level of Evidence (LoE) and the Grade of Recommendation (GoR) see text. The grading was performed according to Hasan et al. (2019).

[a]Topiramate is contraindicated in pregnancy and in women of childbearing potential if not using a highly effective method of contraception. Green shading: Best possible recommendations for BN.

Table 5. Depicts the results of the literature review of pharmacological studies in BED.

Author	Year	Age	*N*	Agent	Treatment setting	Study design	Randomisation	Placebo controlled	Double blind	Treatment duration	Positive outcomes/superior to placebo	Unfavourable or non-significant outcomes	Psychotherapy
Antidepressants													
Tricyclic antidepressants													
Alger et al.*	1991	32.5 (NR)	69 (33 obese bingers, 22 BN)	Imipramine 250 mg/day; Naltrexone 100–150 mg/day	Mixed	RCT	Yes	Yes	Yes	8 weeks	Imipramine significantly reduced binge duration in obese bingers. Naltrexone significantly reduced binge duration in BNs	Binge frequency in BN and obese bingers	No
Laederach-Hofmann et al.	1999	38.2 (20–60)	31 obese-BE	Imipramine 75 mg/day	Outpatients	RCT	Yes	Yes	Yes	8-week, 6 months (open phase)	Imipramine was superior to placebo in weight loss (8 weeks, 6 months). Imipramine was superior to placebo in reducing depression at follow-up (6 months)	depression (8 weeks) and frequency of BE	Yes, behavioural-oriented psychological support including individualised and group therapy
McCann and Agras	1990	NR	23 non-purging BN	Desipramine 100–300 mg/day	Volunteers	RCT	Yes	Yes	Yes	12 weeks	BE frequency, disinhibition, hunger, and restraint scores on TFEQ,	BDI, weight, BMI, BTS	No
Selective serotonin reuptake inhibitors													
Arnold et al.	2002	41.9 (18–60)	60	Fluoxetine 20–80 mg/day	Outpatients	RCT	Yes	Yes	Yes	6-week	Frequency of BE, BMI, weight, CGI-S, HAM-D	NR	No
Devlin et al.	2005	43 (18–70)	116 Obese and overweight patients with BED	Fluoxetine 20–60 mg/day	Volunteers	RCT	Yes	Yes	Yes	20-week	Fluoxetine was effective in reducing depressive symptoms	CBT effective in reducing BE remission/frequency	Yes, fluoxetine/placebo with or without CBT
Devlin et al. (same study as Devlin et al. 2005)	2007	43 (18–70)	116	Fluoxetine 20–60 mg/day	Volunteers	RCT	Yes	Yes	Yes	5-month initial phase of treatment and 2-year maintenance phase	Fluoxetine effective in reducing depressive symptoms in follow-up period	CBT effective in reducing BE remission/frequency in follow-up period	Yes, fluoxetine/placebo with or without CBT
Grilo et al.	2006	44.0 (18–60)	108	Fluoxetine 60 mg/day	Outpatients	RCT	Yes	Yes	Yes	16-week	Rapid response related to better treatment outcome, CBT > fluoxetine	CBT superior to fluoxetine and placebo in BE remission/frequency No between group difference in rapid response	Yes, fluoxetine/placebo with or without CBT,
Grilo, Crosby, et al.	2012	44.2 (18–60)	81 overweight patients with BED	Fluoxetine 60 mg/day	Outpatients	RCT	Yes	Yes	Yes	12-month	NR	CBT with placebo or with fluoxetine superior to fluoxetine-only in BE remission/frequency, EDE-Q subscales and BDI. No added benefit to fluoxetine with CBT. No group difference in weight/BMI	Yes, fluoxetine with or without CBT, placebo with CBT
Grilo, Masheb, et al. (same study as Grilo et al. 2006)	2012	44.0 (18–60)	108	Fluoxetine 60 mg/day	Outpatients	RCT	Yes	Yes	Yes	16-week	Younger participants had greater binge-eating reduction with fluoxetine	Lower self-esteem, negative-affect, and overvaluation of shape/weight indicated better improvements with CBT	Yes, fluoxetine/placebo given with or without CBT
Grilo, Masheb, Wilson (same study as Grilo et al. 2006 and Grilo, Masheb, et al. 2012)	2005	44 (21–59)	108	Fluoxetine 60 mg/day	Outpatients	RCT	Yes	Yes	Yes	16-week	NR	CBT with placebo or with fluoxetine superior to fluoxetine-only/placebo	Yes, CBT

(*continued*)

Table 5. Continued.

Author	Year	Age	*N*	Agent	Treatment setting	Study design	Rando misation	Placebo controlled	Double blind	Treatment duration	Positive outcomes/superior to placebo	Unfavourable or non-significant outcomes	Psychotherapy
Leombruni et al.*	2008	NR (21–57)	42 obese-BED	Fluoxetine 40–80 mg/day; sertraline 100–200 mg/day	Outpatients	Randomised trial, but no placebo arm.	NR	NR	NR	24 weeks	Significant improvement in binge-eating and weight loss during treatment with both, sertraline and fluoxetine.	No difference between sertraline and fluoxetine groups.	NR
Marcus et al.	1990	39.0 (18–50)	45 obese (22 BE, 23 No—BE)	Fluoxetine 60 mg/day	Volunteers	RCT	Yes	Yes	Yes	52-week	Fluoxetine superior to placebo regarding weight loss	No drug effect on frequency of BE, BDI or EDI	Behaviour modification program with placebo/fluoxetine
Ricca et al.*	2001	25.9 (18–45)	108	Fluoxetine 60 mg/day; Fluvoxamine 300 mg/day	Outpatients	Open trial	Yes	No	No	24-week, 1 year	CBT + fluvoxamine superior to CBT + fluoxetine and fluvoxamine alone in EDE total scores. CBT, fluvoxamine, and CBT + fluvoxamine superior to fluoxetine and CBT + fluoxetine in STAI scores.	At 24 weeks all CBT groups superior to medications alone in binge-eating frequency, weight and EDE scores. BDI reduced in all groups. At 1 year FU EDE scores remained unchanged. BMI higher than at 24 weeks.	Yes, CBT with or without fluoxetine or fluvoxamine
de Zwaan et al.	1992	39 (19–54)	64 obese (22 with BE episodes	Fluvoxamine 100 mg	Outpatients	Open trial	No	Yes	No	NR	Greater improvement in HAM-D with fluvoxamine	Weight loss, BDI, BDQ,	Yes, CBT
Hudson et al.	1998	42 (18–60)	85	Fluvoxamine 50–300 mg/day	Outpatients	RCT	Yes	Yes	Yes	9 weeks	Reduction rate in frequency of binge-eating episodes, CGI improvement rate, BMI reduction rate	Rate of decrease in HAM-D	No
Pearlstein et al.	2003	41 (NR)	25	Fluvoxamine 239 mg/day	Volunteers	RCT	Yes	Yes	Yes	12 weeks	NR	No drug effect in any of the variables.	No
Grant et al.	2019	40 (18–65)	80	Vortioxetine 10–20 mg/day	Outpatients	RCT	Yes	Yes	Yes	12 weeks	Not superior to placebo	Most common adverse events includes nausea, dry mouth, headache and dizziness	No
Guerdjikova et al.	2008	38.9 (18–60)	44 BED and obesity	Escitalopram 10–30 mg/day	Outpatients	RCT	Yes	Yes	Yes	12-week	Weight reduction, BMI, frequency of BE, binge days and severity of BED	Obsessive-compulsive symptoms	No
McElroy et al.	2000	42.0 (18–60)	34	Sertraline 50–200 mg/day	Outpatients	RCT	Yes	Yes	Yes	6 weeks	Greater rates of decrease in frequency of BE episodes, decrease in severity of illness, increase in global improvement, and BMI reduction	NR	No
Leombruni et al.*	2008	NR (21–57)	42 obese-BED	Sertraline 100–200 mg/day; Fluoxetine 40–80 mg/day	Outpatients	Randomised trial, but no placebo arm.	NR	NR	NR	24 weeks	Improvement in binge-eating, weight loss, BES and BDI during treatment with both, sertraline and fluoxetine.	No difference between sertraline and fluoxetine group.	NR
Leombruni, Pierò, et al.	2006	41.3 (18–65)	32 obese (14 BED)	Sertraline 100 or 200 mg/day	Outpatients	Open trial	No	No	No	24 weeks	Improvement over time of binge frequency, weight loss, BES, BDI, CGI	NR	No
McElroy, Hudson, et al.	2003	NK	38	Citalopram 20–60 mg/day	Outpatients	RCT	Yes	Yes	Yes	6 weeks	Frequency of BE, binge days, BMI CGI-S, YBOCS-BE, HAM-D	NR	No
Other selective monoamine reuptake inhibitors													
Malhotra et al.	2002	45.9 (28–68)	35 BED, overweight or obesity	Venlafaxine 75–300 mg/day	Outpatients	Case series	No	No	No	120 days	BE frequency, CGI-S, weight, BMI, waist circumference, and diastolic blood pressure	Dry mouth, sexual dysfunction, insomnia, and nausea	No
Silveira et al.	2005	33.3 (NR)	9 BED and obesity	Reboxetine 8 mg/day	Outpatients	Open trial	No	No	No	12 weeks	BE frequency, weight, BMI, BES, BES, CGI-S , WHOQOL-BREF improved in overall quality of life, general health, and psychological domain	NR	No

(*continued*)

Table 5. Continued.

