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REVIEW

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Treatment interventions for Severe and Enduring Eating Disorders: Systematic review

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Abstract

Objective: Approximately 20% of people with Anorexia Nervosa (AN) and 10% with Bulimia Nervosa (BN) will eventually develop a long-standing illness. Although there is no set definition for Severe and Enduring eating Disorder (SE-ED), the common criteria relate to a long duration of the disorder and a number of unsuccessful treatment attempts. Research evidence for treatment of SE-ED remains limited, thus the objective of this systematic review was to describe different treatment interventions and their effects on SE-ED-related outcomes.

Method: A systematic search for quantitative treatment studies of adult participants with SE-ED was conducted in June 2019 (PROSPERO, CRD42018115802) with no restriction on eating disorder type. Altogether, 2,938 studies were included for title and abstract screening.

Results: After systematic searches and article screening, 23 studies (3 randomized controlled trials, 3 open-label studies, 8 naturalistic follow-up studies, 8 case series and case studies, and 1 partially blinded pilot study) were included in the analysis and data extraction. Methodological quality of the included studies was generally low. Inpatient treatment programs (n = 5) were effective in short-term symptom reduction, but long-term results were inconsistent. Outpatient and day-hospital treatment programs (n = 5) seemed promising for symptom reduction. Drug interventions (n = 5) showed some benefits, especially as adjuvant therapies. Brain stimulation (n = 6) led to improvements in depressive symptoms. Other treatments (n = 2) produced mixed results.

Discussion: This is the first systematic review to examine all of the different treatment interventions that have been studied in SE-ED. The results will inform future interventions in research and clinical practice.

KEYWORDS

anorexia nervosa, eating disorders, intervention, Severe and Enduring Eating Disorders, treatment

1 | INTRODUCTION

More advanced treatment options for Severe and Enduring Eating Disorders (SE-ED) are needed, as so many patients have a longstanding trajectory of the disorder. The lifetime prevalence for Anorexia Nervosa (AN) is 1.4%, for Bulimia Nervosa (BN) 1.9% and for Eating Disorder Not Otherwise Specified (EDNOS) 4.3% in women (Galmiche, Déchelotte, Lambert, & Tavolacci, 2019). It has been estimated that approximately 50–80% of people diagnosed with AN will make a full or partial recovery (Steinhausen, 2002). However, for almost 20% of the patients, the disorder prolongs and becomes enduring (Keel & Brown, 2010). Despite a better prognosis for BN, it is estimated that approximately 10% of individuals diagnosed with this type of eating disorder will eventually develop a long-standing illness (Keel & Brown, 2010).

There is currently no clear consensus on the definition of a SE-ED. The most common defining criteria for SE-ED relate to duration of the disorder and number of unsuccessful treatment attempts (Broomfield, Stedal, Touyz, & Rhodes, 2017). Cut-off point in duration is commonly set at 7 years (Treasure, Stein, & Maguire, 2015), with some variation between studies. Despite these variations, follow-up studies reported increased mortality rates in individuals with an enduring disorder as the time to follow-up increased; however, some deaths occur due to causes not directly resulting from the eating disorder itself (e.g., suicide) (Steinhausen, 2002). Importantly, it is possible for a person to achieve a full recovery even after suffering from an eating disorder for as long as 10–20 years (Noordenbos, Oldenhave, Muschter, & Terpstra, 2002).

Compared to other eating disorders, Severe and Enduring Anorexia Nervosa (SE-AN) has been more widely investigated. For example, in a recent study (Ambwani et al., 2020), outpatients with SE-AN (characterized by high current distress and illness duration of at least 7 years) reported worse eating disorder symptomology, more lifetime hospitalizations and less social wellbeing compared to patients with shorter illness duration. In addition, patients in the SE-AN group were found to have less improvement in eating disorder symptoms, body mass index (BMI), and social adjustment over time. However, the definition of SE-AN also remains somewhat ambiguous.

The lack of an empirically derived definition of SE-ED makes the combined efforts to investigate and manage the condition challenging. Furthermore, the lack of definition hinders the recognition of the disorder in health care policies and practice and may delay the provision of tailored care for individuals with SE-ED. For example, more unconventional treatment attempts instead of traditional treatment methods could be utilized for patients in this group.

Recently, the treatment options for SE-ED have been extensively discussed, although research evidence on the topic remains limited and the methodological quality of the studies is generally low (Treasure, Cardi, Leppanen, & Turton, 2015; Wonderlich et al., 2012). Traditionally, the first step in treatment of eating disorders is improvement of nutritional status that is emphasized before psychological treatment can be successfully implemented. In SE-ED, experts have suggested a differing approach to treatment (Strober, 2004; Treasure, Cardi, et al., 2015; Wonderlich et al., 2012). For example, it is suggested for the main focus to be on quality of life, social adjustment, and vocational issues, and not on the assertive pursuit of significant reduction in eating disorder symptoms (Wonderlich et al., 2012). This is because overly challenging or demanding treatment goals may be overwhelming, promote resistance, and lead to harmful consequences among patients, including increasing the risk of suicide (Strober, 2004).

Furthermore, starvation is an important maintaining factor in eating disorders. Long-term poor nutritional status and disordered eating behavior alter the structure and functions of the brain (Fonville, Giampietro, Williams, Simmons, & Tchanturia, 2014). Due to this, SE-ED patients might benefit from novel innovational treatment options, such as brain stimulations designed to change the factors maintaining the disorder (Treasure, Cardi, et al., 2015). In addition, although response to drug treatments has been poor in eating disorders, especially in AN (Crow, 2019), it has been suggested that SE-ED patients might benefit from medications, especially medications that induce weight gain (such as olanzapine) (Bosanac et al., 2003; Hansen, 1999), or stimulate appetite (such as cannabinoid dronabinol) (Andries, Frystyk, Flyvbjerg, & Støving, 2014). However, even after months of treatment attempts, the outcomes on disordered eating behavior and weight recovery have been poor.

A previous review on the definitions and treatment of SE-ED concluded that emerging psychological therapies show promise, although most of the studies had recruited only underweight participants (Hay & Touyz, 2015). In addition to treatment results, it also focused on the conceptualization of recovery, clinical care, presentations and treatment experiences, and problems of treatment resistance and involuntary care in SE-ED patients. The authors noted the model of illness staging in SE-ED, particularly in SE-AN, similar to these in other medical conditions, as potentially informative in the therapeutic process. Shifting focus away from weight restoration and addressing comorbid factors, such as cognitive inflexibility, was suggested as a promising strategy. The review, however, was limited to randomized controlled treatment studies and open trials of novel approaches.

To the best of our knowledge, there is no previous systematic review summarizing all the available treatment interventions for SE-ED and their effects on SE-ED-related outcomes. Thus, treatment of SE-ED has not been extensively investigated. Treatment outcomes need to be investigated in relation to illness duration and severity in order to finally find more targeted approaches to ensure that care pathways better fit patients' needs. Therefore, the objective of this systematic review was to describe different treatment interventions with quantitative study design and their potential efficacy or effectiveness on SE-ED-related outcomes, such as body weight, BMI, eating disorder symptomology, general psychological symptomology, quality of life, compensatory or compulsive behavior, and menstruation. Safety and acceptability of the treatments were also summarized.

2 | METHODS

2.1 | Information sources and search strategy

A systematic search guided by the recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-analysis

(PRISMA) Statement (Moher, Liberati, Tetzlaff, & Altman, 2009) was conducted in consultation with a librarian at the University of Eastern Finland. Separate search strategies were developed for the six electronic databases: PubMed, PsycInfo, Web of Science, Scopus, Cinahl, and Cochrane Central Register of Controlled trials. MeSH terms, key words and Boolean operators were used as appropriate for each of the databases. The search was conducted in June 2019 and all relevant articles published in English language from January 1998 to the time of the search were assessed for eligibility. The search terms included "anorexia nervosa" OR bulimi* OR "binge-eating" OR "binge eating" OR "eating disorder*" OR EDNOS OR osfed OR "other specified feeding or eating disorder*" AND "severe and enduring" OR "chronic*" OR "long-standing" OR "long-term," OR "long-time," OR "long-lasting," OR "treatment-resistant," OR "long standing," OR "long term," OR "long time," OR "long lasting" OR "treatment resistant" OR "treatment failure, AND "nutrition therapy," OR "diet therapy," OR "dietary therapy," OR "diet modification," OR "dietary modification," OR "diet treatment," OR "dietary treatment," OR "nutrition treatment," OR "drug treatment," OR "drug therapy," OR "pharmacotherap*," OR "medicat*," OR "medicines," OR "psychotherap*," OR "behavior therapy," OR "behaviour therapy," OR "behavioral therapy," OR "behavioural therapy," OR "cognitive therapy," OR "mindfulness," OR "intervention*." Additionally, the reference lists of included articles were scanned for eligible articles.

In order to identify eligible articles, two independent researchers (EK and AR) examined the titles and abstracts of the articles identified in the search. Then, the full texts of the articles that met the inclusion criteria (Table 1) were evaluated by the two researches (EK and AR). Disagreements were resolved through discussions, and the third reviewer (MW) was involved if needed.

2.2 | Eligibility criteria

Detailed inclusion and exclusion criteria for article screening are presented in Table 1. Studies including adult participants with SE-ED were considered for eligibility. Only original English language studies with full-text version available were accepted. There were few restrictions in study design, so quantitative studies of any design, including randomized controlled trials (RCTs), observational and case studies, were considered. Moreover, studies with different types of treatment interventions were encompassed in the review. These involve drug trials, nutritional therapies, psychological therapies, surgery, and behavioral therapies. Both inpatient and outpatient treatments were considered.

2.3 | Data extraction

Data extraction were performed by two independent authors (EK and AR) using pre-set extraction criteria, including author, publication year, country, study design and settings, sample size, follow-up, participant characteristics, outcome measures, and adverse events. The extracted data were cross-checked for accuracy. Quantitative analysis of results was not carried out due to the high heterogeneity of included articles in terms of treatment characteristics and study design.

