Psychological Medicine

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Advances in the treatment of anorexia nervosa: a review of established and emerging interventions

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Invited Review

Cite this article: Brockmeyer T, Friederich H-C, Schmidt U (2018). Advances in the treatment of anorexia nervosa: a review of established and emerging interventions. *Psychological Medicine* **48**, 1228–1256. https://doi.org/10.1017/S0033291717002604

Received: 31 March 2017
Revised: 29 July 2017
Accepted: 9 August 2017
First published online: 11 September 2017

Key words:
Anorexia nervosa; randomised controlled trial; treatment

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Abstract

Background. Anorexia nervosa (AN) is a disabling, deadly and costly mental disorder. Until recently, treatment recommendations were based on expert opinion and limited evidence. The aim of this systematic review is to synthesise recent evidence on established and emerging AN treatments and to forecast trends for future developments.

Methods. We systematically review trials of established treatments and associated process outcome studies from the last 5 years, published since a previous review in this journal. 'Established' treatments were those that are widely used in AN, recommended by guidelines and/or have been tested in at least one large randomised controlled trial. Secondly, we summarise emerging treatments for AN, i.e. those that have only been (or are currently being) tested in proof-of concept, feasibility or pilot trials.

Results. We identified 19 published trials of established treatments (15 of high or moderate quality), mostly assessing psychological therapies ($n = 17$). We also found 11 published trials of emerging treatments, and a total of 34 registered, as yet unpublished trials. Promising emerging treatments include cognitive remediation therapy, exposure therapy and non-invasive neuromodulation.

Conclusions. Evidence generation on the treatment of AN has dramatically accelerated, with our understanding of the role of family-based approaches for adolescents more nuanced and a range of psychological approaches available for the treatment of adults. Evidence on emerging treatments and from forthcoming trials suggests that there is a shift towards more targeted brain-based interventions. Future studies need to focus on elucidating mechanisms of action of treatments and what works best for whom.

Introduction

Anorexia nervosa (AN) is one of the most common chronic disorders in adolescence, with incidence rates at least as high as that of type 1 diabetes (Gonzalez *et al.* 2007). It affects up to 4% of women during their lifetime (Keski-Rahkonen & Mustelin, 2016). The peak age of onset of AN is from age 15 to 19, i.e. at a developmentally sensitive time (Micali *et al.* 2013). Average illness duration is about 6 years. Whilst overall the incidence of AN is thought to be stable in Western countries (Keski-Rahkonen & Mustelin, 2016), improved detection may have contributed to reported increases in rates and decreases in age of onset noted in some studies (Steinhausen & Jensen, 2015). Core symptoms of AN include persistent severe food restriction, especially of high caloric foods, leading to significant underweight. In a proportion of cases, there are episodes of loss-of-control or binge eating. Associated weight control behaviours (such as excessive exercise, self-induced vomiting, laxative abuse) are driven by an extreme fear of food, eating or weight gain. Psychological and physical comorbidities are common, and the mortality rate is the highest of any mental disorder (Treasure *et al.* 2015*c*; Schmidt *et al.* 2016*a*). In 15–24-year olds, the mortality risk is also higher than for other serious diseases in adolescence, such as asthma or type 1 diabetes (Hoang *et al.* 2014). Thus, the disease burden for patients, their caregivers and society is high (Schmidt *et al.* 2016*a*).

The aetiology of AN is complex, with evidence for multiple biopsychosocial risk and maintenance factors (Treasure *et al.* 2015*c*; Zipfel *et al.* 2016). Data suggest that environmental and psychological factors interact with and influence the expression of genetic risk to cause eating pathology (Culbert *et al.* 2015). Increasingly, there is a broad acceptance of AN as a brain-based disorder and of neurobiological overlaps between AN, anxiety disorders and addictions (O'Hara *et al.* 2015). Neuroimaging studies have revealed differences in the structure and function of the brain in acute stage AN and in recovery. For example, systematic reviews in adolescents and adults have reported reduced grey and white matter volumes, increased cerebrospinal fluid and altered white matter structure in acute AN compared with healthy

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individuals (Martin Monzon *et al.* 2016; Seitz *et al.* 2016) with some changes persisting in recovery (Martin Monzon *et al.* 2016). In acute stage AN, functional differences have been observed in ventral limbic regions involved in the assignment of emotional significance to stimuli, arousal and generation of emotional responses (i.e. the amygdala, ventral striatum, insula, ventral anterior cingulate cortex (ACC), orbitofrontal cortex) and dorsal regions implicated in higher level evaluative cognitions (including the dorsolateral prefrontal cortex (DLPFC), parietal cortex, dorsal ACC) (Kaye, 2008; Kaye *et al.* 2009, 2011; Zhu *et al.* 2012). As a result of these findings, differences in brain structure and function are being incorporated into aetiological models of eating disorders (EDs). In particular, researchers have implicated alterations in neural circuits involved in reward processing (Frank, 2013; Wierenga *et al.* 2014*b*; O'Hara *et al.* 2015; Wu *et al.* 2016), negative affect and stress (Connan *et al.* 2003), appetite regulation (Kaye *et al.* 2009, 2011), cognitive (self-regulatory) control (Zastrow *et al.* 2009; Friederich *et al.* 2013; Wierenga *et al.* 2014*a*) and socio-emotional processes (Zhu *et al.* 2012; McAdams & Smith, 2015).

Additionally, there is growing evidence to support a stage model of illness for AN, with neurobiological progression and some suggestion that outcomes become poorer once illness duration exceeds 3 years (Currin *et al.* 2005; Treasure *et al.* 2015*b*; Schmidt *et al.* 2016*b*).

Available treatments are largely psychological and/or focus on nutritional rehabilitation (Hay, 2013; Kass *et al.* 2013; Watson & Bulik, 2013; Hay *et al.* 2015; Zipfel *et al.* 2016). For adolescents with AN, there is clear evidence that ED-focused family therapy is superior to individual therapy and thus the treatment of choice (Hay *et al.* 2014; Zipfel *et al.* 2016). In contrast, for adults, there is no leading treatment, recovery rates are low to moderate, and attrition and relapse rates are high (Treasure *et al.* 2015*c*; Zipfel *et al.* 2016). Evidence for the efficacy of any pharmacological treatments of AN (Aigner *et al.* 2011; Flament *et al.* 2012; Hay & Claudino, 2012; Kishi *et al.* 2012; de Vos *et al.* 2014) is weak, with some studies finding olanzapine to show promise in reducing illness preoccupations and meal-time anxiety (Kishi *et al.* 2012; Lebow *et al.* 2013; de Vos *et al.* 2014). This situation calls for the development of novel treatment approaches (Martinez & Craighead, 2015; Le Grange, 2016; Schmidt *et al.* 2016*a*).

The aims of this review are as follows: Firstly, we summarise the main findings of clinical trials on established AN treatments, that have been reported since a previous review on this topic in this journal (Watson & Bulik, 2013). We consider treatments as 'established' that are widely used in AN treatment, recommended by guidelines and/or have been tested in at least one large randomised controlled trial (RCT), with a minimal sample size of $n = 100$ (Friedman *et al.* 2015). Secondly, we review associated process outcome studies, which shed light on active ingredients of existing treatment approaches. Thirdly, we review emerging treatments for AN, i.e. those that have only been (or are currently being) tested in feasibility or pilot trials so far. Finally, we also attempt to forecast future developments by assessing forthcoming as yet unpublished trials.

Methods

To provide an overview of recent RCTs of established and emerging AN treatments, we conducted a systematic literature search in PubMed, Scopus and Web of Science using a simple search strategy (Royle & Waugh, 2005), which has high sensitivity (97%) and precision (29%) (McKibbon *et al.* 2009). This uses the search terms 'random*' (all fields) and 'anorexia' (article titles). We limited our search to articles, published in English or German between Oct 2011 (as the review by Watson & Bulik, 2013 covered the literature up until then) and 31/12/2016. We excluded trials where the main focus of the study was on illness complications, such as osteoporosis, or other non-ED outcomes. Secondary analyses of trials published before Oct 2011 were also not considered. For established treatments, the methodological quality of included trials was assessed according to the Cochrane handbook (Higgins & Green, 2014) and the National Institute of Health criteria for quality assessment of controlled intervention studies (National Institute of Health, 2014). Risk of bias was rated by two independent researchers (US and TB) by using the following criteria: RCT design, sample size $n > 30$ in each condition, *a priori* power analysis, lack of recruitment (selection) bias, similarity of groups at baseline, drop-out rate below 20%, intent-to-treat analysis, reporting of all relevant outcomes, validated and reliable outcome measures, adequate method of randomisation, allocation concealment, blinding of assessors, CONSORT statement, registration in clinical trial registry, good adherence to intervention protocols, avoidance of or similar other interventions in the different conditions, representative population, relevant intervention, clinically relevant primary endpoint. Disagreements were resolved by discussion.

To provide an overview of forthcoming and as yet unpublished trials, we searched major national and international clinical trials registries, including the World Health Organization's International Clinical Trials Registry, clinicaltrials.gov, ISRCTN registry, the Australian and New Zealand Clinical Trials Registry, ANZCTR, and the German trials registry, DRKS (search term: anorexia).

PART I: Review of *established* treatments

Trials in adolescents

We identified eight published ($n = 833$ patients) and six unpublished trials. In published trials treatment completion rates vary from 64% to 90%. In these studies remission/recovery rates range from 17.2% to 50% at last recorded follow-up (6 to 24 months post-randomisation) (see Table 1 for details).