Author	Year	Age	*N*	Agent	Treatment setting	Study design	Rando misation	Placebo controlled	Double blind	Treatment duration	Positive outcomes/superior to placebo	Unfavourable or non-significant outcomes	Psychotherapy
Antiepileptics and mood stabilisers													
Appolinario et al.	2002	32.6 (NR)	8	Topiramate 150 mg/day	Outpatients	Open trial	No	No	No	16 weeks	BE frequency, BES, weight loss	Paraesthesia, fatigue, and somnolence	No
Claudino et al.	2007	NK (18–60)	73	Topiramate 200 mg/day	Outpatients	RCT	Yes	Yes	Yes	21 weeks	Weight loss, BE remission	BE frequency, BES scores, and BDI scores. Paraesthesia and taste disturbance	Yes, CBT with topiramate or placebo
Guerdjikova et al.	2005	47.3 (43–55)	3	Topiramate (after bariatric surgery) 25–1000 mg/day	Outpatients	Case report	No	No	No	10 months	Amelioration of BE symptoms and weight loss	NR	No
Kalaria et al. (article based on data from McElroy, Arnold, et al. 2003)	2020	40.8 (NR)	61 obese-BED	Topiramate 50-600 mg/day	Outpatients	RCT	Yes	Yes	Yes	14 weeks	The identified dose-response relationship demonstrated a daily dose of 125 mg needed to exhibit a marked reduction in BE frequency	NR	No
McElroy, Arnold, et al.	2003	40.8 (18–60)	61	Topiramate 25–600 mg/day	Outpatients	RCT	Yes	Yes	Yes	14 weeks	BE frequency (BMI, weight, CGI, Y-BOCS-BE	Headache ($N = 3$) and paraesthesia's ($N = 2$)	No
McElroy, Hudson, et al.	2007	44.5 (18–65)	394	Topiramate 25–400 mg/day	Outpatients	RCT	Yes	Yes	Yes	16 weeks	BE frequency, BE remission, weight loss, BMI	Paraesthesia, upper respiratory tract infection, somnolence, and nausea	No
McElroy, Shapira, et al.	2004	40.9 (18–60)	43	Topiramate 25–600 mg/day	Volunteers	RCT	Yes	Yes	Yes	42 weeks	BE frequency	Nonadherence ($N = 17$) Adverse events ($N = 14$)	No
Guerdjikova et al.	2009	(18–65)	51	Lamotrigine	Outpatients	RCT	Yes	Yes	Yes	16 weeks	BE frequency, CGI-S, YBOCS-BE, MADRS, EDE-Q, BIS, TFEQ	Significant reduction in fasting levels of glucose, insulin, and triglycerides	No
Guerdjikova, Blom, Martens, et al.	2013	32.6 (21–40)	12 BN	Zonisamide 420 mg/day	Volunteers	Open trial	No	No	No	NR	BE frequency, weight loss, BMI, Y-BOCS-BE, TFEQ	Weight loss, high discontinuation rate. Panic attacks ($N = 1$)	No
McElroy et al.	2006	NK	60 BED	Zonisamide 100–600 mg/day	Outpatients	RCT	Yes	Yes	Yes	16 weeks	BE frequency, weight loss, BMI, CGI-S, Y-BOCS-BE, TFEQ	Bone fracture ($N = 2$), psychological complaints ($N = 2$), and cognitive complaints ($N = 2$)	No
McElroy, Kotwal, et al.	2004	36.8 (18–60)	15	Zonisamide 100–600 mg/day	Outpatients	Open trial	No	No	No	12 weeks	BE frequency, BMI, weight, CGI-S, YBOCS-BE total scores, and TFEQ hunger and disinhibition scores.	NR	No
Ricca et al.	2009	35.4 (18–60)	28 BED (subthreshold too)	Zonisamide	NR	Open trial	No	No	No	24 weeks, 1 year	24 weeks: BES, BMI, EDE-Q total, BDI 1 year: BMI, BE frequency, BES, EDE-Q restraint, STAI	NR	Yes, CBT groups with or without zonisamide
Anti-ADHD medication and stimulants													
Guerdjikova et al.	2016	37.7 (18–55)	50	Lisdexamfetamine 20–70 mg/day	Outpatients	RCT	Yes	Yes	Yes	12-week	Longitudinal analysis: BMI, fasting triglycerides Endpoint: BE frequency, BMI	Longitudinal analysis: BE frequency, CGI-S, YBOCS-BE Endpoint analysis: CGI, YBOCS-BE. Serious cardiovascular event.	No
Hudson et al.	2017	38.7 (18–55)	275 Lisdexamfetamine responders	Lisdexamfetamine 50–70 mg/day	Volunteers	RCT	Yes	Yes	Yes	26-week	Lisdexamfetamine superior to placebo regarding time to relapse	NR	No
McElroy et al.	2016	37.9 (18–55)	745	Lisdexamfetamine 50–70 mg/day	Volunteers	RCT	Yes	Yes	Yes	11-week		TEAEs 1% placebo, 0.6–1.6% LDX	No

(*continued*)

Table 5. Continued.

Author	Year	Age	*N*	Agent	Treatment setting	Study design	Rando misation	Placebo controlled	Double blind	Treatment duration	Positive outcomes/superior to placebo	Unfavourable or non-significant outcomes	Psychotherapy
											Change in BE, BE cessation, weight, CGI-I, YBOCS-BE, blood triglycerides		
McElroy et al.	2015	38.7 (18–55)	255	Lisdexamfetamine 30–70 mg	Volunteers	RCT	Yes	Yes	Yes	11-week	BE frequency (50 mg, 70 mg), BE cessation (50 mg, 70 mg), weight, CGI-I, TFEQ, BES, YBOCS-BE	BE frequency (30 mg) BE cessation (30 mg) HAM-A, MADRS. TEAEs: 59% placebo, 81–86% LDX	No
McElroy, Guerdjikova, et al.	2007	43.1 (18–65)	40	Atomoxetine 40–120 mg/day	Outpatients	RCT	Yes	Yes	Yes	10 weeks	BE frequency, weight, BMI, CGI-S, YBOCS-BE TFEQ hunger subscale	Increased depressive symptoms ($N = 1$), constipation ($N = 1$), and nervousness ($N = 1$)	No
Grilo et al.	2021	37.6	491	Dasotraline 4 or 6 mg/d.	Outpatients	RCT	Yes	Yes	Yes	12 weeks	Endpoint: Treatment associated with significant improvement in the number of binge-eating days/week on the dose of 6 but not 4 mg/d. Improvement observed for 6 and 4 mg/d, respectively on several measures of BED psychopathology	The most common adverse events were insomnia, dry mouth, headache, decreased appetite, nausea, and anxiety	No
McElroy et al.	2020	38.3 (18–55)	315	Dasotraline 4, 6, or 8 mg/d	Outpatients	RCT	Yes	Yes	Yes	12 weeks	Treatment with dasotraline was associated with a significantly greater reduction in binge-eating days/week and led to 4 weeks cessation of binge-eating	The most common adverse events were insomnia, dry mouth, decreased appetite, and anxiety. Discontinuation was due to adverse events occurred in 11.3% of treated patients.	No
Quilty et al.	2019	(18–50)	49	Methylphenidate	Outpatients	Randomised trial	Yes	No	No	12 weeks	Greater BMI decrease with methylphenidate	Similar results with CBT and methylphenidate in objective and subjective BE, BES, QOLI	Yes, as a comparison group
Appetite modulators													
Appetite suppressants													
Appolinario et al.	2003	35.9 (18–60)	60	Sibutramine 15 mg/day	Outpatients	RCT	Yes	Yes	Yes	12 weeks	BE frequency, weight loss, BES, BDI	Dry mouth and constipation	No
Bauer et al.	2006	41.9 (18–75)	73 obese (29 subclinical BED)	Sibutramine 10–15 mg/day	Volunteers	RCT	Yes	Yes	Yes	16 weeks	BWL programs + Sibutramine superior to BWL in weight loss	Binge frequency	Yes, cognitive-behavioural weight loss, BWL
Grilo et al.	2014, 2015	43.9 (18–65)	104 obese-BED	Sibutramine 15 mg/day	Volunteers	RCT	Yes	Yes	Yes	16 weeks	Weight loss sibutramine/placebo	BE remission an frequency, EDE, BDI Milano et al. 2005	Yes, self-help, CBT, shCBT with and without
NR (24–36)	20	Sibutramine	10 mg/day	Outpatients	RCT	Yes	Yes	Yes	12	weeks	BE frequency, weight loss	Dry mouth and constipation	No
Wilfley et al.	2008	41.9 (18–65)	304	Sibutramine 15 mg/day	Volunteers	RCT	Yes	Yes	Yes	24 weeks	BE frequency, weight loss, BMI, BE frequency, weight, TFEQ disinhibition and hunger subscales abstinence from BE	TFEQ cognitive restraint subscale, quality-of-life. Sibutramine was associated with significantly higher incidence of headache, dry mouth, constipation, insomnia, and dizziness	No
Stunkard et al.	1996	NR	28	d-Fenfluramine 15 mg/day	Volunteers	RCT	Yes	Yes	Yes	8 weeks	Patients on d-fenfluramine three times more rapidly in	Increase of binge frequency at 4-mounth follow-up	No

(*continued*)

Table 5. Continued.

Author	Year	Age	*N*	Agent	Treatment setting	Study design	Randomisation	Placebo controlled	Double blind	Treatment duration	Positive outcomes/superior to placebo	Unfavourable or non-significant outcomes	Psychotherapy
											remission of BE than those on placebo		
Opioid Antagonists													
Alger et al.*	1991	32.5 (NR)	69 (33 obese bingers, 22 BN)	Naltrexone 100–150 mg/day; Imipramine 250 mg/day	Mixed	RCT	Yes	Yes	Yes	8 weeks	Imipramine significantly reduced binge duration in obese bingers Naltrexone significantly reduced binge duration in BNs	Binge frequency in BN and obese bingers	No
GLP-1 agonists													
Robert et al.	2015	34 (NR)	44 obese-BE	Liraglutide 1.8 mg	Volunteers	Open trial	Yes	No	No	12 weeks	Liraglutide group showed improvement in BES, weight, BMI, waist circumference, systolic blood pressure, fasting glucose and total cholesterol. Ghrelin levels were significantly increased	BES improved with placebo	No
GABAergic medications													
Broft et al.	2007	31.7 (18–45)	7 (4 BED, 3 BN)	Baclofen 60 mg/day	Volunteers	Open trial	No	No	No	10 weeks	Baclofen reduced BE frequency, food craving	Weight, BDI	No
Corwin et al.	2012	NR	12	Baclofen 60 mg/day	Volunteers	Crossover	No	Yes	Yes	48 days	BE frequency	Increase in depression symptoms (HADS), FMDF, BES, FC-II, weight Tiredness, fatigue and upset stomach	No
de Beaurepaire et al.	2015	50.2 (42–60)	5	Baclofen 50–180 mg/day	Outpatients	Case series	No	No	No	NR	All the patients reported that baclofen suppressed their craving for food. All patients lost weight	Hypomania (n = 1)	No
Ricoux et al.	2019	60	1	Baclofen 70–300 mg/day	Outpatient	Case report	No	No	No	NR	BE frequency, weight loss	Distorted perception of time, cognitive disorders, intermittent short-term memory loss, and irritability, delusions, aggressiveness	No
McElroy et al.	2011	45.1 (21–65)	10	Sodium Oxybate 7.1 g/day	Volunteers	Open trial	No	No	No	22 weeks	BE frequency, binge days, weight, BMI, CGI-S, CGI-I, YBOCS-BE, TFEQ, FCI	MADRS Insomnia and racing thoughts, chest pain (N = 1), headache and paraesthesia (N = 1)	9 received psychotherapy
Intestinal enzyme blockers													
Grilo and White	2013	46.32 (21–65)	79 (40 obese-BED, 39 obese no-BED)	Orlistat 360 mg/day	Inpatients	RCT	Yes	Yes	Yes	4 months	Orlistat-plus-BWL produced significantly greater weight-loss in non-BED group and a moderate weight loss in BED group	The addition of orlistat to BWL was not associated with greater improvements in BED group. No drug effect for EDE, BDI	No (but addition of behavioural weight loss, BWL)
Grilo, Masheb, Salant	2005	47.0 (35–60)	50	Orlistat 360 mg/day	Volunteers	RCT	Yes	Yes	Yes	12 weeks	BE remission rates higher for orlistat + CBTgsh than placebo + CBTgsh at posttreatment but not at 3-month follow-up 5% weight loss higher for orlistat + CBTgsh than placebo + CBTgsh at posttreatment and 3-month follow-up	NR	Yes, CBT delivered as guided self-help, CBTgsh

(*continued*)

Table 5. Continued.

