Anorexia nervosa: aetiology, assessment, and treatment

Stephan Zipfel, Katrin E Giel, Cynthia M Bulik, Phillipa Hay, Ulrike Schmidt

Anorexia nervosa is an important cause of physical and psychosocial morbidity. Recent years have brought advances in understanding of the underlying psychobiology that contributes to illness onset and maintenance. Genetic factors influence risk, psychosocial and interpersonal factors can trigger onset, and changes in neural networks can sustain the illness. Substantial advances in treatment, particularly for adolescent patients with anorexia nervosa, point to the benefits of specialised family-based interventions. Adults with anorexia nervosa too have a realistic chance of achieving recovery or at least substantial improvement, but no specific approach has shown clear superiority, suggesting a combination of re-nourishment and anorexia nervosa-specific psychotherapy is most effective. To successfully fight this enigmatic illness, we have to enhance understanding of the underlying biological and psychosocial mechanisms, improve strategies for prevention and early intervention, and better target our treatments through improved understanding of specific disease mechanisms.

“The want of appetite is, I believe, due to a morbid mental state...I prefer—the more general term 'anorexia' 'nervosa', since the disease occurs in males as well as females, and is probably rather central than peripheral.”

Sir William Gull, 1874

(Transactions of the Clinical Society of London 7: 22–28)

Introduction

Anorexia nervosa is a highly distinctive serious mental disorder. It can affect individuals of all ages, sexes, sexual orientations, races, and ethnic origins; however, adolescent girls and young adult women are particularly at risk. This disorder is characterised by an intense fear of weight gain and a disturbed body image, which motivate severe dietary restriction or other weight loss behaviours such as purging or excessive physical activity. Additionally, cognitive and emotional functioning are markedly disturbed in people with this disorder. Serious medical morbidity and psychiatric comorbidity are the norm. Anorexia nervosa in adults and older adolescents commonly has a relapsing or protracted course, and levels of disability and mortality are high, especially without treatment. Even partial syndromes (ie, sub-syndromal anorexia nervosa) are associated with adverse health outcomes. Quality of life is poor and the burden placed on individuals, families, and society is high.

This Review, like the Lancet Seminar published in 2010, which included all eating disorders, focuses on factors associated with anorexia nervosa that are of particular relevance to clinicians, such as recent developments in diagnosis, epidemiology, pathogenesis, treatment, and prognosis.

Classification and diagnosis

Low bodyweight or low body-mass index (BMI) is the central feature of anorexia nervosa. Tables 1 and 2 give an overview of diagnostic criteria for anorexia nervosa according to DSM4 and ICD10. Restricting and binge-purge subtypes and remission and severity specifiers exist. Amenorrhoea is no longer required in the new DSM-5 diagnostic criteria and is also expected to be dropped in ICD-11. Main reasons for eliminating this criterion are based on conflicts with inclusion of male individuals, adolescents who have not yet reached menarche, and women who use exogenous hormones into the diagnostic criteria. This change is also based on a large body of accumulated evidence showing no meaningful clinical differences between women with anorexia who menstruate and those who do not. DSM-5 also classifies an atypical anorexia nervosa, which includes restrictive behaviours without meeting the low weight criterion.

In DSM-5, severity of anorexia nervosa is classified along four levels by use of the individual’s BMI: extreme (BMI <15 kg/m²), severe (BMI 15–15.99 kg/m²), moderate (BMI 16–16.99 kg/m²), and mild (BMI ≥17 kg/m²). A systematic review from 2015 reported evidence for distinct illness trajectories and neurocognitive features for eating disorders characterised by severe restriction (eg, inflexibility) or by overeating (eg, impulsivity and risk of substance use disorders) and evidence for effective secondary prevention or early treatment. Preliminary evidence also exists for a specific shift in focus of treatment to quality of life as primary outcome in patients with long-standing or intractable anorexia nervosa.

Epidemiology

In high-income countries, the lifetime prevalence of anorexia nervosa in the general population is reported to be around 1% in women and less than 0.5% in men. Accurate point prevalence has been more difficult to calculate, with studies often failing to identify any cases of DSM-IV-defined anorexia nervosa. If the broader DSM-5 criteria A and C (low weight in the presence of overvaluation of weight or shape) are applied, the point prevalence is about 0.3–0.5%. Some studies, but not all, report higher rates of the disorder. In children, the sex ratio is 1.8, with more female individuals affected. In children, the sex distribution is less skewed. Outcomes differ across age groups, with higher rates of full recovery and lower mortality in adolescents than in adults (mean mortality 2% vs 5%).

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**Comparison of diagnostic criteria for anorexia nervosa according to DSM-IV versus DSM-5**

<table>
<thead>
<tr>
<th>DSM-IV</th>
<th>DSM-5*</th>
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<tbody>
<tr>
<td>A. A refusal to maintain bodyweight at or above a minimally normal weight for age and height (eg, weight loss leading to a maintenance of bodyweight less than 85% of that expected, or failure to make expected weight gain during period of growth, leading to bodyweight less than 85% of that expected).</td>
<td>A. Restriction of energy intake relative to requirements, leading to a significantly low bodyweight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected.</td>
</tr>
<tr>
<td>B. Intense fear of gaining weight or becoming fat, even though underweight.</td>
<td>B. Intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight.</td>
</tr>
<tr>
<td>C. Disturbance in the way in which one's bodyweight or shape is experienced, undue influence of bodyweight or shape on self-evaluation, or denial of the seriousness of the current low bodyweight.</td>
<td>C. Disturbance in the way one's bodyweight or shape is experienced, undue influence of body shape and weight on self-evaluation, or persistent lack of recognition of the seriousness of the current low bodyweight.</td>
</tr>
<tr>
<td>D. In postmenarchal females, amenorrhoea—ie, the absence of at least one period or more consecutive menstrual cycles. (A woman is considered to have amenorrhoea if her periods occur only following hormone—eg, oestrogen administration).</td>
<td>D.</td>
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**Table 1: Comparison of diagnostic criteria for anorexia nervosa according to DSM-IV versus DSM-5**

