Eating disorders

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Eating disorders are disabling, deadly, and costly mental disorders that considerably impair physical health and disrupt psychosocial functioning. Disturbed attitudes towards weight, body shape, and eating play a key role in the origin and maintenance of eating disorders. Eating disorders have been increasing over the past 50 years and changes in the food environment have been implicated. All health-care providers should routinely enquire about eating habits as a component of overall health assessment. Six main feeding and eating disorders are now recognised in diagnostic systems: anorexia nervosa, bulimia nervosa, binge eating disorder, avoidant-restrictive food intake disorder, pica, and rumination disorder. The presentation form of eating disorders might vary for men versus women, for example. As eating disorders are under-researched, there is a great deal of uncertainty as to their pathophysiology, treatment, and management. Future challenges, emerging treatments, and outstanding research questions are addressed.

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Introduction

Eating disorders are serious psychiatric disorders characterised by abnormal eating or weight-control behaviours. Disturbed attitudes towards weight, body shape, and eating play a key role in their origin and maintenance. The form of these concerns varies by gender; in men for example, body image concerns might focus on muscularity, whereas in women, these concerns might focus more on weight loss. Obesity per se is not framed as an eating disorder.[1] All eating disorders considerably impair physical health and disrupt psychosocial functioning.[2] Both the Diagnostic and Statistical Manual (DSM-5) and the International Classification of Diseases (ICD-11) encompass six main feeding and eating disorders.[3] These include the familiar diagnostic categories of anorexia nervosa, bulimia nervosa, and binge eating disorder. In addition, three disorders—previously mainly viewed as childhood disorders—have been included. These are avoidant-restrictive food intake disorder, pica, and rumination disorder. DSM-5 also provides subtype qualifiers, severity indicators, and definitions of remission.

Anorexia nervosa is a highly distinctive serious mental disorder characterised by an intense fear of weight gain or a disturbed body image, or both, which motivates severe dietary restriction or other weight loss behaviours (eg, purging, excessive physical activity). Concerns about weight and shape distinguish anorexia nervosa from avoidant-restrictive food intake disorder. Additionally, cognitive and emotional functioning are markedly disturbed.[4,5] Medical complications of anorexia nervosa affect all organs and systems, and are generally due to malnutrition, weight loss and purging behaviours.[6] Gastrointestinal symptoms, affecting the whole gastrointestinal tract, are particularly common and bothersome.[7]

Bulimia nervosa can occur at normal or elevated weight (if weight is less than the threshold for bulimia nervosa, then a diagnosis of anorexia nervosa is given with binge purge subtype as specifier). Bulimia nervosa is characterised by recurrent episodes of binge eating (ie, eating large amounts with loss of control) and compensatory behaviours to prevent weight gain.[8] The most common compensatory behaviour is self-induced vomiting, but inappropriate use of medicines, fasting, or extreme exercise are also used. These behaviours are driven by negative self-evaluation related to weight, body shape, or appearance.

Binge eating disorder is characterised by distressing, recurrent episodes of binge eating, with fewer compensatory behaviours than in bulimia nervosa.[9] Both bulimia nervosa and binge eating disorder are often accompanied by, or lead to, obesity (30–45%)[10,11] and related metabolic disorders. Other specified feeding or eating disorders (DSM-5 and ICD-11) are a residual category.

Avoidant-restrictive food intake disorder is now recognised as an age-neutral disorder in DSM-5 and ICD-11. Core symptoms are food avoidance or restriction (regarding volume or variety), together with one or more of the following: weight loss or faltering growth, nutritional deficiencies, dependence on tube feeding or nutritional supplements for sufficient intake, and psychosocial impairment.[12] Symptoms might arise in the context of an overall absence of interest in food and eating, food selectivity based on sensory sensitivity, and fear of negative consequences of eating related to aversive experiences such as choking or vomiting.[13]

Pica involves eating non-nutritive or non-food substances for a period of a month or more. The main triggers are the taste of the substance, boredom, curiosity, or psychological tension.[14]

Rumination disorder involves regurgitation of food after eating in the absence of nausea, involuntary retching, or disgust.

Psychiatric comorbidities are the norm in people with eating disorders (>70%). The most common psychiatric comorbidities include mood and anxiety disorders, neurodevelopmental disorder, alcohol and substance use disorders, and personality disorders.[15,16] People with diabetes have an increased prevalence of eating disorders.[17–19] This high prevalence produces an increased risk of diabetic complications and premature death, especially if insulin omission is used to compensate for eating.[20,21] Bidirectional associations between eating disorders and autoimmune disorders such as coeliac and Crohn's disease have been observed.[22]

Differential diagnosis and assessment

The diagnosis of anorexia nervosa is usually straightforward, particularly if informants are used. Inflammatory bowel disease (Crohn's disease or ulcerative colitis), malignancies, thyrotoxicosis, and diabetes can sometimes be mistaken for anorexia nervosa. Rarely, anorexia nervosa can be mimicked by a cerebral tumour. Diagnosis of anorexia nervosa can be difficult in patients with major depressive or schizophrenic illnesses. Indeed, severe depression can be associated with weight loss from a loss of appetite or the patient's belief that they do not deserve food. A patient with schizophrenia might avoid food because of delusions of being poisoned.