2.4 | Quality assessment

Two researchers (EK and MW) independently assessed the methodological quality of the included articles. According to the Center of Evidence-based Medicine (Aardoom, Dingemans, Spinhoven, & Furth, 2013; Burns, Durkin, & Nicholas, 2009), studies were graded into one of the following levels of evidence (the lower the level, the higher the methodological quality): level I, double-blind RCTs; level II, open RCTs; level III, observational studies (a: nonrandomized, controlled studies; b: large ($n > 100$) nonrandomized, uncontrolled studies; c: medium-sized ($100 > n > 50$) nonrandomized, uncontrolled studies); level IV, small ($50 > n > 10$) observational studies, nonrandomized, uncontrolled; level V, case series, case reports, and expert opinions. In addition, the methodological quality of RCTs was assessed by a 13-item evaluation form (Van Den Berg, Schoones, Vliet, & Theodora, 2007; modified based on Van Tulder, Koes, & Bouter, 1997). Equal weight was given to all criteria in the list resulting in a methodological score of 0–13. If the score was 9 or higher, the study was rated as being of

TABLE 1 Inclusion and exclusion criteria for the studies in this systematic review

Inclusion criteria	Exclusion criteria
• Original full-text studies in English language • Any design (randomized controlled trials, observational and case studies) • Any types of treatment interventions (drug trials, nutritional therapies, psychological therapies, surgery and behavioral therapies) • Inpatient and outpatient settings • Participants 18 years old and older with eating disorder as a primary diagnosis • Participants with at least 7 years of illness duration (at least a 7-year mean illness duration was accepted when a study included more than 10 patients), AND had several unsuccessful treatment attempts; OR authors defined the eating disorder as "severe and enduring/chronic" with at least 7 years of illness duration (or defined the eating disorder as "severe and enduring/chronic")	• Qualitative studies • Follow-up studies for treatment studies already included in the analysis • Insufficient description of treatment procedures; description of the characteristics of the patients but not the specific treatments nor the treatment outcomes in detail. • Main treatment provided for disorder other than an eating disorder (such as psychotic disorder) • Treatment provided to somatic, acute complications related to eating disorder (such as gastrointestinal manifestations, dehydration etc.) or other comorbidities

good methodological quality as per criteria described elsewhere (Anastasiadou, Folkvord, & Lupiañez-Villanueva, 2018).

3 | RESULTS

3.1 | Study selection

A flow chart of the selection process is reported in Figure 1. The systematic search identified a total of 5,512 articles. After removing duplicates, titles and abstracts of 2,938 articles were screened for eligibility. At this point 2,851 articles were excluded as irrelevant. The full texts of 85 articles were then evaluated. One additional article was identified through reference lists of the included articles. After reviewing full-texts, 64 articles were excluded with specified reasons. The main reasons for exclusion were: unsuitable study population (for example, duration of ED <7 years); study design (for example, qualitative studies); outcome or publication type (see the numbers in PRISMA diagram in Figure 1). Other exclusion reasons were being a follow-up study for a previously included study (n = 1); inadequate information given about the treatment (n = 1); and treatment given primarily to another condition (n = 1).

3.2 | Study characteristics

A total of 23 studies published between 1998 and 2018 were included in this review (Tables 2-7). The included studies were conducted in the UK, Norway, the USA, Australia, Canada, Italy, Israel, and Denmark. Additionally, one multi-site study was performed in Australia and the UK. Three studies were RCTs (Andries et al., 2014; Dalton et al., 2018; Touyz et al., 2013); eight studies had naturalistic follow-up design (Abbate-Daga et al., 2015; Brown et al., 2018; Calugi, El Ghoch, & Dalle Grave, 2017; George, Thornton, Touyz, Waller, & Beumont, 2004; Long, Fitzgerald, & Hollin, 2012; Rø, Martinsen, Hoffart, & Rosenvinge, 2003; Rø, Martinsen, Hoffart, & Rosenvinge, 2004; Rø et al., 2005); another eight were case studies (Bosanac et al., 2003; Bratland-Sanda et al., 2018; Christensen & Averbuch, 2009; Latzer, Eysen-Eylat, & Tabenkin, 2000; Levinson, Rapp, & Riley, 2014; Hansen, 1999; McClelland et al., 2013; McClelland, Kekic, Campbell, & Schmidt, 2016); and three were open-label studies (Lipsman et al., 2017; Lipsman et al., 2013; Mills, Park, Manara, & Merriman, 1998). In addition, one study was a partially blinded pilot study (Van Den Eynde, Guillaume, Broadbent, Campbell, & Schmidt, 2011). Inclusion criteria and indication of SE-ED for each of the individual studies are presented in Table 2.

Majority of the participants in the included studies were women with only four studies (Brown et al., 2018; Calugi et al., 2017; Rø et al., 2004; Rø et al., 2005) recruiting both men and women. The sample size ranged from n = 1 (case studies) to n = 164 participants. Mean age ranged between the ages of 20–40. The mean duration of the eating disorder was reported in 18 studies and was approximately 19 years (range 9–35).

The studies investigated a broad range of treatments. Inpatient treatment programs were investigated in five studies (Calugi et al., 2017; Long et al., 2012; Rø et al., 2003; Rø et al., 2004; Rø et al., 2005). Psychotherapeutic outpatient or day-hospital treatments were examined in another five studies (Abbate-Daga et al., 2015;

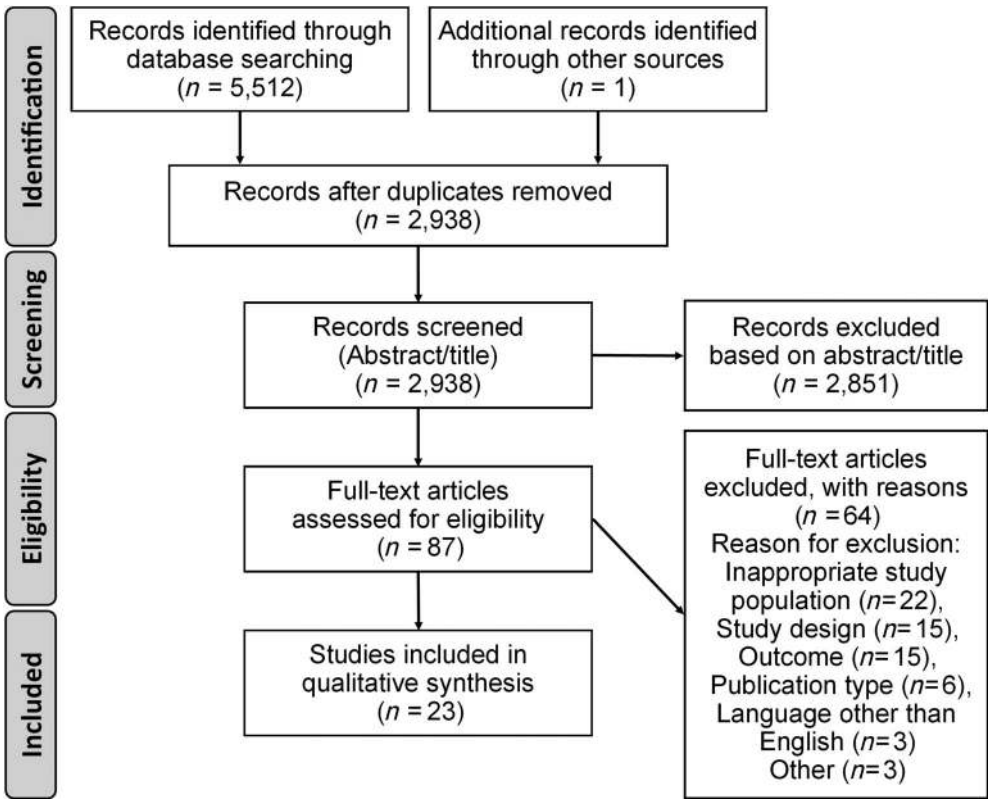

FIGURE 1 PRISMA flow chart of the article selection process

TABLE 2 Inclusion criteria, indication of SE-ED, duration of the eating disorder and previous treatments in the studies included in this review

First Author Year Country	Treatment type	Inclusion criteria for individual studies	SEED indication based on	Duration of the illness (mean, years)	Previous treatments
	Randomized controlled trials				
Touyz 2013 Australia & the UK	CBT-SE-AN compared to SSCM	Female, aged ≥18 years, met DSM-IV criteria for AN, excluding criterion D (amenorrhea), and had an illness duration of at least 7 years	Long illness duration. Authors' view ("severe and enduring anorexia nervosa")	16.6	NR
Andries 2014 Denmark	Dronabinol/placebo	Women aged ≥18 years who fulfilled the DSM-IV-TR criteria for AN for at least 5 years and attended both psychiatric and somatic therapy as an in- or outpatient	Long illness duration. Authors' view ("severe and enduring anorexia nervosa")	≥5	NR
Dalton 2018 The UK	rTMS	Right-handed community-dwelling adults (≥18 years) with a current DSM-5 diagnosis of AN and BMI >14 kg/m2. Illness duration of ≥3 years and completion of at least one previous course of treatment (e.g. NICE 18-recommended specialist psychotherapy or specialist day-patient or inpatient treatment for their ED). Participants needed agreement from their ED clinician or general practitioner	Long illness duration, several treatment attempts. Authors' view ("severe and enduring anorexia nervosa")	14.1	Number of previous ED hospitalizations, mean = 2.18 times; Number of previous ED inpatient stays, mean = 10.49 mo
	Open label studies				
Mills 1998 The UK	Ketamine (with nalmefene)	The patients selected were all severely affected and selected because other forms of treatment failed to produce a remission. They were older than the normal eating disorder patients and were in a chronic refractory state	Long duration, failed treatment attempts over many years, were in were in a chronic refractory state.	NR (range 7–21 years)	All had failed to respond to various forms of treatment over many years, not otherwise specified
Lipsman 2013 Canada	DBS	Female or male aged 20–60 years; diagnosis of AN, restricting or binge–purging subtype (DSM-IV-TR); chronicity or treatment resistance shown by some or all of: 1. A pattern of 3 years' duration of relentless unresponsiveness to repeated voluntary hospital admissions, characterized by failure to complete treatment or immediate weight relapse after treatment 2. A pattern of increasing medical instability, accompanied by refusal to participate in or a pattern of poor response to intensive expert treatment and increasing medical acuity, lasting at least 2 years and including at least two episodes of involuntary feeding 3. A pattern of chronic stable AN that has lasted at least 10 years	Illness duration ≥10 years, authors' description ("treatment-refractory")	18.0	All patients currently, or had previously, had several medical complications directly related to AN. Other previous treatment not reported.