<table>
<thead>
<tr>
<th>ICD-10</th>
<th>ICD-11 (proposed criteria)*</th>
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<tr>
<td>A. Weight loss, or in children a lack of weight gain, leading to a bodyweight of at least 15% below the normal or expected weight for age and height.</td>
<td>A. Significantly low bodyweight for the individual's height, age, and developmental stage (BMI less than 18.5 kg/m² in adults and BMI-for-age under fifth percentile in children and adolescents) that is not due to another health condition or to the unavailability of food.</td>
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<td>B. The weight loss is self-induced by avoidance of &quot;fattening foods.&quot;</td>
<td>B. Low bodyweight is accompanied by a persistent pattern of behaviours to prevent restoration of normal weight, which may include behaviours aimed at reducing energy intake (restricted eating), purging behaviours (eg, self-induced vomiting, misuse of laxatives), and behaviours aimed at increasing energy expenditure (eg, excessive exercise), typically associated with a fear of weight gain.</td>
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<tr>
<td>C. A self-perception of being too fat, with an intrusive dread of fatness, which leads to a self-imposed low weight threshold.</td>
<td>C. Low bodyweight or shape is central to the person's self-evaluation or is inaccurately perceived to be normal or even excessive.</td>
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<tr>
<td>D. A widespread endocrine disorder involving the hypothalamic-pituitary-gonadal axis, manifest in the female as amenorrhoea, and in the male as a loss of sexual interest and potency (an apparent exception is the persistence of vaginal bleeding in anorexic women who are on replacement hormonal therapy, most commonly taken as a contraceptive pill).</td>
<td>D.</td>
</tr>
<tr>
<td>E. Does not meet criteria A and B of bulimia nervosa (F50.2).</td>
<td>E.</td>
</tr>
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</table>

ICD criteria have been taken from the WHO International Statistical Classification of Diseases. *Proposed ICD-11 criteria have been taken from ICD-11 Beta Draft. BMI=body-mass index.

**Psychiatric and physical comorbidity**

Nearly three-quarters of patients with anorexia nervosa report a lifetime mood disorder, most commonly major depressive disorder. Between 25% and 75% of patients with anorexia nervosa report a lifetime history of at least one anxiety disorder, which typically precedes anorexia nervosa and starts in childhood. Obsessive-compulsive disorder occurs in 15–29% of individuals with anorexia nervosa, with up to 79% experiencing obsessions or compulsions at some point in their lives. In population-based studies, the prevalence of alcohol misuse or dependence in individuals with anorexia nervosa is between 9% and 25% for anorexia nervosa and typically lower in those with the restricting subtype. Register-based studies confirmed aggregation of autism spectrum disorder in probands with anorexia nervosa and in their relatives; however, the relation between anorexia nervosa and autism spectrum disorder seems to be non-specific.

Advances in studies of comorbidity are emerging from the genetic literature with intriguing significant positive genetic correlations emerging between anorexia nervosa and schizophrenia (r=0.19) and between anorexia nervosa and obsessive-compulsive disorder (r=0.55). These methods have taken us one step beyond reporting the frequency with underlying mechanisms of co-occurrence—in this case, by identifying shared genetic factors.

Patients with anorexia nervosa display a broad variety of somatic complications in several organ systems (figure) across various stages of illness. In the acute state, patients with anorexia nervosa present with many common complaints such as dizziness, fatigue, or even a syncope. In patients with a chronic course, almost every organ system can be affected because of malnutrition or the presence of binge-eating and purging behaviour. Although changes in multiple endocrine axes are mostly adaptive (ie, to optimise energy expenditure), up to 21% of patients with anorexia nervosa have osteoporosis and more than 54% have osteopenia of the lumbar spine.

Patients with anorexia nervosa have an increased lifetime prevalence of autoimmune disease, most prominently type 1 diabetes. Type 1 diabetes often precedes the onset of anorexia nervosa, is associated with insulin purging, poor glycaemic control, diabetic complications, and very high mortality. In children with paediatric acute-onset neuropsychiatric syndrome (PANS) or paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS), food restriction also occurs and has been deemed to be a variant of childhood onset anorexia nervosa.