Investigations can reveal widespread abnormalities as a result of starvation or purging in anorexia nervosa. A full blood count often reveals leukopenia. Asymptomatic low blood glucose might occur. Raised liver enzymes, cholesterol, and endocrine changes—such as mild hypothyroidism, low levels of oestrogen or testosterone, and hypersecretion of corticotrophin-releasing hormone and growth hormone—are often present. Salivary amylase could be elevated from vomiting. Hypokalaemic alkalosis can be a consequence of purging. The electrocardiogram might show ST-segment and T-wave changes, which are usually secondary to electrolyte disturbances; emaciated patients might have hypotension and bradycardia. The majority of these abnormalities respond to symptomatic improvement, most do not need further investigation, although some (such as prolongation of the QTc interval, hypoglycaemia, hypokalaemia, and hypophosphataemia) can negatively affect management (panel).[23,24] A comprehensive account of medical management is outside the scope of this review but is available in the Management of Really Sick Patients with Anorexia Nervosa (MARSIPAN) guidelines.[24]

For bulimia nervosa and binge eating disorder, there might be an overlap with atypical depression (as overeating and oversleeping often occur in low-light months in people with depression).[25] About 50% of patients with bulimia nervosa or binge eating disorder feature symptoms of attention deficit hyperactivity disorder (ADHD), and around 15% of patients have multiple comorbid impulsive behaviours, including substance abuse, impulse buying, compulsive shopping, and multiple sexual relationships.[26,27] These patients might also self-harm, display intense emotions, and have chaotic sleeping patterns. Furthermore, they might meet criteria for borderline personality disorder or other personality disorders and, often, bipolar II disorder.

Avoidant-restrictive food intake disorder can be mistaken as picky eating, but functional changes such as concomitant low weight or inability to grow along their developmental trajectory might signify the presence of an eating disorder. Patients with avoidant-restrictive food intake disorder are susceptible to the same medical complications as patients with anorexia nervosa. Comorbidity with neurodevelopmental or anxiety disorders often occurs.

Pica can also be observed in individuals with autism, intellectual disability, schizophrenia, or particular physical disorders (eg, Kleine-Levin syndrome). In such instances, pica should be noted as an additional diagnosis only if the problem is severe enough to warrant clinical attention.

The differential diagnosis for rumination disorder includes psychogenic vomiting, purging eating disorders (not yet recognised as a separate eating disorder category), and various somatic disorders.

Panel: Physical findings in the main eating disorders

Anorexia nervosa*

All systems of the body are affected by starvation, and the damage accumulates over time. Also, if there are additional purging behaviours, the risk of the following conditions is increased:

- Cardiovascular: hypotension, bradycardia, prolonged QT, arrhythmias, cardiomyopathy
- Dermatological: dry scaly skin and brittle hair (hair loss), lanugo (ie, fine downy body hair)
- Endocrine and metabolic: hypoglycaemia, hypokalaemia, hyponatraemia, hypothermia, altered thyroid function, hypercortisolaemia, amenorrhoea, delay in puberty, arrested growth, osteoporosis
- Gastrointestinal: prolonged gastrointestinal transit (delayed gastric emptying, altered antral motility, gastric atrophy, decreased intestinal mobility), constipation
- Haematologic: anaemia, leukopenia, thrombocytopenia
- Neurological: peripheral neuropathy, loss of brain volume: ventricular enlargement, sulcal widening, cerebral atrophy (pseudoatrophy—corrects with weight gain)
- Oral: dental caries
- Skeletal: osteopenia
- Renal: renal calculi, acute kidney injury (from dehydration and purging)
- Liver: transaminitis, liver failure
- Reproductive: amenorrhoea, infertility, low birthweight infant

Bulimia nervosa and binge eating disorder

Physical findings mainly due to the effects of starvation or vomiting:

- Often similar to anorexia nervosa, but less severe
- Specific problems related to purging include:
  - Cardiovascular: arrhythmias, cardiac failure (sudden death)
  - Endocrine and metabolic: electrolyte disturbances (K^+, Na^+, Cl^-, metabolic acidosis [laxatives] or alkalosis [vomiting])
  - Gastrointestinal: constipation or steatorrhoea, gastric or duodenal ulcers, pancreatitis, oesophageal or gastric erosions or perforation
  - Haematological: leukopenia or lymphocytosis
  - Oral: dental erosion
  - Renal: acute renal injury

K=Potassium. Na=Sodium. Cl=Chlorine. *It is beyond the scope of this Seminar to detail a full medical assessment and management. For the most part, these anomalies are linked to symptomatic behaviours and resolve when these behaviours are reduced. Further details are available in the Management of Really Sick Patients with Anorexia Nervosa (MARSIPAN) guidelines, which are regularly updated.[23,24]

Epidemiology

Eating disorders can affect individuals of all ages, genders, sexual orientations, ethnicities, and geographies. Adolescents and young adults are particularly at risk, with anorexia nervosa starting earlier than bulimia nervosa or binge eating disorder. Onset after age 30 years is rare for anorexia nervosa.[28,29] Age of onset for anorexia nervosa

appears to be decreasing.[30] In adult populations, the clinical profile is dominated by binge spectrum disorders with less gender differences than in the adolescent population, and a higher than average risk in ethnic minorities and individuals with higher weight.[31]

At a primary care level, incidence rates have been stable in the past decades for anorexia nervosa, stable or declining for bulimia nervosa, and rising for binge eating disorder and unspecified eating disorders.[32,33] Globally, the prevalence of eating disorders has increased by 25%, but only about 20% of affected individuals present for treatment.[34,35] Duration of untreated eating disorder before the start of first treatment is variable, but shorter for anorexia nervosa than for bulimia nervosa or binge eating disorder (ie, 29·9 months for anorexia nervosa, 53·0 months for bulimia nervosa, and 43·8 months for binge eating disorder), and shorter for children than for adolescents or adults (ie, 9·8 months for children and 34·7 months for adolescents or adults; Schmidt U, unpublished).