TABLE 2 (Continued)

First Author Year Country	Treatment type	Inclusion criteria for individual studies	SEED indication based on	Duration of the illness (mean, years)	Previous treatments
Lipsman 2017 Canada	DBS	Female or male aged 20–60 years; diagnosis of AN, restricting or binge–purging subtype (DSM-IV-TR); chronicity or treatment resistance shown by some or all of: 1. A pattern of 3 years' duration of relentless unresponsiveness to repeated voluntary hospital admissions, characterized by failure to complete treatment or immediate weight relapse after treatment 2. A pattern of increasing medical instability, accompanied by refusal to participate in or a pattern of poor response to intensive expert treatment and increasing medical acuity, lasting at least 2 years and including at least two episodes of involuntary feeding 3. A pattern of chronic stable AN that has lasted at least 10 years	Illness duration ≥10 years, nonresponse to treatments. Authors' description ("treatment-refractory")	18	All patients had a clinically significant history of treatment nonresponse, which included multiple hospital admissions for acute medical stabilization, medical treatment, and outpatient follow-up in the community
	Naturalistic follow-up studies				
Rø 2003 Norway	A multicomponent program based on CBT and IPT (group and individual sessions)	Admitted to a specialized unit at a psychiatric hospital; symptoms of BN impairing daily functioning, previous local treatment failures and age >18 years	Long duration of illness, previous treatment failures.	16.4	Duration of psychiatric treatment 3.1 ± 2.2 years (0.6–10); Previous inpatient treatment *N* = 26 (52%)
George 2004 Australia	2-day MET-CBT focused DH (5 h/d)	Having a primary diagnosis of AN for a minimum of 7 years and that the illness had not remitted despite multiple previous treatment interventions	Illness duration ≥ 7 years and previous treatment failures	18.0	Multiple failed in- and outpatient treatments
Rø 2004 Norway	A multicomponent program for AN based on CBT and IPT	Admitted to a specialized unit at a psychiatric hospital; symptoms of AN impairing daily functioning, nonresponse to previous treatment and age >18 years	Long duration of illness and previous treatment failures	11.0	All had received psychiatric treatment on an average of 2.3 years, and *N* = 16 (67%) had previously received inpatient treatment
Rø 2005 Norway	Specialized group treatment program for chronically ill ED patients (multicomponent)	Adult patients admitted to a specialized eating disorder unit at a psychiatric hospital (Modum Bad)	Authors' view ("chronically ill"), unsuccessful treatment attempts	NR	*N* = 71 (99%) had received psychiatric treatment (mean duration 2.6 ± 1.8 years) and *N* = 36 (55%) had previously received inpatient treatment
Long 2012 The UK	CBT program	Consecutive adult (+18 years) referrals to the inpatient treatment unit who fulfilled DSM-IV diagnostic criteria for AN. The main indications for admission: (1) BMI < 17.5 kg/m2; (2) very rapid weight loss; (3) life-threatening physical complications; (4) suicide risk; and (5) chronic failure to benefit from outpatient treatment	Long duration. Authors' view ("chronic anorexia nervosa")	13.0	*N* = 3 (9%) had no previous psychiatric inpatient admissions, *N* = 15 (44%) had one previous admission, *N* = 6 (18%) had more than one previous admission for an ED. *N* = 2 (6%) had never attended any outpatient sessions for their ED, *N* = 17 (50 %) had attended 0–20, *N* = 10 (29%) had attended 20–40, *N* = 5 (15 %) had attended 40+. *N* = 5 (15 %) had previously been discharged against medical advice

(Continues)

TABLE 2 (Continued)

First Author Year Country	Treatment type	Inclusion criteria for individual studies	SEED indication based on	Duration of the illness (mean, years)	Previous treatments
Abbate-Daga 2015 Italy	Psychodynamic, emotionally focused 5-day DH-program	AN patients who were consecutively admitted to the DH of the Eating Disorders Program at the San Giovanni Battista Hospital of the University of Turin in Turin, Italy from September 2009 to August 2012	Long duration. Authors' view ("severe and treatment-resistant patients")	11.7	*N* = 42 (75 %) had failed previous treatments such as residential (*N* = 5, 11.9%), outpatient (*N* = 16, 38.1%) and combined (*N* = 21, 50%) treatments
Calugi 2017 Italy	Enhanced cognitive behavioral therapy for eating disorders CBT-E	Adult patients with AN admitted to the inpatient ED unit. For admission, patients had to be 18–65 years; to meet the DSM-IV diagnostic criteria for AN (except the amenorrhea criterion); and to require inpatient treatment, either because the ED could not be managed safely on an outpatient basis, or due to previous outpatient treatment failures. Inpatient admission criteria: (i) poor response to well-delivered outpatient-based treatment; and (ii) presence of features that make outpatient eating disorder treatment inappropriate (e.g. BMI < 14; marked medical complications, such as pronounced oedema, severe electrolyte disturbance or hypoglycaemia; significant suicide risk; and/or marked interpersonal difficulties)	Long duration. Authors' view ("severe and enduring anorexia nervosa," previous treatment failures)	12.3	Recent failure to respond to treatment (yes) *N* = 30 (88%)
Brown 2018 The USA	6-day PHP program (6–10 h/d, individual, family & group therapy)	Adult patients diagnosed with AN or BN who were admitted to the University of California San Diego (UCSD) PHP. Criteria for admission to PHP conformed to the APA medical, psychiatric, and behavioural criteria guidelines	Long duration. Authors' view ("highlighting the severe and enduring nature of the sample")	AN-BP 11.3 BN 10.2	NR
	Feasibility and pilot studies				
Van den Eynde 2011 The UK	rTMS	Right-handed people with DSM-IV-TR diagnosis of AN (restricting and binge-purging type)	Long duration. Authors' description ("The EDE-Q scores indicate severe eating disorder psychopathology)	10.0	NR
	Case studies and case series				
Hansen 1999 The UK	Olanzapine	NR	Long duration of illness and several treatment attempts in the past	35	Several hospital admissions in the past
Latzer 2000 Israel	Total parenteral hyperalimentation	NR	Long duration and treatment resistance	11	Refused to have any treatments
Bosanac 2003 Australia	Olanzapine	Patients with DSM-IV AN admitted to the Eating Disorders Unit at the Austin and Repatriation Medical Centre between 1996 and 2001, and who were prescribed olanzapine	Long duration of illness, authors view ("Most had a chronic illness")	10.5	NR

TABLE 2 (Continued)

First Author Year Country	Treatment type	Inclusion criteria for individual studies	SEED indication based on	Duration of the illness (mean, years)	Previous treatments
Christensen 2009 The USA	Duloxetine	BN patient referred to an outpatient clinic	Long duration, several treatment attempts. Authors' view ("Chronic Bulimia nervosa")	From late adolescence (35 years old patient)	Serial pharmacologic trials and long-term psychotherapy
McClelland 2013 The UK	rTMS	No contraindications to rTMS and BMI between 14–18,5 kg/m^2	Long duration, unsuccessful treatment attempts. Authors' view ("Severe and enduring anorexia")	23.5	Patient A: 12 years inpatient treatment; Patient B: 6 mo daycare and about 3 years outpatient treatment
Levinson 2014 The USA	CBT with imaginal exposure therapy	A patient admitted to a PHP after failing to gain weight in family-based treatment	Long duration, several treatment attempts. Authors' view ("… diagnosed with AN-restricting type, with a chronic history")	Since adolescence (34 years old patient)	Had been in outpatient therapy with a variety of therapists for many years and had never achieved a period of remission
McClelland 2016 The UK	rTMS	A diagnosis of AN and BMI between 14–18.5 kg/m2. Due to a time delay between the RCT and starting this case series, the BMI of one participant increased to 19.2 kg/m2; thus, she was sub-threshold AN: however, she was still included	Long duration, several treatment attempts. Authors' view ("Enduring anorexia")	24.3	All had multiple unsuccessful treatment attempts
Bratland-Sanda 2018 Norway	Maximal Strength Training 3 x w	A woman meeting the DSM-5 criteria for AN and the International Society for Clinical Densitometry criteria for osteopenia	Long duration, several treatment attempts. Authors' view ("Long-standing anorexia nervosa")	9	From the age of 19 (to approx. 2 months prior to intervention, so about 6 years prior) she maintained continuous outpatient treatment in addition to the two separate periods of daycare treatment. She had visited several therapists (duration ranged from a few months to several years).

Abbreviations: AN, Anorexia nervosa; AN-BP, Anorexia nervosa, binge-purging type; APA, American Psychological Association; Approx., Approximately; BMI, Body Mass Index; BN, Bulimia nervosa; CBT, Cognitive-behavioral therapy; CBT-AN, Cognitive behavioral therapy for anorexia nervosa modified for severe and enduring form; D, Days; DBS, Deep brain stimulation of the subcallosal cingulate; DH, Day-hospital; DSM, Diagnostic and Statistical Manual of Mental Disorders; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders 4th Edition, Text Revision; ED, Eating disorder; E.G., For example; H, Hours; IPT, Interpersonal therapy; Kg/m2, Kilograms per square meter; MET-CBT, Motivational enhancement and schema-focused cognitive behaviour therapy; Mo, Months; NR, Not reported; PHP, Partial hospital program; rTMS, Repetitive transcranial magnetic stimulation; RCT, Randomized controlled trial; SEED, Severe and enduring eating disorder; SSCM, Specialist supportive clinical management; W, Weeks.

