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Specific psychological therapies versus other therapies or no treatment for severe and enduring anorexia nervosa (Review)

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[Intervention Review]

Specific psychological therapies versus other therapies or no treatment for severe and enduring anorexia nervosa

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ABSTRACT

Background

Anorexia nervosa is a psychological condition characterised by self-starvation and fear or wait gain or other body image disturbance. The first line of treatment is specific psychological therapy; however, there is no consensus on best practice for treating people who develop severe and enduring anorexia nervosa (SEAN). Notably, there is no universal definition of SEAN.

Objectives

To evaluate the benefits and harms of specific psychological therapies for severe and enduring anorexia nervosa compared with other specific therapies, non-specific therapies, no treatment/waiting list, antidepressant medication, dietary counselling alone, or treatment as usual.

Search methods

We used standard, extensive Cochrane search methods. The last search date was 22 July 2022.

Selection criteria

We included parallel randomised controlled trials (RCTs) of people (any age) with anorexia nervosa of at least three years' duration. Eligible experimental interventions were any specific psychological therapy for improved physical and psychological health in anorexia nervosa, conducted in any treatment setting with no restrictions in terms of number of sessions, modality, or duration of therapy. Eligible comparator interventions included any other specific psychological therapy for anorexia nervosa, non-specific psychological therapy for mental health disorders, no treatment or waiting list, antipsychotic treatment (with or without psychological therapy), antidepressant treatment (with or without psychological therapy), dietary counselling, and treatment as usual as defined by the individual trials.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. Our primary outcomes were clinical improvement (weight restoration to within the normal weight range for participant sample) and treatment non-completion. Results were presented using the GRADE appraisal tool.

Main results

We found two eligible studies, but only one study provided usable data. This was a parallel-group RCT of 63 adults with SEAN who had an illness duration of at least seven years. The trial compared outpatient cognitive behaviour therapy for SEAN (CBT-SEAN) with specialist supportive clinical management for SEAN (SSCM-SE) over eight months. It is unclear if there is any difference between the effect of CBT-SEAN versus SSCM-SE on clinical improvement at 12 months (risk ratio (RR) 1.42, 95% confidence interval (CI) 0.66 to 3.05) or treatment non-completion (RR 1.72, 95% CI 0.45 to 6.59). There were no reported data on adverse effects. The trial was at high risk of performance and detection bias.

We rated the GRADE level of evidence as very low-certainty for both primary outcomes, downgrading for imprecision and risk of bias concerns.

Authors' conclusions

This review reports evidence from one trial that evaluated CBT-SEAN versus SSCM-SE. There was very low-certainty evidence of little or no difference in clinical improvement and treatment non-completion between the two therapies. There is a need for larger high-quality trials to determine the benefits of specific psychological therapies for people with SEAN. These should take into account the duration of illness as well as participants' previous experience with evidence-based psychological therapy for anorexia nervosa.

PLAIN LANGUAGE SUMMARY

Psychological therapies for people with severe and enduring anorexia nervosa

Key messages

1. One small study of people with severe and enduring anorexia nervosa compared two therapies: cognitive behaviour therapy and specialist supportive clinical management.
2. There is not enough evidence to say with certainty if any specific therapy is more effective than any other.
3. There is a need for larger studies to investigate the benefits of treatment for people with SEAN.

Why is this review important?

Anorexia nervosa is an eating disorder and serious mental illness. People with anorexia nervosa normally have a very low bodyweight, an intense fear of gaining weight, and a distorted perception of their weight. The main treatment for anorexia nervosa is specific psychological therapy combined with multidisciplinary physical and nutritional health care. The main available therapies are cognitive behaviour therapy (CBT), specialist supportive clinical management (SSCM), the Maudsley therapy for adults with anorexia nervosa (MANTRA), and focal psychodynamic therapy (FPT). They all provide advice and counselling on nutrition and physical care, but they differ in their psychological focus. CBT addresses the thoughts (cognitions) that underpin the behaviours of anorexia nervosa, such as fear of fatness, and provides active behavioural strategies (e.g. gentle reintroduction of foods that cause anxiety). SSCM provides supportive therapy and goal setting. MANTRA focusses on helping the person think more freely and finding reasons for change. FPT helps the person work through past relational experiences and explore parts of their identity that underpin the eating disorder. Some people with anorexia nervosa do not improve with usual treatments and develop a severe and enduring form of the illness that is very debilitating. There is very little published evidence to help clinicians manage people with severe and enduring anorexia nervosa (SEAN); in fact, there is not even a universal definition for this condition.

Who will be interested in this review?

People with lived experience of SEAN and those who care for them, including healthcare providers, will be most interested in this review. People more broadly affected by anorexia nervosa and other eating disorders will also be interested.

What did we want to find out?

We wanted to find out if any specific psychological therapies could improve the mental and physical health of people with SEAN. Specifically, we wanted to know if any specific psychological therapy could help people with SEAN to gain weight or complete treatment. We also wanted to find out if specific psychological therapies were associated with any unwanted effects.

What did we do?

We searched for studies that investigated any specific psychological therapy compared with any other specific psychological therapy, a non-specific psychological therapy for mental health disorders, no treatment or waiting list, antipsychotic or antidepressant medication, dietary counselling, or treatment as usual. We compared and summarised the results of the studies and rated our confidence in the evidence based on factors such as study methods and sizes

What did we find?

We found two eligible studies, but only one study in 63 adults provided data we could use in our review. It found that weight gain and completion of treatment improved with cognitive behaviour therapy and specialist supportive psychological therapy, but that neither therapy was better than the other. Both therapies had been adapted for people with SEAN. There was no information on unwanted effects of treatment.

What are the limitations of the evidence?

This review did not find adequate evidence to determine whether any form of therapy is more effective than any other. We have very little confidence in the evidence because it came from a single study that included only 63 people, and because the people in the studies knew which treatment they were getting. There is a need for larger studies to investigate the benefits of treatment for people with SEAN.

How up to date is this evidence?

The evidence is current to July 2022.

SUMMARY OF FINDINGS

Summary of findings 1. Specific psychological therapy compared to alternative specific psychological therapy for severe and enduring anorexia nervosa

Specific psychological therapy compared to alternative specific psychological therapy for severe and enduring anorexia nervosa

Patient or population: people with severe and enduring anorexia nervosa
Setting: Australia, UK, and USA, outpatient
Intervention: CBT-SEAN
Comparison: SSCM-SE

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)[b]	
				Risk with alternate specific psychological therapy	Risk difference with Specific psychological therapy
Clinical improvement: weight restoration to within the normal weight range for participant sample Follow-up: 12 months	63 (1 study)	**Very low**[a]	**RR 1.42** (0.66 to 3.05)	**Study population**	
				250 per 1000	105 more per 1000 (85 fewer to 513 more)
Treatment non-completion: proportion of participants who did not complete treatment	63 (1 study)	**Very low**[a]	**RR 1.72** (0.45 to 6.59)	**Study population**	
				68 per 1000	68 more per 1000 (52 fewer to 524 more)
Proportion of study dropouts or non-completers due to an adverse event or experience	63 (1 study)	No data available	No data available	No data available	No data available

CBT-SEAN: cognitive behavioural therapy for severe and enduring anorexia nervosa; **CI:** confidence interval; **RR:** risk ratio; **SSCM-SE:** specialist supportive clinical management for severe and enduring anorexia nervosa.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

[a] Downgraded one level for study limitations (high risk of performance and detection bias) and two levels for imprecision (single study with 63 participants, wide 95% CI).
[b] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI) i.e. are based on the differences between therapy groups in proportions of people experiencing the outcomes.

