Anorexia nervosa: diagnosis, risk factors and evidence-based treatments

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As part of the series on managing neurological and psychiatric conditions in children and adolescents, Dr Sara Kakhi and Dr Jacinta McCann cover recent updates in epidemiology, risk factors, common comorbidities and treatment options for anorexia nervosa.

Anorexia nervosa (AN) is a severe psychiatric disorder with substantial morbidity and the highest mortality of all mental disorders. The standardised mortality rate for AN is higher than that for asthma or type 1 diabetes mellitus. About one-fifth of those who die do so by suicide. Additionally, the estimated financial cost associated with disability-adjusted life years attributable to eating disorders is higher than that of depression and anxiety combined.

Eating disorders are the third most common chronic illness among adolescents, after obesity and asthma. The peak age of onset occurs between 14 and 19 years. Although approximately 10% of the general population suffers from some type of eating disorder, only a minority of these individuals ever seek treatment.

Several studies were able to demonstrate that the highest incidence rates are found in the 15–19 years age group, with approximately 40% of all new cases appearing between 15–19 years of age. There is some evidence that the age of onset of AN has been decreasing in recent decades and that childhood and adolescent AN are on the rise.

Prevalence rates among females remain significantly higher than males. In clinical samples, increasing prevalence of AN is found in males, but there are few population prevalence data. A greater proportion of younger males present with restrictive eating disorders. Although incidence rates of AN have largely been stable, there has been a notable increase in incidence in 15- to 19-year-old females. UK study based on primary care data demonstrated that the incidence of the diagnosed eating disorder was highest for girls aged 15–19 years and for boys aged 10–14 years.

Increased prevalence rates have been found in males and ethnic/racial minorities (Latino, Asian American and Latinos in the US population), as well as in countries where eating disorders were not previously reported such as India, China and Japan.

F (50.0): ICD 10 diagnostic criteria for anorexia nervosa (World Health Organization, 1992 – Clinical Descriptions and Diagnostic Guidelines)

- Actual body weight at least 15% below expected weight, or body mass index 17.5 or less (in adults)
- Weight loss is caused by the avoidance of high-calorie foods and at least one of the following:
  - Self-induced vomiting
  - Self-induced purging
  - Excessive exercise
  - Use of appetite suppressants and/or diuretics
- Distorted body image as a specific psychological disorder
- Endocrine disorder, manifest in the female as amenorrhea and in the male as a loss of libido
- If onset is pre-pubertal, the puberty in boys and girls may be delayed (growth ceases; in girls the breasts do not develop).

DSM-5 diagnostic criteria – American Psychiatric Association (2013)

A. Restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significant low weight is defined as a weight that is less than minimally normal.

B. Intense fear of gaining weight or becoming fat or persistent behaviour that interferes with weight gain even though at a significant low weight.

C. Disturbance in a way which one’s body weight or shape is experienced, under influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current body weight.

Anorexia nervosa: DSM-IV to DSM-5

There have been major changes from DSM-IV to DSM-5, leading to a potential increase in the prevalence of anorexia nervosa and bulimia nervosa.

The most important changes from DSM-IV to DSM-5 are:
- Removal of a specific weight threshold for diagnosis
• Increased reliance on behavioural manifestations in addition to cognitive symptoms
• Elimination of amenorrhea as a criterion necessary for the diagnosis.

Overall DSM-5 has taken a less restrictive approach, compared with the last version of DSM, towards the criteria threshold for eating disorders. Guideline suggests that being underweight must take into consideration the ‘context of age, sex, developmental trajectory and physical health’.

**Risk factors**
A national Danish study of risk factors for AN concluded that AN risk factors are: having a sibling with AN; affective disorders in family members, and comorbid affective, anxiety, obsessive-compulsive personality, or substance use disorders. Furthermore, female sex and ascending year of birth were significantly associated with having AN. Urbanisation was not related to the family load of AN and case relatives did not develop AN earlier than control relatives.

The aetiology of disordered eating and eating disorder is likely to involve a complex interplay of biopsychosocial effects. Genetic and environmental/nongenetic influences on eating disorders do not operate in isolation. Indeed, environmental experiences (e.g. abuse history) and developmental changes appear to interact with and influence the expression of genes.

• Confirmed risk factors for eating disorders include sociocultural influences, specifically media exposure, pressures for thinness, thin-ideal internalisation, thinness expectancies and nonspecific personality factors, including negative emotionality/neuroticism, perfectionism, negative urgency.