TABLE 3 Characteristics and outcomes of included studies examining inpatient treatment programs in treatment of severe and enduring eating disorders

First Author Year Country	Study design	Participants *N* Diagnosis Mean baseline BMI (*SD*) Ethnicity/race	Mean age (Mean duration of illness, *SD*), years	Type of treatment Treatment duration, Follow-up	Outcome measures	Main findings	QA
Rø 2003 Norway	Naturalistic follow-up	*N* = 54 BN (AN-BP *n* = 1, EDNOS *n* = 13) 23.0 (6.6) Ethnicity/race NR	30.9 (16.4, 8.3)	A multicomponent program based on CBT and IPT (group and individual sessions) Duration: 4 mo	ED symptoms (EDE, EDI) General psychopathology (SCL-90-R, GSI) Frequency of bulimic episodes	Improvements in all EDE subscales at EOT. Large effect size for e.g. "dietary restraint" (ES 0.9), "eating concern" (ES 1.1), "weight concern" (ES 0.8), "drive for thinness" (ES 0.8) "bulimia" (ES 1.2). No changes at the FU. Improvements in almost all EDI subscales at EOT, no changes at the FU. Improvements in SCL-90-R and GSI at EOT (none in FU). Reduction in bulimic episodes from pre-treatment to FU (75% in median values). Increase in binging, vomiting, and laxative misuse from EOT to FU.	Level III
Rø 2004 Norway	Naturalistic follow-up	*N* = 25 AN, BN, EDNOS 16.9 (2.5) Ethnicity/race NR	28.2 (11.0, 6.8)	A multicomponent program for AN based on CBT and IPT Duration: 22–23 w FU: 1 year	Weight gain ED symptoms (EDE, EDI) General psychopathology (SCL-90-R) Treatment response	A time effect on weight gain (F (2,11) =4.5) with an average increase of 4.3 ± 5.6 kg (patients with BMI<17.5). Weight gain was 1.7 ± 4.7 kg at EOT. At FU the gain was 2.6 ± 7.6 kg. Negative correlation between weight changes during treatment and FU (r = 0.68). Improvement on EDE subscales "eating concern," "weight concern," and "restraint" but not on "shape concern" subscale at EOT. EDI subscales "body dissatisfaction," "perfectionism," "maturity and "fear" decreased at EOT. Time effect (F (2,21) = 4.3) and reduction on SCL-90-R subscales "somatization," "depression" and "anxiety" at EOT. At FU 2 patients (8%) recovered, 8 (33%) improved while 14 (58%) had a poor outcome. In the first group (BMI <17.5): 1 recovered, 4 improved and 8 had poor response. In the second group (BMI>17.5): 1 recovered, 4 improved and 6 had poor response.	Level IV
Rø 2005 Norway	Naturalistic follow-up	*N* = 72 AN, BN, EDNOS BMI NR Ethnicity/race NR	30.2 (NR)	Specialized group treatment program for chronically ill ED patients (multicomponent) 22–23 w for AN and 15 w for BN FU 1 & 2 years	ED symptoms (EDE, EDI) General psychopathology (SCL-90-R) Weight gain IP Problems (IIP) Treatment response Compensatory behavior	Improvements in all EDE subscales at EOT. No change in other scales than eating concerns at the FU. Improvements in all EDI subscales (except Interpersonal distrust) at EOT. Improvements also in sum scores and subscale scores of Interpersonal distrust, Interceptive awareness, Drive for thinness at FU. *N* = 18 (BMI value <17.5 at admission) had a weight gain from admission to 2-year FU with a mean increase of 8.6 kg (11.0 kg). At FU, 8/18 were still underweight (BMI <17.5). Improvements in all assessment points in SCL-90-R and IIP. At 2 years FU *N* = 9 (14%) had recovered and *N* = 8 (12%) were subthreshold, *N* = 46 (71%) had improved (at 1 year, 43% had improved). 76% reduction of binging, 71% reduction of purging and 77% reduction of laxative misuse from admission to the 2 years FU.	Level III

TABLE 3 (Continued)

First Author Year Country	Study design	Participants *N* Diagnosis Mean baseline BMI (*SD*) Ethnicity/race	Mean age (Mean duration of illness, *SD*), years	Type of treatment Treatment duration, Follow-up	Outcome measures	Main findings	QA
Long 2012 The UK	Naturalistic follow-up	*N* = 34 AN-R & AN-BP 14.1 (1.3) Ethnicity/race NR	33 (13, 8.6)	Cognitive behavioral psychotherapy program Average length 102 d FU: 4 years	Weight gain ED symptoms (MRAS, EDI, BSQ) Illness severity and self-esteem	The mean BMI increased from 14.1 to 19.5 (EOT) to 19.6 (FU). Changes in MRAS from 3.2 (1.5) to EOT 6.8 (2.0) to FU 9.0 (2.4). Discharge: in 7 EDI subscales reduction, one scale (Perfectionism) no change. FU: 4 subscales further decreased. BSQ: Change from 1.7 (0.7) to EOT 0.9 (0.4) to FU 0.9 (0.6). T-test: 6.2 (admission-discharge). Illness severity decreased and self-esteem improved.	Level IV
Calugi 2017 Italy	Naturalistic follow-up	*N* = 66 (*n* = 32 SE-AN, *n* = 32 non-SE-AN) SE-AN: 15.2 (2.0) Ethnicity/race NR	29.4 (12.3, 4.7) (SE-AN)	Enhanced cognitive behavioral therapy for eating disorders CBT-E Duration: 20 w FU: 6 mo & 12 mo	Weight gain ED symptoms (EDE-Q) General psychopathology (GSI) Acceptability of therapy	Similar large increases in BMI for both groups. BMI for SE-AN from 15.2 (2.0) to EOT 19.1 (1.6) to 6 mo FU 18.4. (1.8) to 12 mo FU 17.8 (1.9). EDE-Q and GSI improved in both groups. High acceptability, 85% completed the study.	Level III

Abbreviations: AN-BP, Anorexia nervosa, binge-purging type; AN-R, Anorexia nervosa, restricting type; BN, Bulimia nervosa; BSQ, Body Shape Questionnaire; CBT, Cognitive-behavioral therapy; D, Days; ED, Eating disorder EDE, Eating Disorder Examination interview; EDE-Q, Eating Disorder Examination –Questionnaire; EDI, Eating Disorder Inventory; EDNOS, Eating disorder not otherwise specified; EDI, Eating Disorder Inventory; EOT, End of treatment; ES, Effect size FU, Follow-up; GSI, The Global Severity Index; IIP, The Inventory of Interpersonal Problems 64 –Questionnaire; IP, Interpersonal IPT, Interpersonal therapy; Mo, Months; MRAS, Morgan-Russell Assessment Schedule; NR, Not reported; QA, Quality assessment, SCL-90-R, Symptom Check List; SE-AN, Severe and enduring anorexia nervosa; W, Weeks.

TABLE 4 Characteristics and outcomes of included studies examining outpatient or day-hospital treatment programs in the treatment of severe and enduring eating disorders

First Author Year Country	Study design Setting	Participants N Diagnosis Mean baseline BMI (*SD*) Ethnicity/race	Mean age (Mean duration of illness, *SD*), years	Type of treatment Treatment duration, Follow-up	Outcome measures	Main findings	QA
George 2004 Australia	Naturalistic follow-up DH patients	*N* = 8 AN & EDNOS 16.5 (1.6) Ethnicity/race NR	36 (18, NR)	2-day MET-CBT focused DH (5 h/day) Duration: 6 months no FU	Readiness to recover (ANSOCQ) ED symptoms (EAT) General Health (GHQ-28) Early maladaptive schema (YSQ) Weight gain	Increase in their readiness to recover (Z = 2.37, two-tailed p = 0.02). No change in EAT or GHQ-28. No change in YSQ scales. No change in BMI.	Level V
Touyz 2013 Australia & the UK	RCT Outpatients	*N* = 63 AN-R & AN-BP 16.2 (1.3) Ethnicity/race NR	33.4 (16.6, 8.5)	CBT-SE-AN compared to SSCM Duration: 8 mo (30 sessions) FU: 6 mo & 12 mo	Quality of life (EDQOL, SF-12) Mood (BDI) Social adjustment (WSAS) Weight gain ED symptoms (EDE Readiness to recover (ANSOCQ)	At EOT and FU, both groups showed improvement in EDQOL and SF12 MCS, but not in SF-12 PCS. At EOT and FU both groups showed improvements in BDI. At the 6-month FU CBT-AN had higher score on WSAS. Weight gain was oobserved in both groups (although not in CBT in 6 mo). At EOT and FU, both groups showed improvement in EDE scores. CBT-AN had lower EDE Global scores at 12 mo FU ($F_{1,57} = 8.90$, $p = 0.004$, $\eta 2$ $p = 0.135$). At EOT and FU, both groups showed improvement in ANSOCQ. At 12-month FU CBT-AN had higher readiness for recovery on ANSOCQ ($F_{1,57} = 6.59$, $p = 0.013$, $\eta 2$ $p = 0.104$).	Level I
Levinson 2014 The USA	Case study DH patient	*N* = 1 AN-R 16.8 Caucasian	34 (since adolescence)	CBT with imaginal exposure therapy 28 d (12 sessions) FU: 1 w & 1 mo	ED symptoms (EDE-Q) Clinical impairment (CIA) Weight gain Anxiety (SUDS)	EDE-Q score decreased from admission to EOT to 1 mo FU. CIA decreased from intake to EOT to 1 mo FU (intake = 41, FU = 32). Weight increased over treatment, maintained at 1 mo FU. (Admission BMI = 16.75, 1 mo FU = 18.47). Anxiety decreased (1st exposure SUDS = 8.5/10, final exposure SUDS = 5/10) even as the script became harder.	Level V
Abbate-Daga 2015 Italy	Naturalistic follow-up DH patients	*N* = 31 SE-AN (Total 56) AN-R & AN-BP 15.0 (1.7) Caucasian	28.4 (11.7, 3.9)	Psychodynamic, emotionally focused 5-day DH-program Duration: 6 mo FU: 12 mo	ED symptoms (EDI-3) Weight gain (BMI) Binge-purge behaviour	At the EOT, 3 (10.7%) had a good outcome, 20 (71.4% had an intermediate outcome, 5 (17.9 %) had a poor outcome. AT 12 mo FU, 7 (26.9%) had a good outcome (*n* = 1 achieved recovery, 3.8%), 10 (38.5%) had an intermediate outcome and 9 (36.4%) had a poor outcome. SE-AN patients were less likely to achieve recovery compared to others.	Level III
Brown 2018 The USA	Naturalistic follow-up DH-patients	*N* = 164 SE-ED (Total 243) AN-BP & BN	AN-BP 26.5 (11.3, 9.6)	6-day PHP program (6–10 h/day, individual, family & group therapy)	Weight gain ED symptoms (EDE-Q)	Improvement in weight in AN-BP at EOT and FU. Improvements in EDE-Q Global score and all the other subscales except Shape/Weight in AN-BP. EDE-Q	Level III