Author	Year	Age	*N*	Agent	Treatment setting	Study design	Randomisation	Placebo controlled	Double blind	Treatment duration	Positive outcomes/superior to placebo	Unfavourable or non-significant outcomes	Psychotherapy
Golay et al. Combinations	2005	40.9 (18–65)	89	Orlistat 360 mg/day	Outpatients	RCT	Yes	Yes	Yes	24 weeks	Weight loss, EDI-2	NR	No
Grilo, Lydecker, et al.	2021	50.4 (18–65)	22	Naltrexone 50 mg and bupropion 300 mg	Outpatients	RCT	Yes	Yes	Yes	12 weeks	The percentage of patients who attained 3% weight loss was significantly greater in patients treated with naltrexone/bupropion than with placebo (45.5 *vs.* 0%).	most outcomes (binge-eating, eating-disorder psychopathology, depression) were not statistically different from placebo.	No
Guerdjikova et al.	2018	45.3 (28–57)	10 BED, obese or overweight	Phentermine 3.75–7.5 mg/day; Topiramate 23–46 mg/day	Volunteers	Open trial	No	No	No	12 weeks	BE frequency, CGI-S, weight, EDE-Q, YBOCS-BE	Dysgeusia	No
Safer et al.	2020	42.9 (18–60)	22 (18 BED, 4 BN)	Topiramate 23–92 mg/day, Phentermine 3.75–15 mg/day	Outpatients	Double-blind crossover study	Yes	Yes	Yes	34 weeks	BE days, weight, EDE-Q global, eating and shape concern subscales, TFEQ hunger subscale, PHQ-9,	EDE-Q dietary restraint and weight concern subscales, TFEQ cognitive restraint and disinhibition subscale	No

NR: not reported; NA: not applicable; BDI: Beck Depression Inventory; BDQ: Body Distortion Questionnaire; BE: Binge-eating; BES: Binge-eating Scale; BMI: Body Mass Index; BTS: BN Thoughts Scale; BWL: behavioural weight loss treatment; CBT: cognitive behavioural therapy; CGI: Clinical Global Impression Scale; CGI-S: Clinical Global Impressions-Severity of Illness Scale; EDE: Eating Disorder Examination; EDE-Q: Eating Disorder Examination-Questionnaire; EDI: Eating Disorder Inventory; EDI-2: Eating Disorder Inventory-2; FCI: Food Craving Inventory; gsh-CBT: guided self-help CBT; HAM-D: Hamilton Rating Scale for Depression; STAI: State-Trait Anxiety Inventory; TEAEs: treatment-emergent adverse events; TFEQ: Three-Factor Eating Questionnaire; WHOQOL-BREF: World Health Organisation Quality of Life Assessment Scale; YBOCS-BE: Yale-Brown Obsessive Compulsive Scale Modified for BE.
Mean and range of age were reported where available.
*Study mentioned twice in the table.

vs. the placebo treated group was found (Laederach-Hofmann et al. (1999). Anticholinergic effects (constipation, dry mouth, blurred vision) were significantly more often reported in the imipramine group. As both RCTs were small and single-centre studies, there is a risk of bias in both studies. Additionally, the results were to some extend contradictory as the binge frequency was not significantly different from the effect of placebo in the RCT performed by Alger et al. (1991). Thus, there is limited evidence (LoE: B) that imipramine is effective. Due to the reported anticholinergic side effects, the recommendation to use imipramine in BED is weak (GoR: 3).

Desipramine. McCann and Agras (1990) published a small, single-centre, 12-week RCT with 23 women with 'non-purging bulimia' to test desipramine and found a significantly greater reduction in binge-eating and more abstinence from binge-eating in the desipramine compared to the placebo condition. As this is the only RCT testing desipramine in BED, the level of evidence is moderate (LoE: B). Although there was good acceptability of the potential for anticholinergic side effects, meant that only a weak recommendation was made (GoR: 3).

Selective serotonin reuptake inhibitors

Fluoxetine. Regarding fluoxetine, an RCT by Grilo, Masheb, Wilson (2005) included 108 patients with BED. They were randomised to four 16-week individual treatments with 27 patients per trial arm: fluoxetine (60 mg/day), placebo, CBT plus fluoxetine (60 mg/day) or CBT plus placebo. In this RCT, fluoxetine was not superior to placebo, CBT plus fluoxetine and CBT plus placebo did not differ, and both CBT conditions were superior to fluoxetine and to placebo. Several further analyses were published based on the data of this trial (Grilo et al. 2006; Grilo, Crosby, et al. 2012; Grilo, Masheb, et al. 2012). These data analyses showed that study participants with rapid response within the first four treatment weeks were more likely to achieve binge-eating remission, had greater improvements in eating-disorder psychopathology, and had greater weight loss (Grilo et al. 2006), that in the follow-up after 12 months from baseline, CBT plus placebo was superior to fluoxetine-only, and that adding fluoxetine to CBT did not improve the outcome compared to adding placebo to CBT (Grilo, Crosby, et al. 2012), that overvaluation of weight and shape was associated with lower remission rates if receiving medication only (Grilo, Masheb, et al. 2012).

A 2-armed RCT with a high-quality SIGN rating (Arnold et al. 2002) had 30 patients per trial arm found a significantly greater reduction in the frequency of binge-eating, BMI, and illness severity in the fluoxetine arm compared with placebo-treated subjects. In a 4-armed RCT by Devlin et al. (2005) which included 116 obese/overweight patients with BED, there was a significant effect of individual CBT, but not of medication on end-of-treatment binge frequency. Further analyses were published by Devlin et al. (2007) which showed that subjects who received individual CBT maintained a lower binge frequency over a two-year follow-up period.

An RCT performed by Marcus et al. (1990) with 45 people with obesity of which 22 had binge-eating problems. Patients treated with fluoxetine plus behaviour modification lost significantly more weight than those treated with placebo plus behaviour modification only. However, fluoxetine did not appear to have a benefit for binge-eaters.

In summary, fluoxetine was found significantly beneficial for people with BED in one RCT (Arnold et al. 2002), but three RCTs did not show any statistically significant benefit (Marcus et al. 1990; Devlin et al. 2005; Grilo, Masheb, Wilson 2005). In summary, we have contradicting results from RCT with the majority indicating no benefit of fluoxetine in comparison to placebo. As there is no meta-analysis available, this result was deemed as limited evidence against fluoxetine (LoE: −B) with a limited grade of recommendation (GoR: −2) against fluoxetine.

Fluvoxamine. Two RCTs (Hudson et al. 1998; Pearlstein et al. 2003) and two open trials (de Zwaan et al. 1992; Ricca et al. 2001) have been published on the effect of fluvoxamine in BED. In the RCT performed by Hudson et al. (1998) with 85 outpatients with BED, fluvoxamine was associated with a significantly greater rate of reduction in the frequency of binge-eating episodes and rate of reduction in CGI severity scores compared to placebo. However, a significantly greater proportion of patients receiving fluvoxamine than those receiving placebo discontinued treatment because of an adverse medical event. In the smaller and hence lower quality RCT by Pearlstein et al. (2003) which included only 20 patients, there were no significant differences for any treatment outcome variables between fluvoxamine and placebo. The evidence was rated as limited (LoE: B). As significantly more patients discontinued the RCT in the fluvoxamine arm in Hudson et al. (1998), the recommendation for fluvoxamine is weak (GoR: 3).

Escitalopram. In an RCT with 44 patients with BED, subjects receiving escitalopram and those receiving placebo had similar rates of reduction in binge-eating episodes and binge-eating days per week (Guerdjikova et al. 2008). Escitalopram was associated with statistically significant reductions in weight, BMI, and global severity of illness scores. However, there was no significant difference in the frequency of binge-eating episodes and binge-eating days. Thus, there is limited evidence against the use of escitalopram in BED (LoE: −B) and a limited recommendation (GoR: −2) against escitalopram in BED.

Sertraline. One RCT published by McElroy et al. (2000) included 34 outpatients with BED who were randomly assigned to receive either sertraline or placebo in a 6 week long RCT. Compared with placebo, sertraline was associated with a significantly greater reduction in the frequency of binge-eating episodes and BMI and significantly greater global clinical improvement. One further RCT over 24 weeks compared sertraline and fluoxetine but found no statistical differences in their effectiveness (Leombruni et al. 2008). And one open study (Leombruni, Pierò, et al. 2006) tested 32 patients with obesity of which 14 had BED, and found a significant improvement regarding binge-eating and significant weight loss which was maintained across 24 weeks. Thus, we have limited evidence (LoE: B) for the effectiveness of sertraline, and the recommendation to use it for BED is therefore limited as well (GoR: 2).

Citalopram. In an RCT with 38 outpatients with BED, subjects receiving citalopram had a significant reduction in the frequency of binge-eating, frequency of binge days, BMI, and severity of illness (McElroy, Hudson, et al. 2003). As this is the only RCT (LoE: B), only a limited recommendation for its use in BED can be made (GoR: 2).

Other selective monoamine reuptake inhibitors

Venlafaxine. In an open study with 35 patients with BED who received venlafaxine, weekly binge frequency, the severity of binge-eating, and BMI showed statistically significant decreases over time (Malhotra et al. 2002). Thus, we have low evidence (LoE: C1) for the effectiveness of venlafaxine in BED with a weak recommendation (GoR: 3) in BED.

Reboxetine. Nine outpatients with BED and obesity received reboxetine for 12 weeks in an open study published by Silveira et al. (2005). The mean binge days per week was significantly reduced at the end of

the study, mean BES scores and the mean BMI were decreased. Thus, a low level of evidence (LoE: C2) and a weak recommendation (GoR: 3) for reboxetine in BED can be made.

Vortioxetine. Grant et al. (2019) reported a 12-week RCT in 80 adults with BED where participants received vortioxetine (10 mg/day for 1 week, then increasing to 20 mg/day) or placebo. Vortioxetine was not more effective than placebo in the treatment of BED. Thus, there is limited evidence against the use of vortioxetine in BED (LoE: −B) and a limited recommendation (GoR: −2) against vortioxetine in BED.

Antiepileptics and mood stabilisers

Topiramate. A large multi-centre, RCT with 407 patients with BED by McElroy, Hudson, et al. (2007) with high quality according to the SIGN rating showed that topiramate reduces binge-eating frequency, leads to weight loss, and improves BED symptoms significantly compared to placebo. A previous RCT with 61 patients by McElroy, Arnold, et al. (2003) which yielded similar findings had an open-label extension (McElroy, Shapira, et al. 2004), and the data were re-analysed (Kalaria et al. 2020) substantiating the results of the initial RCT. An independent RCT by Claudino et al. (2007) which investigated CBT plus topiramate *vs.* CBT plus placebo in 73 patients with obesity and BED found significant weight loss and a significantly greater number of patients who attained binge remission in the CBT plus topiramate group compared to patients taking placebo. Earlier case series studies by Appolinario et al. (2002) and Guerdjikova et al. (2005) supported topiramate's ability to decrease binge-eating, to help lose weight, and to improve BED symptoms. The level of evidence for using topiramate in BED is high (LoE: A) as is the grade of recommendation (GoR: 1). However, topiramate is contraindicated during pregnancy.

Lamotrigine. Guerdjikova et al. (2009) performed an RCT on 51 outpatients with BED who received either lamotrigine or placebo for 16-weeks. Lamotrigine and placebo had similar rates of reduction of weekly frequency of binge-eating episodes and binge days, body weight, and eating pathology. However, lamotrigine was associated with a numerically greater amount of weight loss and significant reductions in fasting levels of glucose, insulin, and triglycerides. It was well tolerated. As this study showed an unusually high placebo response and as it is likely that it was underpowered because of the numerical but not statistically significant mean weight difference, we cannot count the obtained evidence as for or against the use of lamotrigine in BED (LoE: D) which makes no recommendation possible (GoR: 4).

Zonisamide. One 16-week, single-centre RCT with 60 patients with BED published by McElroy et al. (2006) tested zonisamide *vs.* placebo. Compared with placebo, zonisamide was associated with a significantly greater rate of reduction in binge-eating episode frequency, BMI and BED psychopathology. Eight patients on zonisamide discontinued the treatment.

The most common reasons for discontinuing zonisamide were accidental injury with bone fracture ($N = 2$), psychological complaints ($N = 2$), and cognitive complaints ($N = 2$). The authors concluded that zonisamide was efficacious, but not well tolerated. Two open studies were published by Ricca et al. (2009) and McElroy, Kotwal, et al. (2004). In the latter open study, 7 of 15 subjects discontinued zonisamide treatment prematurely due to lack of response ($N = 1$), protocol nonadherence ($N = 2$), and adverse events ($N = 4$). Even though there is limited evidence (LoE: B) for the effectiveness of zonisamide in BED, the recommendation is weak (GoR: 3) because of the poor acceptability.