Long-term follow-up studies (>20 years) of patients with anorexia nervosa or bulimia nervosa show that about a third of these patients have a persistent eating disorder, with a median illness duration of about 10 years for anorexia nervosa.[36] The standardised mortality rate for anorexia nervosa is 5·9, for bulimia 1·9, and for binge eating disorder 2·3. However, these data are often derived from patients admitted to hospital in the past, and early intervention and active engagement might reduce this figure.[37]

In a population-based study of German children aged 7–14 years, 4·98% of participants displayed a recurrent pica behaviour and 1·49% displayed a rumination behaviour.[38] These behaviours showed a significant small correlation with one another and with symptoms of avoidant-restrictive food intake disorder. One study examined the clinical characteristics and frequency of DSM-5 pica and rumination disorder among individuals seeking treatment for either eating disorders and obesity. Only 1·3% of the patients with eating disorders and none of the patients seeking treatment for obesity met DSM-5 criteria for pica. 7·4% of patients with eating disorders and 2% of those seeking treatment for obesity endorsed rumination behaviour.[39]

Pathophysiology

There is considerable uncertainty about how to conceptualise eating disorders: are they problems of eating or body image, or are they neurotic, psychotic, or psychosomatic disorders?[40] Work in progress suggests that divergence exists in the underlying aetiology between anorexia nervosa and binge spectrum disorders. Therefore, we have, when possible, summarised the findings into these two broad categories.

Animal models

Plausible animal models for both subtypes of eating disorders are available. For anorexia nervosa, the most established model is the starvation-induced hyperactivity, which develops in rodents placed on a restricted feeding schedule with access to a running wheel. A proportion (predominately female rodents with a sensitivity to fear) exposed to this environment choose to exercise rather than eat even to the point of death.[41,42] In another model of anorexia nervosa in female adolescent mice, a combination of a genetic susceptibility to anxiety, social isolation, and caloric restriction results in severe self-imposed, sometimes fatal dietary restriction.[43]

Animal models of binge eating include features implicated in the human condition, such as dietary changes (eg, periods of food restriction, addition of sucrose to drinking water, intermittent access to highly palatable food) and stress.[44] Animals exposed to these environmental changes show bio-behavioural changes similar to those found in addictions. This finding has led some to conceptualise the binge spectrum disorders as a form of food addiction.[45,46]

Human studies

There are limitations in research about risk factors in humans. The portfolio of evidence differs between eating disorders. Currently, the strongest genetic evidence is for anorexia nervosa, whereas longitudinal studies revealed more power for the binge spectrum disorders. Cross-sectional clinical studies provide mainly correlational information and might be confounded by secondary effects, which could contribute to symptom persistence as described in staging models.[47] Thus the clinical picture becomes more complex over time and the profile of eating disorders in childhood might differ from that of adults in the later stages of illness.

Genome-wide association studies involving large international cooperative efforts have identified eight loci associated with anorexia nervosa.[48,49] The relevance of these signals to the mechanisms that underpin anorexia nervosa is unclear. However, the positive polygenic correlations with various brain-related behaviours (ie, psychiatric disorders [especially obsessive-compulsive disorder], personality traits [neuroticism], educational attainment, and activity) align with the typical clinical features. Surprisingly, this study also revealed negative polygenic correlations with traits associated with the metabolic syndrome (ie, body mass index [BMI], insulin sensitivity, and cholesterol levels). Work is in progress to obtain a meaningful genome-wide association study on people with binge spectrum disorders, which have slightly lower levels of heritability (0·35–0·45) than those found in anorexia nervosa, and positive genetic correlations with alcohol problems and obesity.[50] A systematic review on the field of epigenetics found mainly small studies, which often focused on one candidate gene. Thus, genome-wide studies are needed.[51]

Longitudinal studies from case registers or cohort studies have revealed risk factors and correlates of psychopathology. Early signals of anomalies in growth

and eating behaviour align with the genetic findings discussed above, in that picky eating and leanness are associated with anorexia nervosa, and a robust appetite and overweight with binge spectrum disorders.[27,52,53] Moreover, longitudinal studies suggest that environmental influences in the perinatal period are of relevance for anorexia nervosa, whereas problems in early childhood are associated with binge spectrum disorders.[54–58] A sociocultural context in which food and body image are highly salient also serves to shape the illness.