Family interventions

Since the previous review (Watson & Bulik, 2013), three large RCTs have examined variants of family therapy for adolescents with AN. These include multi-family group therapy (Eisler *et al.* 2016) and separated (parents only) family therapy (Le Grange *et al.* 2016), both of which had advantages over ED-focused family therapy in the short term. A third RCT found no significant differences between ED-focused family therapy and systemic family therapy (which focuses on general family processes) in weight gain and other outcomes (Agras *et al.* 2014). These findings suggest that non-specific factors, such as mobilisation of the family and provision of a coherent treatment model are likely to play a role in effecting change in family therapy (Jewell *et al.* 2016). Having said that, it seems that giving parents the opportunity to learn from other families (Eisler *et al.* 2016) or to discuss their difficulties without their child being present (Le Grange *et al.* 2016) is helpful. Building on these findings, a novel adjunct to family therapy (termed *Intensive Parental Coaching*) has been developed for parents of 'poor early

https://doi.org/10.1017/S0033291717002604 Published online by Cambridge University Press

Table 1. RCTs of established treatments in adolescent or predominantly adolescent populations

Author(s) (year)	*n*	Inclusion criteria	Setting	Stand-alone or adjunctive treatment	Comparison groups	Dose	Main findings	Additional findings and comments	Study quality
Family interventions – published									
Eisler *et al.* (2016)	169	Adolescents and emerging adults (age 13–20), a DSM-IV diagnosis of AN or EDNOS (restricting type)	Out-patient	Stand-alone	(1) SFT *v.* (2) MFT	12 months treatment period. SFT: Number and frequency of sessions determined by clinical need, starting weekly and then spread out to 3–4 weekly. MFT: 10 days of MFT plus Individual family meetings at intervals	Just under 60% SFT patients *v.* 75% of MFT patients achieved good or intermediate outcome on Morgan–Russell scale (primary outcome) EOT (OR = 2.55 95%; CI 1.17–5.52; $p = 0.019$). At FU (18 months post baseline) the difference between treatments was no longer significant	SFT: median number of outpatient sessions attended was 19 (IQR 12–27); MFT: median 18.5 out-patient sessions; (IQR 11–24) and a median of 7 MFT days (IQR 1–10) Significant improvements on most secondary outcomes in both groups, with no differences between groups. *Treatment completion definition and rates*: Definition: none provided; FT-AN: 73/83 (88%); MFT-AN: 76/86 (88.4%) *Recovery definition and rates at final follow-up:* Definition: none provided; MR outcome: FT-AN – 33% good, 24% intermediate; MFT-AN 45% good; 33% intermediate at 18 months post-randomisation	High
Agras *et al.* (2014)	164	Adolescents (aged 12–18 years) of both sexes; DSM-IV diagnosis of AN (except for amenorrhea)	Out-patient	Stand-alone	(1) FBT focusing on weight gain *v.* (2) SyFT, addressing general family processes	In both groups 16 1-h sessions over 9 months	No differences between groups for primary outcome [% of ideal body weight and for other outcomes, such as remission (⩾95% of IBW)], ED symptoms or comorbid psychiatric disorders at EOT or FU	FBT: faster weight gain early in treatment, significantly fewer days in hospital, lower treatment costs per patient in remission at EOT. SyFT: greater weight gain for participants with more severe obsessive-compulsive symptoms. *Treatment completion definition and rates*: Definition: none provided; FBT: 55/82	High

								(67.1%); SyFT: 53/82 (64.6%) *Recovery definition and rates at final follow-up:* Definition: ⩾95% IBW; FBT: 40.7%; SyFT: 39.0% at 20 months post-randomisation	
Le Grange *et al.* (2016)	107	Adolescents aged 12–18 years, a DSM-IV diagnosis of AN or partial AN	Out-patient	Stand-alone	(1) FBT *v.* (2) PFT	In both groups 18 sessions over 6 months (10 min weight monitoring and support of the adolescent + 50 min. of family or parental sessions)	Remission at EOT (primary outcome) higher in PFT than in FBT at EOT (43% *v.* 22%; $p = 0.016$, OR = 3.03, 95% CI = 1.23–7.46), but did not differ statistically at 6-month, or 12-month FU	*Treatment completion definition and rates*: Definition: ⩾9 sessions (i.e. 50% of dose); FBT: 46/55 (83.6%); PFT: 44/52 (84.6%) *Recovery definition and rates at final follow-up:* Definition: ⩾95% mBMI and EDE Global score ⩽1.59; FBT: 29%; PFT: 37% at 24 months post-randomisation	Moderate
Lock *et al.* (2015)	45	Adolescents (12–18 years), DSM IV diagnosis of AN	Out-patient	Stand-alone	(1) standard FBT ($n = 10$) *v.* (2) FBT + intensive parental coaching ($n = 35$)	FBT: 15 sessions; FBT + parental coaching: 18 sessions	No differences between groups in attrition rates, suitability, expectancy ratings, and most clinical outcomes	This is a feasibility trial. *Treatment completion definition and rates*: Definition: none provided FBT: 8/10 (80%); FBT/IPC: 28/35 (80%) *Recovery definition and rates at final follow-up:* Definition: ⩾95% IBW FBT: 5/10 (50% in ITT sample); FBT/IPC: 17/35 (48.6% in ITT sample) at 6 months post-randomisation	
Family interventions – in progress									
Rhind *et al.* (2014)	175	Adolescents (aged 13–21), a DSM-IV diagnosis of AN	Out-patient	Adjunct to TAU	(1) ECHO self-help intervention plus TAU *v.* (2) ECHO plus telephone coaching plus TAU *v.* (3) TAU alone	ECHO self-help intervention: book and DVDs with carer skills training ECHO plus coaching: 10 sessions per family TAU: psychological treatment plus	Not published yet Primary outcome: ED symptom score and BMI		

(*Continued*)

Table 1. (*Continued.*)

Author(s) (year)	*n*	Inclusion criteria	Setting	Stand-alone or adjunctive treatment	Comparison groups	Dose	Main findings	Additional findings and comments	Study quality
						physical monitoring			
Zucker (2008)	124	Adolescents with AN (age 11–18)	Out-patient	Not known	(1) Skills group for parents that provides psychoeducation for EDs and skills in behaviour management, self-regulation, and emotion regulation *v.* (2) family therapy	Intervention intensity not known	Not published yet Primary outcome: BMI at 12 months		
Interventions for relapse prevention – published									
Godart *et al.* (2012)	60	Adolescents and emerging adults, age 13–21, female sex, DSM-IV diagnosis of AN; aged <19 at illness onset, AN duration ⩽3 years at admission to hospital, no previous FT	Out-patient post-hospitalisa-tion	Adjunct to in-patient treatment	(1) TAU alone *v.* (2) TAU + family therapy (FT)	TAU: out-patient individual and family sessions as needed FT: 90 min sessions every 3–4 weeks over 18 months	TAU + FT was superior to TAU alone on Morgan–Russell outcome categories (primary outcome) and on % of patients achieving a normal BMI and menstruating	FT focused on family dynamics, not on ED symptoms. *Treatment completion definition and rates*: Definition: none provided; FT + TAU: 26/30 (86.7%); TAU: 27/30 (90.0%) *Recovery definition and rates at final follow-up:* Definition: MR good or intermediate outcome; FT + TAU: 12/30 (40%); TAU: 5/29 (17.2%) at 18 months post-randomisation	Moderate
Different treatment settings or intensities – published									
Herpertz-Dahlmann *et al.* (2014)	172	Adolescents (age 11–18), a DSM-IV diagnosis of AN	In-patient or day-patient	Stand-alone	(1) In-patient (IP) treatment *v.* (2) short (3 weeks) IP treatment followed by day-patient (DP) treatment	Patients were discharged from IP or DP when they achieved/maintained their target weight (15^{th}–20^{th} age-adjusted percentiles) for 2 weeks	DP non-inferior to IP regarding primary outcome (mean difference between baseline and 12-month BMI 0·46) in favour of DP (95% CI, −0·11 to 1·02; *p* non-inferiority <0·0001). DP resulted in a mean cost-saving of 20%	This is a non-inferiority trial. DP appears to be a safe and less costly alternative to IP. *Treatment completion definition and rates*: Definition: none provided; IP: 65/75 (86.7%); DP: 62/87 (71.3%) *Recovery definition and rates at final follow-up:* Definition: nono provided; IP: MR good:	High

								19/75 (25.3%); MR intermediate: 14/75 (18.7%); DP: MR good: 25/82 (30.5%); MR Intermediate: 8/82 (9.8%) at 12 months FU	
Madden *et al.* (2015)	82	Adolescents (aged 12–18), a DSM-IV diagnosis of AN	In-patient	Stand-alone	(1) Shorter IP treatment for medical stabilisation (MS) *v.* (2) longer IP treatment for weight restoration (WR)	Refeeding for all patients started with nasogastric feeds. Participants in the MS arm discharged to 20 sessions out-patient FBT if medically stable. Participants in WR arm continued in hospital on supported meals once they were medically stable, until they reached 90% EBW before discharge to 20 sessions out-patient FBT	No difference between groups in primary outcome (number of hospital days following initial admission, at 12-months post-randomisation). More total hospital days used and post-protocol FBT sessions in WR group. Rates of full remission similar in both groups	Prolonged admission to the point of weight restoration had no clinical advantages and was more costly. *Treatment completion definition and rates*: Definition: 20 sessions or achieving treatment goals prior to this (Phase 2 treatment); MS: 36/41 (87.8%); WR 33/41 (80.5%) *Recovery definition and rates at final follow-up:* Definition: EBW > 95% and EDE global score within 1 s.d. of expected norms; MS: 30%; WR: 32.5% at 12 months FU (i.e. approx. 13 months post-randomisation)	Moderate
Different treatment settings or intensities – in progress									
Huss & Kolar (2016)	30	Adolescent AN	Out-patient	Adjunct to TAU	(1) TAU out-patient treatment *v.* (2) TAU plus a smartphone app (mealtime protocols, emotion regulation strategies)	TAU = biweekly out-patient sessions during waiting for in-patient treatment	Not yet published Primary outcome: BMI change after 3 months		
Nutritional interventions – published									
O'Connor *et al.* (2016)	36	10–16 years with a BMI categorised as moderately malnourished and losing weight	In-patient paediatric	Adjunct	Random allocation to (1) start refeeding at 1200 kcal/day *v.* (2) 500 kcal/day ($n = 18$, control).	In both groups energy intake was increased daily by 200 kcal until it was around 80% of estimated	Greater weight gain in high-energy group (mean difference between groups after 10 days of refeeding, −1.2% BMI; 95% CI, −2.4% to 0.0%; $p = 0.05$), but randomised	Refeeding adolescents with higher energy intake appeared safe and led to greater short-term weight gain. No longer term follow-up (beyond 10 days) is given.	Moderate

(*Continued*)

Table 1. (*Continued.*)