**Prognosis**

Regarding the core anorexia nervosa-psychopathology, Steinhausen and colleagues analysed 119 studies covering 5590 patients with anorexia nervosa and reported that 59–6% of those patients showed a weight normalisation,
accompanied by a normalisation of menstrual status in 57–60%, and a normalisation of eating behaviour in 46–8% of the whole group of patients with anorexia nervosa. In general, patients with an illness onset before their 17th birthday achieve a better outcome than adult onset, whereas prepubertal onset confers a worse course.61 Long-term follow-up studies62,63 have confirmed two broad outcome groups with either a good outcome or chronic course with a high risk of premature death. Regarding the time course, several follow-up studies have shown that at least in adult patients with full syndrome anorexia nervosa, time to complete remission is between 5 and 6 years.64

In a meta-analysis65 of excess mortality in the 1990s, anorexia nervosa was associated with the highest rate of mortality among all mental disorders.66 Another meta-analysis67 showed a crude mortality rate (number of deaths within the study population over a specified period) of 5.1 deaths per 10000 person-years and the standardised mortality rate of 5.9 with a mean follow-up period of 14–2 years. Although most deaths due to anorexia nervosa are a direct consequence of starvation-related medical complications, particularly cardiac complications and severe infections, one in five deaths in patients with this disorder results from suicide.68 Data for the course and outcome in male patients with anorexia nervosa are scarce; however, an older age and lower BMI at admission, and a purging subtype of anorexia nervosa led to an increased risk of death in male individuals with anorexia nervosa.69

Pathogenesis
Genetic factors
Anorexia nervosa is strongly familial43 and heritability estimates range from 28% to 74%.60 Two genome-wide association studies (GWAS),45,46 currently understood to be underpowered in view of the presumed genetic architecture of anorexia nervosa, predictably did not detect genome-wide significant loci. Boraska and colleagues62 conducted sign tests to compare results from the discovery sample with those from the replication sample, and 76% of the results from the replication sample were in the same direction as the discovery sample, a result highly unlikely to be due to chance (p=4×10−6). This observation is similar to the discovery sample, a result highly unlikely to be due to chance (p=4×10−6). These impairments have also been noted in unaffected sisters of people with anorexia nervosa and to some extent persist after recovery.66 Evidence suggests that both illness stage or duration and severity affect performance.67 People with anorexia nervosa also have difficulties in socio-emotional processing, showing attentional biases, impaired emotion recognition, regulation, and expressivity, and poor theory of mind.68 These difficulties are present both in the ill state and in muted form after recovery. Prospective longitudinal studies of children with a high familial risk of eating disorders suggest that some neurocognitive and social cognitive vulnerabilities are present from an early age.69

Neurocognitive and social cognition
Neurocognitive markers of anorexia nervosa include set shifting difficulties (ie, difficulties switching between different tasks or task demands)66 and poor central coherence (ie, a preference for local [detail-focused] over global [bigger picture] processing).66 These impairments have also been noted in unaffected sisters of people with anorexia nervosa and to some extent persist after recovery.66 Evidence suggests that both illness stage or duration and severity affect performance.67 People with anorexia nervosa also have difficulties in socio-emotional processing, showing attentional biases, impaired emotion recognition, regulation, and expressivity, and poor theory of mind.68 These difficulties are present both in the ill state and in muted form after recovery. Prospective longitudinal studies of children with a high familial risk of eating disorders suggest that some neurocognitive and social cognitive vulnerabilities are present from an early age.69

Structural neuroimaging
Patients with acute anorexia nervosa have been reported to have global reductions in grey and white matter, increased cerebrospinal fluid and regional grey matter decreases in the left hypothalamus, and in reward-related regions of the basal ganglia and the somatosensory cortex.63 Studies in patients who recovered from anorexia nervosa and longitudinal studies (before and after treatment) suggest that brain tissue abnormalities might recover with weight regain.64,65 Many earlier structural studies have methodological limitations (eg, not correcting for age or...
overall brain volume, not taking anorexia nervosa-subtype or comorbidities into account; results being confounded by effects of dehydration or starvation). A series of studies by Frank and colleagues\(^{56,57}\) addressing these limitations reported increased grey matter volume of the medial orbitofrontal cortex gyrus in both adolescents and adults with anorexia nervosa, which persisted into recovery. Similar changes were found in bulimia nervosa, whereas obese adults showed reduced orbitofrontal cortex gyrus rectus volume. The orbitofrontal cortex assesses quality and value of reward stimuli, such as food, and is implicated in regulating sensory-specific satiety. Additionally, participants with anorexia nervosa had increased right insula grey matter compared with controls. The right anterior insula is associated with self-recognition and interoceptive awareness. Longitudinal studies in at-risk populations are needed to fully assess whether these changes are biomarkers of the illness.

**Functional neuroimaging**

Studies using visual food cue models have found differences between anorexia nervosa and controls in prefrontal areas and in limbic and paralimbic circuits, associated with salience and reward processes with some inconsistencies between studies due to methodological differences.\(^8\) Findings from studies\(^{45,47}\) using taste stimuli to assess neural processing of food reward show that people who recovered from anorexia nervosa have a reduced functional brain response to predictably given, but an increased response to unpredictably given, sugar solutions with insula, striatum, or orbitofrontal cortex response distinguishing anorexia nervosa from controls. The same authors, contrasted people with anorexia nervosa, bulimia nervosa, or obesity who underwent a solutions with insula, striatum, or orbitofrontal cortex predilections with insula, striatum, or orbitofrontal cortex dysregulations that interact with neurotransmitter systems,\(^9\) suggesting that anorexia nervosa might lie in hormonal changes and dysregulations that interact with neurotransmitter systems,\(^9\) and the subsequent shift to compulsive or habitual behaviours\(^{61,62}\) as key factors in the persistence of the illness.