Anti-ADHD medication and stimulants

Lisdexamfetamine (LDX). Four RCTs examined the effects of LDX in patients with BED. McElroy et al. (2015) performed a 4-armed study with 260 patients allocated to LDX at dosages of 30, 50, or 70 mg/d or placebo. At week 11, binge-eating frequency decreased significantly in the 50 mg/d and the 70 mg/d LDX treatment groups but not the 30-mg/d group compared with the placebo group. In two further RCTs with 383 and 390 participants, respectively published in one article (McElroy et al. 2016), LDX at a dose of 50 or 70 mg/d was superior to placebo in decreasing binge-eating frequency and improving binge-eating-related key secondary endpoints. More than 10% of LDX participants experienced dry mouth, insomnia, or headache. In a 12-week, single-centre RCT which included 50 patients with BED, Guerdjikova et al. (2016) found that LDX was associated with significantly decreased BMI compared to placebo. LDX was also associated with statistically significant reductions in binge-eating frequency and BED symptoms. Hudson et al. (2017) performed a multinational RCT including 418 participants who received LDX open label and were then allocated to LDX or placebo to investigate LDX's ability to prevent relapse. The findings demonstrated significantly longer time to relapse in the LDX group than in the placebo group. Thus, there is evidence from four RCTs

and one relapse-prevention RCT that LDX is effective in the treatment of BED (LoE: A). As the safety results in people with BED appear consistent with the known safety profile of LDX, a strong recommendation to use LDX in BED can be made (GoR: 1).

Atomoxetine. A ten-week, single centre RCT using atomoxetine in 40 patients with BED showed that compared with placebo, atomoxetine was associated with a significantly greater rate of reduction in binge-eating episode frequency, binge day frequency and BMI (McElroy, Guerdjikova, et al. 2007). This has led to a grading of limited evidence of efficacy (LoE: B) and a limited recommendation (GoR: 2) for its use in BED.

Dasotraline. McElroy et al. (2020) performed a 12-weeks RCT with in 315 patients with BED who were randomised to 4, 6, or 8 mg/d of dasotraline or placebo. Treatment with dasotraline was associated with a significantly greater reduction in binge-eating days per week and 4-week cessation of binge-eating. The most common adverse events in the dasotraline groups *vs.* the placebo group were insomnia, dry mouth, decreased appetite, and anxiety. Discontinuation due to adverse events occurred in 11.3% of patients on dasotraline *vs.* 2.5% on placebo.

Grilo, McElroy, et al. (2021) reported a 12 weeks of RCT with fixed doses of 6 mg/d dasotraline ($N = 162$), 4 mg/d dasotraline ($N = 161$), or placebo ($N = 162$). At week 12, treatment with dasotraline was associated with significant improvement in the number of binge-eating days per week on the dose of 6 mg/d *vs.* placebo, but not 4 mg/d. Improvement *vs.* placebo was observed for dasotraline 6 and 4 mg/d, respectively, on several measures of BED psychopathology. The most common adverse events on dasotraline were insomnia, dry mouth, headache, decreased appetite, nausea, and anxiety.

Thus, two independent RCTs showing the efficacy of dasotraline in BED treatment have been reported. Because of the side effects, the taskforce graded the evidence of efficacy as limited (LoE: B).

In May 2020, Sunovion Pharmaceuticals Inc. announced that it has withdrawn the new drug applications for dasotraline for the treatment of BED and ADHD. As the medication is not available, no recommendation (GoR: 4) for or against the use of dasotraline in BED can be given.

Methylphenidate. There is one randomised but open label trial of methylphenidate *vs.* CBT in 49 female outpatients with BED (Quilty et al. 2019). Participants were randomised to receive methylphenidate or CBT for 12 weeks. Both treatments reduced BE but only methylphenidate was associated with weight loss. As there was no placebo group, this study provides level C1 evidence that methylphenidate is effective, and a weak recommendation (GoR: 3) for its use in BED can be made.

Appetite modulators

Appetite suppressants

Sibutramine. Several RCTs have tested sibutramine in BED. One RCT was published by Grilo et al. (2014, 2015). It compared the effectiveness of self-help cognitive behavioural therapy (shCBT) and sibutramine alone and in combination in 104 obese patients with BED in a four-armed study: sibutramine ($N = 26$), placebo ($N = 27$), shCBT plus sibutramine ($N = 26$), shCBT plus placebo ($N = 25$). They found significant weight loss in the sibutramine groups, but neither shCBT nor sibutramine showed significant long-term effectiveness relative to placebo regarding BED symptoms. Another RCT 73 (Bauer et al. 2006) tested sibutramine in obese participants, 29 with and 44 without subclinical BED. In this study, a behavioural weight loss programme (BWL) plus sibutramine led to a higher weight loss compared with that in patients who had undergone the BWL alone. A small RCT published by Milano et al. (2005) included 20 patients with BED and found that the binge frequency among patients given sibutramine was significantly lower than that among those given placebo. Another RCT published by Appolinario et al. (2003) tested sibutramine *vs.* placebo in 60 patients with obesity and BED there was a significant reduction in the number of days with binge episodes in the sibutramine group compared with the placebo group which was associated with an important and significant weight loss, a significantly greater rate of reduction in binge-eating symptoms. Dry mouth and constipation were more significantly more common adverse reactions in the sibutramine group compared to the placebo group. The largest RCT testing sibutramine was published by Wilfley et al. (2008). They included 304 patients with BED who were randomly assigned to 24 weeks of double-blind sibutramine or placebo treatment. Compared with subjects receiving placebo, participants who received sibutramine had a significantly greater reduction in weekly binge frequency and binge days, and greater weight loss. However, the change in quality-of-life scores was not significant, and sibutramine was associated with a significantly higher incidence of headache, dry mouth, constipation, insomnia, and dizziness.

In summary, we have several high quality-RCTs which documented the superiority of sibutramine compared to placebo regarding the reduction of binge-eating frequency, weight loss, and reduction of BED symptoms (LoE: A). However, there is strong negative evidence (LoE: −1) against its use in patients with BED due to sibutramine's various side effects which have led not to its withdrawal from the market in most countries.

d-Fenfluramine. Stunkard et al. (1996) conducted an 8-week RCT of d-fenfluramine with 28 severely obese female patients with BED. In this RCT, d-fenfluramine reduced the frequency of binge-eating significantly compared to placebo and was well tolerated. Thus, there is limited evidence for the effectiveness of d-fenfluramine (LoE: B). As already explained in the section on BN, d-fenfluramine, and fenfluramine were removed from the market because of an association with valvular heart disease (Connolly et al. 1997; Graham and Green 1997). Therefore, we recommend against (GoR: −1) its use in BED.

Opioid antagonists

Naltrexone. The three-armed RCT published by Alger et al. (1991) which tested imipramine and naltrexone *vs.* placebo in patients with BN and in patients with obesity plus binge-eating did not find a significant reduction in binge-eating frequency or weight loss during treatment with naltrexone in patients with obesity and binge-eating compared to placebo. Thus, we have limited evidence (LoE: −B) against the use of naltrexone in BED and no recommendation (GoR: −2) for its use in BED.

GLP-1 agonists

Liraglutide. One open study by Robert et al. (2015) examined the effects of liraglutide in an open study in 44 patients with obesity and binge-eating which were randomly assigned to either liraglutide or placebo. Participants who received liraglutide showed significant improvement in binge-eating, accompanied by a reduction in BMI, systolic blood pressure, glucose, and cholesterol plasma concentrations. This open study suggests low-level evidence (LoE: C1) that liraglutide is effective. As it was well tolerated, this level of evidence translates into a weak recommendation (GoR: 3) for its use in BED.

GABAergic medications

Baclofen. Corwin et al. (2012) performed a placebo-controlled, double-blind, crossover study on 12 participants self-reported binge-eating. Up to 60 mg baclofen phase was given over 48 days. Baclofen significantly reduced binge frequency relative to placebo, but it also led to an increase in depressive symptoms. In an open study by Broft et al. (2007) testing the GABA-B agonist baclofen, four women with BED and three women with BN took 60 mg/d baclofen for 10 weeks. Of the four patients with BED, three demonstrated 50% or greater reduction in frequency of binge-eating from beginning to end of the study. De Beaurepaire et al. (2015) treated five patients with BED with between 120 and 140 mg/d baclofen with positive results regarding binge-eating, but several adverse events, e.g. nocturnal dyspnoea and insomnia, fatigue and sleepiness, gastric acid reflux, decrease in libido, balance disorder with falls, and difficulties in verbal expression. Ricoux et al. (2019) described a patients treated with 300 m/d baclofen who developed acute psychosis during the treatment with baclofen. Thus, in balance the available literature suggests that there is level B evidence for its effect on BED, but due to the reported psychiatric side effects, a weak recommendation against its use was given (GoR: −3).

Sodium oxybate. An open-label, prospective, 16-week, study of the narcolepsy medication sodium oxybate in BED was published by McElroy et al. (2011). Of the 12 participants, five completed the study. Sodium oxybate was associated with significant reductions in frequency of binge days and binge episodes, as well as measures of clinical severity, eating pathology, obsessive-compulsive symptoms, food cravings, and body weight. However, the medication was associated with a high discontinuation rate. Thus, we have low evidence (LoE: C1) for the effectiveness of sodium oxybate in BED, which leads to a weak recommendation (GoR: 3), partly because of the poor acceptability.

Intestinal enzyme blockers

Orlistat. Grilo, Masheb, Salant (2005) tested orlistat in addition to guided self-help cognitive behaviour therapy in 50 patients with obesity and BED over 12-week in an RCT and found that remission rates, as well as weight loss, were significantly greater in the treatment arm receiving orlistat. Golay et al. (2005) performed a 24 weeks long RCT in 89 patients with clinically diagnosed BED and obesity who received either 120 mg of orlistat or placebo three times daily, in combination

with a mildly reduced-calorie diet. The mean weight loss for orlistat-treated patients and the improvement in ED psychopathology were significantly greater than for patients receiving placebo. A 4 months RCT published by Grilo and White (2013) tested whether the addition of orlistat to a behavioural weight loss programme for obesity in obese people with ($N = 40$) and without ($N = 39$) BED. They found that adding orlistat to the behavioural weight loss programme produced greater weight loss than adding placebo among patients with obesity who did not have BED but not among those with BED. In the subgroup of participants with BED, there were no significant differences regarding remission rates and changes in ED psychopathology between the orlistat group and the placebo group *vs.* placebo did not differ significantly.

Various studies tested orlistat in adolescent patients with obesity but not BED or without specifically investigating BED symptoms (e.g. McDuffie et al. 2002, 2004; Norgren et al. 2003; Chanoine et al. 2005; Yancy et al. 2010). However, these studies did not specifically evaluate patients with BED or BED symptoms and therefore, have no relevance to these guidelines.

In summary, we have somewhat contradictory evidence from two RCTs (Golay et al. 2005; Grilo, Masheb, Salant 2005) showing significant superiority of orlistat regarding weight loss and improvement in BED psychopathology. However, one RCT by Grilo and White (2013) did not find a statistically significant advantage of orlistat in the subgroup of patients with BED. Thus, in contrast to the previous WFSBP guidelines (Aigner et al. 2011), the level of evidence must be reduced to C1 in accordance with Hasan et al. (2019). In recent years, reports of severe adverse effects under orlistat have been published, including liver damage, diarrhoea, nausea, dry mouth, faecal incontinence, flatulence, and steatorrhoea. Furthermore, orlistat decreases the absorption of lipid-soluble vitamins, contraceptive medications, thyroid hormones, and antiepileptic drugs (Ahmed 2010; Sall et al. 2014; Martínez Insfran et al. 2019; Tak and Lee 2021). Balancing the potential benefits and the possible risks, a recommendation for or against its use in BED cannot be made (GoR: 4).