Author(s) (year)	*n*	Inclusion criteria	Setting	Stand-alone or adjunctive treatment	Comparison groups	Dose	Main findings	Additional findings and comments	Study quality
						average requirements	groups did not differ in QTc interval and other outcomes	*Treatment completion definition and rates*: 100% of patients completed the 10-day refeeding programmes. *Recovery definition and rates at final follow-up:* Not applicable	
Nutritional interventions – in progress									
Golden (2015)	120	Age 12–24	In-patient	Adjunct	(1) High Calorie Refeeding *v.* (2) Low Calorie Refeeding	High Calorie Refeeding: beginning with 2000 kcal and advanced 200 kcal/day; Low Calorie Refeeding: beginning at 1400 kcal/day and advanced 200 kcal every other day	Not yet published Primary outcome: Clinical remission at 12 months		
Froreich (2016)	84	Females with AN, age 16+	In-patient	Adjunct	(1) Open weighing *v.* (2) 'blind' weighing	In both conditions patients are weighed twice a week. Open weighing: The weight is communicated to and discussed with the patient and this information is used in treatment (e.g. in tailoring the meal plan and/or individual psychotherapy) 'Blind' weighing: Information about the patient's weight is only shared with the treating team, not the patient	Not yet published Primary outcome: mealtime anxiety		

Medication trials-in progress							
Moya (2010)	60	Adolescents (age 12–18), a DSM-IV diagnosis of AN, BMI 14–17.5	In-patient	Adjunct	(1) Aripiprazole *v.* (2) placebo	Aripiprazole 10 mg qds *v.* placebo over 26 weeks	Not yet published Primary outcome: EDs symptoms

Within classes of interventions, studies are ordered by sample size, starting with the largest. EDNOS, eating disorder not otherwise specified; EOT, End of treatment. FU, Follow-up; FBT, family-based treatment; FT, family therapy; ED, eating disorders; MR, Morgan–Russell Scale; IQR, Interquartile range; MFT, multi-family group treatment; PFT, parent-focused treatment; SFT, single-family therapy; SyFT, systemic family therapy; TAU, treatment as usual; ECHO, Expert Carers Helping Others; IP, in-patient treatment; DP, day-patient treatment; MS, medical stabilisation; WR, weight restoration; EBW, expected body weight.

responders' to increase parental self-efficacy regarding refeeding. This has shown promise in a small pilot RCT (Lock *et al.* 2015). Two as yet unpublished trials (Zucker, 2008; Rhind *et al.* 2014) also focus on parental skills training.

Interventions for relapse prevention

One trial found adjunctive post-hospitalisation outpatient family therapy focusing on family dynamics but not symptoms to be superior to treatment-as-usual (TAU) alone in terms of weight gain and other AN symptoms (Godart *et al.* 2012).

Different treatment settings or intensities

Two recent RCTs have examined different treatment settings or intensities for adolescents with AN. One of these showed that day-patient treatment after brief inpatient admission was not inferior to longer inpatient treatment in terms of body weight at 12-months follow-up and regarding serious adverse events (Herpertz-Dahlmann *et al.* 2014). This suggests that day-care is a safe and less costly alternative to longer inpatient treatment for adolescent patients with non-chronic AN. Another RCT yielded similar results, i.e. shorter hospitalisation of adolescents with AN (for medical stabilisation) had similar outcomes to longer hospitalisation (until weight restoration) (Madden *et al.* 2015). A trial evaluating a supportive app whilst waiting for treatment is in progress (Huss & Kolar, 2016).

Nutritional interventions

One small trial in severely underweight adolescents with AN admitted to paediatric in-patient units assessed the impact of two different refeeding regimes (500 *v.* 1200 kcals/per day) on weight gain and refeeding-related complications (O'Connor *et al.* 2016). The high-energy regime led to greater weight gain, but not higher rates of complications. Two further trials of different feeding (Golden, 2015) and weighing regimes (Froreich, 2016) are in progress.

Medication

No medication trials were published during the last 5 years, one study on aripiprazole is in progress (Moya, 2010).

Trials in adults

We identified 11 published trials ($n = 1257$ patients) and eight unpublished trials since the previous review. In published trials, treatment completion rates vary from 56% to 93.3%. In these studies remission/recovery rates range from 13% to 42.9% at last recorded follow-up (12–24 months post-randomisation) (see Table 2).

Individual therapy

Six RCTs have evaluated individual psychotherapies, five of these in out-patients. These include: ED-focused variants of cognitive behavioural therapy (CBT) (four trials); focal psychodynamic psychotherapy (FPT) where therapeutic foci (e.g. intra-personal conflicts, maladaptive interpersonal patterns and difficulties in psychological functioning) are derived from an in-depth psychodynamic interview (Friederich *et al.* 2014) (one trial); the Maudsley Model of Anorexia Nervosa Treatment for Adults (MANTRA; three trials), a novel anorexia-specific psychobiologically informed therapy, centred around a patient manual, which targets cognitive, socio-emotional and interpersonal maintenance factors and meta-beliefs about the utility of AN (Schmidt *et al.*

https://doi.org/10.1017/S0033291717002604 Published online by Cambridge University Press

Table 2. Trials of established treatments in adults or predominantly adult populations

Author(s) (year)	*n*	Inclusion criteria	Setting	Stand-alone or adjunctive treatment	Comparison groups	Dose	Main findings	Additional findings and comments	Study quality
Individual therapies-published									
Outpatient trials									
Zipfel *et al.* (2014)	242	Adults (age ⩾ 18), a DSM-IV diagnosis of (subthreshold) AN, BMI 15 to 18.5 kg/m^2	Out-patient	Stand-alone	(1) CBT-E or (2) FPT *v.* (3) optimised TAU (TAU-O)	CBT-E and FPT: 40 sessions over 10 months. TAU-O: patients were monitored by their family doctor and given contact details for psychotherapists with expertise in the treatment of AN	At EoT and at 12 months FU patients in all groups had increased in BMI (primary outcome) with no difference between groups	Higher recovery rate at 12-months FU in FPT compared to optimised TAU (35% *v.* 13%; $p = 0{\cdot}036$). *Treatment completion definition and rates:* Definition: ⩾27 sessions (i.e. 67.5%); CBT-E: 65/80 (81.3%); FPT: 53/80 (66.3%); TAU-O: N.A. *Recovery definition and rates at final follow-up:* Definition: PSR score of 1 or 2 and BMI > 18.5 kg/m^2 at 22 months post-randomisation; FPT: 34.6%; CBT-E: 21.0%; TAU-O: 13%	High
Schmidt *et al.* (2015, 2016*a*, *b*, *c*)	142	Adults (age ⩾ 18), a DSM-IV diagnosis of AN or EDNOS-AN; BMI < 18.5 kg/m^2	Out-patient	Stand-alone	(1) MANTRA *v.* (2) SSCM	Both groups: 20 once weekly sessions plus four follow-up sessions. Patients with a BMI < 15 kg/m^2 were offered 30 weekly sessions plus follow-ups	No difference between groups in BMI outcomes (primary outcome) at 12 months (EoT) or 24 months post-randomisation. Patients in both groups significantly improved on BMI and a range of other measures	MANTRA was more acceptable to patients and showed an advantage over SSCM in more severely ill patients with a BMI of <17.5 kg/m^2 at baseline. One SSCM patient died. *Treatment Completion definition and rates:* Definition: ⩾15 sessions (i.e. 75%); MANTRA: 54/72 (75%); SSCM 41/70 (58.6%) *Recovery definition and rates at final follow-up:* Definition: EDE global score of <1 s.d. above community mean and a BMI > 18.5 kg/m^2; MANTRA: 18/72 (25%);	High

								SSCM: 13/70 (18.6%) at 24 months post-randomisation	
Byrne *et al.* (2017)	120	Adolescents and adults (age ⩾ 17), a DSM-5 diagnosis of AN; BMI ⩾ 14.0 and < 18.5 kg/m^2	Out-patient	Stand-alone	(1) CBT-E *v.* (2) MANTRA *v.* (3) SSCM	In all 3 groups patients were offered 25–40 sessions over 10 months titrated depending on BMI	No differences between groups in BMI and ED psychopathology (primary outcomes), remission rates, general psychopathology and psychosocial impairment at EoT or FU	Follow-up rates were very low (52.5% at 12 months). *Treatment Completion definition and rates:* Definition: progression through all treatment stages; CBT-E: 26/39 (66.7%); MANTRA: 23/41 (56.1%); SSCM: 23/40 (57.5%) *Recovery definition and rates at final follow-up:* Definition: BMI > 18.5, Global EDE < 1.8 and absence of binge eating/purging behaviours; CBT-E: 12/39 (30.8%); MANTRA: 9/41 (22%); SSCM: 13/40 (32.5%) at 22 months post randomisation	Moderate
Schmidt *et al.* (2012)	70	Adults (age ⩾ 18), a DSM-IV diagnosis of AN; BMI < 18.5 kg/m^2	Out-patient	Stand-alone	(1) MANTRA *v.* (2) SSCM	Both groups: 20 once weekly sessions plus 4 follow-up sessions. Patients with a BMI < 15 kg/m^2 were offered 30 weekly sessions plus follow-ups	No differences between groups in BMI (primary outcome) and other continuous outcomes at 6 or 12 months post-randomisation. Patients in both groups improved significantly over time	This was a pilot trial which used an early version of the MANTRA manual. *Treatment Completion definition and rates:* not reported *Recovery definition and rates at final follow-up:* Definition: EDE global score <1 s.d. above community mean (i.e. below 1.74) and BMI > 18.5 kg/m^2; MANTRA: 4/29 (13.8%); SSCM: 5/27 (18.5%) at 12 months post-randomisation	High
Touyz *et al.* (2013)	63	Severe and enduring DSM-IV AN (>7 years of illness	Out-patient	Stand-alone	(1) CBT *v.* (2) SSCM	30 individual sessions over 8 months in both groups. CBT and SSCM were adapted to the needs of	Significant improvements in both groups, no differences on primary (quality of life) or secondary	One patient allocated to CBT died during follow-up. *Treatment Completion definition and rates:*	High

(*Continued*)

Table 2. (*Continued.*)