BACKGROUND

Description of the condition

Anorexia nervosa is a psychological disorder of self-starvation and a specific psychopathology of fear of weight gain or other body image disturbance. The earliest accounts of anorexia nervosa date back to the 19th century (Gull 1874; Lasegue 1873). Today, it is common in low- and middle-income countries as well as in high-income countries (Makino 2004). One systematic review of 12 cumulative incidence studies found an estimated mean yearly incidence in the general population of 18.5 per 100,000 (standard deviation (SD) 21.01) in women and 2.25 per 100,000 (SD 2.63) in men (Pawluck 1998). General population household surveys have found that 0.9% of women in the USA and 0.48% of women across six European countries have experienced anorexia nervosa at some point in their lifetime (Gamiche 2016; Hudson 2007; Preti 2009). The estimated prevalence is 10 times higher in females than in males (Hudson 2007). It appears that anorexia nervosa became more common over the second half of the 20th century (Lucas 1991; Pawluck 1998), although the incidence may have since plateaued (Keski-Rahkonen 2016).

A comprehensive review of 119 studies in 5590 people with follow-up ranging from one to 29 years reported that 47% of people with anorexia nervosa recover (range 0% to 92%), 34% improve (range 0% to 75%), 5% die (range 0% to 22%), and 21% develop a chronic eating disorder (range 0% to 79%) (Steinhausen 2002). Another study reported that 62.8% of people with anorexia nervosa had recovered at 22 years of follow-up (Eddy 2017). Those who do not recover are considered to have severe and enduring anorexia nervosa (SEAN), which is one of the most challenging disorders in mental health care (Strober 2004). People with SEAN have the highest mortality rate of any mental illness (20% at 20 years; Steinhausen 2002), and a markedly reduced life expectancy (Harbottle 2008). Nevertheless, many have persistent illness, with one study showing a higher rate of purging behaviours and older age in people with SEAN compared to those with anorexia nervosa that was not severe or enduring (Calugi 2013). SEAN also imposes a heavy burden on health and other public services. People with the disorder are often unemployed and on sickness benefits with multiple medical complications such as renal failure, liver failure, cardiac failure, and osteoporosis (Birmingham 2010; Robinson 2009). In addition, they require repeated admissions to general and specialist medical facilities and are frequent users of general practitioner services (Birmingham 2010; Robinson 2009). Furthermore, they place a significant burden on parents and others who care for them (Treasure 2001).

SEAN is challenging to define. Although most authors concur that one key feature is persistence of illness despite treatment, there are other important characteristics to consider, such as poor quality of life (Wildes 2017). One potential cause of SEAN is lack of personalised treatment (Gutiérrez 2021, Wonderlich 2020). Most experts agree that recovery or even meaningful symptomatic improvement in longstanding anorexia nervosa is less likely than in an illness with a shorter duration (NICE 2017; Zipfel 2015). However, this assumption is based on extrapolations from general longitudinal follow-up data or clinical consensus (Tierney 2009), or on treatment outcomes of programmes devised for recent-onset anorexia nervosa, where people with longer illness duration have poorer outcomes (Steinhausen 2002). This may lead to unwarranted therapeutic nihilism with regard to treatment. Furthermore, anorexia nervosa treatment has a small evidence base (Lock 2009; NICE 2017; Zipfel 2015; Zeeck 2018), and many people who become chronic have either failed to ever present for treatment (up to 50% in one study) or appear to have benefitted little from treatment (Keski-Rahkonen 2007). Several trials (e.g. Calugi 2017; Raykos 2018), as well as one systematic review from 2020 (Radunz 2020), have found no association between illness duration and outcomes.

Description of the intervention

The recommended treatment for anorexia nervosa is multimodal and multidisciplinary, combining psychological therapy with nutritional and physical rehabilitation (APA 2006; NICE 2017; RANZCP 2014). Nutritional and physical rehabilitation includes refeeding and medical care of the consequences of starvation (Birmingham 2010). Adjunct to psychological therapy is a range of medications, including antidepressants and antipsychotics, which may be prescribed to reduce cognitive and emotive psychological symptoms. However, the evidence base for medications in anorexia nervosa is limited, mostly based on small randomised controlled trials (RCTs) of antipsychotics such as olanzapine (Hay 2012a; Lebow 2013; Monteleone 2022; Zipfel 2015).

A range of psychological therapies are available for anorexia nervosa. These specific therapies address core psychological issues, either for the individual or their family, or both. Some also incorporate nutritional advice and care, although a dietitian may provide this separately. They are usually conducted in face-to-face sessions over a defined period of time. There is limited evidence for the superiority of any specific therapy over any other (Zeeck 2018; Monteleone 2022).

The earliest specific psychological therapies for anorexia nervosa used a psychoanalytic or psychodynamic framework based on the seminal work of Bruch (Bruch 1973). Important elements of this therapy include helping people to redefine their understanding of food and find alternatives to anorexic self-experience and self-expression. Later developments of the psychodynamic approach included focal psychoanalytic psychotherapy (FPT) and self-psychological therapy for eating disorders (Dare 2001; Goodsitt 1985). Time-limited therapies have also been developed. Integrative time-limited therapies include cognitive analytical therapy (CAT; Dare 2001) and interpersonal psychotherapy (IPT; Wilfley 2003). Other time-limited therapies are manualised cognitive behavioural therapy (CBT; Fairburn 2008), family-based therapy (FBT) with and without individual therapy (Le Grange 2005), the Maudsley Model of Anorexia Nervosa Treatment for Adults (MANTRA; Schmidt 2014), and specialist supportive clinical management (SSCM; McIntosh 2006).

For detailed descriptions of these therapies, see Types of interventions. Descriptions of the development and content of these treatments are also found in concurrent Cochrane Reviews on family therapy (Fisher 2018), individual psychological therapies (Hay 2015a), self-help (Perkins 2006), antidepressants (Claudino 2006), and the effects of treatment setting (Hay 2019). These reviews focus on the treatment of acute anorexia nervosa and do not address the management of chronic or treatment-resistant anorexia nervosa.

There is growing interest in the development and modification of treatment strategies for severe and enduring eating disorders,

including anorexia nervosa (Robinson 2009; Zhu 2020). One RCT (involving authors of this review, namely ST, DLG, JL, and PH) developed and compared two specific psychological therapies for SEAN: a modified SSCM aimed at helping people to make any changes that could improve their quality of life and physical well-being (not only weight change) versus cognitive behavioural therapy for anorexia nervosa (CBT-AN) with modifications to focus on quality of life as a primary outcome for people with a chronic disorder (Touyz 2013).

How the intervention might work

Psychological therapies in anorexia nervosa work by reducing aetiological features or maintaining factors, or both, particularly fear of weight gain and rigid and restrictive eating patterns. The approach to achieving this goal can be direct (as in CBT) or indirect (as in psychodynamic psychological therapy and IPT). New developments in anorexia nervosa therapies for people with severe and enduring problems aim to address difficulties consequent to chronic illness, namely poor motivation, cognitive rigidity, impaired interpersonal function, and poor physical health (Brockmeyer 2021; Robinson 2009; Strober 2004; Wonderlich 2012).

The version of SSCM developed in Touyz 2013 (SSCM-SE) is tailored to the specific needs of people with SEAN. SSCM-SE de-emphasises weight gain and a goal weight, focusing instead on strategies that can improve quality of life (e.g. reducing social isolation and improving general physical health). Similarly, Williams and colleagues have described an alternative approach for people with SEAN, namely the Community Outreach Partnership Program (COPP; Williams 2010). COPP aims to improve quality of life and minimise harm, with each patient setting their own goals and pace of therapy.