Combinations

Phentermine and topiramate. One RCT with a crossover design by Safer et al. (2020) evaluated the efficacy and safety of the combination of phentermine and topiramate extended release in adult patients with BED ($N = 18$) or BN ($N = 4$). Participants were randomised to 12-weeks combination of phentermine and topiramate or placebo followed by 2-weeks drug washout, then 12-week crossover. Binge-eating episodes and weight gain decreased significantly, and the difference in BED symptoms and weight was statistically significant when the combination of phentermine and topiramate was compared to placebo. Responses were not significantly different for BED *vs.* BN. The combination of phentermine plus topiramate was well tolerated. In addition to this small RCT, one open trial was published by Guerdjikova et al. (2018). This study included only four participants with BN. Therefore, we only mention it in the BED results section.

As only one small RCT on the combination of phentermine and topiramate is available in BED, there is only limited evidence (LoE: B) that this combination is effective, which would theoretically translate into a limited recommendation for its use. However, the Committee for Medicinal Products for Human Use of the European Medicines Agency found in an examination and a re-examination of this combination that the benefits of Qsiva did not outweigh its risks and recommended that it be refused marketing authorisation. As we do not have the data available on which this decision had been based, the task force cannot make any recommendation (GoR: 4).

Naltrexone and bupropion. Grilo, Lydecker, et al. (2021) tested the combination of naltrexone and bupropion in 22 adult patients with BED who were randomised to receive 12 weeks of double-blind treatment with fixed dose of 50 mg naltrexone plus 300 mg bupropion or placebo. The percentage of patients who attained 3% weight loss was significantly greater in patients treated with naltrexone/bupropion than with placebo (45.5 *vs.* 0%). Overall, however, most outcomes (binge-eating, eating-disorder psychopathology, depression) were not statistically different from placebo.

As only this single small pilot RCT on the combination of naltrexone and bupropion is available in BED, and as the results are inclusive, there is no sufficient evidence to advise for or against the use of naltrexone and bupropion (LoE: D; GoR: 4).

Combination of pharmacotherapy with weight management programs

Regarding the combination of a weight management programme with psychopharmacological treatment, Laederach-Hofmann et al. (1999) found that the addition of low doses of imipramine helped with weight loss in participants with BED. de Zwaan et al. (1992) found that fluvoxamine had no effect on weight loss

for BED participating in weight loss programs. Thus, there is no clear evidence to recommend the addition of pharmacotherapy to weight loss programs in patients with BED. Table 6 summarises LoE and the GoR of studies on BED.

Avoidant restrictive food intake disorder

Avoidant/Restrictive Food Intake Disorder (ARFID) was added to DSM-5 (American Psychiatric Association 2013) as a new diagnosis and thus far evidence for therapeutic and pharmacological interventions for ARFID have been limited. The criteria for diagnosis are avoidance or restriction of food intake which leads to either weight loss, nutritional deficiencies, or dependence on feeding supplements, with an impact on psychosocial functioning. Disturbed body image or preoccupation with shape and weight do not feature in ARFID. A multimodal approach is usually involved with admission or partial admission when warranted, medical management, nutritional meal plan for weight restoration, individual and family therapy which may

Table 6. Binge-eating disorder: level of evidence and grade of recommendation.

	LoE			GoR		
Medication	Evidence that the intervention is effective	No sufficient evidence	Evidence that the intervention is NOT effective	Recommendation for using the Intervention	No recommendation possible	Recommendation AGAINST using the intervention
Antidepressants						
Tricyclic antidepressants						
Imipramine	B			3		
Desipramine	B			3		
Selective serotonin reuptake inhibitors						
Escitalopram			−B			−2
Citalopram	B			2		
Fluvoxamine	B			3		
Fluoxetine			−B			−2
Sertraline	B			2		
Vortioxetine			−B			−2
Other selective monoamine reuptake inhibitors						
Venlafaxine	C1			3		
Reboxetine	C2			3		
Antiepileptics and mood stabilisers						
Topiramate	A			1[a]		
Zonisamide	B			3		
Lamotrigine		D			4	
Anti-ADHD medication and stimulants						
Lisdexamfetamine	A			1		
Dasotraline	B				4	
Atomoxetine	B			2		
Methylphenidate	C1			3		
Appetite modulators						
Appetite suppressants						
Sibutramine	A					−1
d-Fenfluramine	B			−1		
Opioid antagonists						
Naltrexone			−B			−2
GLP-1 Agonists						
Liraglutide	C1			3		
GABAergic medications						
Baclofen	B					−3
Intestinal enzyme blocker						
Orlistat	C1				4	
Other medications						
Sodium oxybate	C1			3		−3
Combinations						
Naltrexone and bupropion		D			4	
Phentermine and topiramate	B				4	

The rows for lisdexamfetamine and topiramate are shaded green, because these are the best possible recommendations for BED.
LoE: A: Strong evidence that the intervention is effective; B: Limited evidence that the intervention is effective; C(1–3): Low evidence that the intervention is effective; D: No evidence; −A: Strong evidence that the intervention is NOT effective; −B: Limited evidence that the intervention is NOT effective; −C(1–3): Low evidence that the intervention is NOT effective.
GoR: 1: Strong recommendation for using the intervention; 2: Limited recommendation for using the intervention; 3: Weak recommendation for using the intervention; 4: No recommendation possible; −1: Strong recommendation AGAINST using the intervention; −2: Limited recommendation AGAINST using the intervention; −3: Weak recommendation AGAINST using the intervention.
Please note: For details regarding the grading of the Level of Evidence (LoE) and the Grade of Recommendation (GoR) see text. The grading was performed according to Hasan et al. (2019).
[a]Topiramate is contraindicated in pregnancy and in women of childbearing potential if not using a highly effective method of contraception. Green shading: Best possible recommendations for BED.

include elements of CBT and family-based therapy (FBT), and finally pharmacotherapy (Katzman et al. 2019).

From the literature search, we included seven articles relevant to the guidelines (see Table 7). Since Aigner et al. (2011) did not include this disorder, none of the studies reported in this 2023 update had been included in the previous WFSBP EDs guidelines.

Pharmacological treatment approaches have included SSRI as an anti-anxiety medication because of the high comorbidity of ARFID and anxiety disorders, olanzapine due to its efficacy in AN which shares many of the feature of ARFID, and mirtazapine due to appetite-inducing and weight gain properties and effects for depression and anxiety symptoms (Brewerton and D'Agostino 2017; Gray et al. 2018; Mahr et al. 2022). Current evidence is descriptive, including case reports and case series, and interpretation of results is limited as many of the cases involve treatment with polypharmacy.

The largest study on pharmacological intervention in ARFID to date is a retrospective chart review of 53 children and adolescents in a partial hospitalisation program, treated with SSRIs as a single medication or in combination with hydroxyzine (Mahr et al. 2022). Improvements from admission to discharge were noted in weight, eating behaviours, mood, anxiety, and fears of food.

In a case series by Spettigue et al. (2018), six patients were treated with a combination of olanzapine and SSRI: fluoxetine in five cases and fluvoxamine in one case, which was supplemented with cyproheptadine in two cases. The medication was added to medical monitoring, family therapy, and CBT, and all cases achieved their target weight.

Dolman et al. (2021) reported another case of combined treatment with olanzapine and SSRI medication, sertraline. Medication along with elements of FBT and CBT enabled an 11-year-old male with rigid ARFID to achieve goal weight and introduce new foods.

Treatment was adjunctive olanzapine was the focus of a retrospective chart review in which nine children and adolescents were treated for ARFID with a behavioural nutritional plan, individual and family therapies as well as non-olanzapine pharmacotherapy, which was not specified in the paper (Brewerton and D'Agostino 2017). Patients who did not demonstrate sufficient weight gain were offered low-dose olanzapine (0.6–2.5 mg/day) with benefits noted in eating, weight gain, symptoms of anxiety and depression and cognitive impairment.

Mirtazapine was found effective in a 12-year-old girl with ARFID who'd had two previous failed paediatric ward admissions. She responded to treatment on the third admission when mirtazapine was added to FBT treatment resulting in weight gain (Naviaux 2019). Naguy et al. (2021) reported a case of a 15-year old inpatient with ARFID and type 1 diabetes mellitus who was treated with mirtazapine 7.5–30 mg/day with improvement in eating patterns, weight, mood, phobic avoidance, glycemic control, and socialisation.

A retrospective chart review by Gray et al. (2018) examined 14 patients aged 7–23 who received mirtazapine as part of a partial hospital weight restoration treatment program. Six patients received mirtazapine as monotherapy and the remaining eight received SSRI, SNRI, cyproheptadine, clonidine, olanzapine, or stimulants. Mirtazapine was safe and well tolerated with sedation being the most notable side effect. A significant increase in weight gain rate was observed after initiation of mirtazapine.

Mahr et al. (2022) did not report the specific SSRIs. Therefore, the taskforce decided not to draw any recommendations regarding SSRIs from this study.

In summary, studies of ARFID for SSRIs, olanzapine, and mirtazapine fall within the category of low evidence (LoE: C2) and weak recommendation for the use of SSRIs, olanzapine, and mirtazapine (GoR: 3). Table 8 summarises the recommendations for the pharmacological treatment of ARFID.

Pica

Pica is defined as persistent eating of non-nutritive, non-food substances over a period of at least one month (American Psychiatric Association 2013). This eating behaviour is usually not an independent phenomenon but appears in the context of another mental disorder, nutritional deficiencies, or medical conditions. For pica to be diagnosed, it needs to be severe enough to necessitate specific attention and treatment.

From the literature search, we included eight articles relevant to the guidelines (see Table 9). Since Aigner et al. (2011) did not include this disorder, none of the studies reported in this report were included in the previous WFSBP guidelines paper.

Pharmacological interventions for PICA appear in the literature as single case reports, and in the context of the disorder with which it presents. You et al. (2021) described a case of a 34-year-old male with a past history of schizophrenia, who developed pica during an episode of psychotic decompensation and responded to treatment with paliperidone and olanzapine with the improvement of psychotic symptoms as

Table 7. Depicts the results of the literature review of pharmacological studies in ARFID.