**Neurobiological models of anorexia nervosa**

Based on these neuroimaging findings, and integrating additional evidence from studies on cerebrospinal fluid (CSF) measures of metabolites, PET, and SPECT brain imaging studies, Kaye and colleagues\(^{61,62}\) suggest that some childhood temperamental and personality traits, such as anxiety, obsessions, and perfectionism might reflect neurobiological risk factors for the development of anorexia nervosa. Restrictive eating thus might be a means of reducing negative affect caused by imbalance between serotoninergic (aversive or inhibitory) and dopaminergic (reward) systems. Other neurobiologically informed models of anorexia nervosa have highlighted the role of stress, fear, and anxiety,\(^{63}\) the rewarding nature of anorexia nervosa symptoms,\(^{64}\) and the subsequent shift to compulsive or habitual behaviours\(^{61,62}\) as key factors in the persistence of the illness.

**Developmental factors**

Several adverse experiences occurring around universal stages and transitions of development are associated with an increased prevalence of anorexia nervosa. These developmental risk factors include adverse prenatal, perinatal, and neonatal events, such as dysmaturity or prematurity\(^{65,66}\) as well as feeding and sleeping difficulties in infancy.\(^67\) Throughout childhood, emerging personality traits associated with anxiety, depression, perfectionism, and autism spectrum\(^68\) have been identified as risk factors for anorexia nervosa. Puberty and adolescence are characterised by profound changes, vulnerabilities, and the transition to adulthood, and they represent the period of first onset of anorexia nervosa. A possible explanation for the crucial role of puberty for the onset of anorexia nervosa might lie in hormonal changes and dysregulations that interact with neurotransmitter functioning, brain maturity, and genetic factors.\(^69\)

**Environmental factors**

Female gender has consistently been shown to be a risk factor for anorexia nervosa.\(^45\) The increase of anorexia nervosa in low-income and middle-income countries suggests that cultural transitions associated with industrialisation, urbanisation, and globalisation might be associated with environmental risk constellations for the development of anorexia nervosa.\(^70\) These constellations might include the adoption of the so-called western lifestyle, including nutritional habits and thin ideal internalisation. However, although body dissatisfaction has been identified as a risk factor for the development of any eating disorder,\(^71\) risk factors associated with thin ideal internalisation and associated sociocultural pressures have not been confirmed for anorexia nervosa. Appraising the potential influence of environmental factors, it has to be taken into account that the incidence of anorexia nervosa is relatively low worldwide despite these pervasive sociocultural pressures to be thin.\(^72\) It is possible that these western influences could simply increase the number of...
individuals who engage in behaviours such as strict dieting or excessive exercise, which can then trigger eating disorders in genetically susceptible individuals.

Treatment

Initial assessment and investigations

Initial assessment of the patient with anorexia nervosa includes an in-depth interview, a physical examination, and investigations to establish severity and nature of eating disorder symptoms and diagnosis, comorbid psychological and physical symptoms, diagnoses and risk, past treatments, current motivation for treatment, and available supports. An early task is to build good rapport with the patient, as they are often highly ambivalent about and fearful of treatment.72 Whenever possible, it is important to involve significant others (family, partners) in assessment and subsequent treatment. Table 3 summarises recommended physical investigations to be done at assessment. We have also formulated indicators of high risk, requiring rapid intensive specialist consultation and intervention (panel 1).

Pathways (levels) of care

A Finnish epidemiological study74 reported that about 50% of people with anorexia nervosa in the community do not access treatment. Those who do engage in treatment typically show varying degrees of ambivalence about change.73 However, with treatment, at least 40% of people with anorexia nervosa (and more in younger samples) will make a full recovery.21 Additionally, access to care from a specialist service with expertise in anorexia nervosa might be associated with better outcomes.76 Thus it is important that health-care practitioners at all levels are competent to identify anorexia nervosa and that there is early access to secondary and tertiary levels of care. This early access is particularly important in view of evidence that there is a critical window for effective intervention in the early stages of illness (ie, duration of <3 years) beyond which full recovery becomes much more difficult to achieve.77 Despite this critical window, there should not be therapeutic nihilism in those who develop severe and enduring anorexia nervosa and have a very high risk of disability or death. Findings from a randomised trial of outpatient psychotherapy75 supported the efficacy of modifying psychological approaches in longstanding illness such that the focus shifts from weight regain and recovery to improved quality of life.

<table>
<thead>
<tr>
<th>Essential</th>
<th>Optional</th>
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<tbody>
<tr>
<td>Medical and psychiatric history</td>
<td>Full examination</td>
</tr>
<tr>
<td>Physical assessment</td>
<td>BMI, heart rate, blood pressure, temperature</td>
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<tr>
<td>Blood profile</td>
<td>Full blood count, blood sedimentation rate</td>
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<tr>
<td>Biochemical profile</td>
<td>Sodium, potassium, calcium, magnesium, phosphate, creatinine, urea, liver enzyme profile, blood glucose</td>
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Table 3: Investigations recommended at initial assessment, on admission, or at regular intervals over the course of refeeding.