• Rodhe et al. reported that elevated body dissatisfaction at ages 13, 14, 15 and 16 years predicted DSM-5 eating disorders onset in the four-year period after each assessment. BMI did not predict eating disorders at any age.

• Correlational studies of adult women and experimental studies of animals provide evidence for the effects of reproductive hormones on the emergence of eating disorder symptoms.

• In an 18-year follow-up study of adolescent AN subjects, difficulties in mentalising tasks remained in several subjects after recovery and were independent of body weight loss and the duration of the eating disorder. Wentz et al. showed that autistic traits in childhood were found to be predictive of a poor global outcome in the eating disorder in adulthood.

• A large multigenerational Swedish study (n=286 232), found that eating disorder in either parent is independently associated with eating disorder developing in their female children (hazard ratio [HR] 1.97 (95% confidence interval [CI]: 1.17–3.33), p=0.01) and that eating disorder in mothers is independently associated with eating disorder in their female children (HR 2.35 [95% CI: 1.39–3.97] p=0.001).

**Treatment**

**NICE recommendations**

• In assessing whether a person has AN, attention should be paid to the overall clinical assessment (repeated over time), including rate of weight loss, growth rates in children, objective physical signs and appropriate laboratory tests.

• Patients with enduring AN not under the care of a secondary care service should be offered an annual physical and mental health review by their GP.

• Children and adolescents with AN should be offered individual appointments with a healthcare professional separate from those with their family members. The therapeutic involvement of siblings and other family members should be considered in all cases because of the effects of AN on other family members. Outpatient psychological treatment for AN should normally be of at least six months’ duration.

• For inpatients with AN, a structured symptom-focused treatment regimen with the expectation of weight gain should be provided in order to achieve weight restoration. It is important to carefully monitor the patient’s physical status during refeeding. The length of outpatient psychological treatment and physical monitoring following inpatient weight restoration should typically be at least 12 months.

• When a young person with AN refuses treatment that is deemed essential, consideration should be given to the use of the Mental Health Act 1983 or the right of those with parental responsibility to override the young person’s refusal.

• Relying indefinitely on parental consent to treatment should be avoided. It is recommended that the legal basis under which treatment is being carried out should be recorded in the patient’s case notes, and this is particularly important in the case of children and adolescents.

• Feeding against the will of a patient should be an intervention of last resort in the care and management of AN. NICE recommended that this ‘is a highly specialised procedure requiring expertise in the care and management of those with severe eating disorders and the physical complications associated with it’, also that there needs to be a clear legal basis for this action and that the relevant mental health legislation and associated procedures are followed.
Outpatient treatment (OP)
Outpatient setting remains the ideal setting for management of AN. NICE recommends outpatient treatment for most patients with AN, with a special modification for young patients (‘the need for IP and the need for urgent weight restoration should be balanced alongside the educational and social needs of the young person’).

Inpatient treatment (IP)
In the UK, admission rates for AN have increased substantially in recent years. From 2012 to 2013, there was a national rise of 8% in the number of admissions to hospital for an eating disorder in comparison with the year before, which had already seen an increase. In addition, the length of hospital stays increased substantially during the last decade.36
• Gowers et al. compared IP with two different forms of outpatient care (a specialised eating disorder outpatient treatment with emphasis on cognitive behavioural therapy [CBT] and treatment as usual in child and adolescent mental health services).37 There were no differences in clinical outcomes between the three groups. The study faced a limitation of poor treatment adherence in the IP arm.
• Recent research supports initiating higher caloric prescription on admission to the hospital, starting patients on 1400–2000kcal per day with close medical monitoring.38 This is reported to shorten hospital stay39,40 and increase the rate of weight gain39,41 without increasing the rate of refeeding syndrome.
• The rates of dropout from IP programs are up to 25%.42,43

Recommendations for weekly weight gain
NICE guidelines recommend 0.5–1.0kg weekly weight gain in an inpatient setting, 0.5kg in an outpatient setting. NICE only mentions an additional amount of 3500–7000 calories per week without differentiating between in- and outpatient treatment or between adolescents and adults. An expert group of the Royal College of Psychiatrists (Junior MARSIPAN [Management of really sick patients with anorexia nervosa]) estimated 20kcal/kg body/weight/day as safe, but advised less (5–10kcal/kg body weight) for individuals with very low initial weight or comorbid somatic disorders.44
Weight gain during inpatient or outpatient treatment and the maintenance of weight gain after discharge from treatment have been proven to be important prognostic factors for the short- and long-term course of adolescent AN.45–47