Author(s) (year)	*n*	Inclusion criteria	Setting	Stand-alone or adjunctive treatment	Comparison groups	Dose	Main findings	Additional findings and comments	Study quality
		duration); BMI < 18.5 kg/m^2				patients with severe and enduring illness	outcomes at EoT. Greater improvements on ED symptoms and readiness to change at 12 months in CBT	Definition: ⩾15 sessions; SSCM: 30/33 (90.9%); CBT: 28/30 (93.3%) *Recovery definition and rates at final follow-up:* not reported	
In-patient trials									
Dalle Grave *et al.* (2013)	80	Adolescents and adults (age 14–65 years), DSM-IV diagnosis of AN	In-patient	Adjunct to in-patient treatment	(1) Enhanced focused CBT (CBT-Ef) *v.* (2) enhanced broad CBT(CBT-Eb)	CBT-Ef focuseson ED pathology whereas CBT-Eb also addresses mood intolerance, perfectionism, low self-esteem and interpersonal difficulties. CBT sessions givenduring 13 weeks in-patient and 7 weeks day-patient treatment	Patients in both programmes showed significant improvements in weight, ED and general psychopathology, no differences between groups	*Treatment Completion definition and rates:* Definition: none provided; CBT-Ef:37/42 (88.1%); CBT-Eb:35/38 (92.1%) *Recovery definition and rates at final follow-up:* Definition: BMI > 18.5 at 17 months post-randomisation; CBT-Ef: 18/42 (42.9%); CBT-Eb: 14/38 (36.8%)	Moderate
Individual therapy trials – in progress									
Cardi *et al.* (2015)	150	Adolescents and adults, a DSM-5 diagnosis of AN (age ⩾ 16)	Out-patient	Adjunct to out-patient treatment	(1) Recovery-MANTRA (guided self-care plus peer mentorship) plus TAU *v.* (2) TAU alone	6 sessions of Recovery-MANTRA over 6 weeks	Not yet published Primary outcome: BMI		
Nevonen (2015)	80	Adolescents and adults with AN (age 17–25)	Out-patient	Stand-alone	(1) Individual CBT *v.* (2) Family therapy	60 sessions (60 min) *v.* 40 sessions (90 min)	Not yet published Primary outcome: BMI		
Interventions for relapse prevention-published									
Fichter *et al.* (2012)	258	Adolescents and adults (age ⩾ 16), aDSM-IV diagnosis of AN; weight gain of 1–2 BMI points during in-patient	Out-patient; post-hospitalisation	Adjunct to out-patient treatment	(1) Internet-based CBT relapse prevention *v.* (2) TAU	Internet-based CBT delivered over 9-months post-discharge (9 modules, online self-monitoring, electronic message boards and monthly	No difference between groups on BMI change at EoT (ITT), minor differences favouring internet based CBT. A higher proportion of CBT patients needed	9-month follow-up data only reported for completers. CBT completers continued to gain weight during FU whereas partial completers were no different from TAU	Moderate

		treatment, no previous history of prolonged in-patient admissions without weight gain				1-h online group 'chats' with a therapist)	additional in-patient treatment up to EoT (21% *v.* 10%; p = 0.047)	participants. *Treatment Completion definition and rates:* Definition: ⩾4 of 9 sessions; Internet-based CBT: 97/128 (75.8%); Control group: 122/130 (93.8%) *Recovery definition and rates at final follow-up:* Not reported
Sternheim (2017)	41	Adolescents and adults (age ⩾ 16), post-inpatient treatment	Out-patient; post-hospitalisation	Adjunct to TAU	(1) Manual-based e-mail guided self-care plus TAU *v.* (2) TAU alone	The manual was based on MANTRA and was adapted for a post-hospitalisation population	No difference between groups in outcomes at 6 months post-randomisation. At 12 months, higher BMI and lower levels of depression and anxiety in self-care group. Rehospitalisation rates were similar in both groups	This is a feasibility study. Therefore no primary outcome was defined a priori. *Treatment Completion definition and rates:* not reported *Recovery definition and rates at final follow-up:* not reported
Interventions for relapse prevention- in progress								
Treasure (2016)	380	Adolescents or adults (age ⩾ 17), a DSM-5 diagnosis of AN	In-patient or day-care	Adjunct to TAU	(1) Web-based intervention for patients and carers *v.* (2) web-based symptom monitoring and feedback.	Web-based intervention for patients and carers combining a workbook, library of short video-clips, eight online group forum sessions and up to six joint Skype sessions (patient-carer) with a health professional. Control arm: Regular online symptom monitoring and visual feedback of scores.	Not yet published Primary outcome: Patients' depression, anxiety and stress levels	
Dalle Grave (2012)	80	Female adolescents and adults (age 13–65) with weight	In-patient	Adjunct to TAU	(1) Group based (eight-session) relapse prevention intervention +	The relapse prevention programme is based on cognitive dissonance theory	Not yet published. Primary outcome: BMI at 1 year	

(*Continued*)

Table 2. (*Continued.*)

Author(s) (year)	*n*	Inclusion criteria	Setting	Stand-alone or adjunctive treatment	Comparison groups	Dose	Main findings	Additional findings and comments	Study quality
		recovered AN; BMI ⩾ 18.5			TAU *v.* (2) TAU alone				
Carer or family interventions – published									
Hibbs *et al.* (2015); Magill *et al.* (2016)	178	Adolescents and adults with AN; age ⩾ 13 together with their carers	In-patient and post-hospitalisation	Adjunct to TAU	(1) Carers skills training (ECHO) + TAU *v.* (2) TAU alone	Carers skills training involved carers being given a book, DVDs and five telephone coaching sessions per caregiver, i.e. up to 10 sessions per family. Phone sessions were up to 40 min long and occurred every other week	No difference between groups in time to relapse (primary outcome). Patients whose caregivers received the ECHO intervention had significantly reduced ED psychopathology and improved quality of life at 6 months (both small effects) and reduced in-patient bed days (7–12 months post-discharge)	Caregivers in the skills training group had reduced carer burden, expressed emotion and time spent care giving compared to those in the TAU group at 6 months, but effects lessened at 12 months. At 24 months FU patients and carers in the skills training group showed further improvement *Treatment Completion definition and rates:* Definition: 4/10 calls (per family) or 75% of the book read; 91/134 (67.9%) *Recovery definition and rates at final follow-up:* not reported	High
Whitney *et al.* (2012)	48	Adults (age ⩾ 18) with AN	In-patient	Adjunct to in-patient treatment	(1) Family workshops plus TAU *v.* (2) individual family therapy plus TAU	Family workshops: two families seen over 3 days. Individual family therapy: Approx. 18 treatment sessions (1–2 h each)	Patients in both groups improved similarly in BMI (primary outcome) with no difference between groups at EoT or FU	Small sample size, insufficient sample description, no ITT analysis, no trial registration. *Treatment Completion definition and rates:* Definition: none provided; Family workshops: 22/25 (88%); Individual family therapy: 20/23 (87%) *Recovery definition and rates at final follow-up:* Not reported	Low
Carer or family interventions – in progress									
Schmidt (2017)	302	Adolescents or adults (age ⩾	Out-patient	Adjunct to TAU	(1) We Can (Web-based Skills Training	Eight session web-intervention plus weekly support for 3	Not published yet Primary Outcome: Carer depression and		

		16) with AN and their carers			for Carers of People with AN delivered on its own or (2) with support from a moderated chat group or (3) with support from a therapist via email	months delivered in addition to TAU	anxiety. Patient outcomes are secondary		
Bulik (2012)	100	Adults with AN (age ⩾ 18), BMI 15 to 19 kg/m^2, and their partner	Out-patient	Stand-alone	(1) Cognitive behavioural couples therapy + individual CBT *v.* (2) individual CBT only	44 sessions both	Not published yet Primary outcomes: BMI and EDE Global Score		
Medication trials – published									
Powers *et al.* (2012)	15	Adult (age ⩾ 18) males and females, a DSM-IV diagnosis of AN	Not specified	Adjunct to TAU	(1) Quetiapine plus TAU *v.* (2) placebo plus TAU	8 weeks medication, dosage or tapering not described	No difference between quetiapine and placebo on core ED symptoms (primary outcome) or weight gain	Small effect sizes suggest that a higher number of participants would not increase significant differences between groups. *Treatment Completion definition and rates:* Definition: none provided; Placebo: 6/9 (66.7%); Quetiapine: 4/6 (66.7%) *Recovery definition and rates at final follow-up:* Not reported	Low
Medication trials – in progress									
Attia (2010)	152	Adults with AN	Out-patient	Stand-alone	(1) Olanzapine *v.* (2) placebo	10 mg/16 weeks	Not yet published Primary outcome: BMI		
Trials of treatment setting – in progress									
Attia (2008)	41	Adolescents and adults with a DSM-IV diagnosis of AN (age ⩾ 16); BMI < 18.5	In-patient	Stand- alone	(1) Inpatient treatment until full weight recovery + 2 weeks weight maintenance *v.* (2) stepped care (initial in-patient treatment followed by day-care, when patient reaches		Not yet published Primary outcome: BMI		

(*Continued*)

Table 2. (*Continued.*)

Author(s) (year)	*n*	Inclusion criteria	Setting	Stand-alone or adjunctive treatment	Comparison groups	Dose	Main findings	Additional findings and comments	Study quality
					a number of health benchmarks or if these are not reached automatically after 28 days of inpatient treatment)				

Within classes of interventions, studies are ordered by sample size, starting with the largest. TAU, treatment as usual; CBT-E, Enhanced Cognitive Behavioural Therapy; FPT, Focal Psychodynamic Therapy; PSR, Psychiatric Status Rating Scale; SSCM, specialist supportive clinical management; MANTRA, Maudsley Model of Anorexia Treatment for Adults; ITT, intention to treat analysis; EoT, end of treatment; FU, Follow-up; EDE, Eating Disorders Examination; ED, eating disorders; BMI, Body Mass Index; ECHO, expert carers helping others.

2014); and Specialist Supportive Clinical Management (SSCM; four trials), a pragmatic a theoretical treatment (McIntosh *et al.* 2006).

The largest of these trials, the ANTOP study, compared (a) an ED specific form of CBT (enhanced CBT; CBT-E) and (b) FPT with (c) an optimised form of TAU (Zipfel *et al.* 2014). All three treatments were similarly effective in terms of BMI increase. CBT-E was associated with more rapid weight gain than TAU, and FPT had a more favourable global outcome at follow-up than TAU. FPT was also the most cost-effective option (Egger *et al.* 2016).

Two other trials compared MANTRA with SSCM (Schmidt *et al.* 2012, 2015, 2016*c*), a third compared these treatments with CBT-E (Byrne *et al.* 2017), and a fourth trial compared a different version of CBT with SSCM in patients with severe and enduring AN (SEED-AN) (Touyz *et al.* 2013). Finally, one trial compared two different versions of CBT-E in in-patients with AN (Dalle Grave *et al.* 2013).