Author	Year	Mean age (age range)	*N*	Agent	Treatment setting	Study design	Rando misation	Placebo-controlled	Double-blind	Treatment duration	Weight gain	Favourable outcomes/superiority to placebo	Unfavourable or non-significant outcomes	Psychotherapy
Antidepressants														
Mirtazapine														
Gray et al.	*2018*	15.2 ± 5.5 (7–23)	14	Mirtazapine 25.5 ± 17.9 mg	Outpatients	Retrospective chart review Case series	NA	NA	NA	13.7 ± 5.2 weeks	Yes	Average change in BMI after starting olanzapine significantly higher than pre-treatment BMI change	Drowsiness, Sedation and anxiety	No
Naviaux	2019	12	1	Mirtazapine 7.5 mg	Inpatient	Case report	NA	NA	NA	NR	No	Fluctuating weight gain and loss	NR	Family-based therapy
Naguy A. et al.	2021	15	1	Mirtazapine 7.5 mg	Outpatient	Case report	NA	NA	NA	NR	Yes	Improvement in eating patterns, weight, mood, phobic avoidance, glycemic control, and socialisation	NR	Dialectical behavioural therapy
Selective serotonin reuptake inhibitors (SSRIs)														
Mahr et al.	2022	NK	53	SSRIs	NK	Retrospective chart review	NA	NA	NA	NR	Yes	Improvement in weight, eating behaviours, mood, anxiety and fear of food	NK	NK
Spettigue W. et al.	2018	12.9 ± 1.13	6	Fluoxetine 10–40 mg, Olanzapine 2.5–7.5 mg cyproheptadine 2–4 mg and fluvoxamine 25 mg.	Inpatients	Case report	NA	NA	NA	NA	Yes	Improvement in weight and anxiety	NR	Family therapy and cognitive behavioural therapy
Dolman et al.	2021	11	1	Sertraline 25–75 mg, olanzapine 0.625–5 mg	Inpatient	Case report	Na	NA	NA	7 weeks	Yes	Improvement in weight and dietary patterns,	NR	Cognitive behavioural therapy and family-based therapy
Antipsychotics														
Atypical antipsychotics														
Brewerton and D'Agostino	2017	14.4 ± 4.1 (9–19)	9	Olanzapine	Inpatients	Case series	NA	NA	NA	53.4 ± 22.4 days	Yes	Improvement in weight, anxiety, depressive symptoms and cognitive functioning.	NR	Structured behavioural therapy
Spettigue W. et al.	2018	12.9 ± 1.13	6	Olanzapine 2.5–7,5 mg/day, fluoxetine 10–40 mg/day, cyproheptadine 2–4 mg and fluvoxamine 25 mg/day.	Inpatients	Case report	NA	NA	NA	NA	Yes	Improvement in weight and anxiety	NR	Family therapy and cognitive behavioural therapy
Dolman et al.	2021	11	1	Olanzapine 0.625–5 mg/day and sertraline 25–75 mg/day	Inpatient	Case report	Na	NA	NA	7 weeks	Yes	Improvement in weight and dietary patterns	NR	Cognitive behavioural therapy and family-based therapy
Appetite modulators														
Appetite stimulants														
Spettigue W. et al.	2018	12.9 ± 1.13	6	Cyproheptadine 2–4 mg/day, olanzapine 2.5–7.5 mg/day, fluoxetine 10–40 mg/day and fluvoxamine 25 mg/day.	Inpatients	Case report	NA	NA	NA	NA	Yes	Improvement in weight and anxiety	NR	Family therapy and cognitive behavioural therapy

NR: not reported; NA: not applicable; NK: not known.
Lightly shaded rows indicate the inclusion of children and adolescent. Mean and range of age were reported where available.

Table 8. Avoidant restrictive food intake disorder: level of evidence and grade of recommendation.

	LoE			GoR		
Medication	Evidence that the intervention is effective	No sufficient evidence	Evidence that the intervention is NOT effective	Recommendation for using the intervention	No recommendation possible	Recommendation AGAINST using the intervention
Antidepressants						
Mirtazapine	C2			3		
SSRIs						
Fluoxetine	C2			3		
Sertraline	C2			3		
Antipsychotics						
Atypical antipsychotics						
Olanzapine	C2			3		
Appetite modulators						
Appetite stimulants						
Cyproheptadine	C2			3		

LoE: C2: Low evidence that the intervention is effective.
GoR: 3: Weak recommendation for using the intervention.

well as resolution of pica. Along these lines, in a recent case of a 17-year-old female who had a family history of schizophrenia and school and interpersonal difficulties, and a habit of eating plastic, diagnoses of ultra-high risk for psychosis, depression, and pica were made (Fekih-Romdhane and Cheour 2022). With paroxetine treatment and CBT pica was resolved, depression and anxiety symptoms improved but she remained at ultra-high risk for psychosis.

In the affective disorders category, a case of a 27-year-old female with a depressive episode at 18 and pica symptoms since age 20 was described by (Peña-Salazar and Kazah 2020). After treatment attempts with mood stabilisers, antiepileptics and antipsychotics, lithium and olanzapine decreased frequency of pica symptoms which allowed to observe them occurring near depressive and hypomanic symptoms, leading to a diagnosis of bipolar disorder. Topiramate was added to treat impulsivity resulting in further decrease in pica episode frequency and severity and euthymic mood. Choure et al. (2006) described a case of a 13-year-old girl who developed baking soda pica in the context of major depression. Treatment with fluoxetine 10 mg/day resulted in complete remission of both conditions.

Pica has been suggested as a symptom of obsessive-compulsive disorder (OCD) or a part of the OCD spectrum disorders. In a case of a 35-year-old female who developed an impulse to ingest chalk under stressful situations, pica presented under stress with an impulse-compulsion trait (Bhatia and Gupta 2009). She was treated with SSRI medication, escitalopram, and with clonazepam, with improvement in mood and pica symptoms. Similarly, Upadhyaya and Sharma (2012) described a case of a 26-year-old female who developed pica manifested as compulsions of eating uncooked rice or wheat, understood as the presentation of OCD, with complete response to fluoxetine 40 mg/day within three months of treatment, without behavioural therapy.

Pica can also appear in neurodegenerative diseases, such as frontotemporal dementia (FTD) and Alzheimer's disease (AD). In clinical trials of trazodone and fluvoxamine for FTD symptoms, eating disorder behaviours improved although not classified as pica per se (Ikeda et al. 2004; Lebert et al. 2004). In a recent case report, an 80-year-old female with AD and pica was treated with fluvoxamine and trazodone based on these findings with complete remission from pica symptoms (Kanamori et al. 2021).

A single case report described pica as a presenting manifestation of ADHD. An eight-year-old boy was referred for psychiatric assessment because of eating carpet and cloth fibres for 3 years (Hergüner and Hergüner 2010). He was diagnosed with ADHD and treated with successfully methylphenidate with complete resolution of pica symptoms. A case of a 17-year-old female with autistic spectrum disorder (ASD) and pica was treated with risperidone due to her disruptive behaviours with partial response. Treatment with aripiprazole 7.5 mg/day led to a decrease in disruptive and compulsive behaviours, and complete resolution of pica symptoms (Hergüner and Hergüner 2016).

To summarise, the approach to pica treatment depends on the causative factor with no pica-specific medications studied. After ruling out nutritional deficiencies or a medical cause, psychiatric assessment should indicate the psychiatric diagnosis for treatment, i.e. SSRI medication in depression and OCD cases or antipsychotics in patients with psychosis or ASD behavioural symptoms. Thus far, cases are presented in case report form only, which are considered low

Table 9. Depicts the results of the literature review of pharmacological studies in Pica.

Author	Year	Mean age (age range)	*N*	Agent	Treatment setting	Study design	Rando misation	Placebo-controlled	Double-blind	Treatment duration	Weight gain	Favourable outcomes/superiority to placebo	Unfavourable or non-significant outcomes	Psychotherapy
Antidepressants														
SSRIs														
Fekih-Romdhane and Cheour	2022	17	1	Paroxetine 20 mg/day	Outpatient	Case report	NA	NA	NA	6 months	NR	Pica was resolved, depression and anxiety symptoms improved	Remained at risk for psychosis	CBT
Choure et al.	2006	13	1	Fluoxetine 10 mg/day.	Outpatient	Case report	NA	NA	NA	4 weeks	NR	Complete remission of pica and depression	NR	Psychodynamic psychotherapy
Bhatia and Gupta	2009	35	1	Escitalopram 5 mg/day and clonazepam 0.25 mg/day	Outpatient	Case report	NA	NA	NA	3 weeks	NR	Improvement in mood and pica symptoms	NR	No
Upadhyaya and Sharma	2012	26	1	Fluoxetine 40 mg/day	Outpatient	Case report	NA	NA	NA	3 months	NR	Improvement after treatment targeted for OCD, and not pica.	NR	No
Kanamori et al.	2021	80	1	Fluvoxamine 75 mg and trazodone 50 mg/day	Inpatient	Case report	NA	NA	NA	NR	NR	complete remission from pica symptoms	NR	No
Antipsychotics														
Atypical antipsychotics														
You et al.	2021	34	1	Paliperidone 234 mg IM and olanzapine 10–20 mg/day	Inpatient	Case report	NA	NA	NA	NR	NR	Improvement of psychotic symptoms as well as resolution of pica.	NR	No
Peña-Salazar and Kazah	2020	27	1	Lithium 1200 mg/day, olanzapine 25 mg/day and topiramate 450 mg/day	NR	Case report	NA	NA	NA	3 months	NR	Decreased severity and frequency of pica	Achypsychia, tachylalia, hyperthymia, inappropriate laughing, increased socialisation, and decreased need for sleep	No
Hergüner and Hergüner	2016	17	1	Risperidone 1 mg/day and afterwards aripiprazole 7.5 mg/day	Outpatient	Case report	NA	NA	NA	3 weeks	NR	Decrease in disruptive and compulsive behaviours, and complete resolution of pica symptoms	No side effects reported with aripiprazole	No
Antiepileptics and mood stabilisers														
Peña-Salazar and Kazah	2020	27	1	Topiramate 450 mg/day, lithium 1200 mg/day and olanzapine 25 mg/day	NR	Case report	NA	NA	NA	3 months	NR	Decreased severity and frequency of pica	Disturbance of the perception of time, tachylalia, hyperthymia, inappropriate laughing, increased socialisation, and decreased need for sleep	No
Benzodiazepines														
Bhatia and Gupta	2009	35	1	Clonazepam 0.25 mg/day and escitalopram 5 mg/day	Outpatient	Case report	NA	NA	NA	3 weeks	NR	Improvement in mood and pica symptoms	NR	No
Anti-ADHD medication and stimulants														
Hergüner and Hergüner	2010	8	1	Methylphenidate	Outpatient	Case report	NA	NA	NA	3 weeks	NR	complete resolution of pica symptoms	NR	No

NR: not reported; NA: not applicable; CBT: cognitive behavioural therapy.
Mean and range of age were reported where available.
Lightly shaded rows indicate the inclusion of children and adolescents.

evidence level (LoE:C2) and weak recommendations (GoR: 3). Table 10 summarises the recommendations for the pharmacological treatment of pica.

Rumination disorder

RD is an effortless regurgitation of ingested food, which is not attributed to another medical condition or another eating disorder (American Psychiatric Association 2013). The study of RD lies between psychiatric and gastrointestinal disciplines. It is estimated to be underrecognized.

From the literature search, we included two articles relevant to the guidelines (see Table 11) which were not yet mentioned in Aigner et al. (2011).

The first line of treatment is behavioural modification with diaphragmatic breathing exercises (Vachhani et al. 2020). Evidence for pharmacological interventions is limited. Baclofen, a γ-aminobutyric acid agonist, acting as an antispasmodic was examined in a double-blind crossover study of 20 adults with RD. A reduction in postprandial manometry was noted and 63% of patients reported symptom improvement in the baclofen period whereas 26% reported improvement in the placebo period (Pauwels et al. 2018). When prescribed for other EDs, baclofen has been reported to have caused serious side effects, such as psychosis (Ricoux et al. 2019), increase in depressive symptoms (Corwin et al. 2012), nocturnal dyspnoea and insomnia, fatigue and sleepiness, gastric acid reflux, decrease in libido, balance disorder with falls difficulties in verbal expression (de Beaurepaire et al. 2015). Thus, even though we have limited evidence for its use in RD (LoE: B), only a week recommendation (GoR: 3) can be made for baclofen.

In an open prospective study of the antipsychotic levosulpiride, a selective dopamine D2-receptor antagonist with prokinetic activity, improvement was reported by 38% who were treated with the medication for several months along with supportive therapy (Lee et al. 2007).