The primary goal of medical hospitalisation is to safely restore physiological stability through nutritional rehabilitation. This process should be approached with caution as it can result in the refeeding syndrome.48–50

Refeeding syndrome
This is characterised by a variety of metabolic and clinical features, including but not limited to hypophosphatemia, cardiac arrest, and delirium.51–53 Refeeding syndrome primarily develops during the first fortnight after starting refeeding. Most guidelines recommend a stepwise increase of daily intake such as 200kcal/day.44

Recent studies have not found any difference in the rates of refeeding syndrome between adolescents who were started on a low-calorie diet compared with those on a high-calorie diet.54,55 Hypophosphatemia, a major symptom of refeeding syndrome, was associated with low BMI at intake but not related to the amount of calories consumed.54,56

Patient motivation to change is an important predictor of short-term outcome. A study by Hillen et al. reports those patients with a greater motivation to change at admission exhibited a higher weekly weight gain during treatment but did not show better outcome in eating disorder-specific psychopathology and depression.54

Does admission to hospital for eating disorders under the Mental Health Act increase mortality rates?
Approximately 20 years follow-up in a UK mortality study demonstrated that although the mortality in the five years following a compulsory admission was higher than non-compulsory patients, this difference was attenuated over time. The standardised mortality rate in the compulsory treatment group no longer differed significantly from that of the non-compulsory group. The suicides were not linked with compulsory admission.55

Box 1. Three stages of family-based treatment
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Day patient treatment (DP)
DP for anorexia may be an alternative to IP or may be useful as an approach following IP.\textsuperscript{56} It is certainly a less restrictive option and is helpful in building family and patient confidence.

Herpertz-Dahlamann et al. investigated the safety and efficacy of day treatment settings, after short inpatient care, compared with continued inpatient in a multicentre, randomised, open-label trial in Germany. They concluded that DP was not inferior to IP with respect to symptom reduction, BMI at the 12-month follow-up.\textsuperscript{57}

Two small uncontrolled studies from Australia and the US demonstrated preliminary efficacy of a day patient program in younger patients.\textsuperscript{58} The authors reported that the 12–18-year-old Australian female patients enrolled in the study benefitted from DP, as evidenced by their significant weight gain and reduction in eating disorder behaviour.\textsuperscript{59} In a US family-centred day patient program for children with a mean age of 13 years, participants showed significant improvement in weight and psychological outcomes at discharge. Unfortunately, there was no follow-up assessment in either study.\textsuperscript{58}

Psychological interventions
Most therapeutic recommendations are primarily based on mainstream expert opinion with little empirical evidence. Only 12 papers in the top 100 cited papers published in the AN field address therapeutic strategies.\textsuperscript{60}

So far studies have provided little support for specialised psychotherapies or pharmacotherapies, conducted with both underweight and weight-restored individuals.\textsuperscript{61–69} However, the Maudsley family-based therapy approach is one of the few empirical, evidence-based studies showing effectiveness in young people with AN under the age of 18 years.\textsuperscript{70,71}

Cognitive behavioural therapy (CBT)
Due to some diagnostic uncertainties, an enhanced, ‘transdiagnostic’ approach to CBT has been established (CBT-E).\textsuperscript{72} CBT-E for adolescents consists of three phases:
1. Thinking afresh on the current state and maintaining processes of the eating disorder, including analyses of pros and cons.
2. Modification of concerns surrounding weight and shape.
3. Maintaining changes and developing strategies to handle setbacks.\textsuperscript{73}

Cognitive remediation therapy (CRT)
CRT was developed with the aim of improving cognitive flexibility and thereby functioning. The focus of CRT is on how patients think, rather than on what patients think. It is hypothesised that CRT training works by proliferating and refining neural connections and by teaching new, adaptive strategies, thus making individuals more flexible in the way they think and behave.\textsuperscript{74}

Preliminary results show small to medium effects of CRT on various measures of cognitive flexibility in adolescents, both in groups or individual settings, as an adjunct to other treatments.\textsuperscript{75,76}

Randomised controlled trials (RCTs) demonstrate that CRT has the potential of enhancing the effectiveness of current treatments, reduce attrition, increase cognitive set-shifting abilities and quality of life, as well as reduce eating disorder psychopathology.\textsuperscript{77}

Family-based treatment (FBT)
FBT is an outpatient-based intervention that has the strongest evidence of effect in adolescents with AN (see Box 1).\textsuperscript{73,78}

The Maudsley FBT is the most established treatment model for adolescents with AN, and several RCTs have demonstrated evidence for symptom remission and weight rehabilitation.