Panel 1: Indicators of high medical risk and other reasons for considering inpatient treatment

Weight
- BMI <14 kg/m² or rapid weight loss (adults) or <75% of expected bodyweight or rapid weight loss (adolescents)

Medical status
- Heart rate <50 bpm
- Cardiac arrhythmia
- Postural tachycardia (increase >20 bpm)
- Blood pressure <80/50 mm Hg
- Postural hypotension >20 mm Hg
- QTc >450 ms
- Temperature <35.5°C
- Hypokalaemia <3.0 mmol/L
- Neutropenia
- Phosphate <0.5 mmol/L

Additional indicators
- Severe bingeing and purging (eg, several times daily)
- Failure to respond to outpatient or daypatient treatment
- Severe psychiatric comorbidity
- Suicidality

These indicators are only a guide and do not replace the need for individual clinical judgement (adapted from Hay and colleagues, 2014,73 and Treasure and colleagues, 20104). QTc=corrected QT.
Evidence-based psychological treatment in adolescent and adult patients with anorexia nervosa

Based on comprehensive systematic reviews and complemented by well designed and sufficiently powered treatment studies, we have reported on the first-line behavioural treatments for adolescent and adult patients with anorexia nervosa separately (table 4) and have supplemented this by interventions for relapse prevention and aftercare as well as specific interventions for carers. Additionally, we have added information (panel 2) on the setting, structure, and content of psychotherapeutic interventions applied in randomised trials since 2010.

First, the overall evidence base for the treatment of adolescent patients with anorexia nervosa is increasing. However, the number of empirically supported psychosocial treatments trials opposed to the number of treatments for adolescent anorexia nervosa remains scarce. In total, 12 randomised trials (n=1060 patients) have compared different psychological treatments in adolescent patients with the disorder (age <19 years). Lock concluded in a systematic review on psychological treatments in children and adolescents that there is clear and growing evidence to support the efficacy of family treatment in adolescent anorexia nervosa compared with individually based approaches, and that there is evidence that supports family-based treatment (FBT) with a focus on eating disorder behaviour and weight gain as opposed to more general family processes.

Second, over the past 30 years, 12 randomised trials (n=1157 patients) comparing different psychological treatments in adult patients with anorexia nervosa (age >18 years) have been done in outpatient settings. Since the 2010 review, several well designed and sufficiently powered treatment studies for adult patients with anorexia nervosa have been published, reporting substantial weight gain and clear improvements of eating disorder and general psychopathology at the end of treatment and at follow-up. The largest of these trials (n=242) compared three different first-line treatments: focal psychodynamic psychotherapy (FPT), enhanced cognitive behaviour therapy (CBT-E), and an optimised treatment as usual, including psychotherapy as well as medical care by the family doctor. Weight gain was similar in all three groups. Considering a combined outcome (weight and eating disorder psychopathology), FPT proved advantageous in terms of recovery at 12-month follow-up, whereas CBT-E was more effective with respect to speed of weight gain and improvements in eating disorder psychopathology than the other treatments. Results from one trial (n=56) showed that by the end of treatment, an intervention that combined supportive therapy with sound clinical management delivered by eating disorder specialists (specialist supportive clinical management, SSCM) was superior to two specific psychotherapies (cognitive behavioural therapy [CBT] and interpersonal psychotherapy [IPT]). However, a long-term follow-up of this trial did not support the superiority of any treatment. Findings from another randomised trial (n=63) showed that patients with anorexia nervosa with severe and enduring course can make meaningful improvements with both CBT or SSCM. A novel anorexia nervosa-specific outpatient therapy (Maudsley model of anorexia nervosa therapy for adults, MANTRA) has been compared against SSCM in two trials (n=214). Although overall outcome did not differ between groups, patients preferred MANTRA to SSCM, and patients with a more severe illness had a greater weight gain in the MANTRA group than in the...
Panel 2: Novel and effective psychological treatments in anorexia nervosa

Family-based treatment (FBT)
Family-based treatment is a three-phase treatment for adolescent patients with anorexia nervosa and their families over 16 1-h sessions and a 9-month period (initially of 10 h during 6 months). In the first phase, therapy is characterised by attempts to absolve the parents from the responsibility of causing the disorder and by complimenting them on the positive aspects of their parenting. Families were encouraged to work out for themselves how best to help restore the weight of their child with anorexia nervosa. In phase 2, parents were helped to transition eating and weight control back to the adolescent in an age-appropriate manner. The third phase focused on establishing a healthy relationship between the adolescent and the parents. 24 1-h sessions were provided over the 1-year period (Lock and colleagues, 2010 and Agras and colleagues 2014; appendix).

Specialist supportive clinical management (SSCM)
This treatment should be delivered by therapists specialised in the treatment of eating disorders and should provide a standardised form of usual outpatient treatment. Patients with anorexia nervosa and a BMI of 15 kg/m² or lower receive up to 30 once-weekly individual therapy sessions and four monthly follow-up sessions. In those patients with a BMI >15 kg/m² the number of sessions could be reduced to 20. It combines clinical management (ie, giving information, advice, and encouragement) with a supportive therapeutic style designed to build a positive therapeutic relationship and to foster change. Therapy content includes assessment, identification, and regular review of target symptoms; psychoeducation; monitoring of physical status; establishment of a goal weight range; and nutritional education and advice. The aim is to help patients make a link between their clinical symptoms and their abnormal eating behaviour and weight, and to support patients in a gradual return to normal eating behaviour and weight. Additional therapy content is determined by the patient (McIntosh and colleagues 2006, appendix).