Overall, none of these specialised psychotherapies were clearly superior to each other or to SSCM. Some advantages over optimised TAU or SSCM have been reported for CBT-E, FPT and MANTRA in terms of the speed of weight gain (Zipfel *et al.* 2014), long-term global outcomes (Touyz *et al.* 2013; Zipfel *et al.* 2014) and weight gain in patients with a more severe form of the illness (Schmidt *et al.* 2012, 2015), respectively. However, the overall picture remains that there is no single psychotherapy that is substantially superior to another (Hay, 2013; Kass *et al.* 2013; Le Grange, 2016). All mentioned psychological treatments lead to significant improvements in body weight and reductions in AN symptoms, distress levels and clinical impairment. Two further trials of individual therapies are in progress (Cardi *et al.* 2015; Nevonen, 2015).

Relapse prevention

One small trial found addition of manual-based e-mail supported guided self-care to show promise compared with TAU alone (Sternheim, 2017). One large trial tested internet-based CBT added to TAU *v.* TAU alone in the post-hospitalisation phase of treatment (Fichter *et al.* 2012). Whilst there was no difference between groups on the primary outcome (weight gain) in intention-to-treat analysis, CBT-completers showed greater BMI improvement than those receiving TAU only. Two further trials of relapse prevention are in progress, one of them assessing a web-based relapse prevention programme focusing on both patients and carers (Treasure, 2016), the other using a group-based approach (Dalle Grave, 2012).

Carer interventions

Two trials tested interventions for carers and reported outcomes in patients. An exploratory RCT compared family workshops with individual family work and found similar improvements in patients' body weight and carer's distress in both conditions (Whitney *et al.* 2012). A second large-scale trial compared a brief post-hospitalisation carers skill intervention (delivered by book, DVD and telephone coaching) added to TAU with TAU alone (Hibbs *et al.* 2015; Magill *et al.* 2016). There were no statistically significant effects of the intervention in terms of the primary outcomes (patient relapse; caregiver distress), although differences were in the anticipated direction. Effects for all secondary outcomes (including bed usage) for both caregiver and patient were small, but all favoured the skills training group. Two further trials are in progress (Bulik, 2012; Schmidt, 2017).

https://doi.org/10.1017/S0033291717002604 Published online by Cambridge University Press

Table 3. Emerging treatments

Author(s) (year)	*n*	Inclusion criteria	Setting/format	Stand-alone or adjunctive treatment	Comparison groups	Main findings	Additional findings and comments
CRT trials-published							
Dingemans *et al.* (2014)	82 ED patients (proportion of AN patients not reported but all analysed participants had a BMI < 19)	Adult/adolescents with a DSM-IV diagnosis of an ED; age ⩾ 17	In-patient/ individual format	Adjunct to TAU	(1) 10 sessions CRT + TAU *v.* (2) TAU only	CRT + TAU superior to TAU only in improving ED-related quality of life from baseline to EoT and in reducing ED psychopathology (primary outcome) from baseline to 6-month follow-up	No differences between groups on neuropsychological functioning
Davies *et al.* (2012)	81	Adults with a DSM-IV diagnosis of AN; age ⩾ 18	In-patient/ individual format	Adjunct to TAU	(1) 10 sessions CREST + TAU *v.* (2) TAU only	At EoT there were no group differences in BMI (primary outcome) or set-shifting, central coherence and emotion recognition. No follow-up data reported	This was a non-randomised controlled clinical trial, not an RCT
Lock *et al.* (2013)	46	Adults/adolescents with a DSM-IV diagnosis of AN; age ⩾ 16; BMI ⩽ 90 percentile	Out-patient/ individual format	Adjunct to CBT	(1) 8 sessions CRT + 16 sessions CBT *v.* (2) 24 sessions CBT	By session 8, lower drop-out rate (primary outcome) and (in part) greater improvements in cognitive set-shifting and central coherence in the CRT condition. No group differences in attrition rate, set-shifting, central coherence and ED psychopathology at EoT, 6- and 12-month follow-up	
Brockmeyer *et al.* (2014)	40	Adults with a DSM-IV diagnosis of AN; age ⩾ 18	In- and out-patient individual format	Adjunct to TAU	(1) 30 sessions CRT + TAU *v.* (2) 30 sessions NNT + TAU	CRT superior to NNT in terms of improved set-shifting (primary outcome) at EoT. Clinical outcomes (weight, ED symptoms) not reported. Follow-up data not reported	Treatment completers only were analysed. 11/20 (55%) in CRT group and 14/20 (70%) in control group included in analysis
Steinglass (2015)		This trial is detailed below under exposure treatments					
CRT-trials – in progress							
Brockmeyer (2015)	168	Adults/adolescents with a DSM-5 diagnosis of (atypical) AN; age ⩾ 17	In-patient/ group format	Adjunct to TAU	(1) 10 sessions CRT + TAU *v.* (2) 10 sessions art therapy + TAU	Not yet published Primary outcomes: BMI, ED psychopathology, and ED-related quality of life	
Ringuenet (2013)	120	Adult/Adolescent females with a DSM-IV		Adjunct to TAU	(1) 10 sessions CRT + TAU *v.* (2) 10 sessions SHAM	Not yet published Primary outcomes:	

(*Continued*)

Table 3. (*Continued.*)

Author(s) (year)	*n*	Inclusion criteria	Setting/format	Stand-alone or adjunctive treatment	Comparison groups	Main findings	Additional findings and comments
		diagnosis of AN; age 15–40	In-patient/ individual format		(physical activity, emotion recognition, interpersonal functioning) + TAU	Neuropsychological functioning and clinical outcomes (Morgan–Russell Scales)	
Timko (2016)	80	Adolescents with a DSM-5 diagnosis of (sub-threshold) AN; age 12–18	In-patient/not reported	Adjunct to TAU	(1) 6–8 sessions CRT + 3–4 sessions Teach the Parent + TAU *v.* (2) 6–8 sessions CRT + 3–4 sessions Family Fun Time + TAU *v.* (3) TAU only	Not yet published Primary outcomes: treatment engagement and motivation	
Van Passel *et al.* (2016)	130 (64 with AN)	DSM-IV diagnosis of (sub-threshold) AN or OCD	Not reported/ individual format	Adjunct to CBT	(1) 10 sessions CRT + CBT *v.* (2) 10 sessions supportive counselling therapy + CBT	Not yet published Primary outcome: Eating Disorder Examination Questionnaire	
Asch (2015)	60	Female adolescents with a DSM-IV diagnosis of AN-R; age 8–16	In- and out-patient/ single + group format	Adjunct to TAU	(1) 10 sessions CRT + TAU *v.* (2) 10 sessions relaxation therapy + TAU	Not yet published Primary outcome: cognitive flexibility	
Cook (2012)	40	Adult women with an ICD-10 diagnosis of (atypical) AN; age ⩾ 18	Out-patient/ individual format	Adjunct to CBT	(1) Six sessions CRT + 6 sessions CBT *v.* (2) 6 sessions CBT only	Not yet published Primary outcome: Eating Disorder Examination Questionnaire	
Lock (2014)	30	Adolescents with DSM-IV AN (age 11–19)	Out-patient	Adjunct to FBT	(1) FBT + CRT *v.* (2) FBT + art therapy (15 sessions of each)	Not yet published Primary Outcome: Full remission from AN	
Exposure-based treatment trials – published							
Steinglass *et al.* (2014)	32	Adults/adolescents with former AN (weight-restored), BMI ⩾ 18.5, age 16–45	In-patient/ mainly individual format	Adjunct to behaviour therapy	(1) 12 sessions (ood) Exposure and Response Prevention + Behaviour therapy *v.* (2) 12 sessions CRT + Behaviour Therapy	Target intervention led to greater increase in caloric intake during test meal (primary outcome); attrition rate 6%	Neurocognitive or clinical outcomes (BMI, ED symptoms) not reported. No follow-up data
Levinson *et al.* (2015)	36	Adults with former DSM-IV AN (weight restored)	Partial hospitalisation	Adjunct	TAU + Exposure Therapy plus (1) 250 mg D-cycloserine ($n = 20$) or (2) placebo ($n = 16$). Participants completed psycho-education and four sessions (45 min) of group exposure therapy (2–5 participants supervised by a therapist during their lunch time meal which was standardised). Medication was given prior to the first three exposure sessions	Participants in the D-cycloserine group had significantly greater weight gain than those in the placebo group after the four exposure sessions. At 1-month follow-up BMI in the D-cycloserine group continued to increase, whereas in the placebo group it decreased. In both groups, mealtime anxiety decreased over time	

Exposure-based treatment trials – in progress							
Pham-Scottez (2011)	100	Adults with AN; age ⩾ 18; BMI ⩾ 16	In-patient/ individual format	Adjunct to TAU	(1) 10 sessions correction of body size perception with Anamorphic Micro software + TAU *v.* (2) 10 sessions of conventional body image therapy + TAU	Not yet published Primary outcome: Body Shape Questionnaire	
Hildebrandt & Sysko (2016)	90	Adolescents with AN (age 12–18)	Not reported	Not reported	(1) Six sessions of interoceptive exposure *v.* (2) Six sessions of Family Based Therapy with weight gain control. During Interoceptive exposure, participants are provided with a meal replacement shake of 'unknown' kcal or macronutrient content and are asked to mindfully observe the sensations (aversive taste, texture, bloating, icky feeling) and associated emotional states (i.e. disgust) with the empathetic support of parents/therapist in session	Not yet published Primary outcome: Change in the emotional responses from facial muscle movements to food pictures and non-food pictures as measured with fMRI-EMG	
Khalsa (2017)	50	Adults/adolescents with a current or lifetime DSM-5 diagnosis of AN; BMI 17–35	Not reported	Not reported	(1) Infusions of isoproteronol *v.* (2) saline as enhancers of exposure therapy (number of planned sessions not reported)	Not yet published Primary outcomes: Anxiety and sensation intensity (heart beat and breathing)	Isoproterenol is a sympathmimetic agent. This will be used to repeatedly trigger cardiorespiratory sensations and anxiety during meal anticipation to facilitate the development of a reduction of the anxiety/ fear response
Neuromodulation trials – published							
McClelland *et al.* (2016)	60	Adults (⩾ age 18) with a DSM-5 diagnosis of AN; BMI 14–18.5	Out-patient	Adjunct to TAU	(1) TAU + 1 session of real *v.* (2) TAU + sham rTMS applied to the DLPFC	In completers (n = 49), real rTMS led to greater short-term reduction in ED symptoms and improved reward-related decision-making (delay discounting)	This is a proof of concept trial
Lackner *et al.* (2016)	22	Adolescents with a DSM-5 diagnosis of AN (age 12–18)	In- or out-patient	Adjunct to TAU	(1) 10 sessions of EEG Alpha-neurofeedback twice a week over 5 weeks + TAU *v.* (2) TAU alone	Significant training effects were shown in eating behaviour, emotion regulation, and in some EEG parameters	Rationale: alpha neurofeedback is supposed to be stress reducing
Neuromodulation trials – in progress							
Downar & Woodside (2016)	240	Adults with AN, binge-purge type or BN; age 18–65; Failed to	Out-patient	Not reported	(1) 20 Hz *v.* (2) 1 Hz *v.* (3) sham rTMS targeting the DMPFC, delivered twice	Not yet published Primary outcome: Weekly binge-purge frequency on	