Le Grange suggests that most young patients with AN require, on average, no more than 20 treatment sessions over the course of 6–12 months.\textsuperscript{80}

The Maudsley approach holds great promise for most adolescents who have been ill for a relatively short period of time (e.g. less than three years). This can prevent hospitalisation and assist the adolescent in her/his recovery, provided that parents take an active role in treatment.\textsuperscript{81}

Eisler et al. showed that approximately two-thirds of adolescent AN patients are recovered at the end of FBT while 75–90% are fully weight recovered at five-year follow-up.\textsuperscript{82}

The majority of trials only report mean participant ages in the 12–18 years range. It should be noted that these findings come only from a small number of trials with small sample sizes, where risk of bias is notable.\textsuperscript{83}

Dynamic family therapy
A RCT by Godart et al. involving 60 female adolescents with DSM-IV AN, aged 13–19 years, compared ‘treatment as usual’ (TAU) with adjunctive family therapy. This included sessions for the adolescent alone and sessions with a psychiatrist for the adolescent with her parents (TAU + FT), which included a family therapy component targeting intrafamilial dynamic but not eating disorder symptoms. Results showed that focusing on the intrafamilial dynamic improves treatment effectiveness in severe AN patients even after 13 years follow up.\textsuperscript{84}
Multiple family therapy (MFT)

Preliminary research suggests that MFT, which involves several families being treated together as a group, may be an effective intervention for adolescent AN. Marzola et al. followed up 54 adolescents, 30 months after a brief intensive MFT intervention, reporting 59.3% remission (>95% expected body weight [EBW]) rates and a further 27.7% partial remission (>85% EBW). MFT-AN is a highly acceptable intervention to families, with more than 90% completing the treatment, with significant improvement in weight and other patient symptoms, improvements in parents’ mood and better family relationships.

Pharmacological treatment – efficacy of antidepressants and atypical antipsychotics

NICE does not support medication as a primary or only treatment for AN. However, use of medication such as olanzapine might be necessary intermittently in highly anxious and agitated patients who otherwise would resist refeeding.

In AN, atypical antipsychotics and selective serotonin reuptake inhibitors (SSRI) are the most commonly used medications.

Recent studies did not support effectiveness of adjunctive treatment with second-generation antipsychotics on weight-related outcomes or eating disorder-specific psychopathology.

In a double-blind placebo-controlled study of risperidone, 40 adolescent patients were randomised to receive risperidone or placebo plus the normal eating disorder program. After nine weeks there were no significant differences between the treatment groups.92

In a placebo-controlled pilot study of adjunctive olanzapine for adolescents the percentage change in median body weight did not differ between the two treatment groups.92

In a recent systematic review and meta-analysis of the effects of olanzapine, risperidone, and amisulpride in both adolescent and adult samples, no significant increase in BMI or decrease in the drive for thinness and body dissatisfaction was found.93

There is no clear evidence of whether, and under what conditions, SSRIs may be beneficial in the treatment of AN. Fluoxetine has been examined during the weight restoration process and the weight maintenance phase of therapy. SSRIs may be considered if there is comorbid depressive disorder.

In two early studies, no effect on weight gain was found. In a study of relapse prevention, 93 weight-restored patients including females 16 years or older were enrolled in a controlled multicentre study combining CBT and pharmacotherapy with fluoxetine. As an adjunctive medication, fluoxetine was not more effective than the placebo, even for depressive and anxiety symptoms.96

Novel pharmaceutical substances targeting hormonal circuits of appetite control and food intake may also be important agents in the future treatment of AN.97

Outcomes of AN

In a recent meta-analysis based on 36 studies, the standardised mortality rates were 5.86 for AN, 1.93 for bulimia nervosa (BN), and 1.92 for eating disorder not otherwise specified (EDNOS) (according to DSM-IV criteria). The mortality rates for AN showed a significant association with age but not with BMI, underlining the danger of a long-lasting illness.

The severity and physical consequences depend on the extent and rapidity of weight loss, the current degree of underweight, the duration of the eating disorder, the intensity of purging, and the age of the patient.