Several temperamental traits (in part related to developmental disorders) are considered to be part of a predisposing phenotype. These traits are in turn associated with anomalies in neurocognitive function, many of which are accentuated by weight loss. A compilation and critical analysis of systematic reviews of neurocognition provides an excellent overview.[59] Low self-esteem is common to all forms of eating disorders.[60] In anorexia nervosa, problems with social cognition, social anxiety, social anhedonia, and insecure attachment are possibly linked to autistic spectrum disorder and anxiety traits.[61–63] High levels of perfectionism are associated with obsessive compulsive personality.[64] Problems with emotional processing can be associated with a tendency to ruminate and with anomalies in metacognition.[65–67] Anomalies in social cognition include decreased facial expressivity and reduced theory of mind, both of which limit the capacity to interpret and reciprocate in social interactions.[68] Furthermore, there is an increased sensitivity to social ranking and threat.[69] These factors contribute to the relationship ruptures and social isolation, which are core maintaining factors of anorexia nervosa.[70]

Abnormal eating behaviour might also be underpinned by differences within the inhibition or disinhibition behavioural spectrum, and the salience and processing of rewards (ie, food and body image rewards). People with bulimic spectrum disorders have anomalies with attention and impulsivity, which might be part of the association with attention deficit hyperactivity disorder.[26] Anomalies in reward learning are thought to allow behaviours of habitual eating disorder to become embedded.[71] People with anorexia nervosa can delay responding to rewards, whereas the opposite is the case for binge eating disorder.[72] People with a binge spectrum eating disorder show increased attention and approach to food cues, whereas disengagement or avoidance occurs in anorexia nervosa. This approach to food aligns with the behavioural susceptibility theory, which suggests that there is a genetic vulnerability to the differential relationship to food.[73] The salience of these cues (ie, food or body image) might be learned responses, which become more extreme and habitual in the later stages of illness.[74]

These behavioural changes are associated with functional changes in brain circuits and connectivity associated with reward, habit learning, interoception, and the construction of self (default mode network).[75–77] Studies have examined the biological footprint in the prodromal and early phase of illness (IMAGEN).[78] A narrative review of the circuits associated with the range of anorexia nervosa symptoms is available, alongside a systematic review of circuits associated with the binge spectrum disorders.[78,79] These findings support the idea that there is a relative imbalance between top-down and bottom-up regulation of appetite. In line with the widespread impact of starvation, in anorexia nervosa there are reversible, structural reductions in brain tissue.[80]

Of particular interest, given the genetic profile described above, are anomalies in insulin and lipid metabolism.[81] There is burgeoning curiosity into the possible links with the microbiome (see systematic or narrative reviews of the increasing number of small-scale studies).[82,83] Descriptive studies report a lower than average faecal microbial diversity in people with anorexia nervosa, with an increase in mucin degraders. Various mechanisms that potentially maintain this condition have been proposed, including perturbations of nutritional metabolites, increased gastrointestinal permeability (complicated by immunological reactions), and changes in gut motility. Other secondary features can serve to maintain the illness through the psychosocial consequences of starvation. For example, the regression of the hypothalamic gonadal axis reduces the drive to form intimate relationships, which can contribute to isolation, a key maintaining factor.

Summary of pathophysiology

The underlying mechanisms of eating disorders are the subject of active research. It is probable that interactions between genetic and environmental factors at a crucial period in development add to the complexity of modelling these disorders. Families requested help to understand the illness, and the Academy of Eating Disorders offered up "nine truths about eating disorders", accompanied by a paper explaining the scientific rationale behind them.[84] Figures 1 and 2 summarise the current status and divide the causes into predisposing (background vulnerabilities), precipitating (the environmental context at the time of onset), and perpetuating factors (secondary aspects of the illness that cause the illness to be valued and maintained).

Treatment and management of eating disorders

Eating is an important social activity and social support can provide an important scaffold for recovery. Impaired social functioning can lead to social isolation or increased social media use (such as pro-anorexia nervosa websites), which could be harmful.[85] The form and structure of social support differs by age and developmental stage. For example, families are encouraged to be involved in managing symptoms in adolescents, whereas the form and content of family involvement is modified to suit the needs of adult patients. Carers themselves often experience high burden and stress,[86] and benefit from psychoeducation and skills training.[87]

In evidence-based practice, high-quality evidence is set within the context of clinical diversity and patient

preference.[88] The generalisability of evidence from trials is uncertain as the inclusion or exclusion criteria are often highly selective (eg, most of the evidence comes from a handful of centres in high-income countries), whereas the clinical presentation of eating disorders is diverse. For example, in anorexia nervosa, factors impacting care planning and prognosis include: child or adult onset, acute or chronic presentation, severe or mild malnourishment, and comorbid or simple anorexia nervosa. Furthermore, the comorbidities of the eating disorder spectrum (eg, developmental disorders, depression and anxiety, trauma) are an important part of the formulation. Thus, these caveats need to be considered.

In the following section, we first summarise the main findings of clinical trials on established psychological, pharmacological, and nutritional treatments, focusing mainly on trials reported in the past 5 years. We define "established treatments" as treatments that are widely used, recommended by guidelines, or have been tested in at least one large randomised controlled trial (RCT), with a minimal sample size of 100 participants. We also briefly describe treatments that are emerging and promising—ie, those treatments only tested in feasibility or pilot trials so far.