(*Continued*)

Table 3. (*Continued.*)

Author(s) (year)	*n*	Inclusion criteria	Setting/format	Stand-alone or adjunctive treatment	Comparison groups	Main findings	Additional findings and comments
		achieve clinical response to at least one pharmacological or behavioural treatment in current episode			daily, 5 days a week over 3 weeks	the EDE at EoT and follow-up (15 weeks post-randomisation)	
Vicari (2015)	160	Adolescents aged 13–18 with either a DSM-5 diagnosis of AN (BMI below 5th percentile) or BED with BMI > 85th percentile	Not reported	Adjunct to TAU	AN: (1) TAU + excitatory tDCS over left prefrontal cortex (anode left/cathode right) *v.* (2) TAU + sham BED: (1) TAU + excitatory tDCS over right prefrontal cortex (anode left/cathode right) *v.* (2) TAU + sham Both groups: 18 treatment sessions over 6 weeks	Not yet published Primary outcome: Proportion of patients in each treatment arm with change of ⩾1 point of the total score of the EDI-3 at 6 weeks	The hypothesis is that tDCS may alter/reset inter-hemispheric balance in these two disorders and thus improve ED behaviours
Chastan (2012)	54	Restrictive AN (age 18–80) with BMI < 16 and illness duration between 1 and 3 years	Out-patient	Adjunct to TAU	(1) TAU + rTMS applied to the inferior parietal cortex (2000 ten-Hz stimulations per session, applied at 90% of the resting motor threshold) *v.* (2) TAU + sham rTMS; Both groups: 10 sessions in 2 weeks	Not yet published Primary outcome: Body Shape Questonnaire at EoT	
Bartholdy *et al.* (2015)	30	Adults with a DSM-5 diagnosis of AN; BMI 14–18.5; ⩾1 previous failed adequate course of treatment, illness duration ⩾3 years	Out-patient	Adjunct to TAU	(1) TAU + 20 sessions real *v.* (2) TAU + sham rTMS applied to the DLPFC	Not yet published Primary outcome: none defined as this is a feasibility trial	
Gao (2015)	10	Adults with a DSM-IV diagnosis of AN (age 18–65); BMI < 16	Not reported	Not reported	(1) Continuous deep brain stimulation of bilateral nucleus accumbens *v.* (2) fluoxetine	Not yet published Primary outcome: BMI at 6 months	
Medication trials – published							
Andries *et al.* (2014)	25	Adult (age ⩾ 18) women with a DSM-IV diagnosis of AN, ⩾5 years illness duration	In-patient and out-patient	Adjunct to TAU	(1) Dronabinol 2.5 mg twice daily over 1 month + TAU *v.* (2) placebo + TAU. Patients were randomly assigned to one of two treatment sequences dronabinol-placebo or placebo dronabinol. There was a 4-week washout period between the two treatment phases	Regardless of the drug sequence received, the participants gained 0.76 kg (95% CI 0.23–1.29, $t = 2.98$, df = 22, $p < 0.01$) more during the first treatment period than the second period	
Medication trials – in progress							
Russell (2016)	120	Adult/adolescent AN patients (age 16–50)	In-patient	Adjunct to TAU	(1) TAU + Intra-nasal oxytocin (36IU/day; one spray in each nostril	Not yet published Primary outcome: Eating	

		needing refeeding in hospital			morning and night) *v.* (2) TAU + placebo nasal spray over 28 days	Concern subscale of the EDE	
Piróg-Balcerzak (2012)	60	Adolescents with a DSM-IV or ICD-10 diagnosis of AN (age 12–19)	In-patient	Adjunct to TAU	(1) TAU + Omega-3 Fatty Acids Oral Capsules *v.* (2) TAU + Placebo over 10 weeks	Not yet published Primary outcome: BMI at day 70	
Bonny (2013)	40		In-patient	Adjunct to TAU	(1) TAU + 4 fish oil capsules (eicosapentaenoic acid) (2120 mgs)/ docosahexaenoic acid (600 mg) daily *v.* (2) TAU + 4 placebo pills daily over 12 weeks	Not yet published Primary outcome: fish oil tolerability	Rationale: improvement in anxiety and depression
Other interventions – published							
Parling *et al.* (2016)	43	Adults with a DSM-IV diagnosis of AN or EDNOS-AN; age ⩾ 18	Out-patient, after day-care treatment/not reported	Stand-alone	(1) 19 sessions ACT *v.* (2) TAU	Both groups improved in terms of BMI and ED psychopathology (primary outcomes); no group differences at EoT or follow-up (6, 12, 18, 24 months, 5 years)	Only 58.3% of patients completed ACT. One TAU patient died from suicide
Smith *et al.* (2014)	26	Adolescents/adults with AN (age ⩾ 15)	In-patient	Adjunct to TAU	(1) TAU + Acupuncture *v.* (2) TAU + acupressure and massage. Twice weekly sessions for 3 weeks followed by once weekly sessions for 3 weeks	Patients in both groups improved with no difference on primary (BMI) or secondary outcomes	
Other interventions – in progress							
Werthmann (2015)	50	Adults with a DSM-5 diagnosis of AN	Out-patient	Adjunct to TAU	(1) TAU + 3 sessions of computerised attention training to food stimuli *v.* (2) TAU + 3 sessions sham training	Not yet published Primary outcome: attention bias towards food cues assessed with dot probe task	
Steinglass (2015)	20	Adults with a DSM-5 diagnosis of AN; age 18–45	In-patient	Adjunct to TAU	(1) TAU + 12 × 45 min sessions of Supportive Psychotherapy or (2) TAU + REACH (focused on changing routines or habits that have become part of the ED) over 4 weeks	Not yet published Primary outcome: Habit strength assessed by self-report	

AN, anorexia nervosa; BN, bulimia nervosa; TAU, treatment as usual; CRT, cognitive remediation therapy; ED, eating disorders; EoT, end of treatment; CBT, Cognitive Behavioural Therapy; NNT, non-specific neurocognitive therapy; CREST, Cognitive Remediation and Emotion Skills Training; BMI, Body Mass Index; rTMS, repetitive transcranial magnetic stimulation; DLPFC, dorsolateral prefrontal cortex; EEG, electroencephalography; EDE, Eating Disorder Examination; BED, Binge Eating Disorder; EDI-3, Eating Disorder Inventory-3; ACT, Acceptance and Commitment Therapy; EDNOS, eating disorder not otherwise specified.

Medication

A small trial of quetiapine *v.* placebo found no differences in outcome between groups (Powers *et al.* 2012). An as yet unpublished large scale RCT of olanzapine *v.* placebo in adult outpatients with AN found olanzapine to be superior to placebo in terms of weight gain, but without any effect on illness preoccupations (Attia, 2010, 2016).

Treatment settings

No trial was published during the period of interest, but one study is in progress (Attia, 2010).

Process outcomes

One avenue for improving psychological treatments is to focus on the therapeutic process in order to identify elements that might be particularly important for the success of treatment. A recent systematic review (Brauhardt *et al.* 2014) summarised the available literature on process-outcome research across all EDs and addressed issues such as treatment settings and modalities, symptom-orientation, motivational enhancement, therapeutic alliance, response patterns, attendance and duration of treatment. Here, we focus instead on within- and between-session processes and patient/therapist views.

Between-session processes

Secondary analyses of the ANTOP study (Zipfel *et al.* 2014) showed that less favourable treatment outcomes were associated with patients' reporting greater negative between-session preoccupation with their therapy/therapist (Hartmann *et al.* 2016). Further research is needed to clarify whether this is a result of less effective therapeutic intervention or of a more complex and severe form of the disorder.

In-session processes

A study applying computerised quantitative text-analysis to verbatim transcripts of therapy sessions from the ANTOP study, found that patients who expressed more negative emotions during mid-treatment had more favourable end-of-treatment and follow-up BMI and ED-symptom outcomes (Friederich *et al.* 2017). These findings support the idea that increased emotional processing during psychotherapy for AN reduces maladaptive affect regulation mechanisms (e.g. dietary restraint). Importantly, these effects were independent from treatment condition, AN subtype, and illness duration, suggesting that the enhanced expression of negative feelings in psychotherapy constitutes a robust universal action mechanism underlying successful AN treatment.

Patient and therapist views on psychotherapy

Incorporating patients' views on helpful and less helpful elements of psychotherapy can generate valuable ideas for refining existing treatment approaches. Thematic analyses of patients' and therapists' views on MANTRA highlighted strengths of the approach (e.g. clear structure, flexibility and individual tailoring of the treatment) and also yielded testable hypotheses about what might work best for whom, and how this treatment could be improved (Waterman-Collins *et al.* 2014). A complementary analysis of the patients' views echoed these views (Lose *et al.* 2014). Furthermore, written case formulations of therapists delivering MANTRA were rated for their quality. Regression analyses showed that greater adherence to the treatment model was related to better treatment acceptability and greater therapist reflectiveness/respectfulness to greater reductions in ED symptoms (Allen *et al.* 2016). Other qualitative studies of AN treatment found that patients link a good therapeutic relationship to therapist characteristics, such as acceptance, vitality, challenge and expertise (Gulliksen *et al.* 2012). In another study, 132 ED patients (not only AN) and 49 ED experts were asked which elements of treatment they consider to be helpful and effective in facilitating recovery (Vanderlinden *et al.* 2007). Views among patients were divergent but overlapped with those of therapists. Many different factors were considered important. Patients with restricting type AN considered three elements as more important than other patients: gaining autonomy, reducing social isolation and having family support.

