The pharmacological treatment of eating disorders: new guidelines and gender-specific aspects

Hubertus Himmerich[1,2], Cheyenne Lee[1], Victoria Burmester[3], Dasha Nicholls[3], Janet Treasure[1,2]

1. Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
2. South London and Maudsley NHS Foundation Trust, London, UK
3. Division of Psychiatry, Department of Brain Sciences, Imperial College London, London, UK

✉ Corresponding author: Hubertus Himmerich. Email: hubertus.himmerich@kcl.ac.uk

Abstract

Even though psychopharmacology has made substantial progress in many areas of psychiatry since the discovery of antipsychotics and antidepressants in the 1950s, the evidence base for pharmacological treatments in the field of eating disorders has been lagging. The World Federation of Societies of Biological Psychiatry guidelines update 2023 on the pharmacological treatment of eating disorders provides a comprehensive summary of pharmacological studies and recommendations for anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED), avoidant/restrictive food intake disorder, pica and rumination disorder. However, there are very few studies in adolescents, implying that evidence-based recommendations in this population are difficult to make. Gender-specific aspects have also been addressed in the guidelines update, such as the small number of male patients included in pharmacological studies in AN and BN. Furthermore, the guidelines recommend against the treatment of female AN patients with testosterone, mention that topiramate for the treatment of BN and BED is contraindicated during pregnancy and that fluoxetine and its metabolite norfluoxetine inhibit the metabolism of the anti-breast cancer prodrug tamoxifen to its active metabolite endoxifen.

Keywords: eating disorder, anorexia nervosa, bulimia nervosa, binge eating disorder, avoidant/restrictive food intake disorder, pharmacological treatment, gender

1. Historical remarks

1.1 Eating disorders

A cornerstone in the history of eating disorders (EDs) was the meeting of the "Clinical Society of London" in 1873, when Sir William Gull coined the term "anorexia nervosa" (AN) (1). The diagnosis of "bulimia nervosa" (BN) was first suggested by Gerald Russell in a paper published in 1979 (2). Only one year later, in 1980, BN was included into the 3rd edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM). Binge eating disorder (BED) was described in 1959 by psychiatrist Albert Stunkard in his paper, "Eating Patterns and Obesity" (3). The 5th edition of the DSM (DSM-5), which was issued in 2013 (4), finally introduced BED as a separate ED. The DSM-5 also recognises avoidant/restrictive food intake disorder (ARFID), pica and rumination disorder (RD) as autonomous disorders in the respective DSM-5 chapter on "Feeding and Eating Disorders". The diagnoses in the DSM-5 are comparable to those in the more recently published ICD-11 (5).

1.2 Psychopharmacology

From the start of the 19th century up to the 1950s, the psychiatric asylum numbers increased steadily in Europe and North America despite big efforts of deinstitutionalisation. In 1950, however, chlorpromazine, the first antipsychotic drug, was synthesised, and two years later, Pierre Deniker recognised its therapeutic effect on schizophrenia (6). This discovery led to a massive improvement in the therapy of psychosis. Before 1950, only 6% of patients with schizophrenia were ever discharged. However, after the introduction of chlorpromazine, 67% of patients with schizophrenia could be discharged after inpatient treatment; between 1955 and 1968, the residential psychiatric population in the United States decreased by 30% (7). A similar therapeutic breakthrough was achieved in affective disorders based on the discovery of the antidepressant effect of imipramine by Roland Kuhn in 1956 (8). Chlorpromazine, imipramine and other new psychopharmacological drugs allowed the mentally ill to recover, be discharged from psychiatric asylums and hospitals, live in their own homes and obtain employment.

1.3 Psychopharmacology of eating disorders

Because of anecdotal reports of success with antipsychotics, the use of first-generation antipsychotics to treat AN was investigated in open and uncontrolled, and also in randomised controlled trials in the 1970s and 1980s. However, the newly discovered psychopharmacological agents did not gain general acceptance for the treatment of EDs at that time and it seemed like patients with EDs could not benefit from the great breakthrough psychopharmacological therapies had achieved in other areas of psychiatry (9).

Between the 1980s and today, the situation changed due to diagnostic and psychopharmacological advances. Re-

garding new psychopharmacological developments, the selective serotonin reuptake inhibitor (SSRI) fluoxetine came into the market in 1986. It was tested in patients with BN, yielding positive results (10), and approved by the US Food and Drug Administration in 1987.

In AN, however, no pharmacological treatment has been approved. This might be one of the reasons why the prognosis for AN is still poor. A recent cohort study over 22 years published by Eddy and colleagues showed that only just over 30% of patients with AN had recovered after 9 years (11), although the prognosis for early onset AN may be better (12, 13).