Maudsley model of anorexia treatment for adults (MANTRA)
This treatment is an empirically based cognitive-interpersonal treatment, which proposes that four broad factors, linked to underlying obsessional and anxious (or avoidant) personality traits, are central to the maintenance of anorexia nervosa. These are (1) a thinking style characterised by inflexibility, excessive attention to detail, and fear of making mistakes; (2) impairments in the socio-emotional domain (eg, avoidance of emotional experience, regulation, and expression); (3) positive beliefs about how anorexia nervosa helps the person in their life; and (4) unhelpful responses of close others (eg, overinvolvement, criticism, accommodation to symptoms). These factors are targeted in treatment with the aim of improving weight, eating disorder and other symptoms, and psychosocial adjustment. The treatment style is motivational. Treatment is centred around a patient-manual. This manual has core (eg, formulation) and optional modules (eg, module on building a so-called non-anorexic identity). Treatment has a clear structure and hierarchy of therapeutic procedures. Individual tailoring of treatment arises from flexibility on how modules are combined and how much emphasis they are given. Nutrition and other symptom management or behaviour change, information or advice is given if the patient is motivationally ready for this. Differences from other treatments include that the model was developed specifically for anorexia nervosa, it is based on biological and psychological research, and is tailored to characteristic temperamental traits in this disorder. It is unique in its use of a patient workbook, developed in co-production with patients and therapists. It is also unique in its involvement of carers in both the model or formulation and the treatment. Separate carer materials based on the model are available (Schmidt and colleagues, 2015, appendix).

Enhanced cognitive behaviour therapy (CBT-E)
According to Fairburn and colleagues CBT-E is the abbreviation for “enhanced cognitive therapy”, and it refers to a “transdiagnostic” personalised psychological treatment for eating disorders. It was developed as an outpatient treatment for adults but is an intensive version for day patient and inpatient settings, and a version for younger people. As an outpatient therapy treatment CBT-E has four stages and is available in short (20 sessions) and longer version (40 sessions). In stage one, the focus is on gaining a mutual understanding of the person’s eating problem and helping him or her modify and stabilise their pattern of eating. In the brief second stage progress is systematically reviewed and plans are made for the main body of treatment. Stage three focused on the processes that are maintaining the person’s eating problem (eg, addressing concerns about shape and eating). In the last stage the emphasis shifts onto the future. There is a focus on dealing with setbacks and maintaining the changes that have been obtained (Fairburn, 2008; appendix).

Focal psychodynamic psychotherapy (FPT)
The initial manualised treatment was designed as a 40 h outpatient psychodynamic-oriented psychotherapy for moderately ill patients with anorexia nervosa (BMI >15 kg/m²). At the beginning of focal psychodynamic therapy, the therapist identifies psychodynamic relevant foci using a standardised operationalised, psychodynamic diagnostic interview (OPD-II). The psychodynamic treatment manual can be divided roughly into three treatment phases. The first phase focuses mainly on therapeutic alliance, pro-anorectic behaviour and ego-syntonic beliefs (attitudes and behaviour viewed as acceptable), and self-esteem. In the second phase of treatment, main focus is placed on relevant relationships and the association between interpersonal relationships and eating (anorectic) behaviour. The pertinent aspects of the final phase are the transfer to everyday life, anticipation of treatment termination, and parting. Before every treatment session the patient’s weight is assessed and documented (Friederich and colleagues, 2014).

This panel describes effective psychological treatments applied in randomised trials (table 4, including those treatment approaches shown the highest evidence and effectiveness for adolescents and adults and published as randomised trials since the 2010 review by Treasure and colleagues 2010). For references see appendix.
SSCM group. In summary, although the evidence base for the treatment of adults with anorexia nervosa is advancing, thus far no specific approach has shown clear superiority. Across different individual psychotherapies for adults with anorexia nervosa there are common elements. These elements include a psychotherapeutic approach specific to and focused on anorexia nervosa in combination with a focus on weight regain and nutritional rehabilitation.71

Third, few studies have focused on relapse prevention and aftercare in anorexia nervosa, and the little available evidence suggests that patients who have a structured intervention for relapse prevention—based on cognitive-behavioural principles—after inpatient treatment have fewer and later episodes of relapse in anorexia nervosa during the first year after inpatient discharge than do patients without a follow-up intervention.119–125

Finally, in view of the burden of anorexia nervosa on families and partners, and evidence suggesting that carers’ distress and behaviours might inadvertently maintain the illness, several randomised trials have also trialled interventions targeting carers of adults with anorexia nervosa. A new couple-based intervention for anorexia nervosa (Uniting Couples in the Treatment of Anorexia Nervosa)126 also focuses on leveraging the support of close others in the treatment of anorexia nervosa. These studies show that carer outcomes (distress and unhelpful behaviours) can be improved and that this improvement in turn might positively affect relationships with the patient and patients’ clinical outcomes.97,127

Pharmacological treatments
Systematic reviews consistently conclude that antidepressants neither improve weight gain128 nor reduce eating disorder or other psychological symptoms in the re-feeding phase.27 The utility of antidepressants for relapse prevention in the post-weight restoration phase remains uncertain.79 This mixed evidence is based on two trials, one smaller positive trial and a second larger trial that tested the efficacy of adding fluoxetine to CBT on post-weight restoration and found no added benefit in preventing relapse at 1 year (for references on single trials see appendix). A pooled meta-analysis of four placebo-controlled randomised trials on antidepressants (two on a tricyclic and two of fluoxetine) and a relapse prevention trial also failed to find a significant effect on weight gain.28 As a consequence, treatment guidelines27 are cautious in recommending use even for comorbid features such as depression until it is established that these features are not due to the starvation state and remit with weight restoration.