TABLE 4 (Continued)

First Author Year Country	Study design Setting	Participants N Diagnosis Mean baseline BMI (*SD*) Ethnicity/race	Mean age (Mean duration of illness, *SD*), years	Type of treatment Treatment duration, Follow-up	Outcome measures	Main findings	QA
		AN-BP 18.7 (1.5) BN 24.3 (4.6) 74.7% Caucasian, 5.4% Asian, 1.2% African American, 0.4% Native American/Alaskan Native, and 18.3% Other	BN 28.2 (10.2, 9.1)	Average 89.2 days FU: 3 mo/6 mo/1 y/2 y (longest for each participant)	Mood, anxiety (BDI, STAT) Remission status (BMI, binge/purge behavior, EDE-Q) Binge/purge behavior	Global, Restraint, Eating Concern: significant effects of time across discharge and FU, all diagnoses improved through FU. Global scores across all diagnoses at discharge and FU fell within 1 *SD* of the mean of a community sample of women, *M* (*SD*) = 1.52 (1.25). Improvements at EOT in BDI and STAT. 50% (AN-BP), 52% (BN) of patients had clinically meaningful improvements in BDI. 24.1% of AN-BP and 29.3% of BN patients met criteria for full remission (normal BMI, no compensatory behaviors, and normal cognitions) at EOT. 27.3% of AN-BP and 27.3% of BN patients met criteria for full remission at FU. Binge-purging reduced in BN but not in AN-BP.	

Abbreviations: AN-BP, Anorexia nervosa, binge-purging type; AN-R, Anorexia nervosa, restricting type; ANSOCQ, Anorexia Nervosa Stages of Change Questionnaire; BDI, Beck Depression Inventory; BN, Bulimia nervosa; CBT-AN, Cognitive behavioral therapy for anorexia nervosa modified for severe and enduring form; CIA:Clinical Impairment Assessment; DH, Day-hospital; EAT, The Eating Attitudes Test; EDE, Eating Disorder Examination interview; EDE-Q, Eating Disorder Examination—Questionnaire; EDQOL, Eating Disorder Quality of Life Instrument; EOT, End of treatment; FU, Follow-up; GHQ-28, The General Health Questionnaire–28; H, Hours MCS, Mental Component Summary scale; MET-CBT, Motivational enhancement and schema-focused cognitive behaviour therapy; Mo, Months; PCS, Physical Component Summary scale; NR, Not reported; PHP, Partial hospital program RCT, Randomized controlled trial; Severe and enduring anorexia nervosa; SE-ED, Severe and enduring eating disorder; SF-12, Short Form-12 Health Status Questionnaire; SSCM, Specialist supportive clinical management; STAT, State–Trait Anxiety Inventory—Trait subscale; SUDS, Subjective Units of Distress Scale; WSAS, Weissman Social Adjustment Scale; YSQ, The Young Schema Questionnaire.

TABLE 5 Characteristics and outcomes of included studies on drug therapies in the treatment of severe and enduring eating disorders

First Author Year Country	Study design Setting	Participants N Diagnosis Mean baseline BMI (*SD*) Ethnicity/race	Mean age (Mean duration of illness, *SD*), years	Type of treatment Treatment duration, Follow-up	Outcome measures	Main findings	QA
Mills 1998 The UK	Open-label Outpatients	*N* = 14 SE-ED (Total 15) AN, BN (CE) BMI NR Ethnicity/race NR	NR, range 24–42 (NR, range 7–21)	Ketamine (with nalmefene) 20 mg/h for 10 h 2–9 infusions at 5 d–3 w no FU	Compulsive behavior (CQC) Weight Menstruation Mood (CDQ) Compulsive eating and starving (CQE, CQS)	Responders (9/15) improved at EOT in CQS. BN and CE: lost weight, AN: gained weight (responders). Menstruation related to weight changes. In responders (9), 4/5 patients went from complete amenorrhea to return of menstruation. In responders CQD, CQE and CQS scores decreased and in nonresponders no change.	Level IV
Hansen 1999 The UK	Case study Inpatient	*N* = 1 AN 12 Ethnicity/race NR	49 (35)	Olanzapine 10 mg/d, reduced to 5 mg/d 6–7 mo no FU	Weight Mental state (NR)	Initial weight 31.2 kg and at EOT 53.1 kg. Confusion cleared, insight changed.	Level V
Bosanac 2003 Australia	Case series (retrospective) Inpatients	*N* = 14 AN-R & AN-BP 14.2 (1.9) Ethnicity/race NR	NR, range 19–49 (10.5, 7.5)	Olanzapine Mean dosage 9.7 mg/d Mean duration 24.9 d no FU	Weight	BMI increased on average from 14.2 (1.9) to 15.3 (1.2) during treatment.	Level V
Christensen 2009 The USA	Case study Outpatient	*N* = 1 BN Normal Caucasian	35 (from late adolescence)	Duloxetine (an SNRI) 30 mg/d for 3 w, 60 mg/d for 12 w, 30 mg/d for 4 mo no FU	Binge-purge episodes	Binge-purge episodes decreased from at least 2/d to 1/d within 3 w. The patient noted a decrease in "drive" to binge, With 60 mg/d for 12 week episodes decreased to 1/mo. No increase in binge-purge behavior after 4 mo with 30 mg/day.	Level V
Andries 2014 Denmark	RCT Cross-over Inpatients/ Outpatients	*N* = 24 AN BMI NR Caucasian	≥18 (≥ 5)	Dronabinol/placebo 2.5 mg x2 /d 4 w no FU	Weight ED symptoms (EDI-2) Leptin levels	A weight gain of 1 kg (95% CI 0.4–1.6) with dronabinol versus 0.3 kg (95% CI 0.1 to 0.8) during placebo (p = .03) Changes in EDI-2 minimal, no difference between dronabinol and placebo.	Level I

Abbreviations: AN-BP, Anorexia nervosa, binge-purging type; AN-R, Anorexia nervosa, restricting type; BMI, Body mass index; BN, Bulimia nervosa; CE, Compulsive eating; CQC, The Coping Questionnaire's Compulsion scores; CQD, The Coping Questionnaire depression sub-scale; CQE, The Coping Questionnaire eating sub-scale; CQS, The Coping Questionnaire starving sub-scale; D, Day; EDI-2, Eating Disorder Inventory-2; EOT, End of treatment; FU, Follow-up; H, Hour Mg, Milligrams; Mo, Month; NR, Not reported; QA, Quality assessment, SE-ED, Severe and enduring eating disorder.

TABLE 6 Characteristics and outcomes of included studies examining brain stimulation therapies in the treatment of severe and enduring eating disorders

First Author Year Country	Study design	Participants N Diagnosis Mean baseline BMI (*SD*) Ethnicity/race	Mean age (Mean duration of illness, *SD*), years	Type of treatment Treatment duration, Follow-up	Outcome measures	Main findings	QA
Van den Eynde 2011 The UK	Pilot study (partially blinded)	*N* = 10 AN-R & AN-BP 15.7 (NR, range 13.8–17.8) Ethnicity/race NR	25 (10, NR, range 3–30)	rTMS 1 exposure (20 min) FU: 10–15 min after exposure	ED symptoms (EDE-Q) Mood (DASS-21) Safety and acceptability	Sensations of "feeling fat" & "feeling full" decreased (EDE-Q). A decrease in "anxiety," no change in mood (DASS-21). Safe, well-accepted. Discomfort occurred.	Level IV
Lipsman 2013 Canada	Open-label study	*N* = 6 AN-R & AN-BP 13.7 (1.4) Ethnicity/race NR	38 (18, 11)	DBS 6 mo FU: none after EOT	Weight gain Mood (HDRS, BDI) Obsessive-compulsive behavior (YBOCS) Anxiety (BAI) Quality of life Safety	Surgery well tolerated, adverse event did occur. No effect on weight. Improvements in both HDRS and BDI. Mean BDI scores decreased by ≥ 18. Mean YBOCS score decreased by about 12 p. Mean BAI scores fell by about 10 p. Quality of life improved for 3 persons.	Level V
McClelland 2013 The UK	Case series	*N* = 2 AN-R & AN-BP 15.8, 16.4 Ethnicity/race NR	23 (12) 52 (35)	rTMS 5 w FU: 1 mo	Weight gain ED symptoms (EDE-Q) Mood (DASS-21)	No weight gain achieved. EDE-Q scores improved (EOT & FU). DASS-21 scores improved (EOT & FU).	Level V
McClelland 2016 The UK	Case series	*N* = 4 SE-ED (Total *N* = 5) AN-R & AN-BP 14.8, 16.4, 15.4, 14.5 Ethnicity/race NR	23 (12) 52 (35) 41 (31) 30 (19)	rTMS 4–5 w FU: 6 mo & 12 mo	Weight gain ED symptoms (EDE-Q) Mood (DASS-21) Change in remission status.	No change in weight, during FU weight decreased. Improvements in ED symptoms. Improvements in DASS-21. At EOT *n* = 1 recovered, *n* = 3 improved, n =1 unchanged; at 6 mo FU *n* = 3 recovered, *n* = 2 improved. At 12 mo FU *n* = 2 recovered, *n* = 1 improved, *n* = 2 unchanged.	Level V
Lipsman 2017 Canada	Open-label study	*N* = 16 AN-R & AN-BP 13.8 (1.5) Ethnicity/race NR	34 (18, 6)	DBS 1 year FU: none after EOT	Safety and acceptability Weight gain Depression and anxiety (BDI, HAMD) Obsessive-compulsive behavior (YBOCS) Disordered eating (YBC-EDS)	Good acceptability (*n* = 2 wanted device removed). BMI increased over 12 mo. Improvements in both BDI and HAMD scores. Anxiety improved with 4 (25%) of 16 patients showing an improvement of more than 50%. YBOCS scores improved: *n* = 5 (36%) of 14 patients had a decrease of more than 50%. Improvements in some of the YBC-EDS sub-scales (YBC-EDS-we, YBC-EDS-r).	Level IV

(Continues)

TABLE 6 (Continued)