1.4 Guidelines for the pharmacological treatment of eating disorders

In 2011, clinicians and researchers of the World Federation of Societies of Biological Psychiatry (WFSBP) published a comprehensive review of all published psychopharmacological studies in EDs up to then (14). This was the first version of the WFSBP guidelines on the pharmacological treatment of EDs. Since 2011, the DSM-5 was issued in 2013 recognising BED, ARFID, pica and RD as independent feeding disorders/EDs, and in 2019, novel guidance was developed by the WFSBP on how to grade evidence for clinical guideline development (15). According to this guidance, strong evidence that an intervention is effective can only be concluded if two positive, independent, high-quality, randomised controlled trials (RCTs) find that the medication helps in a clinically and statistically significant way. The quality of an RCT can, for example, be assessed using the Scottish Intercollegiate Guidelines Network (SIGN) rating (16). However, a strong recommendation can only be given to a medication with strong evidence if it shows safety, tolerability and a good adherence rate. This guidance was then applied in the new WFSBP guidelines update 2023 on the pharmacological treatment of EDs (17).

2. Eating disorders according to DSM-5 and ICD-11

As already mentioned, both DSM-5 and ICD-11 recognise AN, BN, BED, ARFID, pica and RD as feeding disorders or EDs. The main criteria for the diagnosis of AN are a significantly low body weight in the context of age, sex and physical health, an intense fear of weight gain and a disturbed body perception. In ICD-11, rapid weight loss (e.g., more than 20% of total body weight within 6 months) may replace the low body weight diagnostic feature for AN as long as other diagnostic requirements are met, meaning AN can be diagnosed at any weight. In the DSM-5, this would be atypical AN. Criteria for the diagnosis of BN are recurrent binges, recurrent vomiting, excessive physical activity or fasting and excessive occupation with food, figure and weight. Criteria for the diagnosis of BED are recurrent binge eating with control loss but no compensatory measures for weight reduction. Additional important symptoms are eating without being hungry, feelings of embarrassment, disgust or guilt after a binge and suffering distress due to these eating habits. ARFID is a feeding disorder/ED characterised by restrictions regarding the amount or the range of food consumed, or by a fear of the adverse consequences of eating, such as choking or vomiting. People with ARFID are underweight, have nutritional deficiencies, rely on supplements or enteral feeding and/or have significantly impaired psychosocial functioning as a result of their eating patterns that are more severe than simply being selective with one's food. Unlike those with AN, people with ARFID are not excessively preoccupied with body image, weight or shape. ARFID can occur at any age and any weight. Pica is a compulsive feeding disorder or ED in which people eat non-food items such as dirt, clay, paint, glue, hair, cigarette ashes and faeces. The disorder is more common in young children between the ages of 2 to 6 years. RD is an illness that involves repetitive, habitual regurgitation of food that might be partly digested. The affected patient may re-chew and re-swallow the food or spit it out (4).

3. Pathophysiological considerations

Appetite-regulating neurocircuits: Appetite and body weight are biologically regulated by specific neurocircuits. The three most important neurocircuits are the self-regulatory, the hedonic and the homeostatic systems (18). These systems relate to the reasons why we eat or do not eat. For example, we may adhere to a specific diet because of a certain ideal of beauty or for ethical or somatic reasons (for example, food allergies). This happens in the self-regulatory system because it embeds eating into the social context, creates individual values and performs self-regulatory control. Its main centre lies in the prefrontal cortex.

Another reason for us to eat is enjoyment. The function of the hedonic system is to elicit the desire to eat and to evoke pleasure during food consumption. Its neurons and synapses can be found mainly in the prefrontal cortex, the basal ganglia and the thalamus.

Being hungry also creates an urge to eat to ensure that we consume sufficient energy to keep our body functioning. This hunger originates from the homeostatic system that integrates peripheral signals of food consumption and energy storages and regulates appetite. The hypothalamus plays a prominent role in this system.

Appetite-regulating signal molecules: Figure 1 shows that these neurocircuits are related and which signalling molecules, including neurotransmitters and hormones, they use. Important neurotransmitters of the self-regulation system are serotonin, noradrenaline, acetylcholine, the excitatory transmitter glutamate and the inhibitory messenger gamma-aminobutyric acid (GABA). The main neurotransmitters of the hedonic system are dopamine, opioids and cannabinoids. Signalling molecules of the homeostatic system include peripheral appetite-regulating hormones like

leptin, ghrelin, insulin and glucagon-like peptide-1 (GLP-1), hypothalamic appetite regulators like neuropeptide Y (NPY), agouti-related peptide (AgRP), α-melanocyte-stimulating hormone (α-MSH), cocaine- and amphetamine-regulated transcript (CART) and the neurotransmitter histamine (9). These signal molecules and their receptors can be targeted using pharmacological interventions to influence eating behaviour, food-related thoughts and emotions and body weight.

4. Medication for anorexia nervosa

For AN, the WFSBP guidelines update 2023 identified 70 relevant articles; 38 articles were new since 2011. The highest evidence was found for the antipsychotic agent olanzapine at a daily dose between 2.5 and 10 mg based on four positive RCTs (19-22), but the evidence is restricted to weight gain as an outcome. However, a low adherence rate was found for olanzapine in AN. Furthermore, the effect in young people is not clear as the only small RCT in adolescents showed no significant differences in weight gain, resting energy expenditure and psychological symptoms (23). Therefore, the WFSBP guidelines update 2023 concluded that olanzapine has strong evidence for weight gain only, but only a limited recommendation in AN (17). Olanzapine is an antagonist at dopamine, serotonin and histamine receptors.