The review on eating disorders by Treasure and colleagues4 reported emerging evidence for the use of olanzapine, an atypical antipsychotic in reducing illness preoccupations and anxiety during refeeding. The inconsistent results and inability to achieve significance in pooled meta-analyses of placebo controlled trials for weight gain100–102 have led to a consensus in the medical literature that more, larger, and consistently positive trials of antipsychotics are needed before their use can be recommended.99,100

There has been little advance in evidence for any other psychotropic medication in anorexia nervosa treatment since the review by Treasure and colleagues.’ Other drugs that are currently under investigation for a putative role in anorexia nervosa treatment are tumour necrosis factor, dronabinol (a cannabinoid receptor agonist), and ghrelin agonists103 to promote appetite or antagonists to reduce hyperactivity (for references on single trials see appendix). These drugs do not have an evidence base for their use at this stage.

Nutritional treatments
In moderately ill outpatients with anorexia nervosa, nutritional counselling alone is not an adequate treatment;129 however, dieticians are an important part of a multidisciplinary treatment team. Patients who are substantially underweight and malnourished should be admitted to a specialist inpatient or day-patient eating disorder unit for a combined programme of supervised refeeding and anorexia nervosa-related psychotherapy. First, it is important to accurately assess nutritional and fluid intake and to document premorbid weight and the course of weight loss. Depending on the duration of weight loss and malnutrition, age of the patient, somatic comorbidity, and the severity of purging behaviour, recommended weight gain rates range from 500 g to 1400 g per week.127–129 Evidence exists that substantial weight gain is best achieved in inpatient settings,130 particularly in patients with increased somatic risk. Refeeding syndrome is a serious and potentially fatal medical complication, particularly during the early stages of refeeding in those patients at the highest risk, who have been malnourished and emaciated for a long time.27,29 Due to a switch from fasting gluconeogenesis to carbohydrate-induced insulin release, there is a rapid intracellular uptake of potassium, phosphate, and magnesium with the consequence of a rapid onset of hypophosphataemia, hypomagnesemia, and hypokalaemia.131 In accordance with the RANZP protocol (2014),27 adult patients with anorexia nervosa should start with a refeeding of 6000 kJ/day, increased by 2000 kJ/day every 3 days, until an adequate intake to meet the person’s needs for weight restoration is reached. As a consequence, particularly in the early phase of refeeding, electrolytes should be regularly monitored and this diet should be supplemented by phosphate at 500 mg twice daily and thiamine at least 100 mg daily for the first week, and thereafter as clinically indicated for people at high risk of refeeding syndrome (eg, those with BMI <13). Nutritional therapy includes supervised meals and, if necessary, additional high-protein oral liquid supplements. In severely emaciated patients at high medical risk, nasogastric feeding, including professional and supportive supervision, could be indicated. On very
rare occasions and after failure of the above nutritional strategies, parenteral nutrition might be indicated. In adolescent patients with a short duration of illness, a more rapid refeeding protocol can be applied. In principle, the least intrusive and most physiological normal method of nutrition should be applied.71

Osteoporosis prevention and treatment
The most efficient strategy to improve bone density is to restore weight and, in women, menstrual function. Oestrogen-replacement therapy, primarily via transdermal application, only partially increases bone density in adolescents.15 Oral oestrogen-progesterone combinations are ineffective in increasing bone mineral density in adolescent and adult anorexia nervosa patients.36 Moreover, neuroendocrine changes can have a direct effect on neurocognition and mood as well as on core eating disorder psychopathology.55

Experimental treatments
There is widespread agreement that new interventions are needed to improve outcomes, especially in adults with anorexia nervosa. Such interventions should target specific disease mechanisms.90,114 We describe some of the more promising experimental treatments.

Psychobiological treatments
Cognitive remediation therapy (CRT) for anorexia nervosa targets neuropsychological inefficiencies in executive functioning, chiefly poor set-shifting and weak central coherence (extreme attention to detail at the expense of the bigger picture). Two systematic reviews59,130 identified four small to medium sized (n=32–82 participants) randomised trials of CRT (for references on single trials see appendix). These studies varied in populations, intensity of CRT (8–30 sessions), comparison treatments (CRT, treatment as usual, exposure treatment, non-specific neurocognitive training), and primary outcomes (eating disorder symptoms, test meal consumption, set-shifting, treatment dropout). Therefore no meta-analysis was possible. Two studies found differential short-term improvements in neurocognition for CRT versus comparison treatment. One trial of CRT plus treatment as usual versus treatment as usual alone in inpatients with either anorexia nervosa or bulimia nervosa found greater improvement in quality of life at end of treatment and greater improvement on eating disorders symptoms at 6 months follow-up in the group containing CRT than in the TAU alone group. These findings are promising but well designed large-scale studies of CRT are as yet not available.

Abnormalities in fear conditioning have been thought to be causally implicated in anorexia nervosa. In line with this thought, exposure therapy (to food or body stimuli) might be another promising treatment for anorexia nervosa. One systematic review116 identified one placebo-controlled randomised trial (n=14) of food exposure and D-cycloserine (DCS) in anorexia nervosa, based on evidence that DCS enhances fear extinction during exposure therapy in anxiety disorders (for references on single trials see appendix). DCS compared with placebo had no effect in any of the training or test meals. One further randomised trial (n=32) compared food exposure with CRT in weight-restored anorexia nervosa and found greater test-meal consumption at end of treatment in the exposure treatment group. Other promising psychobiological treatments include cognitive bias modification treatments,113 based on converging evidence suggesting a range of cognitive biases (attention, memory) in relation to illness-relevant and emotional stimuli in anorexia nervosa. However, randomised trials are so far not available.