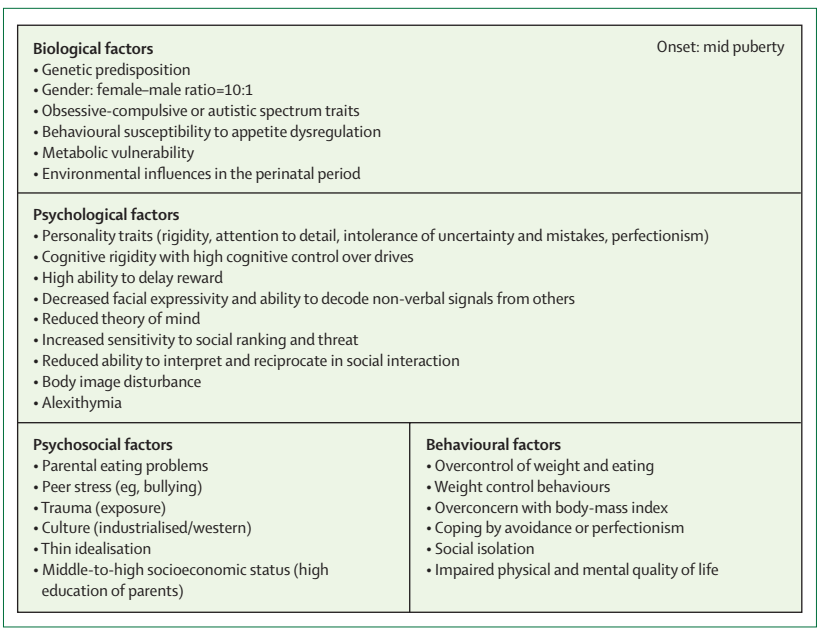

Figure 1: **Aetiology diagram of restrictive-type eating disorders**

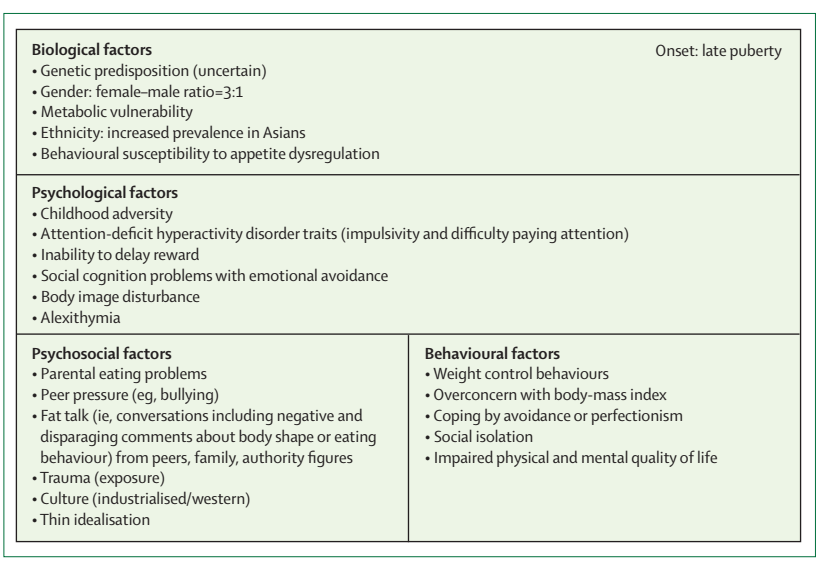

Figure 2: **Aetiology diagram of bulimic spectrum eating disorders**

Psychological treatments for anorexia nervosa across the age spectrum

A meta-analysis on the efficacy of psychological treatments for anorexia nervosa found no differences between psychological treatment and comparison interventions on weight gain, eating disorder psychopathology, and quality of life.[89] This finding is perhaps not surprising as the comparison interventions were mostly specialist psychological interventions. High-quality studies and those studies reporting therapist training had larger effects on weight gain and quality of life than studies of low quality. A network meta-analysis of both uncontrolled and randomised controlled trials of psychotherapy found that family-based approaches dominated interventions for adolescents, and individual psychotherapies dominated in adults, with no superiority of a specific approach.[90] Mean weight gain in inpatient settings was 537 g/week in adults and 615 g/week in adolescents. In outpatient settings, mean weight gain was 105 g/week in adults and 192 g/week in adolescents. A meta-analysis comparing different treatment settings for anorexia nervosa concluded that insufficient evidence exists to guide choice.[91] Having a lower BMI, lower motivation, and binge-purge type anorexia nervosa predicted dropout, whereas greater eating disorder pathology and poorer motivation predicted poorer outcomes.[92]

Psychological and nutritional treatments for adolescents with anorexia nervosa

For adolescents with anorexia nervosa, family-based interventions focused on eating disorders are recommended as first-line treatments by international evidence-based guidelines.[93] However, a Cochrane review suggests that the evidence favouring family-based interventions over standard treatment or other psychological approaches is not very solid, and that different types of family-based interventions do not seem to have different outcomes.[94] Since this review, variants of family-based interventions, such as multi-family group therapy,[95] separate parental interventions,[96] and carer skills training,[97] have been trialed with positive effects on both carer and patient outcomes.

Inpatient treatment involves meal support, which in a proportion of patients might involve nasogastric feeding. A systematic review of nutritional treatment of

adolescents found a large variation in protocols for refeeding, ranging from cautious protocols (shaped by concerns about refeeding syndrome) to those protocols that endorse a more rapid resolution of malnutrition.[98] A later systematic review suggested that some approaches might be too conservative.[99] No systematic review related to the use of oral nutritional supplements or micronutrient augmentation exists yet. Two systematic reviews compiled the evidence for enteral feeding in anorexia nervosa.[100,101] Most included studies were cohort studies reporting an increase in weight gain or a decrease in binging, or both, with few adverse effects. One RCT reported sustained benefits.