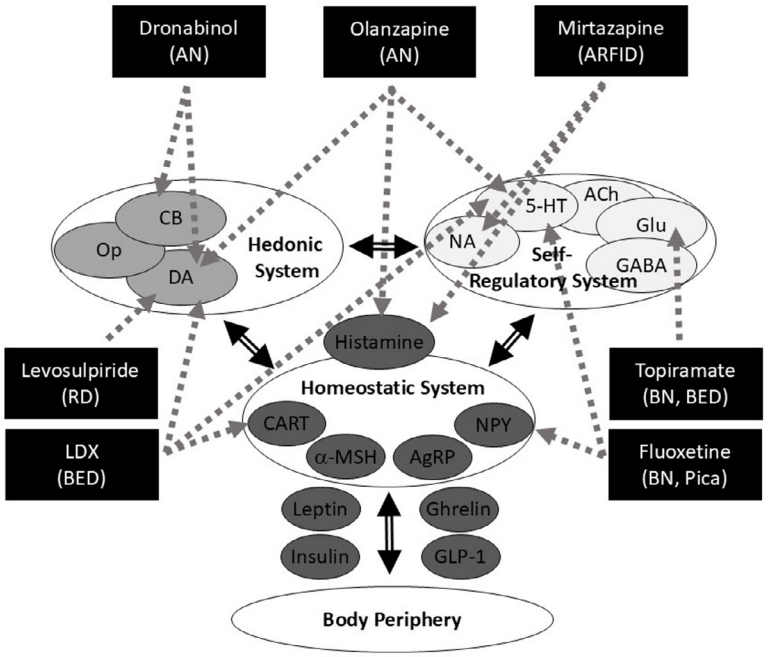

Figure 1: Appetite-regulating neurocircuits (hedonic, self-regulatory and homeostatic systems), related signalling molecules and eating disorder (ED) medications that are discussed in this article. The cannabinoid (CB) receptor agonist dronabinol, which has some evidence for its use in anorexia nervosa (AN), also influences the dopamine (DA) system. Olanzapine is an antagonist at (DA), serotonin (5-HT) and histamine receptors, with strong evidence for weight gain in AN. The antidepressant mirtazapine is an antihistaminergic α2-receptor blocker with evidence for its use in avoidant/restrictive food intake disorder (ARFID) from a retrospective chart review and two case reports. Topiramate influences cellular sodium and calcium channels as well as glutamate (Glu) and gamma-aminobutyric acid (GABA) receptors. It is recommended by the WFSBP guidelines for use in bulimia nervosa (BN) and binge eating disorder (BED). The selective serotonin reuptake inhibitor (SSRI) fluoxetine, which also influences neuropeptide Y (NPY), is approved for the treatment of BN. There is also evidence from case reports for its use in pica. Lisdexamfetamine (LDX) influences serotonin, dopamine and cocaine- and amphetamine-regulated transcript (CART). It has been approved for the treatment of BED in several countries (not the UK). Levosulpiride blocks presynaptic dopaminergic receptors and has helped ~one-third of patients with rumination disorder (RD) in an open study. Further abbreviations: opioids (Op), noradrenaline (NA), acetylcholine (Ach), agouti-related peptide (AgRP), α-melanocyte-stimulating hormone (α-MSH), glucagon-like peptide-1 (GLP-1). The figure is amended from (9).

Regarding children and adolescents with AN, the Canadian practice guidelines for the treatment of children and adolescents with eating disorders (24) have stated that in specific contexts, consideration of olanzapine use may be undertaken for the adjunct treatment of low weight children and adolescents with AN. These guidelines further explain that given its propensity for adverse effects, olanzapine should only be considered with appropriate consultation and monitoring by trained specialists in child and adolescent psychiatry or paediatrics who have expertise in the treatment of children and adolescents with EDs. When utilised, olanzapine should be initiated at a very low dose of 0.625 to 1.25 mg and titrated carefully (24).

The cannabinoid receptor agonist dronabinol has also been tested in people with AN. The daily dose was 5 mg. The beneficial effects on body weight, ED psychopathology and physical activity was published in two articles by Andries and colleagues in 2014 and 2015 (25, 26). Thus, the WFSBP EDs Task Force bestowed a limited level of evidence and a limited recommendation to use dronabinol (17). However, dronabinol is a controlled drug in the UK and is not licenced for the use of AN. Table 1 shows the medications with the highest recommendation and evidence for each ED.

The only medications with a high level of recommendation are fluoxetine and topiramate for BN and topiramate and lisdexamfetamine for BED. The WFSBP guidelines update 2023 reviewed clinical trials across the life span. However, as most RCTs were performed in adults, clinicians treating children and adolescents should consult more specific guidelines such as the Canadian practice guidelines for the treatment of children and adolescents with eating disorders (24).