First Author Year Country	Study design	Participants N Diagnosis Mean baseline BMI (*SD*) Ethnicity/race	Mean age (Mean duration of illness, *SD*), years	Type of treatment Treatment duration, Follow-up	Outcome measures	Main findings	QA
Dalton 2018 The UK	RCT	*N* = 34 AN-R & AN-BP 16.0 (1.4) White *N* = 31; Other *N* = 3	29.7 (14.1, 10.8)	rTMS 4 w FU: 4 mo	Feasibility and safety Weight gain ED symptoms (EDE-Q) Mood (DASS-21, POMS) Quality of life (EQ-5D-5L)	Reten tion rate 93.8 (30/32). Change in BMI greater in intervention group (NS). No difference in ED symptoms. DASS-21: 4 mo total score change −21.3 (24.3) in the intervention group and −3.8 (12.8) in the sham group, a between group effect size of $d = -0.9$ (95% CI −1.62 to −0.17). Improvements in DASS-21 depression and stress subscales, and POMS total mood disturbances scale. Medium between-group effect sizes on change scores in quality of life ($d = 0.52$, 95% CI −0.19 to 1.22) at 4 mo FU.	Level I

Abbreviations: AN-BP, Anorexia nervosa, binge-purging type; AN-R, Anorexia nervosa, restricting type; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; DASS-21, 21-item Depression, Anxiety and Stress Scale; DBS, Deep brain stimulation of the subcallosal cingulate; ED, Eating disorder; EDE-Q, Eating Disorder Examination –Questionnaire; EQ-5D-5L, EuroQol Quality of Life Scale (5-level EQ-5D version); EOT, End of treatment FU, Follow-up; HAMD, Hamilton Depression Rating Scale; HDRS, Hamilton Depression Rating Scale; Min, Minutes; Mo, Months; NR, Not reported; NS, not significant; P, Points; POMS, the Profile of Mood States; QA, Quality assessment; rTMS, Repetitive transcranial magnetic stimulation; SE-ED, Severe and enduring eating disorder; W, Weeks; YBOCS, Yale-Brown Obsessive Compulsive Scale; YBC-EDS, Yale-Brown-Cornell Eating Disorder Scale, YBC-EDS-we, Yale-Brown-Cornell Eating Disorder Scale, eating disorder weight and eating preoccupation subscale; YBC-EDS-r, Yale-Brown-Cornell Eating Disorder Scale, eating disorder rituals subscale.

TABLE 7 Characteristics and outcomes of included studies examining parenteral nutrition and strength training in the treatment of severe and enduring eating disorders

First Author Year Country	Study design Setting	Participants N Diagnosis Mean baseline BMI (*SD*) Ethnicity/race	Mean age (Mean duration of illness, *SD*), years	Type of treatment Treatment duration, Follow-up	Outcome measures	Main findings	QA
Latzer 2000 Israel	Case study Outpatient	*N* = 1 AN-BP 12 Child of middle-class mixed, Ashkenazi-Sapharlic, parents	24 (11)	Total parenteral hyperalimentation Duration: 7 mo FU: 1 year	Weight GI symptoms Menstruation Mood (NR)	Gained 10 kg in 7 mo. FU: maintained stable weight, GI symptoms almost disappeared. FU (1 year): weight gain maintained, not menstruated. Positive change in mood.	Level V
Bratland-Sanda 2018 Norway	Case study Outpatient	*N* = 1 AN-R 17.6 Ethnicity/race NR	25 (9)	Maximal Strength Training 3 x w Duration: 16 w FU: 6 mo	ED symptoms (EDE) Weight BMD (DXA) Muscle strenght Energy intake Compulsive exercise (CET)	No change in EDE or weight. BMD increased by 4% in lumbar spine and right femoral neck, by 3% in left femoral neck. Strength improved by 36% in upper body, and 30% in legs. From EOT to FU strength decreased by 7%. Inability to adhere to adequate energy intake. No change in CET.	Level V

Abbreviations: AN-BP, Anorexia nervosa, binge-purging type; AN-R, Anorexia nervosa, restricting type; BMD, Bone mineral density; CET, Compulsive exercise test; DXA, Dual x-ray absorptiometry; ED, Eating Disorder; EDE, Eating Disorder Examination interview; EOT, End of treatment; FU, Follow-up; GI, Gastrointestinal; Mo, Months; NR, Not reported; W, Week.

Brown et al., 2018; George et al., 2004; Levinson et al., 2014; Touyz et al., 2013); and a separate five of the included studies were drug interventions (Andries et al., 2014; Bosanac et al., 2003; Christensen & Averbuch, 2009; Mills et al., 1998; Hansen, 1999). Brain stimulation therapies were studied in six studies, of which four studied repetitive transcranial magnetic stimulation (rTMS) therapy (Dalton et al., 2018; McClelland et al., 2013; McClelland et al., 2016; Van den Eynde et al., 2011); and two deep brain stimulation (DBS) of subcallosal cingulate (Lipsman et al., 2013; Lipsman et al., 2017). Furthermore, one study employed total parental hyperalimentation (Latzer et al., 2000) and one resistance training (Bratland-Sanda et al., 2018).

The outcome measures varied considerably between the studies. Nineteen out of 23 studies reported a change in weight or BMI as their primary or secondary outcome. Other common outcome measures included a change in eating disorder symptoms or psychopathology (17 studies), and a change in mood (12 studies). Seven studies examined a change in clinical impairment or general symptomology. Safety or acceptability of the treatment was studied in five out of 23 studies. Other outcomes studied were, for example: a change in compensatory behavior in four studies; a change in compulsive behavior in four studies; and menstruation in two studies. Four studies also examined quality of life, and two studied readiness to recover as an outcome measure.

3.3 | Methodological quality

The level of evidence of the included studies ranged from low to high (please see Tables 3–7 for details). Overall, three studies were found to have high Level I evidence (all RCTs), five Level III evidence, five Level IV evidence, and ten Level V evidence. Most of the drug trials had insufficient methodological quality largely due to a case study design (Table 5).

3.4 | Synthesis of results

3.4.1 | Inpatient treatment programs

Inpatient treatment programs were studied in five naturalistic follow-up studies (Calugi et al., 2017; Long et al., 2012; Rø et al., 2003; Rø et al., 2004; Rø et al., 2005) (see Table 3). All reported treatment programs were either completely or in part based on cognitive behavioral therapy (CBT) and consisted of both individual and group sessions with a therapist. Two studies employed nutrition plans aimed at weight restoration in SE-AN patients (Calugi et al., 2017; Long et al., 2012). The use of antidepressants was evaluated individually in two studies, and those patients with, for example, recurrent severe depression were advised to continue their medication (Rø et al., 2003;

Rø et al., 2004). In Calugi et al. (2017), psychotropic drugs were not prescribed as a part of the treatment and those patients taking medication were gradually tapered off them. Programs lasted from three to five months on average. Sample sizes were moderate, between n = 25 and n = 72 patients. Two studies included only participants with AN, and the other three had participants with AN, BN, and EDNOS diagnoses (Table 3).

Eating disorder symptoms, as measured by Eating Disorder Examination Interview, Eating Disorder Examination Questionnaire, and Eating Disorder Inventory, were significantly improved in all five inpatient studies. Most of the reductions in eating disorder symptomology occurred during the inpatient treatment and only two studies found improvements during the follow-up (Calugi et al., 2017; Long et al., 2012). General psychopathology also improved during the treatments in all four reporting studies (Calugi et al., 2017; Rø et al., 2003; Rø et al., 2004; Rø et al., 2005).

Four studies reported weight changes, all of which found significant weight gain (Calugi et al., 2017; Long et al., 2012; Rø et al., 2004; Rø et al., 2005). Calugi et al. (2017) found that weight increased from admission to the end of the treatment (20 weeks), but not during six and 12 months of follow-up. Instead, a decrease in weight was reported during that period; however, the mean weight still remained higher after 12 months of follow-up compared to baseline weight. Moreover, high acceptability of the treatment was observed with 85% of patients completing the study. In a study by Long et al. (2012), the mean BMI increased from 14.1 to 19.5 kg/m^2 during the treatment (mean length 102 days). The increase in BMI was also maintained during a 4-year follow-up. On the contrary, Rø et al. (2004) reported a negative correlation between weight gain during treatment and follow-up, that is those patients with successful weight gain during inpatient treatment tended to lose weight after discharge to follow-up, and those without successful weight gain managed to gain weight during follow-up. Those patients with low weight on admission showed a significant mean weight increase of approximately 4 kg at the follow-up. In a study by Rø et al. (2005), weight also increased particularly during the 2-year follow-up although weight gain during inpatient treatment was not significant.

Two studies assessed changes in binge/purge behavior, and laxative misuse (Rø et al., 2003; Rø et al., 2005). Both found a decrease in these episodes during treatment. However, similarly to weight gain outcomes, compensatory behaviors did not decrease during follow-up, with some tendencies for increase reported.

3.4.2 | Outpatient and day-hospital treatment programs

One RCT (Touyz et al., 2013), three naturalistic follow-up studies (George et al., 2004; Abbate-Daga et al., 2015; Brown et al., 2018), and one case study (Levinson et al., 2014) assessed outpatient or day-hospital treatment programs in the treatment of SE-ED. Table 4 presents details of the study characteristics and main outcomes.

Treatment was specifically modified for SE-ED by prioritizing quality of life and harm minimization associated with eating disorder instead of weight gain and recovery in an RCT by Touyz and colleagues (Touyz et al., 2013). They randomized 31 SE-AN outpatients to CBT-AN treatment arm and 32 SE-AN patients to specialist supportive clinical management. High retention rate (85%) was achieved at a follow-up (6- and 12-month post-treatment) and both treatments were acceptable.

Treatment was also modified for SE-ED in another study by focusing on raising awareness and doubt about living with chronic AN (George et al., 2004). Generally, in outpatient and day-hospital treatment studies, treatments consisted of psychological individual and/or group sessions provided two to six times per week. Two studies also provided weekly sessions with a dietitian (Abbate-Daga et al., 2015; Brown et al., 2018). Programs lasted from one to eight months. Follow-up periods also varied, from no follow-up to one-week to two-year follow-up. There was a high heterogeneity in study sample sizes (from n = 1 to n = 164). Three studies included only participants with AN, one study included participants with AN or BN, and one study with AN or EDNOS diagnoses.