PART II: Review of emerging treatments

Here, we review novel treatment approaches that have not yet been tested in large-scale RCTs but where there is at least one published feasibility or pilot RCT or where there are proof-of-concept studies and/or cases series and the approach is currently being tested in at least one registered RCT (see Table 3). We identified 11 published and 20 ongoing trials. These can broadly be divided into those that: (a) have been translated from basic research and address specific neurocircuit functions considered to underlie core aspects of AN psychopathology; (b) those that are more broad-based; and (c) a small number of miscellaneous other studies.

Treatments targeting neurocircuit functions

Cognitive remediation therapy (CRT)

Neuropsychological inefficiencies are common in AN, in particular poor cognitive set-shifting (Wu *et al.* 2014) and weak central coherence (extreme attention to detail at the expense of the bigger picture) (Lang *et al.* 2014) [for review see (Lindvall Dahlgren & Rø, 2014; Tchanturia *et al.* 2014; Danner *et al.* 2015)]. CRT aims to improve these basic cognitive functions by using a range of exercises designed to strengthen cognitive flexibility and holistic information processing (e.g. switching between different perspectives or rules in visual illusions or Stroop tasks, increasing levels of abstraction by summary tasks) and metacognitive elements (e.g. thinking about one's thinking, reflecting on pros and cons of thinking styles and impact on life). Five small to medium-sized trials have been published. These vary in populations, CRT dose (8 to 30 sessions), comparison treatments (CBT, TAU, exposure treatment, non-specific neurocognitive training) and primary outcomes (set-shifting, ED symptoms, test meal consumption, treatment drop-out).

Two studies found differential short-term improvements in neurocognition for CRT *v.* comparison treatment (Lock *et al.* 2013; Brockmeyer *et al.* 2014). Secondary analyses suggested that CRT in AN may be effective in improving the neural mechanisms underlying poor cognitive flexibility, as it was found to be associated with increased striatal activation during task switching and activation in the dorsolateral prefrontal, sensorimotor and temporal cortex during response inhibition (Brockmeyer *et al.* 2016*b*). One trial of CRT plus TAU *v.* TAU alone in in-patients with either AN or bulimia nervosa (Dingemans *et al.* 2014) found greater improvement in quality of life at end of treatment and greater improvement in ED symptoms at 6 months follow-up. A fourth trial compared CRT to exposure treatment and found less improvement in food intake

https://doi.org/10.1017/S0033291717002604 Published online by Cambridge University Press

in a test meal in CRT (Steinglass *et al.* 2014). A variant of CRT that includes socio-emotional skills training, *Cognitive Remediation and Emotion Skills Training* (CREST), was compared against TAU in a clinically controlled trial in in-patients, but did not show any benefits in terms of neurocognitive, socio-emotional or ED outcomes (Davies *et al.* 2012).

Taken together, these findings are promising but well-designed large scale studies of CRT are needed to assess the clinical utility of CRT in AN further. Several such trials are in progress (Cook, 2012; Ringuenet, 2013; Lock, 2014; Brockmeyer, 2015; Timko, 2016; van Passel *et al.* 2016).

Exposure-based therapy

Abnormalities in fear conditioning, possibly partly related to low oestrogen, are thought to be causally implicated in AN (Guarda *et al.* 2015). In line with this thinking, exposure therapy to illness-related stimuli (food, body, exercise) may be a promising treatment (Koskina *et al.* 2013). Whilst early studies using food exposure to treat EDs were conducted nearly 40 years ago, in the treatment of AN, food exposure was only recently tested in a small RCT (Steinglass *et al.* 2014). In this trial exposure therapy lead to increased caloric intake in a test meal and reduced meal-time anxiety compared with CRT. One further RCT of food exposure in adolescents with AN is in progress (Hildebrandt & Sysko, 2016).

Preliminary evidence from an un-controlled study and a small RCT further suggests that augmentation with D-cycloserine, an *N*-methyl-D-aspartate receptor agonist known to facilitate extinction learning, may improve the effects of exposure and response prevention on weight gain in AN (Steinglass *et al.* 2007; Levinson *et al.* 2015). Ongoing randomised [see Table 3, (Khalsa, 2017)] or open-label studies (Guarda, 2016) use the sympathomimetic agent isoproterenol or oestradiol to augment exposure training in AN.

An alternative target for exposure therapy in AN is body-related fear and anxiety, with preliminary studies suggesting that *in-vivo* body image exposure (Koskina *et al.* 2013) or delivered using novel techniques such as virtual reality (Keizer *et al.* 2016; Gutiérrez-Maldonado *et al.* 2010; Ferrer-Garcia & Gutierrez-Maldonado, 2012) lead to short-term improvements in mood, self-esteem and body-image-related symptoms. Clinical trials on body image exposure in patients with AN are lacking, although one ongoing trial is evaluating the use of morphing techniques (Pham-Scottez, 2011).

Neuromodulation treatments

Improved understanding of the neurocircuitry involved in AN (Lipsman *et al.* 2013*b*) has given rise to the use of neuromodulation treatments, such as deep brain stimulation (DBS), repetitive transcranial current stimulation (rTMS), transcranial direct current stimulation (tDCS) and neurofeedback (Bartholdy *et al.* 2013; Lipsman *et al.* 2013*a*; McClelland *et al.* 2013*a*). Case studies of DBS (targeting the nucleus accumbens, sub-genual cingulate cortex, ventral capsule/ventral striatum or sub-callosal cingulate) to improve AN symptomatology or comorbid symptoms (OCD, depression) have shown promise in highly selected severe and enduring cases. As yet no RCTs have been carried out. Non-invasive methods of brain stimulation (NIBS), i.e. tDCS or rTMS have also shown promise in several case studies (McClelland *et al.* 2013*b*). Candidate targets for NIBS in EDs, based on an 'RDoC formulation' of ED pathology have been described in (Dunlop *et al.* 2016). These include potential targets in the cognitive control, positive and negative valences and social processes systems. To date there is only one published proof-of-concept trial (McClelland *et al.* 2016) of the use of one session of real or sham high-frequency rTMS applied to the left DLPFC in AN. The study found short term reductions in AN-symptoms and improvements in reward-related decision-making assessed via a delay discounting task. One small trial of EEG alpha neurofeedback, which is supposed to be stress reducing, has also been published with promising results, albeit without any change in the targeted alpha waves (Lackner *et al.* 2016).

Five further RCTs are in progress, four on therapeutic use of different NIBS and one small trial of DBS (Chastan, 2012; Bartholdy *et al.* 2015; Gao, 2015; Vicari, 2015; Downar & Woodside, 2016).

Novel medications

A range of different medications has been/is currently being trialled. Dronabinol, a cannabinoid receptor agonist which may promote appetite, has been found to lead to small but significant weight gain above placebo in a pilot RCT in severe and enduring AN (Andries *et al.* 2014, 2015).

Oxytocin is a pituitary neuropeptide hormone, synthesised within the hypothalamus. In addition to its key role in parturition, maternal behaviour and pair-bonding, it also plays a role in regulation of broader social interactions, emotional reactivity and feeding behaviour. As such, it is thought that dysregulation of the oxytocinergic system might be involved in the pathophysiology of psychiatric disorders, such as ED, mood, anxiety and autism spectrum disorders (Romano *et al.* 2015). These authors and others (Maguire *et al.* 2013) suggest that oxytocin may be a useful adjunct to treatment of AN. One RCT of intranasal oxytocin treatment is in progress (Russell, 2016).

Finally, two studies are in progress on fishoils as treatment supplements for AN (Piróg-Balcerzak, 2012; Bonny, 2013), based on widespread interest in this in other neuropsychiatric disorders (Bos *et al.* 2016; Lei *et al.* 2016).

Novel comprehensive treatments and miscellaneous other treatments

Novel comprehensive treatments

A number of so-called 'third wave' behavioural therapies (Churchill *et al.* 2013) have been/are being adapted for AN. One shared rationale for the application of these approaches to AN is evidence of widespread socio-emotional processing difficulties in AN (Oldershaw *et al.* 2011; Brockmeyer *et al.* 2013, 2016*a*; Caglar-Nazali *et al.* 2014; Davies *et al.* 2016).

Most of these treatments, including an adapted version of *Dialectical Behaviour Therapy* that focuses on reducing emotional over-control and increasing appropriate socio-emotional signalling (Lynch *et al.* 2013; Chen *et al.* 2015), interventions using general and eating focused mindfulness interventions (Albers, 2011; Marek *et al.* 2013; Hartmann *et al.* 2015), and *Emotion Acceptance Behaviour Therapy* (Wildes & Marcus, 2011; Wildes *et al.* 2014) have only been evaluated in preliminary uncontrolled studies. A related approach is *Acceptance and Commitment Therapy* (*ACT*), which involves a range of experiential exercises and aims to promote emotional awareness and acceptance as well as adaptive values and goals. ACT has been examined as a potential treatment for AN in one small RCT (Parling *et al.* 2016). No difference was found between ACT and TAU.

https://doi.org/10.1017/S0033291717002604 Published online by Cambridge University Press

Miscellaneous other treatments

One small trial evaluated acupuncture *v.* acupressure and massage in AN, with patients in both groups improving equally (Smith *et al.* 2014). Two ongoing trials focus on reducing food-related cognitive biases and AN-related rules and habits (Steinglass, 2015; Werthmann, 2015).

Discussion

The findings of this review need to be seen in context. There are big differences in health care systems and consequently in treatment availability/accessibility for people with AN and other EDs between different countries and continents. For example, many countries in continental Europe have a much greater emphasis on in-patient treatment than e.g. the UK and this is reflected in the nature of the research questions asked and trials that are being conducted (e.g. Fichter *et al.* 2012; Godart *et al.* 2012; Dalle-Grave *et al.* 2013; Herpertz-Dahlmann *et al.* 2014). Moreover, different psychotherapeutic traditions may affect availability of different treatment modalities, e.g. such as focal psychodynamic therapy (e.g. Zipfel *et al.* 2014). This in turn affects whether such treatments are studied or recommended. A case in point is the fact that recent NICE guidance does not include focal psychodynamic therapy as a first line treatment option for AN, even though the evidence base would support this (NICE, 2017).