Diagnosis	Medication	Daily dose	Level of evidence†	Grade of recommendation‡
Anorexia nervosa	Olanzapine	2.5 - 10 mg	A*	2
	Dronabinol	5 mg	B	2
Bulimia nervosa	Fluoxetine	20 - 60 mg	A	1
	Topiramate	75 - 200 mg	A	1
Binge eating disorder	Lisdexamfetamine	30 - 70 mg	A	1
	Topiramate	75 - 600 mg	A	1
ARFID	Mirtazapine	7.5 - 45 mg	C	3
Pica	Fluoxetine	20 - 60 mg	C	3
Rumination disorder	Levosulpiride	75 mg	C	3

Table 1. Medications with the highest level of evidence and grade of recommendation for each eating disorder according to the WFSBP guidelines update 2023 on the pharmacological treatment of eating disorders (17).

Notes: † Level of evidence: A: strong evidence that the intervention is effective; B: limited evidence that the intervention is effective; C: low evidence that the intervention is effective. ‡ Grade of recommendation: 1: strong recommendation for using the intervention; 2: limited recommendation for using the intervention; 3: weak recommendation for using the intervention. * Evidence restricted to weight gain.

5. Medication for bulimia nervosa

In BN, the task force identified 70 relevant articles. However, only 13 articles have been published since the first WFSBP guidelines in 2011. Thus, there has been limited progress regarding the pharmacological treatment of BN.

Fluoxetine is approved for the treatment of BN. The dose is between 20 and 60 mg per day. Four RCTs with a "high quality" SIGN rating (27-30) found a statistically significant superiority of fluoxetine regarding binge eating and vomiting. Thus, there is strong evidence that fluoxetine is effective in BN, and this leads to a strong recommendation for fluoxetine in BN. However, there is only one study in the adolescent population (31). This open trial of 60 mg fluoxetine daily in 10 young people showed reductions in binge frequency and the medication was well tolerated. For further case series and case reports of the use of fluoxetine in children and adolescents, see (24). The Canadian practice guidelines for the treatment of children and adolescents with eating disorders list fluoxetine as additional promising medication for BN but highlight that more research is required before definitive recommendations can be made (25).

Two RCTs which tested topiramate in BN have shown significant superiority compared to placebo regarding binge eating and vomiting (32-34). Topiramate must be started at a low dose of 25 mg per day to avoid cognitive problems such as impairments in verbal fluency (35), and the dose can be increased to 400 mg per day. As topiramate was well tolerated, it can be recommended for use in BN as well (17). However, it is not approved for the treatment of BN and fluoxetine should be tried first if a pharmacological treatment is necessary.

6. Medication for binge eating disorder

The WFSBP EDs Task Force identified 68 relevant articles pertaining to BED, of which 24 were new. All were in adult patients. Recent RCTs investigated lisdexamfetamine (LDX) at a dose of 50 or 70 mg per day. Evidence from four RCTs (36-39) and one relapse-prevention RCT (37) demonstrate that LDX is effective in the treatment of BED regarding binge eating frequency and body weight. Therefore, the task force bestowed strong evidence and a strong recommendation for the use of LDX in BED. LDX is approved for attention deficit hyperactivity disorder (ADHD) but not BN in the UK. It has, however, been approved for the treatment of BED in the US, Canada, Brazil, Puerto Rico, Mexico and Israel.

Three RCTs have tested topiramate in BED (40-42). The researchers used a dose between 25 and 600 mg per day and they found significant superiority of topiramate regarding binge eating frequency and body weight. Therefore, the task force decided to bestow level A evidence and a grade 1 recommendation to topiramate (17). However, topiramate is not approved for the treatment of BED in the UK.

7. Medication for avoidant/restrictive food intake disorder

Apart from BED, DSM-5 and ICD-11 introduced ARFID, pica and RD as new independent feeding disorders/EDs. No randomised controlled pharmacological study has been performed and published in ARFID. Three of the seven articles on pharmacological treatment for ARFID, most of which referred to children and young people, reported treatment with mirtazapine, namely one retrospective chart review (43) and two case reports (44, 45). Therefore, there is little evidence that mirtazapine is effective in ARFID, and this translates to a weak recommendation for its use in ARFID. Other medications used were antihistamines and antipsychotics, all with low levels of evidence.

8. Medication for pica

Pica is usually not an independent phenomenon but appears in the context of other mental or physical disorders. The task force identified eight articles pertaining to the pharmacological treatment of pica. The successful use of fluoxe-

tine for pica was reported in two case reports of patients with pica and obsessive-compulsive disorder (OCD) (46, 47), and two case reports of patients with pica and a neurodegenerative disorder (48, 49). Thus, there is low evidence that fluoxetine is effective in pica, and this translates to a weak recommendation for its use (17). However, in a patient with pica, it is advisable to examine for psychiatric comorbidities, such as OCD or a neurodegenerative disease, and select the pharmacological treatment taking all available information into account. Further successful single case reports are available for the treatment with SSRIs, antipsychotics and ADHD medication.