All but one of the four studies reporting changes in eating disorder symptoms found significant improvements in symptoms during outpatient or day-hospital treatment (Abbate-Daga et al., 2015; Brown et al., 2018; Levinson et al., 2014; Touyz et al., 2013). Importantly, improvements were not limited to the treatment period and continued also during follow-up (from 1 week to 12 months). For example, BMI significantly increased both during treatment (mean increase of 0.6 kg/m^2) and follow-up (mean increase of 0.1 kg/m^2) in the RCT in SE-AN patients by Touyz et al. (2013). A naturalistic follow-up study by Brown et al. (2018) also reported a clinically significant increase in BMI (mean = 1.7 kg/m^2) in binge/purge SE-AN patients. In Levinson et al. (2014) study, a case with restrictive SE-AN gained weight during CBT with imaginal exposure therapy treatment, which was maintained at 1-month follow-up. George et al. (2004) found neither change in eating disorder symptoms nor in weight during 6 months of a motivational enhancement and schema focused CBT program. However, motivational therapy employed in that study was not aimed at symptom reduction, but rather at increasing the readiness to recover from an eating disorder. Moreover, it included both SE-AN and severe and enduring EDNOS patients.

Treatment seemed to increase participants' motivation to recover from their eating disorder. In the RCT by Touyz et al. (2013), the group that received CBT and the group that received specialist supportive clinical management showed significant improvements during treatment and 12-month follow-up. At follow-up, the group that received CBT had higher readiness to recover than the group that received specialist supportive clinical management. Motivational therapy employed in the study by George et al. (2004) resulted in a significant change in motivation to recover. Many patients reported, for the first time ever, that they were willing to consider making changes, which could be considered a first step in the recovery of eating disorders. Despite this, there were no changes in eating disorder symptoms, life satisfaction, and early maladaptive schemas.

Treatment outcomes such as an increase in BMI (aiming for BMI of at least 17.5 kg/m^2), change in eating disorder symptoms, and change in compensatory behavior were studied in two of the included studies (Abbate-Daga et al., 2015; Brown et al., 2018). A 6-day partial hospital program for an average of 90 days resulted in 24% of patients with binge/purge AN and 29% of patients with BN meeting full recovery, defined by a BMI >18.5 kg/m^2, no fasting, binge/purge behavior in the last 28 days, and Eating Disorder Examination Questionnaire Global scores within one standard deviation of community means (Brown et al., 2018). At mean of 11.5 months follow-up, the proportion of patients with AN in full remission had increased, whilst the proportion of patients with BN had decreased. Abbate-Daga et al. (2015) demonstrated that both binge/purge and restrictive AN patients (n = 31) with long-standing eating disorders were less likely to recover during treatment and follow-up when compared with AN patients with a shorter duration of the illness (n = 25). In their study, at the end of the six-month day-hospital treatment, only 11% of patients with SE-ED met remission criteria, defined by a BMI > 17.5 kg/m^2, the absence of binge/purge episodes, and normal scores on Eating Disorder Inventory 2 subscales 1–3 (drive for thinness, bulimia, and body dissatisfaction).

3.4.3 | Drug trials

Overall, five drug trials met the inclusion criteria for this review and study characteristics and main findings are presented in Table 5. These included one randomized cross-over study (Andries et al., 2014), three case-studies (Bosanac et al., 2003; Christensen & Averbuch, 2009; Hansen, 1999), and one open-label study (Mills et al., 1998). The drugs studied were dronabinol (n = 1 study), olanzapine (n = 2 studies), ketamine (n = 1 study), and duloxetine (n = 1 study). Study populations varied between n = 1 and n = 24 participants, and study durations between three weeks and seven months. Three studies included only participants with AN, one study included participants with AN or BN and one study included a case with BN diagnosis.

Dronabinol was found to promote weight gain in a RCT comparing a 4-week dronabinol treatment to placebo in AN patients (Andries et al., 2014). Dronabinol is a synthetic cannabinoid that in addition to improving appetite as a function of endocannabinoid system also seems to have anabolic effects by interacting with molecular targets involved in peripheral fat metabolism (Cota et al., 2003). Despite small improvements in weight in the dronabinol group, changes in eating disorder symptoms were minimal and did not differ between the groups (Andries et al., 2014). No severe adverse events were reported in either group, whilst reported side effects were similar in dronabinol treatment and placebo groups.

Olanzapine was studied in two case studies that included AN participants only (Bosanac et al., 2003; Hansen, 1999). One was a case series of 14 participants and the other a single case study. Olanzapine was prescribed as it is known to diminish anxiety (Tollefson & Kuntz, 1999) and to alleviate body image perception as well as induce weight gain as a side effect (Powers, Santana, & Bannon, 2002). Both studies reported significant weight gain during the olanzapine treatment (Bosanac et al., 2003; Hansen, 1999). In the case series, the average dosage was 9.7 mg/day (Bosanac et al., 2003). The initial dosage in the case study was 10 mg/day, but it was reduced to 5 mg/day due to patient's complains of tiredness and dizzy spells (Hansen, 1999). Olanzapine was found to increase weight clinically significantly both given alone and in conjunction with other psychotropic drugs.

Ketamine was studied in one open-label study including patients with longstanding AN, BN and compulsive eating (Mills et al., 1998). Two to nine ketamine infusions were given at intervals of five days to three weeks. Ketamine blocks the excitement of the hippocampus by glutamate-NMDA receptors that leads to long-term potentiation (LTP) and thus can affect patients' compulsive drive characterized by frequent recall of anorexic thoughts (Mills & Medlicott, 1992; Stringer & Guyenet, 1983). Nine of the 15 patients responded to the treatment (Mills et al., 1998). Scores for compulsive behavior and compulsive eating and self-starvation decreased for the responders, with no change in the nonresponders. Weight change depended on ED diagnosis. Patients with SE-BN lost weight during treatment whereas those with SE-AN gained weight. All patients except one reported subsequent resumption of menstruation.

One case study assessed duloxetine in the treatment of SE-BN (Christensen & Averbuch, 2009). Duloxetine acts as reuptake inhibitor in serotonin and norepinephrine systems, both of which are presumed to play a part in pathophysiology of BN (Barbarich, Kaye, & Jimerson, 2003; Brambilla, 2001; Kaye, Gendall, & Strober, 1998). The case study reported that binge/purge episodes were decreased from at least two per day to one per day with 30 mg/day of duloxetine for three weeks (Christensen & Averbuch, 2009). After that, the dose was increased to 60 mg/day for 12 weeks. This led to further decrease in binge/purge episodes to one per month. However, due to patient's complaints of jitteriness, the dose was reduced to 30 mg/day. Despite the decrease, episodes were maintained at one per month for the four months of follow-up.

3.4.4 | Brain stimulation therapies

Of the 23 included articles, six assessed brain stimulation therapies as treatment for SE-ED. Of these, four assessed rTMS (Dalton et al., 2018; McClelland et al., 2013; McClelland et al., 2016; Van den Eynde et al., 2011), and two reported DBS of the subcallosal cingulate (Lipsman et al., 2013; Lipsman et al., 2017). Study characteristics and main findings are presented in Table 6.

There was only one RCT included (Dalton et al., 2018), which was a feasibility trial of real versus sham rTMS treatment in adults with SE-AN. They randomized thirty-four participants into two groups (17 per group) and found that the treatment protocol was feasible and acceptable to participants. This study provided preliminary evidence for the therapeutic potential, especially moderate to large effect sizes for mood outcomes, of rTMS in SE-AN.

Generally, in the reviewed brain stimulation studies, the duration of the treatments varied from one 20-minute exposure to repeated

sessions for five weeks in rTMS and from six months to over 1 year continuous stimulation in DBS. Sample sizes were generally small, ranging from n = 2 to n = 34 participants. All six studies included patients with either restricting or binge/purge type of AN. All participants had a long history of eating disorder with a mean duration of 10 years or more.

Only one of the four brain stimulation studies that reported weight changes, found a significant weight gain during the treatment (Lipsman et al., 2017). In this study, the mean BMI increased from 13.8 to 17.3 kg/m^2 over 12 months. However, weight gain did not occur until at least three months after stimulation had started, even though participants' depression and anxiety scores improved prior to the weight gain.

Changes in eating disorder symptoms were assessed in five of six studies examining brain stimulation therapies. No significant difference in eating disorder symptoms were found in a 4-week RCT comparing rTMS with sham rTMS (Dalton et al., 2018). Four studies reported at least some improvements in ED symptomology (Lipsman et al., 2017; McClelland et al., 2013; McClelland et al., 2016; Van den Eynde et al., 2011). Three studies employed the Eating Disorder Examination Questionnaire (Fairburn, 2009) to assess symptoms and one study used the Yale-Brown-Cornell Eating Disorder Scale (Mazure, Halmi, Sunday, Romano, & Einhorn, 1994). Results favored active treatment but were of small effect size. Participants' mood improved significantly in all studies that investigated brain stimulation, although one study found a decrease in anxiety but not in depression scores (Van den Eynde et al., 2011). Most studies assessed mood with the 21-item Depression, Anxiety and Stress Scale (Lovibond & Lovibond, 1995).

Brain stimulation therapies were generally found to be safe and feasible treatment methods and also accepted by the patients (Dalton et al., 2018; Lipsman et al., 2013; Lipsman et al., 2017; Van den Eynde et al., 2011). Side effects of rTMS included a slight buzzing in the head (Van Den Eynde et al., 2011), and occasional mild headaches (McClelland et al., 2016), whilst DBS was linked to pain and nausea (Lipsman et al., 2013; Lipsman et al., 2017). Adverse events, such as electrolyte disturbances and seizures, did occur both during rTMS and DBS, but they were in general related to the underlying disease, not the treatment (Dalton et al., 2018; Lipsman et al., 2013; Lipsman et al., 2017).

3.4.5 | Other treatments

Other interventions included in this review were one case study on total parenteral hyperalimentation (Latzer et al., 2000) and one on exercise (maximal strength training; Bratland-Sanda et al., 2018). Both studies included only one participant with SE-AN. Study characteristics and main outcomes are listed in Table 7.