Established treatments

Huge progress has been made in advancing the evidence-base on treatment of AN, since the previous review by Watson & Bulik (2013). This earlier review identified 48 trials (2013 patients), published during a 30-year period (1981–2011). In contrast, the present review identified 19 trials during a 5-year period (2011–2016) including a comparable number of patients ($n = 2092$), thus more and larger trials have emerged in a much shorter space of time. Of note, the three largest trials published during the last 5 years have been the product of a single research network in one European country, Germany, and four other trials (two large) emanated from a single programme grant in the UK, underscoring the importance of large consortia in the quest for high quality trials.

The focus of recent trials has been mainly on first line psychological interventions. Very little new work has been done in relation to established (antipsychotics or antidepressants) medications, although one large trial of olanzapine *v.* placebo is in progress (Attia, 2010, 2016). Available trials paint a nuanced picture of the relative merits of different types of family-based interventions for adolescents with AN. They also support the use of a range of individual psychotherapies for adults, with little information on what works best for whom. The fact that so far no single psychotherapy has emerged as clearly superior to others in the treatment of adults with AN, suggests that common therapeutic factors may play an important role in facilitating change. Future studies should assess the relative contributions of common factors *v.* specific therapeutic mechanisms in this respect. Of note, there is also a growing number of studies evaluating the impact of involving partners and families of adult patients on these carers and the patients themselves.

Not all studies include a priori definitions of what counts as treatment completion. Where completion rates are reported they range from acceptable to excellent.

Recovery rates vary considerably between studies. In studies of adolescents full recovery rates range from 17.2% to 50% at last recorded follow-up (6–24 months post-randomisation). Recovery rates in adults range from 13% to 42.9% at follow-up (12–24 months post-randomisation). This wide range in recovery rates can be explained by differences between studies in patient mix, length of follow-up and definitions of recovery. Of note, both in studies of adolescents and adults fewer than 50% of patients fully recover during treatment, suggesting that there is considerable room for improvement. As yet, limited data are available on the cost-effectiveness of different first line interventions, with the exception of the ANTOP study, which showed that both focal psychodynamic therapy and CBT-E were more cost-effective than optimised TAU, with focal psychodynamic therapy dominant over CBT-E (Egger *et al.* 2016).

Two studies in children and adolescents examined the impact of treatment setting on AN outcome in more severely ill patients (Herpertz-Dahlmann *et al.* 2014; Madden *et al.* 2015). Both studies cast doubt on the need for costly prolonged hospital admissions for refeeding, where appropriate alternatives are available, i.e. short admission followed by day-care treatment or out-patient family therapy. In fact, in one of these studies (Herpertz-Dahlmann *et al.* 2014), psychosocial outcomes in the group that received day-care were superior to the group that received in-patient treatment, highlighting the potential for iatrogenic effects of prolonged hospitalisation in younger patients.

Whereas earlier trials often combined patients at different developmental (children, adolescents, adults) and illness stages (Watson & Bulik, 2013), in recent years there has been a clearer separation of trials according to developmental stage (see Tables 1 and 2). In addition, analogous to developments in other mental disorders (McGorry *et al.* 2006; Insel, 2007), a stage model for AN has been suggested, ranging from high-risk stage, prodrome and full syndrome through to severe enduring AN (Treasure *et al.* 2015*b*), based on available literature on illness course, neurobiological factors, functional decline, and intervention studies. Stage-matched treatment interventions have begun to emerge (Hay & Touyz, 2015; Brown *et al.* 2016), focusing in particular on SEED-AN with one RCT (Touyz *et al.* 2013) specifically adapting psychological therapies for this group (i.e. less emphasis on weight gain, more emphasis on quality of life and adaptive function) (Hay *et al.* 2012; Wonderlich *et al.* 2012). Others have suggested that a range of emerging treatment approaches such as CRT, NIBS or oxytocin may be useful as adjuncts to treatment of SEED-AN (Treasure *et al.* 2015*a*). Interventions for early stage illness include family-based interventions for children and adolescents, but early stage illness in adults has so far attracted only limited research attention (Schmidt *et al.* 2016*a*). Likewise, research on service-level interventions, e.g. exploring the merits of designated early intervention services for ED, is practically non-existent [but see (Brown *et al.* 2016)] compared with other areas of mental health research such as psychosis.

Very little is known about sequencing or combinations of interventions if first-line treatments for AN fail and during the period considered no trials considering such questions were conducted. There were however several studies (Fichter *et al.* 2012; Godart *et al.* 2012; Hibbs *et al.* 2015; Sternheim, 2017) that assessed interventions to prevent relapse after discharge from in-patient care, a time when patients are particularly vulnerable to relapse. It is likely that some of the emerging treatments, several of which are currently thought of as adjunctive to other interventions may in future be explored in this context.

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Studies exploring within- and between-session processes and patient/therapist views are also appearing, integrated into large-scale studies. These provide valuable pointers on how to improve available treatments. With the availability of novel tools for computational psychotherapy research it is now possible to process much larger amounts of data (Imel *et al.* 2015; Owen & Imel, 2016), using text mining and machine learning approaches to investigate the underlying linguistic structures and semantic themes of psychotherapy sessions and to reveal clinically relevant content including emotional, interpersonal and intervention-related topics. This would also allow one to distinguish between different psychotherapy approaches and thus contribute to ensuring treatment fidelity in trials.

Emerging treatments

It has previously been noted that 'the ED field lags behind other psychiatric disorders in terms of progress in understanding responsible brain circuits and pathophysiology' (Kaye *et al.* 2011) and this has hampered the development of new treatments, especially in relation to AN. It is therefore heartening to see that a group of highly targeted treatments, based on neurobiological data/mechanisms are now emerging. These are currently being explored particularly in relation to patients with SEED-AN, as this is the group that has often unsuccessfully undergone multiple conventional treatments at great cost to the individual, their family and society at large. Unsurprisingly therefore, many of these treatments are being used as add-ons to other often fairly intensive treatments, making interpretation of findings more complicated. However, it is conceivable that at least some of these novel brain-directed interventions may be useful for first episode illness, where brain changes are arguably more malleable. Exploration of some emerging treatments as stand-alone interventions may be more feasible in less entrenched illness.

CRT is the novel treatment which is most advanced in terms of current research activity, with five published clinical trials and seven further in progress, and associated research on mechanisms of action and neural correlates. Thus, it is likely that over the next 5 years we will have a much clearer idea as to what the role of this intervention is in the treatment of AN, and what patients and in what setting might benefit most. Additionally, as several forthcoming studies focus on adolescents we may also be clearer about the illness stage at which CRT might be most effective.

In contrast, exposure treatment, although it has been around for several decades, remains the treatment that has as yet not quite emerged. Astonishingly little research has been done/is in progress to specifically and systematically address food and body-related fears in AN. Referring to recent fear extinction literature, which emphasises the violation of expected feared outcomes instead of mere habituation effects as a key mechanism of action of exposure treatment, Murray and colleagues have recently called for a better differentiation between feared cues and feared outcomes in AN (Murray *et al.* 2016*a*, *b*). Greater clarity in translating extinction theory to the treatment of AN may help facilitate advances in this area. In addition the availability of new morphing and virtual reality technologies may make exposure paradigms more standardised and easier to deliver.

Neuromodulation treatments have huge potential, both as probes of illness mechanisms and as potential interventions in the treatment of AN, but much of this potential is waiting to emerge. Much needs to be learnt about patient selection, intervention parameters, treatment targets and protocols. These technologies continue to evolve, and for example in the case of NIBS are allowing more precise targeting of treatment, use of increasingly briefer and more powerful treatment protocols, probing deeper brain areas and stimulating multiple brain targets simultaneously (Dunlop *et al.* 2016). In relation to tDCS, portable devices are now available, which can be used at home, which constitutes another important advance. There is also emerging evidence suggesting that these kinds of interventions may work synergistically when applied with different forms of cognitive training, as yet this combination treatment is completely unexplored in EDs. Finally, another promising neurotechnology is fMRI neurofeedback, which as yet has not been explored in relation to AN (Bartholdy *et al.* 2013).

In relation to novel medications, the challenges of CNS drug discovery and reinvigorating Big Pharma's interest in psychiatry as a whole, have been noted (Andersen *et al.* 2014). Thus, it is perhaps unsurprising that in AN there are only a handful of trials emerging on a diverse range of novel medications.

Several new multi-component treatments are focusing on improving socio-emotional processing in AN. However, many of the more established treatments also explicitly target these processes. Drop-out from some of these newer treatments appears to be quite high (Wildes *et al.* 2014; Parling *et al.* 2016). All in all, it remains to be seen, whether these new multi-component treatments have specific advantages over other psychological interventions.

Conclusions

Research funding for EDs remains limited. For example, in the UK, only 0.4% of mental health research expenditure is spent on EDs, compared with 7.2% for depression and 4.9% for psychosis (MQ, 2015). At European level no specific calls for EDs are included in the Horizon 2020 initiative (Schmidt *et al.* 2016*a*). Against this background the acceleration in knowledge about treatment of AN made in the last 5 years is remarkable.

In addition, a paradigm shift is occurring away from traditional talking therapies towards a range of novel targeted treatments, thus a transformation of the treatment landscape is taking place. Whilst we are still a long way away from delivering personally tailored mechanism-based precision treatments for AN, the development of neurotechnologies for diagnosis, outcome prediction and treatment, gives rise to considerable optimism for the future of people with this devastating illness. It is our view that in order to make further significant advances in treatment of AN utilisation of the full range of these different research approaches and a greater integration and knowledge transfer between neuroscience and clinical research is required. Additionally, greater investment in large-scale programmatic funding at national or international (e.g. European) level is required. Finally, the progress made in research on treatments for AN will only benefit patients if evidence-based treatments are disseminated from controlled settings to clinical care, in a manner that preserves their quality and ensures that underserved populations are reached. Strategies for addressing these research practice gaps have recently been outlined in relation to EDs (Kazdin *et al.* 2017).

Acknowledgements. Ulrike Schmidt is supported by a National Institute of Health Research (NIHR) Senior Investigator Award and receives salary support from the NIHR Mental Health Biomedical Research Centre at the South London and Maudsley NHS Foundation Trust and King's College London.

Declaration of Interest. None.

https://doi.org/10.1017/S0033291717002604 Published online by Cambridge University Press

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https://doi.org/10.1017/S0033291717002604 Published online by Cambridge University Press