Finally, Schmidt and colleagues have conducted clinical trials into a novel therapy for anorexia nervosa called MANTRA (Schmidt 2014; Schmidt 2015). In this approach, motivational enhancement therapy is used to explore the patient's understanding of anorexia nervosa in the context of their core beliefs, life rules, and values (Treasure 2008). The treatment also aims to reduce cognitive rigidity and engage carers to support the patient and facilitate reduced interpersonal conflict and criticism. The nutritional aspect focusses on health and safety rather than weight regain.

Why it is important to do this review

To reduce the burden of SEAN, it is crucial to determine the most effective treatment approach. The types of treatments that work well in younger people with short duration of illness (e.g. FBT) may not be applicable or may need modification in people who are unresponsive to established therapies. People who have had an eating disorder for many years have normally adopted an eating-disordered lifestyle: they have a severely regimented daily diet, are socially isolated, experience cognitive disturbance, and are either treatment-resistant or at best poorly motivated for therapy (Robinson 2009). All these factors likely influence the effectiveness of treatment in this population. In addition, the goals of treatment should arguably focus as much on improvements in quality of life and eating behaviours as on weight gain and a lower intensity of treatment (Yager 2019).

On the other hand, there is no agreed definition of SEAN (Broomfield 2017), and some studies have found that many people with severe or chronic illness respond to standard treatment (Raykos 2018). Therefore, it is important to evaluate modified approaches in relation to standard care in this population.

Whilst we were aware of one published study that had described outcomes of a specific approach for longstanding anorexia nervosa (Touyz 2013), we thought there may have been more RCTs that had recruited people with a mean duration of illness of three years or more. With this review, we aimed to strengthen the portfolio of Cochrane Reviews on anorexia nervosa (Claudino 2006; Claudino 2007; Fisher 2018; Hay 2015a; Hay 2019).

OBJECTIVES

To evaluate the benefits and harms of specific psychological therapies for severe and enduring anorexia nervosa compared with other specific therapies, non-specific therapies, no treatment/waiting list, antidepressant medication, dietary counselling alone, or treatment as usual.

METHODS

Criteria for considering studies for this review

Types of studies

Parallel RCTs, including cluster-RCTs and cross-over trials.

Types of participants

There is no standard definition of SEAN. For the purpose of this review, we adopted the following criteria.

1. No age limit (adults, children, or adolescents)
2. Anorexia nervosa as defined by the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; APA 2013) or the International Classification of Diseases 11th Revision (ICD-11; WHO 2019). According to the DSM-5, anorexia nervosa is characterised by a relentless pursuit of thinness resulting in weight loss substantially below a normal bodyweight (APA 2013). This is in the context of specific psychopathology, including an intense fear of weight gain or persistent behaviour to avoid weight gain and various manifestations of body image disturbance (e.g. when body shape and weight have an excessive influence on the individual's self-worth or self-regard). There are two subtypes of anorexia nervosa: the restricting subtype (where the individual severely restricts the amount and type of food they consume) and the binge eating and purging subtype (where the individual regularly engages in binge eating or purging behaviour, such as self-induced vomiting or misuse of laxatives). The second subtype of anorexia nervosa is distinct from bulimia nervosa in that people with bulimia nervosa are not underweight.
3. Illness duration of three years or more. To our knowledge, three years is the shortest duration in the current literature pertaining to the defining features of SEAN and is thus the most inclusive time period. We defined the onset of illness as the first episode of weight loss.

We planned to include studies with a treatment-resistant subgroup of participants. We defined treatment resistance as having failed at least two comprehensive attempts at treatment.

If trials with eligible interventions did not report the duration of participants' illness or describe treatment resistance, we contacted the trial authors to request this information. We asked trial authors to provide unpublished data if there was a subsample of participants with illness duration of three or more years or treatment resistance, provided randomisation was stratified by illness duration to avoid baseline imbalances between interventions in such subgroups. If trial authors did not respond to our request, we contacted them again after one month. We planned to include relevant unpublished data in the meta-analyses.

We included studies where participants had concurrent psychological or physical disorders, or both.

Types of interventions

Experimental interventions

Eligible experimental interventions were specific psychological therapies aimed at improving physical and psychological health in SEAN. Interventions could take place in any treatment setting (i.e. hospital or community). There were no restrictions in terms of number of sessions, modality (group versus individual, face-to-face versus telephone/internet), and duration of therapy. We considered the following specific psychological therapies.

1. CBT-AN: CBT-AN is conducted over three phases. The first phase involves psycho-education, assessment of motivation for engagement in treatment, self-monitoring and homework, prescription of normal eating, and negotiation of a target weight range (Pike 2003; Pike 2010). In the second phase, the therapist introduces CBT skills for challenging dysfunctional thoughts and thought restructuring with cognitive schema work. The final phase involves preparation for termination and training in relapse prevention strategies.
2. Enhanced cognitive behavioural therapy (CBT-E): a form of a transdiagnostic CBT for eating disorders developed specifically for anorexia nervosa (Fairburn 2008). It includes modules that address predisposing but, importantly, perpetuating or maintaining factors for the eating disorder, including mood intolerance. Three optional modules address interpersonal relationships, clinical perfectionism, and low self-esteem. In anorexia nervosa, transdiagnostic CBT has an additional core module for the 'underweight and under-eating' patient that is prescriptive of calorie needs for weight gain. CBT-E shares many features with CBT-AN, but focusses more on behavioural change (and monitoring of behaviours that reinforce the eating disorder psychopathology, such as body checking) and less on motivational enhancement strategies (Fairburn 2008; Pike 2010). Weight monitoring is key to both therapies. Another distinguishing feature of transdiagnostic CBT is that caregivers are encouraged to provide psychological and pragmatic support in all matters regarding food and eating, for example by cooking with the patient (Fairburn 2008).
3. Time-limited psychodynamic approaches (CAT or FPT)
   a. CAT is a time-limited therapy ranging from four to 24 weeks, with a usual duration of around 16 weeks. It is tailored to the individual with negotiated goals for change. At its core is an empathetic therapeutic relationship of mutual respect. CAT in anorexia nervosa combines elements of cognitive therapy (mapping out the role of the eating disorder in the patient's life in diagrammatic form) with focused psychodynamic therapy (including transference analysis). There is no manual for CAT. Early life experiences and patterns of interpersonal relating are explored and used with self-observation of moods, thoughts, and symptoms to develop revised or new ways of relating (ACAT 2014).
   b. FPT is a standardised form of time-limited psychoanalytic therapy that may be more readily disseminated and empirically evaluated. The therapist takes a non-directive stance, giving no advice about the eating behaviours or other problems of symptom management. They address first the unconscious and conscious meanings of the symptom in terms of the person's history and family experiences, second the effects of the symptom and its influence on current interpersonal relationships, and third the manifestation of those influences in the person's relationship with the therapist (Dare 2001).
4. IPT: a manualised and time-limited approach (usually 15 to 20 weekly sessions and up to one year for chronic illness). IPT is based on a model developed for both depression and bulimia nervosa. For anorexia nervosa, as for bulimia nervosa, IPT focusses on the person's presentation of eating disorder symptoms to facilitate work on the interpersonal problem(s) that appear to be maintaining the eating disorder through indirect negative effects on mood and self-esteem (Rieger 2010; Wilfley 2003). IPT involves three phases: first, the identification of relevant interpersonal problem areas; second, an intermediate phase in which the therapist and patient work together to help the patient meet interpersonal goals deemed to be relevant for overcoming the eating disorder; and third, a termination phase involving preparation for the end of therapy.
5. SSCM: a manualised therapy that has been tested in two RCTs (McIntosh 2005; Touyz 2013). In McIntosh 2005, SSCM was conducted over 20 weeks and incorporated two core elements: a collaborative identification and regular review within session of 'target symptoms', and the supportive therapy. SSCM involves extensive psychoeducation, strategies for weight maintenance, information about energy requirements, and relearning to eat normally. It thus incorporates elements of nutritional counselling and some behavioural weight restoration strategies, but no specific motivational enhancement strategies. Eating disorder symptoms or other issues or symptoms can be targeted, but weight gain is 'non-negotiable'. The authors of Touyz 2013 modified SSCM for people with SEAN (SSCM-SE) by removing the focus from weight regain.
6. FBT: family therapy for anorexia nervosa includes members of the family of origin or chosen family. It addresses the eating disorder as a problem of family life and engages the family members as active participants in psycho-behavioural change of the patient (Lock 2009). Many individual approaches incorporate some contact with family or carers (Wonderlich 2012). For the purpose of this review, we considered only family therapy that constituted a primary approach. Several RCTs have focused on FBT (Le Grange 2005). It is manualised and has an early goal of empowerment of the family to assist in refeeding and meal provision (Lock 2013). The therapy is conducted over three phases, following an important first session. In this first meeting, the clinician evaluates the family's strengths and weaknesses and ensures that a positive comment is conveyed to each member as the session closes. If there are emergent major problems, such as physical or sexual abuse, substance abuse, or difficulties with another child (e.g. substance abuse or disturbed behaviour), the family should then be referred to