9. Medication for rumination disorder

The task force identified two articles for the pharmacological treatment of RD. One open study in adult patients tested levosulpiride, an antipsychotic with prokinetic activity. Whilst it did not help all patients, more than a third (38%) of the adults included benefitted from this medication (50). As we have evidence from one open study, this translates to a weak recommendation for its use in RD (17).

Another medication tested in RD was baclofen, which is a GABA agonist. In one double-blind crossover study in adult patients, 63% of patients reported symptom improvement with baclofen compared to 26% in the placebo period (51). However, baclofen has been reported to have serious adverse effects such as psychosis, depression, balance disorder with falls, and difficulties in verbal expression. Thus, despite evidence from a double-blind crossover study, the recommendation of the WFSBP for the use of baclofen in RD is weak (17).

10. Gender-specific aspects of the pharmacological treatment of EDs

Gender distribution of ED epidemiology: The prevalence of AN in the general population is about 1% among women and 0.1% in men. Similarly, BN is 10 times more common in females than in males, with a prevalence between 1 and 2% among women. BED is the most prevalent of all the EDs worldwide, with a prevalence of about 3% in the whole population including men and women who have a similar risk of BED (52). The prevalence estimates for ARFID in the general population vary substantially, ranging from 0.3% to 15.5% in children and adolescents and from 0.8% to 4.5% among adults with a sex ratio of ~1:1 (53). There is little epidemiological information on the prevalence of pica and RD.

Lack of studies in male patients with AN and BN: Due to the unbalanced gender distribution of AN and BN, most participants in studies testing medication in AN or BN are female. For example, of the 152 patients with AN included in the largest RCT of olanzapine for AN (22), only seven were male. In the largest RCT for fluoxetine in BN (28), of 398 patients with BN, only 17 were male. Thus, it is questionable whether firm conclusions for the pharmacological treatment of males can be drawn from these studies.

Female sex hormones to treat osteopenia in female patients with AN: The question of whether female sex hormones could help with osteopenia in AN was not addressed in the updated WFSBP guidelines, but it is clinically highly relevant. The evidence for exogenous oestrogen or progesterone to treat osteopenia in AN is scarce. Oral ethinyl oestradiol in the form of the oral combined pill does not appear to be effective, but transdermal 17β-oestradiol may increase bone mineral density. Thus, this treatment may be considered in patients where other options have been exhausted (54). However, endogenous oestrogen production usually follows weight restoration during the recovery from AN.

Testosterone for female patients with AN: Kimball et al. (55) reported an RCT in 90 female patients with AN, testing 300 µg transdermal testosterone daily or a placebo patch for 24 weeks. However, 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, the task force recommended against the use of transdermal testosterone.

Oxytocin for female patients with AN: Russell et al. (56) studied the effect of intranasal oxytocin in two pilot studies of female inpatients with AN. In the oxytocin group, eating concerns and cognitive rigidity were reduced after oxytocin application but no effect on weight was reported. Burmester et al. (unpublished data) found a negative effect of intranasal oxytocin on social cognition in female adolescents with ED who had higher baseline social stress; an effect that was not found in controls whose social stress reduced, as predicted.

Pregnancy: Topiramate has approval for epileptic seizures and migraine. It is contraindicated in pregnancy and in women of childbearing potential if they are not using a highly effective method of contraception.

Breast cancer: Fluoxetine is widely approved for the treatment of BN. However, fluoxetine and its metabolite norfluoxetine are potent inhibitors of the cytochrome P450 (CYP) isoenzymes CYP2D6 and CYP2C19. Therefore, caution is advised when combining fluoxetine with CYP2D6 and CYP2C19 substrates such as amitriptyline, atomoxetine, clomipramine, imipramine, and several antipsychotics. CYP2D6 inhibition also leads to decreased metabolism of the prodrug tamoxifen to its active metabolite endoxifen. Therefore, fluoxetine must not be given to women who receive tamoxifen treatment, a hormone therapy for breast cancer. Finally, fluoxetine should not be combined with monoamine oxidase inhibitors.

11. Discussion

The update of the WFSBP guidelines for the pharmacological treatment of EDs is currently the most comprehensive review of pharmacological studies in EDs. It also provides an evaluation of the reported evidence and makes recom-

mendations for pharmacological treatment. It follows clear and transparent guidance to rate the level of evidence and the grade of recommendation (15, 17). Several other international and national guidelines, such as the National Institute for Health and Care Excellence guideline, "Eating disorders: Recognition and treatment" (57), barely mention specific medications for the treatment of EDs because the evidence is relatively weak. Pharmacological trials in this population are a priority for research.

However, the WFSBP guidelines update 2023 on the pharmacological treatment of EDs has its limitations. It focused on the pharmacological treatment of EDs only. It did not compare the pharmacological treatment with non-pharmacological biological, psychotherapeutic or 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 were neglected, for example, anxiety and sleep disturbances in AN, patient-reported outcome measures or patient-reported experience measures.

Additionally, comorbidities were neglected. This is, for example, important if a patient suffers from depression and AN. The antidepressant bupropion is contraindicated in AN because of weight loss and an increased risk of seizures. If a patient suffers from depression or bipolar disorder and BED, mirtazapine and olanzapine should be avoided due to the risk of weight gain. Information about the treatment for frequent health consequences and comorbidities of EDs can be found in the paper by Himmerich et al. (58).