In conclusion, there is limited evidence (LoE: B) and a weak recommendation (GoR: 3) for baclofen, and low evidence (LoE: C1) and weak recommendation (GoR: 3) for levosulpiride in RD. Table 12 summarises the recommendations for the treatment of RD.

Discussion

Anorexia nervosa

In AN, atypical antipsychotics have been the most studied class of medication for AN in recent years, and olanzapine in particular. Five RCTs, of which four show positive results for weight gain (Brambilla et al. 2007; Bissada et al. 2008; Attia et al. 2011, 2019), provide a strong level of evidence (LoE: A). However, several reservations should be noted. First, the observed drug effect for weight gain is modest, 0.259 increase in BMI over 16 weeks with olanzapine compared with 0.095 in the placebo group, in the largest RCT by Attia et al. (2019). Second, the acceptability of olanzapine is low. Attia et al. (2019) reported 45% dropout rate. Given this poor/moderate acceptability, we judged that a

Table 10. Pica: level of evidence and grade of recommendation.

	LoE			GoR		
Medication	Evidence that the intervention is effective	No sufficient evidence	Evidence that the intervention is NOT effective	Recommendation for using the intervention	No recommendation possible	Recommendation AGAINST using the intervention
Antipsychotics						
Atypical antipsychotics						
Olanzapine	C2			3		
Paliperidone	C2			3		
Risperidone	C2			3		
Aripiprazole	C2			3		
Antidepressant						
SSRIs						
Escitalopram	C2			3		
Fluoxetine	C2			3		
Fluvoxamine	C2			3		
Paroxetine	C2			3		
Antiepileptics and mood stabiliser						
Lithium	C2			3		
Topiramate	C2			3		
Benzodiazepines						
Clonazepam	C2			3		
Stimulants						
Methylphenidate	C2			3		

LoE: C2: Low evidence that the intervention is effective.
GoR: 3: Weak recommendation for using the intervention.

Table 11. Depicts the results of the literature review of pharmacological studies in rumination disorder.

Author	Year	Mean age (age range)	*N*	Agent	Treatment setting	Study design	Randomisation	Placebo-controlled	Double-blind	Treatment duration	Weight gain	Favourable outcomes/ superiority to placebo	Unfavourable or non-significant outcomes	Psychotherapy
Antipsychotics														
Typical antipsychotics														
Lee et al. (2007)	2017	41.9 ± 2.6	21	Levosulpiride 25 mg three times a day	Outpatients	Open prospective study	NA	NA	NA	7.9 ± 0.9 months	NR	Improvement was reported by 38%	NR	Yes, psychotherapy
GABAergic medications														
Pauwels et al. (2018)	2018	18–61	20	Baclofen 10 mg three times a day	Outpatients	RCT	Yes	Yes	Yes	2 weeks	NR	Reduction in postprandial manometry and symptoms improvement in 63%	NR	No

NR: not reported; NA: not applicable.
Mean and range of age were reported where available.

grade 2 recommendation for its use to achieve weight gain in AN is appropriate. However, in EDs in general, dropout rates for treatment have been reported to range between 20 and 50% for inpatient settings and between 30 and 70% for outpatient treatment regardless of the specific treatment applied (Fassino et al. 2009). Thus, the dropout rate reported by Attia et al. (2019) is not unusual for an outpatient ED study. Additionally, meta-analytic research has found that personal reasons or factors associated with a specific study are more common reasons for dropouts than adverse events or metabolic effects (Kan et al. 2020). Thus, the reason for the poor or moderate acceptability of olanzapine in the treatment of AN may not necessarily be related to olanzapine, but rather to ambivalence about treatment for the eating disorder.

Also, it should be emphasised that weight gain was the primary outcome in the studies testing olanzapine. These studies (Brambilla et al. 2007; Bissada et al. 2008; Attia et al. 2011, 2019) did not show a consistent effect on psychopathological components of AN including ED related obsessions and rituals, depression or anxiety. Regarding compulsivity for example, Brambilla et al. (2007) found a significant improvement in compulsivity and rituals in the olanzapine but not in the placebo group; Bissada et al. (2008) found a greater rate of decrease in obsessive symptoms under the treatment with olanzapine compared to placebo; Attia et al. (2011) found that psychological symptoms improved in the olanzapine as well as the placebo group without significant group differences; and a later RCT by Attia et al. (2019) confirmed no significant difference between treatment groups regarding obsessions.

According to the recently published observational naturalistic case–control study by Pruccoli et al. low-dose olanzapine ($\leq$5 mg/day) might be more effective for the treatment of depressive symptoms than a higher dose of olanzapine (Pruccoli et al. 2022).

Three studies examined olanzapine in the adolescent population. Kafantaris et al. (2011) ($n = 20$) who included participants aged between 12 and 21 years in an RCT reported no significant weight change, while an open study by Leggero et al. (2010) ($n = 13$) and an open study with a no-drug comparison group by Spettigue et al. (2018) ($n = 38$) reported a positive effect for weight gain. Thus, there is so far no evidence for or against the use of olanzapine in the paediatric population.

Two RCTs testing the atypical antipsychotics quetiapine (Powers et al. 2012) and risperidone (Hagman et al. 2011), two double-blind crossover studies testing the typical antipsychotics pimozide (Vandereycken and Pierloot 1982) and sulpiride (Vandereycken 1984) did

Table 12. Rumination disorder: level of evidence and grade of recommendation.

	LoE			GoR		
Medication	Evidence that the intervention is effective	No sufficient evidence	Evidence that the intervention is NOT effective	Recommendation for using the intervention	No recommendation possible	Recommendation AGAINST using the intervention
Antipsychotics						
Typical antipsychotics						
Levosulpiride	C1			3		
GABAergic medications						
Baclofen	B			3		

LoE: B: Limited evidence that the intervention is effective; C1: Low evidence that the intervention is effective.
GoR: 3: Weak recommendation for using the intervention.

not find a significant effect on body weight in people with AN. There are accumulating reports on the use of aripiprazole, in the adult (Trunko et al. 2011) and in the adolescent population (Frank 2016; Frank et al. 2017). However, the studies so far do not include RCTs. Thus, the evidence for the use of aripiprazole in AN is graded low (LoE: C1; GoR: 3). Meta-analyses (Kishi et al. 2012; Lebow et al. 2013; de Vos et al. 2014; Dold et al. 2015) did not find a significant effect on weight for atypical antipsychotics as a group.

Mirtazapine is the only antidepressant with a positive recommendation. However, the recommendation is weak (LoE: C3; GoR: 3) and based on only two favourable case reports (Safer et al. 2011; Naguy and Al-Mutairi 2018).

Of newer directions pursued, grade 2 recommendations can be made for dronabinol based on a crossover RCT (Andries et al. 2014). However, so far, no RCTs on dronabinol have been published in children or adolescents.

Most hormonal treatments including growth hormone, ghrelin agonist, and oxytocin have yielded limited or negative results and are not recommended. However, preliminary evidence based on case reports (Milos et al. 2020; Antel et al. 2022; Gradl-Dietsch et al. 2023) led to a weak recommendation for the use of metreleptin. Metreleptin has been approved by the Food and Drug Administration (FDA) under strict regulations exclusively for the treatment of generalised lipodystrophy. However, the recent approval by the European Medicines Agency (EMA) may offer the possibility to treat patients with AN off-label. Metreleptin might be a treatment option for patients with AN and particularly low leptin levels or marked hyperactivity (Hebebrand et al. 2019). However, RCTs are necessary to examine the potential benefits and side effects of metreleptin in people with AN.

Bulimia nervosa

In BN, the current literature prompts a grade 1 recommendation for the use of fluoxetine or topiramate in BN. According to major guidelines (American Psychiatric Association 2012; Hay et al. 2014; NICE 2017; Herpertz et al. 2018), psychological therapies, such as guided self-help and CBT for adults or BN-focussed family therapy for adolescents are first-line treatments in BN (Monteleone et al. 2022). As fluoxetine is widely approved for the treatment of BN and showed strong evidence which leads to a strong recommendation in our literature review, fluoxetine might be the first medication to try in BN if psychotherapy alone is not effective, the patient does not agree to psychotherapy or psychotherapy is not available. Based on published, RCTs (Fichter et al. 1991; Fluoxetine Bulimia Nervosa Collaborative Study Group 1992; Goldstein et al. 1995; Goldbloom et al. 1997; Walsh et al. 2000; Romano et al. 2002) fluoxetine should be started at a dose of 20 mg and can be escalated to 60 mg per day. Beneficial effects have been found for up to 2 years. Potential side effects include insomnia, headache, diarrhoea, nausea, fatigue.

In adolescents (12–18 years) only one small ($n = 10$) open study (Kotler et al. 2003) showed a significant decrease in bingeing and purging. Thus, there is far less evidence in adolescence for the use of fluoxetine compared to adults.

Fluoxetine and its major metabolite, norfluoxetine, are potent inhibitors of the cytochrome P (CYP) 450 isoenzymes CYP2D6 and CYP2C19. Therefore, caution is advised when combining fluoxetine with preferred substrates of CYP2D6 and CYP2C19, such as amitriptyline, atomoxetine, clomipramine, imipramine, sertindole, and several antipsychotics. Due to the inhibition of CYP2D6 by fluoxetine and the consequently reduced metabolism of the prodrug tamoxifen to its active metabolite endoxifen, fluoxetine must not be given to women who receive tamoxifen treatment. Additionally, fluoxetine should not be combined with MAO-Is. Fluoxetine has a long half-life. Thus, the interactions may persist for several weeks after stopping fluoxetine (Hiemke et al. 2018). Asian and particularly sub-Saharan African ancestries have much more variability in CYP2D6 and CYP2C19 genes. Thus, therapeutic drug level should be monitored when prescribing for patients of those

ancestries, particularly when pharmacogenetic testing is not available (Sayer et al. 2021).

Topiramate has also been shown to be effective and well-tolerated in BN at daily doses between 75 and 200 mg. It is recommended that treatment with topiramate should be started with 25 mg per day and slowly increased, for example, a weekly increase of 25 mg per day. Based on the current literature, a recommendation about the duration of the therapy cannot be made. Potential side effects are weight loss, paraesthesia, tiredness, and cognitive disturbances. An FDA report (US Food and Drug Administration 2008) on topiramate suggested that it led to an increased risk of suicide with an odds ratio of ~2.5. Topiramate is a weak inducer of CYP3A4, which may make other medications less effective. At doses of 200–800 mg topiramate per day, there is a possibility of reduced contraceptive effectiveness (Viana et al. 2014).

As topiramate is not approved for the treatment of BN by any major medicine regulatory agency, as there is less experience with topiramate in BN compared to fluoxetine, as topiramate is contraindicated in pregnancy, and because of the increased risk of suicide and of a failure of hormonal contraception, topiramate should not be the first choice of the pharmacological treatment for BN.

If fluoxetine and topiramate are not effective or cannot be prescribed due to their risk profile, contraindications, and interactions, the medications with grade 2 recommendation—trazodone, isocarboxazid, phenelzine, and ondansetron—may be considered by balancing the risks and benefits.

Desipramine was also found statistically effective in the treatment of BN (Hughes et al. 1986; Barlow et al. 1988; Blouin et al. 1988; Walsh et al. 1991), but its poor acceptability leads to a grade 3 recommendation to use in BN. This recommendation is in line with a Cochrane Database Systematic Review (Bacaltchuk and Hay 2003) which concluded that treatment with TCAs is more likely to be interrupted prematurely due to adverse events and that patients treated with TCAs dropped out due to any cause more frequently that patients treated with placebo in studies testing antidepressants in people with BN. This Cochrane Database Systematic Review (Bacaltchuk and Hay 2003) found that the opposite was true for those treated with fluoxetine, suggesting fluoxetine to be a more acceptable treatment than TCAs.