a specialist family therapist. Regular sessions are offered to most family members, or at least the parents of the patient, to elicit the family's assistance in helping the patient. The three treatment phases of FBT comprise parental empowerment to facilitate refeeding the patient (including having a family meal), negotiations for a new pattern of relationships, and the establishment of a healthy adolescent or young adult relationship with the parents, where disordered eating does not constitute the basis of interaction, and the patient has increased personal autonomy. It is important to note that FBT challenges the practical factors maintaining the illness, such as allowing patients to make their own food choices, and makes no assumptions about the cause of anorexia nervosa. It thus does not presuppose a familial pathology, but rather aims to reduce parental and patient self-blame.

7. MANTRA: a manualised modular time-limited therapy delivered in weekly sessions over eight to 10 months. It addresses such putative maintaining factors as rigid thinking styles, perfectionism, obsessive-compulsive personality traits, the avoidance of strong emotion, 'pro-anorectic' beliefs, and responses of close others. It includes remediation of problematic cognitive styles, particularly over attention to detail (weak central coherence) and inflexibility (Roberts 2007). Therapy is set within a motivational interviewing framework (Treasure 2008). It includes individualised case conceptualisation and summary letters from the therapists. In MANTRA, therapy is matched to participants' clinical symptoms, personality traits, and neuropsychological profile (Schmidt 2012, Schmidt 2014).
8. COPP: an outpatient therapy developed for chronic illness. The focus is on symptom management, skill development, and understanding benefits and risks of symptoms. The therapy is also set within the patient's community. Activities include emotion and nutritional counselling, and there are 'non-negotiables' such as medical safety. Motivational interviewing is used to promote a therapeutic alliance that increases patients' self-awareness and self-acceptance, placing the responsibility for change with them (Williams 2010).

Comparators

1. Another specific psychological therapy for anorexia nervosa (e.g. CBT compared to SSCM)
2. Non-specific psychological therapy for mental health disorder (e.g. supportive psychological therapy or CBT that does not address the specific issues of anorexia nervosa)
3. No treatment or waiting list
4. An antipsychotic as sole treatment
5. An antipsychotic as adjunct treatment
6. An antidepressant as sole treatment
7. An antidepressant as adjunct treatment
8. Dietary counselling as sole treatment (i.e. advice on nutrition needed for weight gain provided by a dietitian outside the context of formal psychological therapy)
9. Treatment as usual as defined by trial authors. We included this as an additional comparator and not within comparator 3 (no treatment or waiting list) because trials in anorexia nervosa may use a treatment-as-usual arm to provide an anorexia nervosa-specific specialist-lead therapy of similar intensity or duration to the experimental intervention. This form of treatment as usual is different from no treatment or waiting list.

For the purpose of this review, we planned to organise antidepressants into the following classes.

1. Tricyclic antidepressants (e.g. amitriptyline, imipramine, trimipramine, doxepin, desipramine, protriptyline, nortriptyline, clomipramine, dosulepin, lofepramine)
2. Heterocyclic antidepressants (e.g. amoxapine, maprotiline)
3. Selective serotonin reuptake inhibitors (SSRIs; e.g. zimelidine, fluvoxamine, fluoxetine, paroxetine, sertraline, citalopram, escitalopram)
4. Monoamine oxidase inhibitors (MAOIs)
   a. Irreversible (e.g. phenelzine, tranylcypromine, isocarboxazid)
   b. Reversible (e.g. brofaromine, moclobemide, KP157)
5. Other antidepressants
   a. Noradrenaline reuptake inhibitors (NARIs; e.g. reboxetine, atomoxetine)
   b. Norepinephrine-dopamine reuptake inhibitors (NDRIs; e.g. amineptine, bupropion)
   c. Serotonin–norepinephrine reuptake inhibitors (SNRIs; e.g. venlafaxine, milnacipran, duloxetine)
   d. Noradrenergic and specific serotonergic antidepressants (NaSSAs; e.g. mirtazapine, mianserin)
   e. Serotonin antagonist and reuptake inhibitors (SARIs; e.g. trazodone)
   f. Unclassified (e.g. agomelatine, vilazodone)

We planned to combine drugs in analyses only where they were from the same class. The 'other antidepressants' were to be presented together, but again only drugs of the same class were to be combined to produce a pooled effect (e.g. duloxetine and venlafaxine).

Types of outcome measures

Primary outcomes

1. Clinical improvement: weight restoration to within the normal weight range for participant sample (e.g. for female young adults, body mass index (BMI) 19 to 25; for others, greater than 85% expected weight for age/height) at end of treatment, six months' follow-up, and 12 months' follow-up
2. Treatment non-completion: proportion of participants who did not complete treatment

Secondary outcomes

1. Clinical response: eating disorder symptoms as measured by any validated instrument (e.g. the Eating Disorder Examination; Fairburn 1993) at end of treatment, six months' follow-up, and 12 months' follow-up
2. Eating disorder health-related quality of life (EDHRQoL): eating disorder-specific quality of life score, as measured by any recognised and validated questionnaire or interview (e.g. the Eating Disorder Examination (EDE) Interview or Questionnaire; Fairburn 1993; Fairburn 1994) at end of treatment, six months' follow-up, and 12 months' follow-up
3. Health-related quality of life (HRQoL): general quality of life score, as measured by any recognised and validated questionnaire or interview (e.g. 12-item Short Form Health Survey (SF-12; Ware 1996)) at end of treatment, six months' follow-up, and 12 months' follow-up

4. Participant satisfaction: ratings on any recognised and validated questionnaire or interview (e.g. the Client Satisfaction Survey; Larsen 1972) at end of treatment, six months' follow-up, and 12 months' follow-up
5. Proportion of study dropouts or non-completers due to an adverse event or experience

Search methods for identification of studies

Cochrane Common Mental Disorders Controlled Trials Register (CCMD-CTR)

The Cochrane Common Mental Disorders Group (CCMD) previously maintained two archived clinical trials registers at its editorial base in York, UK: a References Register and a Studies Register. The CCMD-CTR References Register contained over 40,000 reports of RCTs on depression, anxiety, and neurosis. Approximately 50% of these references were tagged to individual, coded trials. The coded trials were held in the CCMD-CTR Studies Register, and records were linked between the two registers using unique Study ID tags. Coding of trials was based on the EU-Psi coding manual, using a controlled vocabulary. Reports of trials for inclusion in the Group's registers were collated from routine (weekly) generic searches of MEDLINE (1950 to 2016), Embase (1974 to 2016) and PsycINFO (1967 to 2016); quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and review-specific searches of additional databases. Reports of trials were also sourced from international trial registers via the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch), pharmaceutical companies, the handsearching of key journals, conference proceedings, and other (non-Cochrane) systematic reviews and meta-analyses.