Inpatient treatment is augmented with various psychosocial, educational, and pharmacological interventions. Two RCTs have examined different treatment settings or intensities for adolescents with anorexia nervosa. Both showed that short hospitalisation of adolescents with anorexia nervosa (for medical stabilisation) followed by family-based treatment or day-treatment had similar outcomes to longer hospitalisation (until weight restoration).[102,103] Another trial found outpatient family therapy, which was offered post-hospitalisation and focused on family dynamics but not symptoms, to be superior to treatment as usual alone in terms of weight gain and other anorexia nervosa symptoms.[104]

Psychological and nutritional treatments for adults with anorexia nervosa

First-line treatments consist of structured individual therapies that focus on eating disorders, including cognitive behavioural therapy (CBT), Maudsley Model of anorexia nervosa, focal psychodynamic psychotherapy, and Specialist Supportive Clinical Management. These therapies have been evaluated in large-scale trials, with little or no differences in efficacy between them.[105–108] This finding is perhaps not surprising as all of them have common elements of behaviour change. All of these therapies lead to considerable improvements in body weight and reductions in anorexia nervosa symptoms, distress levels, and clinical impairment. Roughly 25% of patients recover completely, and 25% do not respond to outpatient treatment in adults.[109]

A higher intensity of care (ie, day or inpatient treatment) is required by about 20–40% of adult outpatients with anorexia nervosa because of high risk or irrresponsiveness to outpatient treatment.[110] Inpatient treatment is effective at improving nutritional health, but a proportion of patients relapse.[92,93] Various modifications have been added to reduce the tendency to relapse after discharge. Augmenting inpatient treatment by digital interventions and encouraging carer support have been found to be of benefit.[110] An exploratory RCT compared family workshops with individual family work and found similar improvements in patients' bodyweight and carers' distress in both conditions.[111] A second large-scale trial compared a brief skill intervention for carers (delivered by book, DVD, and telephone coaching) added to treatment as usual with treatment as usual alone.[112,113] There was a significant reduction in readmissions in the carer intervention group.

Hormonal treatment and pharmacotherapy for anorexia nervosa

A compilation of systematic reviews and meta-analyses is a useful resource describing medications that are used off license or prescribed for comorbidity.[114] High-quality evidence is lacking partly because many drug trials manifest poor and selective recruitment, which is mainly caused by negative expectancies of drug treatment (ie, weight gain) and high levels of attrition due to a sensitivity to side-effects. However, a multicentre outpatient study of olanzapine (10 mg) in adult patients (n=152) with anorexia nervosa (mean duration=10 years; mean BMI=16·7) reported a small positive effect on weight gain and agitation with olanzapine, although no change in general and specific psychopathology was observed.[115] There was no difference between the olanzapine and placebo condition in rates of withdrawal or attrition (45%) and hospitalisation (10%). Larger cohorts might be needed to consider potential harms.

Many of the endocrine anomalies found in people with anorexia nervosa are secondary features.[116] Bone health is of particular interest because of irreversible sequelae.[117] The National Institute for Health and Care Excellence (NICE) guidelines suggest referral to a specialist paediatrician to consider incremental physiological doses of transdermal oestrogen in girls with a chronic illness and a bone age of less than 15 years to mimic pubertal oestrogen increases and prevent later osteoporosis.[118]

Psychological treatments for binge spectrum disorders

In adolescents with bulimia nervosa, family-based therapy is one of the first-line treatments recommended by NICE.[118] CBT is an alternative therapy and, given in the form of guided self-care, produces a more rapid improvement in binge eating than family-based therapy, and has the advantage that the manual can be shared with parents.[119]

In adults with bulimia nervosa, NICE guidelines (from 2017) recommend guided self-help or therapist-delivered CBT as the treatment of choice.[119] Nevertheless, a meta-analysis found that over 60% of patients failed to fully abstain from core bulimia nervosa symptoms even after receiving best available treatments.[120]

In binge eating disorder, a comprehensive meta-analysis found large effects for abstinence from binge eating in trials of CBT compared with waitlist, whereas structured self-help treatment produced medium-to-large effects.[121] A landmark study by de Zwaan and colleagues[122] did a direct comparison of CBT with guided self-help. In this large trial, CBT was found to be more effective and more expensive than guided self-help.[123]

Various so-called third-wave behavioural therapies have been adapted for eating disorders, such as acceptance and commitment therapy, dialectical behaviour therapy, compassion-focused therapy, mindfulness-based interventions, and schema therapy. Several small trials, mainly in binge eating disorder, have been done to examine their efficacy in terms of remission. A meta-analytic review showed that these treatments were not superior to comparison treatments (such as CBT) in terms of reduction of binge eating.[124] A dissonance-based group treatment has been found to be more effective at symptom reduction than mindfulness-based group treatment in a transdiagnostic sample.[125] Other promising treatments include integrative cognitive affective therapy for bulimia nervosa.[126]