Binge-eating disorder

In BED, the current literature prompts a grade 1 recommendation for the use of LDX or topiramate in BED in combination with psychotherapy.

LDX is approved for the treatment of BED in the US, Canada, Brazil, Puerto Rico, Mexico, and Israel. It is a prodrug that is converted to the trace amine-associated receptor 1 (TAAR1) agonist dextroamphetamine (Xu and Li 2020; Himmerich et al. 2021). At a daily dose of 30 to 70 mg/d, it has been shown to lead to a reduction in binge-eating episodes and to weight loss (McElroy et al. 2015; Guerdjikova et al. 2016; McElroy et al. 2016; Hudson et al. 2017). Frequent side effects of LDX include decreased appetite, headache, insomnia, and a dry mouth. LDX can be recommended in countries where its use in BED is approved.

However, there are concerns about the combination of LDX with CBT which has also been proven to be effective in BED (Monteleone et al. 2022), because the effect of the medication (weight loss) runs counter to current CBT approaches (weight maintenance and eating more regularly while eliminating binge-eating). Thus, RCTs testing the combination of LDX with CBT are needed.

Topiramate has also been shown to be effective and well-tolerated in BED at daily doses between 75 and 200 mg as has also been found for BN. As topiramate is not approved for the treatment of BED by any medicine regulatory agency like the FDA or the EMA, as topiramate is contraindicated in pregnancy, and because of the increased risk of suicide and of a failure of hormonal contraception, topiramate should not be the first choice of the pharmacological treatment for BED.

If LDX and topiramate are not effective or cannot be prescribed due to their risk profile, contraindications, and interactions, medications with grade 2 recommendation may be considered by balancing the risks, benefits, and alternative non-pharmacological treatments. These medications include the SSRIs citalopram and sertraline and atomoxetine.

No RCTs are available for the use of LDX or topiramate in children and adolescents. Therefore, we cannot recommend the use of LDX and topiramate in adolescents.

Avoidant restrictive food intake disorder, pica, and rumination disorder

There is only sparce evidence for drug treatment of the relatively new EDs diagnoses ARFID, pica, and RD which have been introduced by DSM-5 (American Psychiatric Association 2013).

Changes compared to the previous guidelines (Aigner et al. 2011)

For the 2023 update of the guidelines on the pharmacological treatment of eating disorders, we reviewed

the literature again, added studies published since 2011, and re-evaluated the old and the novel publications according to the new evidence and the recommended grading system developed for WFSBP treatment guidelines (Hasan et al. 2019). Based on the novel literature and the novel approach in grading, the evidence led to a re-evaluation of the studies included in the first WFSBP guidelines on the pharmacological treatment of EDs (Aigner et al. 2011), This led to differences compared to the previous guidelines.

For example, the grade B evidence for zinc supplementation in AN could not be upheld. For olanzapine, Aigner et al. (2011) obtained grade B evidence. Even though we identified further evidence, e.g. Attia et al. (2019), a limited recommendation was given, because the available evidence was restricted to weight gain, olanzapine's effect on psychopathology is less clear, and the adherence rate was low.

In contrast to Aigner et al. (2011), the current task force assessed the risk of the treatment of BN with tricyclic antidepressants as considerable. Therefore, tricyclic antidepressants are no more recommended for BN. Instead, the new update recommends topiramate for BN, both with a LoE of A and a GoR of 1. Aigner et al. (2011) had given a GoR of 2 only for topiramate. In BED, novel research has led to the recommendation of LDX and topiramate has maintained its high level of recommendation.

The current update of the guidelines includes literature relating to ARFID, pica, and RD. However, firm recommendations cannot be made yet.

Methodological limitations

As in the previous WFSBP guidelines on the pharmacological treatment of eating disorders (Aigner et al. 2011), we used only PubMed as database for the literature search, because we assumed that pharmacological studies of sufficient quality would have been published in journals that are covered in PubMed. However, the next guidelines update might consider using other databases as well, for example, Web of Science™ or PsycInfo.

Some recent meta-analyses (e.g. Hilbert et al. 2020) reviewed pharmacotherapeutic study registers for unpublished studies to avoid the risk of not detecting a potential publication bias. This was not done for the current guidelines.

When reviewing the literature, we focussed on the statistical significance of findings as opposed to clinical significance of reported changes during treatment. This is partly due to the lack of generally accepted standards for clinical significance. However, this approach might lead to misinterpretations and a misunderstanding when it comes to the judgement of whether statistically significant results are also clinically relevant (Sharma 2021).

Hasan et al. (2019) specified various criteria of acceptability including the risk–benefit ratio, the cost–benefit ratio, the applicability in the target population, ethical and legal aspects, preferences of service users, and practicability. However, due to the heterogeneity with which acceptability was reported we were not able to assess these specific aspects of acceptability systematically.

Content-related limitations

Even though this is an up-to-date and comprehensive summary of pharmacological studies on EDs which provides a cutting-edge evaluation of pharmacological studies in EDs, this article cannot cover all aspects of the treatment of patients with EDs. We focussed on the pharmacological treatment of EDs. Even though we added essential information on accompanying psychological treatment in the results tables, we did not compare the pharmacological treatments to non-pharmacological biological, psychotherapeutic, and other treatment approaches.

Whether a study was successful or not was decided with reference to the main outcome and improvement of diagnostic criteria. Other important outcomes for patients were therefore potentially neglected. For example, in the study of Walsh et al. (2006) no difference was found in time-to-relapse between the fluoxetine and the placebo group. However, a drug effect was found for anxiety symptoms. For an individual patient, a reduction of anxiety might be an important outcome. Indeed, most patients with AN would find medication useful if it helped reduce anxiety or sleep problems (Tyrrell-Bunge et al. 2018). Indeed, Patient Reported Outcome Measures (PROMs) and Patient Reported Experience Measures (PREMs) are increasingly perceived as clinically important as they assess the efficacy, safety, and experience of care from a patient perspective (Black et al. 2014). Specific PROMs and PREMS for EDs have not been developed yet. Therefore, future studies and guidelines might be able to take the patients' perspective into account.

Patients with EDs often suffer from various psychiatric co-morbidities, such as social anxiety, affective disorders such depression and bipolar disorder, sleep

disorders, obsessive-compulsive disorder, personality disorders, and suicidality (e.g. Ulfvebrand et al. 2015; Ahn et al. 2019; Catone et al. 2020). Additionally, physical diseases often develop as a consequence of the ED. These co-morbidities might benefit from pharmacological treatment. However, first line treatments for these co-morbidities might be contra-indicated because of the ED. For example, the antidepressant bupropion is contraindicated in AN and BN, because further weight loss can be a side effect and specifically contra-indicated in AN because of the increased risk of seizures; and in BED, the antidepressant mirtazapine and the atypical antipsychotic olanzapine which has also mood-stabilising properties should be avoided due to weight gain as a side effect (Himmerich et al. 2021). Additionally, it is known that not all medications used to treat comorbidity are effective in people with AN. For example, SSRIs medication have little to no effect on depressive and anxious symptoms in underweight patients with AN (Ferguson et al. 1999). For further information on the pharmacological treatment of physical and mental co-morbidities, we refer to the respective review articles, e.g. (Himmerich et al. 2021).

Comorbidities are often exclusion criteria in RCTs. Thus, the high frequency of comorbidities in eating disorders means that the generalisability of studies is questionable. Many trials in BED, for example, exclude patients with extreme obesity, which leaves the question unanswered whether a medication is safe and efficacious in this vulnerable population.

Most pharmacological trials in EDs have a relatively short duration between 6 and 16 weeks. Only few studies have had a follow-up assessment after 12 months (e.g. Schmidt et al. 2004). Thus, the stability of treatment effects, the tendency to relapse, the long-term outcomes, and potential difficulties with the long-term use of medications are unclear for most pharmacological treatments.

The application of the recommendations should be in accordance with the national legal framework in each country and therefore partly depends on the medicines agencies' approval. The legal aspects of the prescription of medications for EDs were not the focus of these guidelines.

Future research perspectives

Major therapeutic challenges for pharmacological therapy research in EDs remain. For example, regarding studies with antidepressants, most previous studies were underpowered. Because of the proximity of AN to obsessive-compulsive disorder, it would be quite conceivable that, for example, high-dose SSRI treatment over three months might have effects like those seen in obsessive-compulsive disorder. However, such studies have never been done. Novel and promising pharmacological developments that might help people with AN include the human recombinant leptin metreleptin (Milos et al. 2020; Antel et al. 2022; Gradl-Dietsch et al. 2023), the dissociative anaesthetic (es)ketamine (Mills et al. 1998; Dechant et al. 2020; Scolnick et al. 2020; Keeler et al. 2021; Schwartz et al. 2021), and the psychedelic psilocybin (Spriggs et al. 2021). However, RCTs are necessary to examine their benefit and potential side effects in AN.

Areas of the pharmacological treatment of EDs that have been neglected so far are health economics, pharmacokinetics, and pharmacogenetics. Even though the economic impact of EDs is huge (Schmidt et al. 2016; Santomauro et al. 2021), the potential economic benefit of pharmacological treatment in EDs is unclear.

The promising role of probiotics to support the treatment of mental health disorders has been investigated in literature (Foster and McVey Neufeld 2013). Only preliminary evidence is available for its use as an adjunctive therapeutic approach in AN (Solis et al. 2002; Nova et al. 2006; Dhopatkar et al. 2023). It has been found that probiotics help with AN comorbidities, such as anxiety and depression (Foster and McVey Neufeld 2013), metabolic disturbance (Green et al. 2020), immune modulation (Azad et al. 2018), and gastrointestinal symptoms (Pugh et al. 2019). As evidence is still scarce, this therapeutic approach might be revisited in the next update of the WFSBP guidelines for the pharmacological treatment of EDs.

Regarding pharmacokinetics and pharmacogenetics, we have already discussed fluoxetine earlier as one example, because this is the one medication that is approved in all countries for use in BN, and we have mentioned fluoxetine and its metabolite norfluoxetine very long elimination half-life (Altamura et al. 1994) and its inhibition of CYP2D6 (Hiemke et al. 2018; Murphy et al. 2022) which catalyses the metabolism of many clinically important drugs including antidepressants, neuroleptics, antiarrhythmics, β-adrenoceptor blockers, and opioids. However, pharmacokinetic interactions should also be considered when prescribing other medications for EDs, and genetic testing might be helpful to identify slow metabolizers (Bertilsson et al. 2002). The focus of these guidelines was to identify the LoE and the GoR for each medication. The interactions of the different medications were beyond the scope of this article but must be taken into

account in clinical practice. However, even though people with EDs have metabolic peculiarities, there is almost no pharmacokinetic or pharmacogenetic research available in this patient group.

Thus, future guidelines and research should thus give guidance on the use of combinations of pharmacological, other biological, and psychotherapeutic treatments; they should also address comorbidities of EDs and the long-term consequences of the use of medication, and consider health economic, pharmacokinetic, and pharmacogenetic aspects of the treatment of EDs.

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ORCID

Hubertus Himmerich http://orcid.org/0000-0003-1209-6073
Andreas Karwautz http://orcid.org/0000-0001-9053-998X
Marta Tyszkiewicz-Nwafor http://orcid.org/0000-0002-0141-4593
Susan L. McElroy http://orcid.org/0000-0002-8879-0865

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