Appendix 1 provides an example of the core MEDLINE search used to inform the register.

Electronic searches

Electronic database searches

The CCMD Information Specialist ran searches on the following bibliographic databases.

1. Cochrane Specialised Register: CCMD-CTR (all years to 11 December 2015; Appendix 2)
2. Ovid MEDLINE (2015 to 12 June 2019)
3. Ovid Embase (2015 to 2019, Week 23)
4. Ovid PsycINFO, (2015 to 12 June 2019)
5. CENTRAL (14 June 2019; Issue 6) in the Cochrane Library (searched again in March 2021)

Appendix 3 shows the search strategies for the main bibliographic databases. We applied no restrictions on the date, language, or status of publication.

We updated the search on 6 March 2021 then again on 22 July 2022 in the following databases.

1. Ovid Embase (2019 to 22 July 2022)
2. Ovid MEDLINE (2019 to 22 July 2022)
3. Ovid PsycINFO (2019 to July Week 2 2022)
4. CENTRAL (2022, Issue 7) in the Cochrane Library (searched 22 July 2022)

International trials registers

We searched the WHO ICTRP and the US National Institutes of Health ongoing trials register ClinicalTrials.gov via CENTRAL (Issue 6, 2019). Records of RCTs from the international trials registers were uploaded to CENTRAL in early 2019.

Searching other resources

We screened the reference lists of appropriate papers and reviews identified in the searches for further relevant trials. We contacted notable researchers requesting information on additional, unpublished, or ongoing studies.

Data collection and analysis

Selection of studies

Two review authors (PH, JZ) independently selected potentially eligible studies by screening the titles and abstracts of the records returned by the searches. We then retrieved the full-text articles of all potentially eligible studies, and the same two review authors read them to determine if they met our eligibility criteria. We resolved any disagreements by discussion or by consulting a third review author (YY) where necessary.

Data extraction and management

Authorship was not concealed at the point of data collection. Two review authors (PH, JZ) independently extracted data from the eligible trials using separate data entry sheets. One review author (JZ) then entered the data into a single Excel spreadsheet and Review Manager 5 software (Review Manager 2014). JZ and YY extracted data from Touyz 2013, as PH was an author on this trial.

We extracted the following data.

1. Study registration, study dates, funding, and conflicts of interest
2. Inclusion and exclusion criteria
3. Number and percentage exclusion rate of participants
4. Diagnostic criteria
5. Type of programme and psychological therapies applied, including intensity and numbers of sessions and any medications included
6. Treatment setting, including the country and any specific cultural aspects
7. Comparison interventions
8. Method of allocation and randomisation (including if cluster randomisation occurred)
9. Risk of bias
10. Outcome of randomisation and comparability of groups
11. Measures used to attempt or ensure blinding of trial participants and key personnel from knowledge of treatment allocation
12. Reporting of reasons for attrition and exclusions
13. Participant flow (and whether a diagram was provided)
14. Type of outcome analyses and whether an intention-to-treat (ITT) approach was applied
15. Reporting of power analysis, follow-up, and primary and secondary outcome data

Main planned comparisons

We planned to evaluate comparisons of a specific psychological therapy versus any of the following comparators.

1. Another specific psychological therapy
2. Non-specific psychological therapy
3. No treatment or waiting list
4. Antipsychotic treatment
5. Antipsychotic treatment plus psychological therapy
6. Antidepressant treatment
7. Antidepressant treatment plus psychological therapy
8. Dietary counselling/advice-only treatment
9. Treatment as usual

Assessment of risk of bias in included studies

Two review authors (PH, JZ) independently assessed the risk of bias of each included study using the original Cochrane risk of bias tool (RoB 1; Higgins 2011). They resolved any disagreements by consulting a third review author (YY). Where PH or JZ were an author, YY was the second reviewer.
For each risk of bias domain (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, other bias), we rated each study at high, low, or unclear risk of bias. We based our judgement on the following criteria.

1. Method of randomisation
   a. Appropriate method of randomisation used
   b. Method of randomisation not described
2. Adequacy of allocation concealment
   a. Adequate concealment
   b. Unclear whether allocation was adequately concealed
   c. Allocation definitely not adequately concealed
3. Blinding
   a. Blinding of both outcome assessor and participant (double-blind)
   b. Blinding of outcome assessor only (single-blind)
   c. No blinding
4. Attrition
   a. Less than 20%
   b. From 20% to 49%
   c. 50% or more
5. Other risk of bias
   a. Treatment fidelity (measured and deemed satisfactory)
   b. Researcher allegiance
   c. Therapist allegiance and qualifications
   d. Comparability of groups after randomisation in terms of age, gender, bodyweight, and severity of illness at study inception (using measures applied at outcome assessment. Although imbalance may occur by chance, it may also be due to inadequate randomisation (or exclusion of participants after randomisation) or inadequate allocation concealment (Higgins 2011). We categorised comparability of groups as follows.
      i. Groups comparable at baseline on demographic and illness severity
      ii. Uncertain comparability or not assessed
      iii. Groups not comparable at baseline.

Measures of treatment effect

We calculated risk ratios (RRs) for dichotomous outcomes and mean differences (MDs) for continuous outcomes, together with the corresponding 95% confidence intervals (CIs). We used RRs because they are less likely to overestimate a treatment effect compared to odds ratios (Higgins 2011).

Unit of analysis issues

Cluster-randomised trials

We planned to deal with cluster-randomised trials by extracting a direct estimate of the required effect measure from an analysis that properly accounts for the cluster design (in the opinion of review author SL), as per the recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We would then have used the generic inverse-variance method in Review Manager 5 to meta-analyse effect estimates and their standard errors (SEs).

Cross-over trials

We planned to deal with cross-over trials according to the recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If carry-over or period effects were not considered a problem, analysis of continuous data from a two-period, two-intervention cross-over trial would have used the paired t-test. This was to evaluate the value of measurement on experimental intervention (E) minus measurement on control intervention (C) separately for each participant. We would have included the effect estimate in a meta-analysis using the generic inverse-variance method in Review Manager 5.

Studies with multiple treatment groups

We planned to deal with multiarm trials according to the recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We would have determined first which intervention groups were relevant to this systematic review, and second which intervention groups were relevant to a particular pair-wise comparison in the meta-analysis. We would have described all intervention groups of multiarm trials in the Characteristics of included studies table. We would have provided a detailed description of interventions relevant to this review and thus potentially used in analyses. If more than two intervention groups had been relevant, we would have combined groups to create a single pair-wise comparison if possible (e.g. if a trial had one inpatient condition and two outpatient conditions, we planned to combine the two outpatient conditions if appropriate). If we could not do this, we planned to determine whether it was possible to split the shared group into two or more groups with smaller sample size, and include two or more (reasonably independent) comparisons. If this was not possible, we would have selected one pair of interventions and excluded the others, and combined groups to create a single pair-wise comparison.