Pharmacological treatments for binge spectrum disorders

A network meta-analysis of treatments for bulimia nervosa revealed that fluoxetine treatment had negligible efficacy in promoting remission in comparison to other treatments.[120] Pharmacotherapy for binge eating disorder (including 30 studies with second-generation antidepressants, CNS stimulants, anticonvulsants, and others) produced greater levels of weight loss, an equivalent reduction in binges (less for abstinence), and a lower reduction in general and eating disorder psychopathology compared with placebo treatment, according to two meta-analyses.[121,127] Most studies of medication only measure short-term effects. A systematic review and exploratory meta-analysis concluded that side-effects and high levels of attrition need to be set against the positive benefits found from lisdexamfetamine, the only medication recommended for binge eating disorder by the US Food and Drug Administration.[128] Many trials of new treatments are registered and include drugs used for obesity, type 2 diabetes management, and addictions.[129] Although obesity is a common complication of binge eating disorder, no studies compared weight loss interventions (including bariatric surgery) with an inactive control comparison in binge eating disorder.[121,127]

Treatments for other specified feeding or eating disorders, avoidant-restrictive food intake disorder, rumination disorder, and pica

NICE guidelines recommend that people with other specified feeding or eating disorders should be treated using treatments for the disorder that it most closely resembles.[118] One small feasibility trial compared family-based treatment with treatment as usual in adolescents with avoidant-restrictive food intake disorder, and it suggested that family-based treatment is an acceptable and efficacious treatment in this group.[130] A novel form of CBT for avoidant-restrictive food intake disorder has also been developed.[131] A systematic review of cyproheptadine concluded that it had some benefits for avoidant-restrictive food intake disorder.[132] There are also reports on the use of mirtazapine and olanzapine in avoidant-restrictive food intake disorder.[133,134] We are not aware of any trials on rumination disorder or pica.

Conclusions from evidence-based practice

Early intervention improves outcomes; therefore, rapid commencement of specialised eating disorder treatment and care rather than watchful waiting is essential.[135] For mild or moderately severe cases, the first step is outpatient psychological treatment involving family members in an age-appropriate manner. If the medical or psychological risk is high or there is an irresponsiveness to outpatient care, then greater intensity of care can be provided by outreach, day, or inpatient facilities. Studies in the UK National Health Service suggest that about 20–35% of patients will need this higher level of care.[97,109] There is uncertainty about the management of patients who continue to be symptomatic following these first-line treatments, although recovery remains possible for more than 60% of patients even after 20 years.[136] Patients often request that their families and treatment teams should not give up on them.[137] New forms of treatments are being considered for this group, but some aspects of management are controversial. Transitions between services for age, educational, or physical reasons need to be carefully managed.

For patients with binge spectrum disorder, it is possible to sequence treatments, which can start with guided self-help and be followed by CBT or pharmacological augmentation, or both.[118] Recovery is possible for more than 60% of patients after 9 years of illness, but no further improvements are seen at 20 years of treatment.[136]

Emerging treatments

Many new augmentation techniques (including cognitive and emotional remediation and various brain-directed treatments) have been introduced to reduce eating disorder habits and promote new learning. However, these techniques are work in progress. Cognitive remediation therapy (CRT) aims to improve neuropsychological inefficiencies commonly found in eating disorders by using exercises that are designed to strengthen cognitive flexibility, holistic information processing, and metacognition.[138] A systematic review identified four trials of CRT with a small-to-medium sample size, which all included patients with anorexia nervosa.[139] These trials varied in populations, CRT dose, comparison treatments, and primary outcomes, and they had variable effects on neurocognition and clinical outcomes.[140] A variant of CRT, involving training on social and emotional skills, has also been piloted.[141] Taken together, findings on CRT show promise but further work is needed.

Computerised trainings, which focus on modification of neurocognitive processes related to inhibition, impulsivity, and associated biases (such as approach or attention biases), have been developed. In binge spectrum disorders,

these trainings have been used to target overeating and weight gain.[142] Several feasibility trials of a variety of such trainings have been done, including attention control training,[143] approach bias modification, and inhibitory control training.[144,145] Neurobiologically informed treatments, which target habits that maintain the underlying condition in anorexia nervosa or impulsivity in binge eating disorder, have been trialled.[146,147]

Learning models suggest that exposure-based therapy could be effective in reducing food fears and undereating in anorexia nervosa, food cue reactivity and overeating in bulimia nervosa or binge eating disorder, and body-related fears across the spectrum of eating disorders. In line with this thinking, exposure interventions to illness-related stimuli (food, body, exercise) have been developed and tested in small trials.[109,148,149] Increasingly, virtual reality environments have been used to tackle food-related or body-related fears in several small trials including patients with eating disorders.[150] One trial explored virtual reality treatment as a second-line treatment for bulimic disorders after unsuccessful CBT.[151,152] Virtual jogging environments for exposure treatment of excessive exercise in eating disorders have also been designed.[153]

Improved understanding of the neurocircuitry involved in eating disorders has given rise to the use of neuromodulation treatments, including deep brain stimulation, repetitive transcranial current stimulation, transcranial direct current stimulation, and neurofeedback, in a handful of small trials only.[154–157] Although deep brain stimulation and non-invasive brain stimulation produce large, early improvements in mood, weight, and eating psychopathology, changes in weight or eating disorder psychopathology take more time to emerge, and might in part be driven by increased motivation to engage with treatment as usual.[155,157]

Controversies in treatment

Service-related controversies

Despite the fact that the peak age of onset of eating disorders includes adolescence and emerging adulthood, in many countries services for children and adolescents are separated from services for adults with eating disorders, with transitions between services at age 18 years. Strictly enforced, this transition could cause distress to patients and families, avoidable delays in commencing or continuing treatment, disruptions to the therapeutic alliance, and even death. Alternative models of services that include all ages might be preferable to provide seamless care.