The WFSBP guidelines cover pica and RD (5) because they appear as feeding disorders and EDs in DSM-5 (4). However, in England, the National Health Service (NHS) children's ED services are generally not commissioned to treat these diagnoses as per NHS England Access and Waiting Time guidance.

Most pharmacological trials in EDs have a relatively short duration of between 6 and 16 weeks. Therefore, we had to develop guidelines without knowing what the long-term effects are.

Gender aspects seem to have particular importance for the pharmacological treatment of EDs for female, male, pregnant and breast cancer patients. Further, gender aspects that should receive more attention by future research are the pharmacological effects in transgender people with EDs as well as the psychological and physical effects of sex hormones in EDs.

Declaration of Interest

Hubertus Himmerich is the chief investigator of a proof-of-concept study testing psilocybin in AN which is an industry cooperation between SLaM, COMPASS Pathfinder Limited and Worldwide Clinical Trials Limited.

Funding

Hubertus Himmerich and Janet Treasure have received salary support from the National Institute of Health and Care Research (NIHR) Mental Health Biomedical Research Centre (BRC) at South London and Maudsley NHS Foundation Trust (SLaM) and King's College London (KCL). DN is supported by the National Institute for Health and Care Research Applied Research Collaboration Northwest London and the Imperial BRC. The views expressed in this publication are those of the author(s) and not necessarily those of the National Institute for Health Research or the Department of Health and Social Care.

References

1. Van Deth R, Vandereycken W. Eating Disorders: Clinical Section. *In:* Berrios G (editor). A History of Psychiatry. London. Routledge (2008). p. 593-601.
2. Russell G. Bulimia nervosa: an ominous variant of anorexia nervosa. Psychological Medicine. 1979;9(3):429-48.
3. Stunkard AJ. Eating patterns and obesity. Psychiatric Quarterly. 1959;33(2):284-95.
4. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5). Arlington, VA. American Psychiatric Association (2013).
5. World Health Organisation (WHO). International Classification of Diseases 11th Revision 2021. Available from: https://icd.who.int.
6. Delay J, Deniker P. Neuroleptic effects of chlorpromazine in therapeutics of neuropsychiatry. Journal of Clinical and Experimental Psychopathology. 1955;16(2):104-12.
7. Thuillier J. Les dix ans qui ont changé la folie. Paris. Robert Laffont (1980).
8. Steinberg H, Himmerich H. Roland Kuhn - 100th Birthday of an innovator of clinical psychopharmacology. Psychopharmacology Bulletin. 2012;45(1):48.
9. Himmerich H, Treasure J. Psychopharmacological advances in eating disorders. Expert Review of Clinical Pharmacology. 2018;11(1):95-108.
10. Freeman C, Hampson M. Fluoxetine as a treatment for bulimia nervosa. International Journal of Obesity. 1987;11:171-7.
11. Eddy KT, Tabri N, Thomas JJ, Murray HB, Keshaviah A, Hastings E, et al. Recovery from anorexia nervosa and bulimia nervosa at 22-year follow-up. The Journal of Clinical Psychiatry. 2017;78(2):17085.
12. Wentz E, Gillberg C, Gillberg IC, Råstam M. Ten-year follow-up of adolescent-onset anorexia nervosa: psychiatric disorders and overall functioning scales. The Journal of Child Psychology and Psychiatry and Allied Disciplines. 2001;42(5):613-22.
13. Herpertz-Dahlmann B, Dempfle A, Egberts KM, Kappel V, Konrad K, Vloet JA, et al. Outcome of childhood anorexia nervosa - the results of a five-to ten-year follow-up study. International Journal of Eating Disorders. 2018;51(4):295-304.
14. Aigner M, Treasure J, Kaye W, Kasper S, Disorders WTFOE. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of eating disorders. The World Journal of Biological Psychiatry. 2011;12(6):400-43.
15. Hasan A, Bandelow B, Yatham LN, Berk M, Falkai P, Möller H-J, et al. WFSBP guidelines on how to grade treatment evidence for clinical