Dealing with missing data

We contacted study authors to request information not available in the published studies (including information needed for

data analyses, subgroup and sensitivity analyses, and quality evaluation), and to obtain the results of unpublished or partly published trials. We contacted study authors on a maximum of two occasions, requesting that they respond within three months of the request. We planned to conduct calculations of unpublished data, such as the SD, where there was sufficient (published or unpublished) information, as per section 7.7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Where study authors provided additional information, we noted this in the risk of bias sections of the Characteristics of included studies table.

We sought any missing statistics from the study authors or calculated them using appropriate methods (e.g. it is sometimes possible to calculate missing SDs from CI values, SEs, or t values). As we expected to include few trials, we planned to attempt imputation only if most trials in a meta-analysis had complete statistics (Higgins 2011).

We planned to impute data for dichotomous outcome variables only. If there was no follow-up information on weight restoration, we would have assumed the participant(s) concerned had not attained normal weight for age and height.

We only included continuous data reported in the study publications or provided by study authors. We planned to consider the potential impact of the missing data on the results, taking into account the amount of missing data, the pooled estimate of the treatment effect, and the variability of the outcomes, which we considered a potential source of heterogeneity. We planned to perform a sensitivity analysis for continuous data using the method described in the *Cochrane Handbook for Systematic Reviews of Interventions*, which is to assume a fixed difference between the actual mean for the missing data and the mean assumed by the analysis (Higgins 2011).

Assessment of heterogeneity

We planned to assess heterogeneity using the Chi^2 test ($P \leq 0.10$) and the observed value of the I^2 statistic. The importance of the I^2 value depends on the magnitude and direction of effects and the strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or a CI for the I^2 statistic). The *Cochrane Handbook for Systematic Reviews of Interventions* provides the following rough guide for interpreting the I^2 statistic.

1. 0% to 40%: might not be important
2. 30% to 60%: may represent moderate heterogeneity
3. 50% to 90%: may represent substantial heterogeneity
4. 75% to 100%: considerable heterogeneity.

Where the I^2 statistic was moderate to high and the direction and magnitude of treatment effects suggested important heterogeneity, we planned to investigate potential sources of inconsistency (Higgins 2011).

Assessment of reporting biases

We planned to minimise any duplicate publication bias by checking with study authors for suspected duplicate publication. We attempted to minimise location, language, and citation bias by comprehensive and systematic searches that were as broad as possible and included non-English language trials.

We planned to investigate systematic differences between reported and unreported findings by inspection of funnel plots (in meta-analyses of 10 or more trials) and statistical tests for funnel plot asymmetry of our primary continuous outcome variable. However, we acknowledge that an asymmetrical funnel plot is not necessarily indicative of publication bias, and that publication bias does not necessarily cause asymmetry.

Data synthesis

We planned to favour the random-effects model where the treatment effect was unlikely to be the same across studies. Where all studies used the same intervention, and we could assume they were estimating the same treatment effect, we planned to use the fixed-effect model.

Subgroup analysis and investigation of heterogeneity

We planned to combine data for all participants in a single meta-analysis of the same outcome for the same intervention comparison. Had data allowed, we would have conducted the following subgroup analyses.

1. Participants who had failed at least two comprehensive attempts at treatment
2. Inpatient, day-patient, or outpatient treatment settings
3. Children and adolescents (age < 16 years)
4. Adults and older adolescents (age ≥ 16 years)

We planned to address identified heterogeneity by first checking that the data were correct. If data were correct and there was a large degree of inconsistency in results, we planned to conduct a sensitivity analysis by sequentially removing trials by sample size, starting with the smallest until three trials remained or heterogeneity became non-significant (P value ≥ 0.1).

Sensitivity analysis

We planned to undertake sensitivity analyses by excluding, in turn, trials that met the following criteria, then repeating the meta-analysis.

1. No blinding of outcome assessment
2. Treatment fidelity not reported or inadequate
3. Attrition greater than 20%

If there had been a large amount of missing continuous data, we would have performed a sensitivity analysis using the method described in the *Cochrane Handbook for Systematic Reviews of Interventions,* which is to assume a fixed difference between the actual mean for the missing data and the mean assumed by the analysis (Higgins 2011).

Summary of findings and assessment of the certainty of the evidence

We created a summary of findings table with GRADEpro GDT to present our key findings (GRADEpro GDT). We planned to create a separate summary of findings table for each eligible comparison.

Our summary of findings table included the following three outcomes.

1. Clinical improvement: weight restoration to within the normal weight range for participant sample (e.g. for female young adults, BMI 19 to 25; for others, greater than 85% expected weight for age/height) at 12 months' follow-up (which we considered the most clinically relevant (longest) time point for people with longstanding illness)
2. Treatment non-completion: proportion of participants who did not complete treatment
3. Proportion of study dropouts or non-completers due to an adverse event or experience

We presented our findings relating to standardised effect size estimates (and 95% CIs) to illustrate comparative risk, the number of studies and participants, and the certainty of evidence based on standards of the GRADE working group (Balshem 2011). The GRADE approach covers five considerations: risk of bias, imprecision, inconsistency, indirectness of study results, and publication bias. Two review authors (PH, JZ) independently conducted the GRADE assessment, consulting a third review author (YY) in the event of any disagreements.

RESULTS

Description of studies

Two trials met the inclusion criteria for this review (Touyz 2013; Zipfel 2014). Zipfel 2014 included 242 people of varying illness duration and stratified randomisation by duration (six years or less versus more than six years). We contacted the study authors to request unpublished data on the outcomes of participants with illness duration of more than 6 years, but we received no response.

Results of the search

After combining the records returned by the different searches and removing duplicates, we screened the titles and abstracts of 1336 records, of which 1229 were clearly ineligible. We retrieved the remaining 101 records for full-text review and excluded 93 for various reasons (Characteristics of excluded studies). We included two trials (eight reports) in the qualitative synthesis (Touyz 2013; Zipfel 2014). Zipfel 2014 provided no data for the quantitative synthesis. Figure 1 presents the study selection process in a PRISMA diagram.

Figure 1. Study flow diagram.