Neurobiological treatments
Improved understanding of the neurocircuity involved in anorexia nervosa111 has given rise to the use of neuromodulation treatments, such as deep brain stimulation (DBS), repetitive transcranial current stimulation (rTMS), and transcranial direct current stimulation (tDCS), especially in severe and enduring anorexia nervosa. We identified two systematic reviews104,125 summarising cases studies and three further case studies describing use of these techniques (for references on single trials see appendix). As yet, no randomised trials of therapeutic use of neuromodulation treatments have been published. Several cases studies or series of DBS (nucleus accumbens, ventral capsule or ventral striatum, or subcallosal cingulate cortex) targeting anorexia nervosa symptomatology directly (n=12) or targeting obsessive-compulsive disorder or depression with parallel improvements in anorexia nervosa symptoms (n=2) have been identified. These studies suggest that DBS might have promise in highly selected severe and enduring cases. Likewise, rTMS (DLPFC) or tDCCS (anodal, DLPFC) case studies (n=13) have shown promise in enduring anorexia nervosa.

Evidence-based prevention programmes
Prevention efforts can be divided into universal, selective, and indicated, depending on whether they address the general population or populations with increased risk (eg, children of eating disordered mothers; elite athletes) or those exhibiting early signs of a disorder. Eating disorder prevention has focused on either risk factors (eg, body dissatisfaction) or eating disorder pathology or caseness. A systematic review106 of eating disorders prevention programmes for young people between the ages of 12 and 25 years identified six reviews and 46 universal prevention trials, with psychoeducation the most commonly tested intervention (26 trials).106 The review also identified six reviews and 40 trials in at-risk populations, where psychoeducation and cognitive dissonance programmes were equally common (12 each).
Adolescents with anorexia nervosa
• Which factors are essential to identify patients at risk and how could we address this target group with adequate and effective prevention programmes?
• What are the predictors, moderators, and mediators of outcome in the treatment of adolescent patients with anorexia nervosa?
• What to do when family-based treatment is unsuccessful or inappropriate (eg, if there is substantial intrafamilial abuse)?

Adults with anorexia nervosa
• How can we improve treatment outcomes—ie, what works and for whom and in what setting?
• What is the best first-line outpatient treatment?
• What treatments should be used as second-line treatments?
• How important is it to involve family members and partners in treatment?
• How can we prevent relapse after inpatient or day-patient treatment?

Across the age range
• What brain circuits are involved in the onset and maintenance of anorexia nervosa?
• Which structures are implicated for which subtypes of anorexia nervosa?
• Are there imaging markers to identify treatment responders and non-responders?
• In view of the typical age of onset of anorexia nervosa, does it make sense to have separate adolescent and adult eating disorder services or should there be seamless services across the ages?
• How should treatment and treatment goals be adjusted for different stages of illness?
• What is an adequate course of treatment for anorexia nervosa?
• How should treatment resistance and palliative care be defined?
• How can we help the subgroup of patients with severe hyperactivity?

Treatment of comorbidities (psychiatric or physical)
• How can we reduce mortality and suicide in individuals with anorexia nervosa?
• How can we help the subgroup of patients with severe psychiatric comorbidities?
• What is the treatment for patients suffering from comorbid post-traumatic stress disorder, personality disorder, developmental disorders (eg, autism spectrum disorder), and alcohol or substance misuse?
• How can we help the subgroup of patients with a severe somatic comorbidity disorder?
• What is the treatment for patients with comorbidities such as diabetes mellitus or inflammatory bowel disease?
• What is the optimum management of osteopenia and osteoporosis in anorexia nervosa?
• What is the treatment for patients with a comorbidity such as food-related allergy?

Panel 3: Key unmet challenges in the management of anorexia nervosa

Meta-analyses of controlled trials from other reviews were summarised as indicating that “prevention programmes generally produce large effects on outcomes related to eating disorder knowledge, and only small net effects for other important prevention targets such as reducing exhibited risk factors, changing attitudes, and reducing eating pathology”.10 The review also found that larger effect sizes are usually seen for studies of at-risk populations and interactive programmes using multi-session formats.

Other systematic reviews117 have specifically examined school-based interventions,130 e-health interventions, and the role of parental involvement131 in eating disorders and body dissatisfaction prevention programmes for children and adolescents, suggesting that these settings and ways of delivery are fruitful avenues to explore in future studies.

Conclusions
The past 5 years have seen substantial advances in the knowledge of anorexia nervosa. Recent treatment studies suggest that patients with anorexia nervosa have a realistic chance of recovery, especially if treated early, or at least, to achieve substantial improvement. However, there is widespread agreement that several challenges remain in the management of anorexia nervosa (panel 3) and new interventions are needed to improve outcomes, especially in adults with the disorder. Such interventions should target specific disease mechanisms. The neuro-psychological constructs introduced within the research domain criteria (RDoC) matrix offer a new systematic basis for determining the neural substrates underlying the biological predisposition to anorexia nervosa.129 A clearer understanding of how anorexia nervosa behaviour is encoded in neural circuits would provide a key for developing more effective treatments. To conclude, we still need to discover how to provide better, faster, and lasting improvements in the management of this enigmatic disorder.

Contributors
All authors contributed to the search and selection of the medical literature and to the writing of the Review.

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