Neurosurgical approaches to treatment of severe, enduring anorexia nervosa

People with severe, treatment-refractory anorexia nervosa and their families can be desperate for new treatment approaches. Yet the evidence base for more invasive treatments, such as deep brain stimulation or brain lesioning, is insufficient.[158] Attempts have been made to develop a neuroethics framework for deep brain stimulation studies.[159] Also, concerns have been raised about the use of brain lesioning approaches without adequate consideration to alternative treatments and appropriate ethical safeguards.[160] The potential from approaches of lesioning and deep brain stimulation needs to be set against long-term risks and benefits, dissemination, and costs.[161]

Ethical issues in treatment-refractory anorexia nervosa

There are many ethical issues relating to the treatment of anorexia nervosa. It took a test case and specific mention in the UK Mental Health Act legislation to ensure that the treatment of anorexia nervosa could be given under the Mental Health Act.[162] The capacity to make decisions about life-saving treatment (eg, nasogastric feeding) might be disturbed because of an inability to appreciate the severity of the illness or the disruption of decision making.[163] However, in some cases, protracted nasogastric feeding is given in the face of active resistance from the patient. This procedure sits uneasily with the values encoded in the laws related to human rights and deprivation of liberty. The question of whether it is ever in the best interest of patients to give up active refeeding is hotly debated in countries where palliative care or assisted suicide are available.[164–166]

Outstanding research questions

Given the size and cost of the problem, research funding for eating disorders is inadequate—for example, in the UK, only 1% of mental health research expenditure is for eating disorders, compared with 9% for depression and 14·2% for schizophrenia and psychosis.[167] This funding disparity is reflected in relatively low research activity in eating disorders compared with other mental disorders.[168] An attempt to list research priorities for anorexia nervosa was made by eating disorder experts from the UK, the USA, Australia, and Germany.[169] In addition, a prioritisation exercise by the James Lind Alliance identified the top ten research priorities for eating disorders from a patient and carer perspective.[170] Their research priorities focused on improving recovery rates, with recommendations to compare the efficacy of different treatment settings, identify factors that might allow personalisation of treatment, assess the merits of individually-tailored versus protocol-driven approaches, and identify the role of carers and the treatment team in recovery. There was also a wish to better understand common comorbidities, such as self-harm, and a recommendation to identify the most effective treatments for people with eating disorders and comorbidities. Finally, the question of identification of modifiable risk factors for eating disorders and their prevention was raised. Several of these priorities are currently being researched in large-scale studies, such as the role of carers in treatment and the merits of

different treatment settings (inpatient *vs* day-patient treatment).

The UK Medical Research Council's Delivery Plan (2019) for mental health research in general also provides a useful road map for research in the eating disorder field.[171] Genome-wide association studies in anorexia nervosa have informed conceptualisations,[172,173] and data from genome-wide association studies on bulimia nervosa and binge eating disorder, as well as genome-wide approaches to the epigenome, are needed.[174,175] Research into the gut–brain axis and inflammatory processes needs to be further developed.[176–178]

Prospective longitudinal studies with sufficient power to consider the interactions of a range of risk factors (biological, environmental, and psychological) in prediction of illness onset or course are sorely needed. To date, only a handful of studies have attempted to follow this approach.[179] A promising variant of this kind of study concerns prospective longitudinal studies with embedded high-risk samples (eg, children of people with an eating disorder) to examine factors associated with risk and resilience.[180]

Other questions centre around how to augment available treatments to improve effectiveness. Novel precision approaches are urgently needed to improve outcomes, but crucially rely on improved understanding of the psychological and biological mechanisms that drive the illness trajectory over time and explain interindividual differences in illness course, severity, and persistence. A range of emerging interventions address behavioural, psychological, and biological aspects of eating disorders for specific populations, such as patient groups at the severe enduring end of the spectrum or patients with serious comorbidities (eg, autism spectrum disorders or type 1 diabetes).

The use of novel technologies in treatment and prevention is of interest, but dropout is high and strategies to increase acceptability are needed.[181,182] The relative merits of different service settings and the value of early intervention approaches are being explored.[183,184] Finally, use of routine data might shed light on outcomes beyond clinical trials, even though the quality of such data could be "FUPS" (flawed, uncertain, proximal, and sparse).[185]

Open research questions and conclusions

Over the past 50 years and in the context of major changes in our environment, eating disorders have evolved into a variety of forms with overlapping and distinct clinical and aetiological features, affecting people of all ages and social classes. The feminist writer Naomi Wolf commented that eating appears to have replaced sex as the neurotic focus of our time. The prevalence of eating disorders is moderately high, although most affected individuals do not present for treatment. Lengthy periods of untreated symptoms can lead to an entrenched form of illness, which is more difficult to treat. In brief, advances are needed to allow more precise elucidation of the mechanisms that underpin these problems and to develop more targeted treatments. At the same time, disseminable and scalable treatments are needed.

Contributors

All authors contributed to the planning, searching, writing, and editing of the Seminar.

Declaration of interests

We declare no competing interests.

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