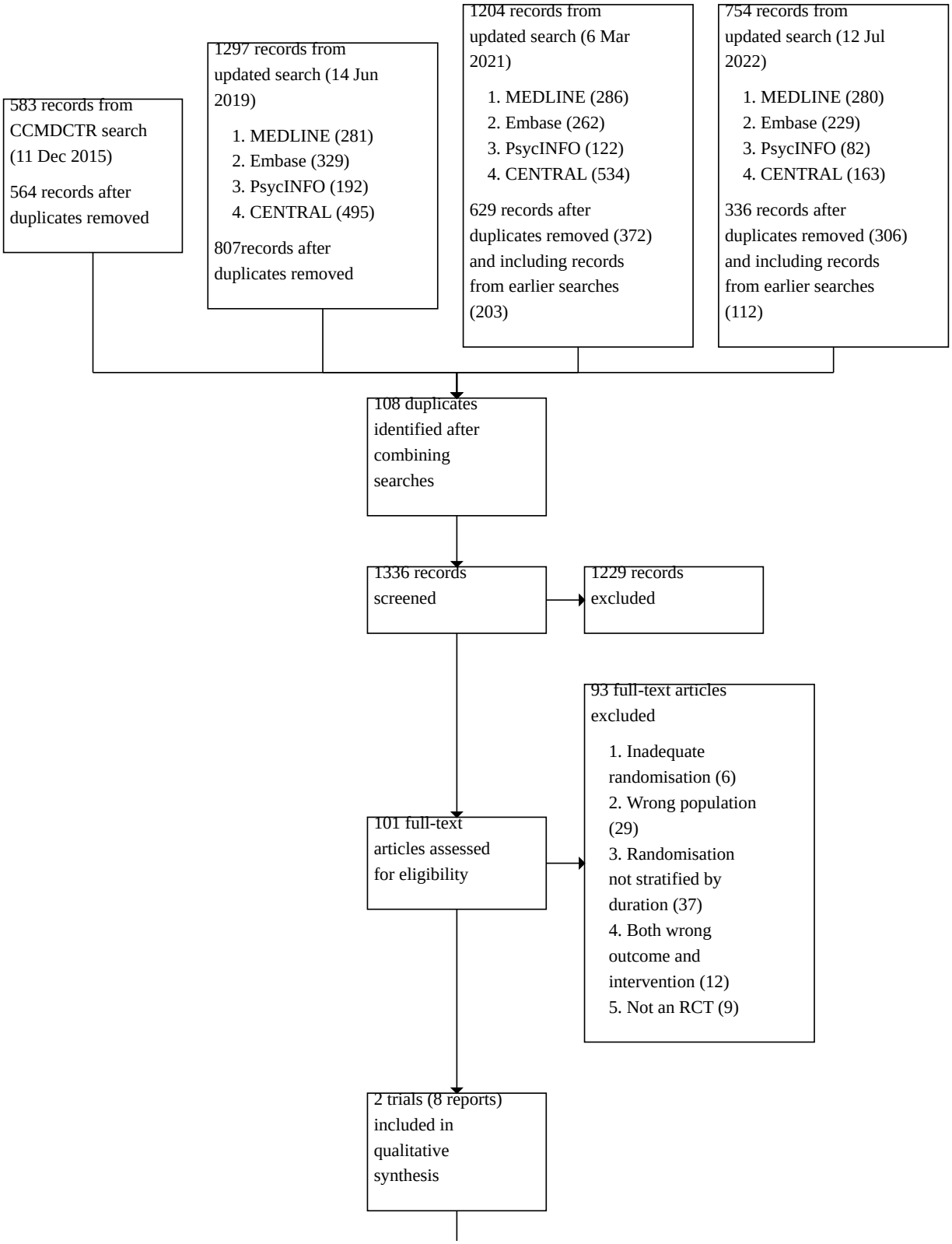
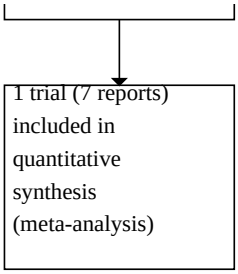


Figure 1. (Continued)



Included studies

Two studies were eligible for inclusion in this review (Touyz 2013; Zipfel 2014). The Characteristics of included studies table provides further information.

Design

Both studies used a randomised controlled parallel-group design. We identified no eligible cluster-randomised or cross-over trials.

Sample sizes

Touyz 2013 enroled 63 people with SEAN. Zipfel 2014 enroled 242 people but did not specify the number of participants with SEAN.

Setting

Touyz 2013 was a multicentre trial; people with SEAN were recruited in Australia and the UK, and data management and analysis took place at a USA site (Chicago). Zipfel 2014 was a multicentre trial set in Germany.

Participants

Touyz 2013 included adults (aged 18 years or older) with anorexia nervosa (according to DSM-5; APA 2013) and an illness duration of at least seven years since onset. Of the 63 participants, 47 (75%) had restricting subtype. Zipfel 2014 provided no data for participants with SEAN.

Interventions

Touyz 2013 compared CBT-AN with SSCM-SE. Both therapies focused on quality of life as the primary goal (Mcintosh 2016; Pike 2016), and both were conducted in 30 face-to-face sessions over eight months. When reporting the results of the interventions in this review, we termed the first intervention CBT-SEAN to distinguish it from CBT for people with anorexia nervosa of any duration. The interventions in Zipfel 2014 were manualised focal psychodynamic treatment, manualised CBT (based on CBT-E) and optimised treatment as usual.

Outcomes

Touyz 2013 assessed our primary outcomes (clinical Improvement and treatment non-completion) and four of our secondary outcomes (clinical response, EDHRQoL, generic HRQoL, and participant satisfaction). Zipfel 2014 assessed clinical improvement and treatment non-completion as well as clinical response and participant satisfaction.

Excluded studies

We excluded 93 studies during the full-text review: six studies had inadequate randomisation or stratification, 29 did not evaluate people with SEAN, 37 included some SEAN participants but did not stratify randomisation by illness duration, 12 had ineligible interventions and outcomes, and nine were not RCTs (see Figure 1). We contacted four authors for additional information on participant eligibility, and all responded to confirm that their trials were not eligible for inclusion in our review (Geist 2000; McIntosh 2005; Parling 2016; Schmidt 2012; Schmidt 2015). The Characteristics of excluded studies table presents the excluded studies that readers may reasonably consider to be eligible.

Ongoing studies

We identified no ongoing trials.

Studies awaiting classification

There are no studies awaiting classification.

Risk of bias in included studies

For details of the risk of bias judgements for each study, see the Characteristics of included studies stable. Figure 2 and Figure 3 present a graphical representation of the risk of bias judgements.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