In the hyperalimentation study, parenteral nutrition was provided for seven months (Latzer et al., 2000). Total parental nutrition is considered as sub-optimal treatment option with many risks, whereas enteral routes of feeding should be prioritized in treatment (Diamanti et al., 2008). The study (Latzer et al., 2000) reported side effects such as local infections, local irritation and an episode of hypokalemia. Patient's weight increased by 10 kg during total parenteral hyperalimentation, and gastrointestinal symptoms mostly resolved (Latzer et al., 2000). Also, a positive change in the patient's mood was reported. At a 1-year follow-up, the patient had maintained her weight gain; however, remained amenorrheic.

In the exercise study, the maximal strength regime was employed for four months (Bratland-Sanda et al., 2018). Maximal strength training regime did not result in significant weight gain nor lead to improvement in disorder symptoms. The patient in the exercise study was unable to adhere to the recommended energy intake of 2,500–2,900 kcal per day. BMI increased from 17.6 to 17.9 kg/m^2 during the study but was not considered clinically significant. Menstrual dysfunctions also persisted. Despite this, the patient's muscle strength and bone mineral density increased, resulting in normal bone density in the course of the treatment, which was considered a significant improvement.

4 | DISCUSSION

This review, presenting a wide variety of treatments interventions on SE-ED with mixed outcomes, identified several encouraging results. Summarized inpatient treatment programs were effective in short-term symptom reduction, but long-term results were inconsistent. The results of outpatient and day-hospital treatment programs seemed promising for symptom reduction as well as other objectives such as readiness to recover from eating disorder. Drug therapies showed to be partly beneficial, especially as adjuvant therapies. Brain stimulation therapies, which are the most novel approach in the treatment of SE-ED, were shown to be safe, feasible and accepted by the patients. Preliminary results also indicate that brain stimulation might lead to improvements especially in depressive symptoms, which are common in these patients. However, the quality level of the included studies was mainly low apart from three high-quality RCTs.

Similarly to work by Hay and Touyz (2015), the present review found that most of the included studies recruited underweight participants, of which a majority had longstanding AN (16/23 included studies). The remaining seven studies recruited participants with AN or EDNOS except for one case study with a BN patient. At present, the field of research is dominated by studies on AN, and less can be concluded about the treatment of other prolonged eating disorders.

In this review, weight was shown to increase clinically significantly during outpatient, day-hospital and inpatient treatments in SE-ED patients (Brown et al., 2018; Calugi et al., 2017; Levinson et al., 2014; Long et al., 2012; Rø et al., 2004; Rø et al., 2005; Touyz et al., 2013). Most of the weight gain occurred during inpatient treatment, but in outpatient settings, improvements were also made during the follow-up. In some studies, such as Rø et al. (2004), patients with successful weight gain during inpatient treatment tended to lose weight after discharge to follow-up, whereas patients without successful weight gain managed to gain weight during follow-up. This highlights

different weight recovery trajectories between individuals with SE-ED.

It has been argued whether weight recovery and symptom reduction should or should not be the primary goal in treating SE-ED. Instead, other objectives, such as improving quality of life, are suggested to be emphasized (Strober, 2004; Treasure, Cardi, et al., 2015; Wonderlich et al., 2012). Surprisingly, only three studies included in this review examined quality of life as their primary or secondary outcome. In the study by Touyz et al. (2013), significant improvements in quality of life were achieved both at the end of the intervention and follow-up. The focus of the treatment was on improving quality of life rather than weight gain per se. Thus, reduced pressure to gain weight may enhance treatment engagement in patients with SE-AN. Concurrently, BMI significantly increased both during the treatment and follow-up which reflects that in SE-AN, improvements in quality of life and weight may be linked. Similarly, Lipsman et al. (2013) found that improvements in quality of life were connected to weight gain, as patients who achieved improvements in BMI also showed improvement in quality of life. In a rTMS RCT by Dalton et al. (2018), quality of life improved in the rTMS group during the 4-month follow-up, but there was no significant change in BMI. The enhancement in quality of life may have linked with the observed improvements in depression, as comorbid depression is known to associate with poor quality of life in individuals with SE-AN (Arkell & Robinson, 2008). These results suggest that in SE-AN the quality of life may be associated with both weight and depressive symptoms.

In this review, it was observed that eating disorder psychopathology was improved during outpatient and day-hospital treatments (Abbate-Daga et al., 2015; Brown et al., 2018; Levinson et al., 2014; Touyz et al., 2013), psychological inpatient treatments (Rø et al., 2003; Rø et al., 2004; Rø et al., 2005; Long et al., 2012), as well as brain stimulation therapies (Calugi et al., 2017; Lipsman et al., 2017; McClelland et al., 2013; McClelland et al., 2016; Van den Eynde et al., 2011). Symptoms continued to improve during follow-up in outpatient and day-hospital treatment programs that specifically aimed to decrease eating disorder symptoms. This result is promising and suggests importance of focus on symptom reduction also in SE-ED patients.

Previous research in AN has suggested that improvements in ED psychopathology are closely related to improvements in starvation, which highlights the important role of nutrition rehabilitation in ameliorating both symptoms (Calugi, Chignola, El Ghoch, & Dalle Grave, 2018). For example, malnutrition is known to influence cognition which might hinder recovery (Fonville et al., 2014). However, in a rTMS treatment study by McClelland et al. (2016), improvements in both ED symptoms and mood were observed despite persistent low weight in SE-AN patients. Therefore, although nutritional rehabilitation and weight restoration is considered as the gold standard treatment for AN, overcoming pharmacological interventions and psychotherapy (Hay et al., 2014), there is a need for novel treatment innovations for SE-ED to adjunct nutritional rehabilitation. However, it is noteworthy that none of the studies included in this review studied the effects of nutritional rehabilitation on SE-ED per se, although nutritional rehabilitation was included in many of the inpatient, day hospital and outpatients programs.

Majority of the reviewed drug trails with olanzapine, dronabinol and ketamine also reported weight gain (Andries et al., 2014; Bosanac et al., 2003; Hansen, 1999; Mills et al., 1998), however, individual studies included only 1–24 participants and only one was an RCT (Andries et al., 2014). Drug trials were generally short in duration and none of the studies included a follow-up period, so long-term effects of these pharmacological interventions remain unclear. However, in the RCT on dronabinol by Andries et al. (2014), disordered eating behavior and symptomatology remained unchanged during the treatment, which suggests that dronabinol may not promote psychoactive effects, and was limited to metabolic effects only. Dronabinol is a synthetic cannabinoid agonist that is suggested to promote orexigenic and metabolic effects. In SE-ED, however, even modest increase in weight without change in psychopathology, may be crucial to the patients. Therefore, this form of interventions with pharmacological therapies should not be overlooked in SE-ED and should be investigated in the future.

Brain stimulation therapies were generally not effective in increasing participants' weight except for one study with DBS that had the longest stimulation period lasting up to 1 year (Lipsman et al., 2017). In this study, authors suggested that preceding changes in limbic functions might be necessary in order to enable weight gain. Thus, the disorder may be maintained by anatomical structures distinct from those governing basal vegetative functions, like appetite and metabolism (Lipsman et al., 2017). A potential target of the treatment interventions should therefore be an alteration of the activity of these structures, which naturally postulates a relatively long duration of the brain stimulation.

Patients with SE-ED are commonly interested in getting help, even if the thought of recovery remains challenging to them (Strober, 2004). Compliance for having active treatments to support recovery, including weight recovery in SE-AN, is more challenging. SE-ED patients struggle with the dilemma of wanting to get better but struggle to commit and take responsibility for recovery as the eating disorder has often become such a crucial part of their identity (Stockford, Stenfert Kroese, Beesley, & Leung, 2019). Studies in this review had only few drop-outs with relatively high reported adherence to treatment. This outcome supports the previously reported motivation and commitment to treatment interventions in patients with SE-ED, however, is limited to patients who want to take part in studies and cannot be generalized to all SE-ED patients.

In the light of the results pertaining to treatment of SE-ED, a question regarding the usefulness of the term SE-ED itself should be further discussed. The previously described staging model, proposed by Hay and Touyz (2015), could provide a helpful guide in management. Furthermore, based on the results of this review, both more traditional and novel treatment methods could be beneficial for this group, particularly when traditional treatments fail to deliver good outcomes even after numerous attempts. Tailored flexible treatment solutions, focused on therapeutic alliance and based on the patients´ ambivalence in relation to treatment and recovery, are urgently needed. Also, as the understanding of eating disorders is deepening,

new innovative treatments might arise. Thus, we need to be open to this opportunity. Moreover, more investigation on the long-term physiological and psychological changes due to undernutrition are needed, as these should be taken into account as a part of treatment.

There are several limitations in this review. There was high heterogeneity in terms of sample size, follow-up periods, treatment methods, and outcomes measured between the studies. As the definition of a SE-ED remains unclear, also the duration of illness of the participants varied between the studies although was generally long (mean duration between 9 and 35 years). Lack of consistency in these and other variables, such as previous treatment attempts and current medications, challenges comparisons and synthesis of the results. Because of the methodological disparities between the studies, comparison of different treatment methods was not conducted. Some studies also had deficiencies in reporting, for example, most of the studies failed to report participants' ethnicity and/or race. Most of the reviewed studies had also suboptimal methodological quality due to nature of study designs (e.g. uncontrolled studies, case studies). However, small study populations and an observational nature are common in ED research (Rocks, Pelly, & Wilkinson, 2014), and RCTs are not always ethically justified in the treatment of this population. However, it is worth noting that this review also identified three RCTs of good methodological quality and more RCTs, whenever possible to conduct, are warranted. In the future, having a clear sense of targeted intervention mechanisms could provide new possibilities for RCTs in this population.

In conclusion, this review identified several potentially beneficial treatment options for SE-ED including inpatient treatments, outpatient and day-hospital treatments, drug and brain stimulation therapies. However, more high-quality research evidence particularly based on RCTs, when possible, is warranted. The question of what the best possible care for someone living with a SE-ED is, remains unanswered. Additionally, it is important to clarify and more consistently apply the definition of SE-ED. Furthermore, future programs in this population may also include other therapeutic goals, such as quality of life, as many of the studies included in this review have focused mainly on traditional treatment responses, such as weight gain and psychopathology. Finally, despite the severity of SE-ED, the reviewed studies reported symptom reduction and increased recovery, which is encouraging for the development and improvement of future therapeutic approaches to treatment.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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