guideline development. The World Journal of Biological Psychiatry. 2019;20(1):2-16.
16. Scottish Intercollegiate Guidelines Network (SIGN). Accessed 03 September 2023. Available from: https://www.sign.ac.uk/.
17. Himmerich H, Lewis YD, Conti C, Mutwalli H, Karwautz A, Sjögren JM, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines update 2023 on the pharmacological treatment of eating disorders. The World Journal of Biological Psychiatry. 2023:1-64.
18. Treasure J. Neuroimaging of eating disorders: commentary. In: Shenton M, Turetsky B, editors. Understanding Neuropsychiatric Disorders: Insights from Neuroimaging. Cambridge. Cambridge University Press (2011). p. 510-6.
19. Brambilla F, Monteleone P, Maj M. Olanzapine-induced weight gain in anorexia nervosa: involvement of leptin and ghrelin secretion? Psychoneuroendocrinology. 2007;32(4):402-6.
20. Bissada H, Tasca GA, Barber AM, Bradwejn J. Olanzapine in the treatment of low body weight and obsessive thinking in women with anorexia nervosa: a randomized, double-blind, placebo-controlled trial. American Journal of Psychiatry. 2008;165(10):1281-8.
21. Attia E, Kaplan A, Walsh B, Gershkovich M, Yilmaz Z, Musante D, et al. Olanzapine versus placebo for out-patients with anorexia nervosa. Psychological Medicine. 2011;41(10):2177-82.
22. Attia E, Steinglass JE, Walsh BT, Wang Y, Wu P, Schreyer C, et al. Olanzapine versus placebo in adult outpatients with anorexia nervosa: a randomized clinical trial. American Journal of Psychiatry. 2019;176(6):449-56.
23. Kafantaris V, Leigh E, Hertz S, Berest A, Schebendach J, Sterling WM, et al. A placebo-controlled pilot study of adjunctive olanzapine for adolescents with anorexia nervosa. Journal of Child and Adolescent Psychopharmacology. 2011;21(3):207-12.
24. Couturier J, Isserlin L, Norris M, Spettigue W, Brouwers M, Kimber M, et al. Canadian practice guidelines for the treatment of children and adolescents with eating disorders. Journal of Eating Disorders. 2020;8:1-80.
25. Andries A, Frystyk J, Flyvbjerg A, Støving RK. Dronabinol in severe, enduring anorexia nervosa: a randomized controlled trial. International Journal of Eating Disorders. 2014;47(1):18-23.
26. Andries A, Gram B, Støving RK. Effect of dronabinol therapy on physical activity in anorexia nervosa: a randomised, controlled trial. Eating and Weight Disorders-Studies on Anorexia, Bulimia and Obesity. 2015;20:13-21.
27. Fluoxetine Bulimia Nervosa Collaborative Study Group. Fluoxetine in the treatment of bulimia nervosa. A multicenter, placebo controlled, double-blind trial. Arch Gen Psychiatry. 1992;49:139-47.
28. Goldstein DJ, Wilson MG, Thompson VL, Potvin JH, Rampey AH, Group FBNR. Long-term fluoxetine treatment of bulimia nervosa. The British Journal of Psychiatry. 1995;166(5):660-6.
29. Walsh BT, Agras WS, Devlin MJ, Fairburn CG, Wilson GT, Kahn C, et al. Fluoxetine for bulimia nervosa following poor response to psychotherapy. American Journal of Psychiatry. 2000;157(8):1332-4.
30. Romano SJ, Halmi KA, Sarkar NP, Koke SC, Lee JS. A placebo-controlled study of fluoxetine in continued treatment of bulimia nervosa after successful acute fluoxetine treatment. American Journal of Psychiatry. 2002;159(1):96-102.
31. Kotler LA, Devlin MJ, Davies M, Walsh BT. An open trial of fluoxetine for adolescents with bulimia nervosa. Journal of Child and Adolescent Psychopharmacology. 2003;13(3):329-35.
32. Hedges DW, Reimherr FW, Hoopes SP, Rosenthal NR, Kamin M, Karim R, et al. Treatment of bulimia nervosa with topiramate in a randomized, double-blind, placebo-controlled trial, part 2: improvement in psychiatric measures. Journal of Clinical Psychiatry. 2003;64(12):1449-54.
33. Hoopes SP, Reimherr FW, Hedges DW, Rosenthal NR, Kamin M, Karim R, et al. Treatment of bulimia nervosa with topiramate in a randomized, double-blind, placebo-controlled trial, part 1: improvement in binge and purge measures. Journal of Clinical Psychiatry. 2003;64(11):1335-41.
34. Nickel C, Tritt K, Muehlbacher M, Pedrosa Gil F, Mitterlehner FO, Kaplan P, et al. Topiramate treatment in bulimia nervosa patients: A randomized, double-blind, placebo-controlled trial. International Journal of Eating Disorders. 2005;38(4):295-300.
35. Mula M. Topiramate and cognitive impairment: evidence and clinical implications. Therapeutic Advances in Drug Safety. 2012;3(6):279-89.
36. McElroy SL, Hudson JI, Mitchell JE, Wilfley D, Ferreira-Cornwell MC, Gao J, et al. Efficacy and safety of lisdexamfetamine for treatment of adults with moderate to severe binge-eating disorder: a randomized clinical trial. JAMA Psychiatry. 2015;72(3):235-46.
37. McElroy SL, Hudson J, Ferreira-Cornwell MC, Radewonuk J, Whitaker T, Gasior M. Lisdexamfetamine dimesylate for adults with moderate to severe binge eating disorder: results of two pivotal phase 3 randomized controlled trials. Neuropsychopharmacology. 2016;41(5):1251-60.
38. Guerdjikova AI, Mori N, Blom TJ, Keck Jr PE, Williams SL, Welge JA, et al. Lisdexamfetamine dimesylate in binge eating disorder: a placebo controlled trial. Human Psychopharmacology: Clinical and Experimental. 2016;31(5):382-91.
39. Hudson JI, McElroy SL, Ferreira-Cornwell MC, Radewonuk J, Gasior M. Efficacy of lisdexamfetamine in adults with moderate to severe binge-eating disorder: a randomized clinical trial. JAMA Psychiatry. 2017;74(9):903-10.
40. McElroy SL, Hudson JI, Capece JA, Beyers K, Fisher AC, Rosenthal NR, et al. Topiramate for the treatment of binge eating disorder associated with obesity: a placebo-controlled study. Biological Psychiatry. 2007;61(9):1039-48.
41. McElroy SL, Arnold LM, Shapira NA, Keck Jr PE, Rosenthal NR, Karim MR, et al. Topiramate in the treatment of binge eating disorder associated with obesity: a randomized, placebo-controlled trial. American Journal of Psychiatry. 2003;160(2):255-61.
42. Claudino AM, Oliveira IRd, Appolinario JC, Cordás TA, Duchesne M, Sichieri R, et al. Double-blind, randomized, placebo-controlled trial of topiramate plus cognitive-behavior therapy in binge-eating disorder. Journal of Clinical Psychiatry. 2007;68(9):1324-32.
43. Gray E, Chen T, Menzel J, Schwartz T, Kaye WH. Mirtazapine and weight gain in avoidant and restrictive food intake disorder. Journal of the American Academy of Child and Adolescent Psychiatry. 2018;57(4):288-9.
44. Naviaux A-F. Management of ARFID (avoidant restrictive food intake disorder) in a 12-year-old on a paediatric ward in a general hospital: use of mirtazapine, partial hospitalisation model and family based therapy. Psychiatria Danubina. 2019;31(suppl 3):421-6.
45. Naguy A, Roshdy R, Al-Mutairi A, Alwetayan S, Alamiri B. Mirtazapine improved eating patterns in avoidant/restrictive food intake disorder. American Journal of Therapeutics. 2023;30(2):173-5.
46. Choure J, Quinn K, Franco K. Baking-soda pica in an adolescent patient. Psychosomatics. 2006;47(6):531-2.
47. Upadhyaya SK, Sharma A. Onset of obsessive compulsive disorder in pregnancy with pica as the sole manifestation. Indian Journal of Psychological Medicine. 2012;34(3):276-8.
48. Ikeda M, Shigenobu K, Fukuhara R, Hokoishi K, Maki N, Nebu A, et al. Efficacy of fluvoxamine as a treatment for behavioral symptoms in frontotemporal lobar degeneration patients. Dementia and Geriatric Cognitive Disorders. 2004;17(3):117-21.