A Finnish study assessed mortality, recovery, and sociodemographic outcomes of AN in a community sample. Women were followed for 10 years after baseline diagnostic assessment (mean age at follow-up 34 years, n=2188). They showed that the long-term prognosis of AN in the community was promising. Weight-restoration is common and sociodemographic outcomes were generally favourable. However, women with a history of AN may be less likely to have children.

Suicidality is one of the most important reasons for premature death in AN. Suicidal ideation is found in about half of adolescent AN patients, and suicide attempts are observed in 3–7%. Although suicidality is much lower in adolescent AN than in adult AN, a strong association between depression, the binge/purge subtype of AN, and the duration of illness has been reported.

Physical complications

Table 1 covers some common physical complications of anorexia.

Psychiatric comorbidities

In more recent studies, up to 60% of adolescent patients with AN display some type of mood disorder.
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Several studies found an association between weight loss and depression; for example, patients with a high degree of starvation also felt more depressed. Anxiety disorders other than OCDs are very common in AN. About 25% of patients with acute AN report one or more anxiety disorders. In many cases, the anxiety disorders begin in childhood and pre-date the eating disorder.

About 25% of AN patients suffer from substance abuse. The most prevalent substance abuse is amphetamine and cocaine dependence, but many patients also abuse nicotine.

Prevention

The role of prevention in the development of eating disorders needs further exploration. Bailey et al. in their review, failed to identify any controlled trials investigating prevention strategies involving families. Potential prevention components may involve education and skills training for parents around talking about and identifying risk factors.

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References are available online at: www.progressnp.com

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Key points

- BMI alone is not a reliable marker for assessment of eating disorders in young people
- The rate of weight loss is important when assessing acute presentation of AN
- Junior MARSIPAN is the reference guideline in medical management of anorexia in the UK
- Community treatment for anorexia nervosa is the setting of choice
- The effectiveness of building up family resilience and skills in managing eating disorder is supported by a strong evidence base
- Safety and utility of pharmacological treatment in anorexia should be considered on an individual basis

Osteopenia and osteoporosis

Low bone density is generally not completely reversible, even after weight rehabilitation. Osteoporosis is not only a problem of females but also of male patients, owing to their deficits in gonadal hormones.

Treatment of bone mineral density (BMD)

- Although calcium and vitamin D supplementation increase BMD in the short term in healthy adolescents, no RCTs have been done in AN
- Oral oestrogen/progestin has not been found to effectively increase BMD in AN
- One study found that physiological doses of transdermal oestrogen increased spine and hip BMD compared with controls
- Although bisphosphonates have been found to increase BMD in adolescents and young adults with AN, the effect is modest and their use is not recommended

Given the increased fracture risk, dual-energy X-ray absorptiometry scans should be obtained when amenorrhea is present for six months or more.

Cardiovascular system

Patients with eating disorders often present with bradycardia, hypotension, arrhythmias and changes in heart rate variability. Hypotension and postural changes in heart rate and blood pressure can result from decreased cardiac mass leading to systolic dysfunction, in addition to volume depletion and autonomic dysfunction.

Endocrine

Girls and boys may present with decelerated linear growth, pubertal delay or pubertal regression, and menstrual dysfunction is common in females. Progesterone level is monotonously low and corresponds to the basal level of first phase of menstrual cycle. Levels of testosterone and androstendione often correspond to the lower limits of normal. Hormonal changes include increase in growth hormone (GH) level and in cortisol concentration in blood plasma as well as a decrease in free thyroxine (T4)

Menstrual function disorder (MFD): Weight loss of 10% or more can lead to MFD and include secondary amenorrhea or oligomenorrhea. This is mainly due to dysfunctional secretion of gonadotropin releasing hormone (GnRH)

Renal

Eating disorder patients can develop dehydration and renal insufficiency due to severe fluid restriction or vomiting. Patients with AN may lose renal concentrating ability, which can result in high urine output and inaccurate specific gravity measurements on urinalyses

Haematological

Bone marrow hypoplasia is seen in low-weight eating disorders, primarily leukopenia and anaemia, with rare cases of thrombocytopenia. All dyscrasias resolve with the reversal of malnutrition. It is important to evaluate for iron and vitamin B12 deficiency in anaemic patients because these are easily reversed with supplementation

Neurological

Severely ill patients with AN have been shown to have reduced brain tissue volume and impaired neuropsychological functioning

Table 1. Common physical complications of anorexia

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Table 1. Common physical complications of anorexia
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