49. Kanamori T, Kaneko Y, Yamada K, Suzuki M. Successful combination therapy of trazodone and fluvoxamine for pica in Alzheimer's disease: a case report. Frontiers in Psychiatry. 2021;12:704847.
50. Lee H, Rhee PL, Park EH, Kim JH, Son HJ, Kim JJ, et al. Clinical outcome of rumination syndrome in adults without psychiatric illness: a prospective study. Journal of Gastroenterology and Hepatology. 2007;22(11):1741-7.
51. Pauwels A, Broers C, Van Houtte B, Rommel N, Vanuytsel T, Tack J. A randomized double-blind, placebo-controlled, cross-over study using baclofen in the treatment of rumination syndrome. American Journal of Gastroenterology. 2018;113(1):97-104.
52. Silén Y, Keski-Rahkonen A. Worldwide prevalence of DSM-5 eating disorders among young people. Current Opinion in Psychiatry. 2022;35(6):362-71.
53. Dinkler L, Bryant-Waugh R. Assessment of avoidant restrictive food intake disorder, pica and rumination disorder: interview and questionnaire measures. Current Opinion in Psychiatry. 2021;34(6):532-42.
54. Zadeh P, Etheridge L. Should teenage girls with anorexia nervosa be offered oestrogen treatment to reduce later risk of osteoporosis? Archives of Disease in Childhood. 2020;105(8):798-802.
55. Kimball A, Schorr M, Meenaghan E, Bachmann KN, Eddy KT, Misra M, et al. A randomized placebo-controlled trial of low-dose testosterone therapy in women with anorexia nervosa. The Journal of Clinical Endocrinology and Metabolism. 2019;104(10):4347-55.
56. Russell J, Maguire S, Hunt GE, Kesby A, Suraev A, Stuart J, et al. Intranasal oxytocin in the treatment of anorexia nervosa: randomized controlled trial during re-feeding. Psychoneuroendocrinology. 2018;87:83-92.
57. National Institute for Health and Care Excellence (NICE). Eating disorders: recognition and treatment. NICE guideline [NG69] 2017. updated 16 December 2020. Accessed 6 October 2023. Available from: https://www.nice.org.uk/guidance/ng69/chapter/Recommendations#identification-and-assessment.
58. Himmerich H, Kan C, Au K, Treasure J. Pharmacological treatment of eating disorders, comorbid mental health problems, malnutrition and physical health consequences. Pharmacology and Therapeutics. 2021;217:107667.