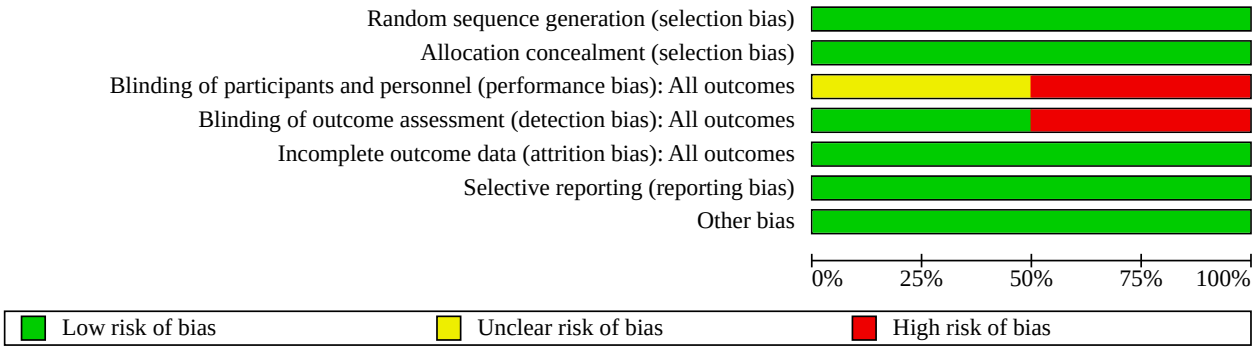
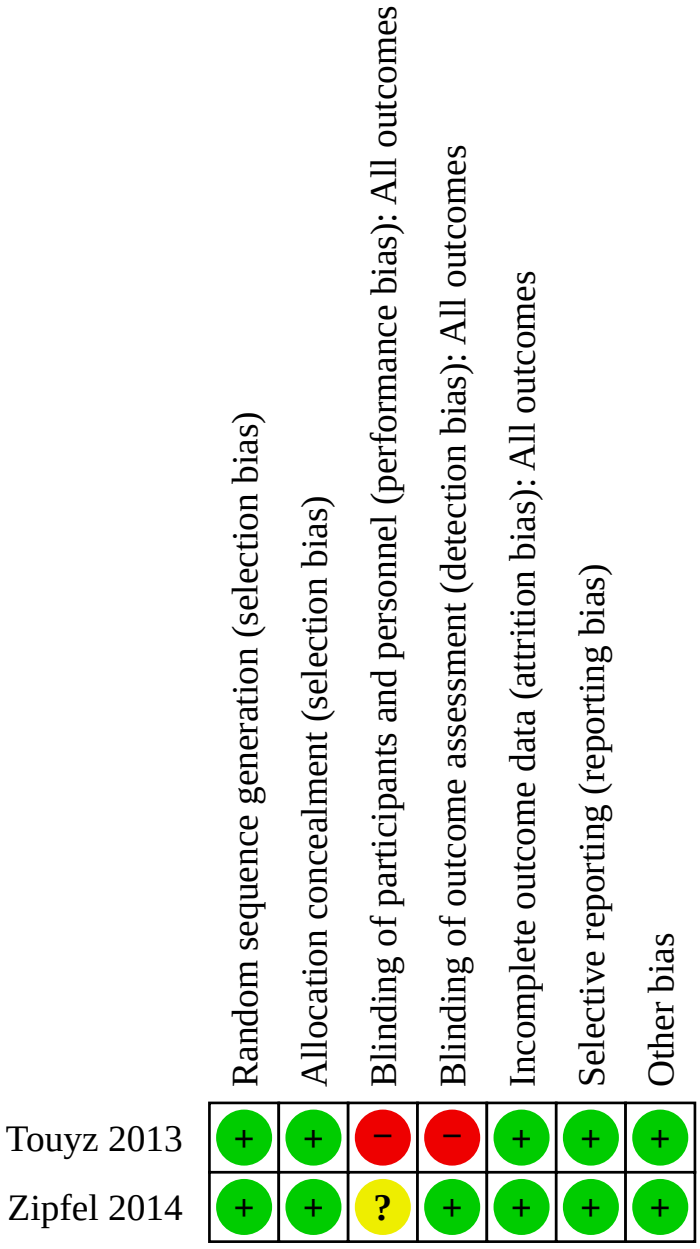


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Both studies were at low risk of selection bias as they both described adequate randomisation and allocation concealment (Crisp 1991).

Blinding

Touyz 2013 was at high risk of performance and detection bias as there was no blinding of participants or therapists and almost all outcomes were self-reported, although one primary outcome (clinical improvement) and one secondary outcome (clinical response) were assessed by independent interviewers blinded to treatment arm. Zipfel 2014 was at unclear risk of performance bias

because complete masking of participants was not feasible (one-third of participants were allocated to optimised treatment as usual and therefore were not treated at respective centres). The study was at low risk of detection bias because outcome assessors were masked.

Incomplete outcome data

Both studies were at low risk of attrition bias because attrition rates were low, and Zipfel 2014 conducted complete data analysis on the primary outcome.

Selective reporting

Touyz 2013 was at low risk of reporting bias because it reported all specified outcome measures. Zipfel 2014 was also at low risk of reporting bias because there was a published protocol with the same outcomes as reported in the trial publication.

Other potential sources of bias

We identified no other potential sources of bias.

Effects of interventions

See: **Summary of findings 1** Specific psychological therapy compared to alternative specific psychological therapy for severe and enduring anorexia nervosa

Comparison 1: specific psychological therapy versus another specific psychological therapy

One study including 63 participants contributed data to this comparison (Touyz 2013). For all outcomes, we downgraded the certainty of the evidence by one level due to study limitations (high risk of performance and detection bias) and by two levels due to imprecision (single study of 63 participants, wide 95% CIs). See Summary of findings 1.

Primary outcomes

Clinical improvement: weight restoration to within the normal range for participant sample

There was no evidence of a difference between the effect of CBT-SEAN versus SSCM-SE on clinical improvement at the end of treatment (RR 0.79, 95% CI 0.41 to 1.54; 63 participants; very low-certainty evidence; Analysis 1.1), at six months' follow-up (RR 0.74, 95% CI 0.26 to 2.08; 63 participants; very low-certainty evidence; Analysis 1.2), or at 12 months' follow-up (RR 1.42, 95% CI 0.66 to 3.05; 63 participants; very low-certainty evidence; Analysis 1.3).

Treatment non-completion

There was no evidence of a difference between the effect of CBT-SEAN versus SSCM-SE on treatment non-completion (RR 1.72, 95% CI 0.45 to 6.59; 63 participants; very low-certainty evidence; Analysis 1.4).

Secondary outcomes

Clinical response: eating disorder symptoms as measured by any validated instrument

Touyz 2013 measured eating disorder symptoms using the EDE global score and the Anorexia Nervosa Stages of Change Questionnaire (ANSCQ).

Eating Disorder Examination global score

There was no evidence of a difference between the effect of CBT-SEAN versus SSCM-SE on clinical response as measured with the EDE global score at the end of treatment (MD −0.50, 95% CI −1.12 to 0.12; 63 participants; very low-certainty evidence; Analysis 1.5) or at six months' follow-up (MD −0.50, 95% CI −1.09 to 0.09; 63 participants; very low-certainty evidence; Analysis 1.6).

In one trial, CBT-SEAN was more effective than SSCM-SE for improving clinical response as measured with the EDE global score at 12 months' follow-up, but the evidence was very uncertain (MD −0.70, 95% CI −1.29 to −0.11; 63 participants; very low-certainty evidence; Analysis 1.7).

Anorexia Nervosa Stages of Change Questionnaire

There was no evidence of a difference between the effect of CBT-SEAN versus SSCM-SE on clinical response as measured with the ANSCQ at the end of treatment (MD −0.20, 95% CI −0.55 to 0.15; 63 participants; very low-certainty evidence; Analysis 1.8), at six months' follow-up (MD 0.00, 95% CI % CI −0.35 to 0.35; 63 participants; very low-certainty evidence; Analysis 1.9), or at 12 months' follow-up (MD 0.40, 95% CI 0.03 to 0.77; 63 participants; very low-certainty evidence; Analysis 1.10).

Eating disorder health-related quality of life: eating disorder-specific quality of life score as measured by any recognised and validated questionnaire or interview

Touyz 2013 assessed EDHRQoL using the Eating Disorder Quality of Life Instrument (EDQOL).

There was no evidence of a difference between the effect of CBT-SEAN versus SSCM-SE on EDHRQoL as measured with the EDQOL at the end of treatment (MD −0.20, 95% CI −0.55 to 0.15; 63 participants; very low-certainty evidence; Analysis 1.11).

In one trial, CBT-SEAN was more effective than SSCM-SE for improving EDHRQoL as measured with the EDQOL at six months' follow-up, but the evidence was very uncertain (MD −0.30, 95% CI −0.57 to −0.03; 63 participants; very low-certainty evidence; Analysis 1.12).

There was no evidence of a difference between the effect of CBT-SEAN versus SSCM-SE on EDHRQoL as measured with the EDQOL at 12 months' follow-up (MD −0.10, 95% CI −0.45 to 0.25; 63 participants; very low-certainty evidence; Analysis 1.13).

Health-related quality of life: general quality of life score as measured by any recognised and validated questionnaire or interview

Touyz 2013 measured HRQoL using the SF-12 Mental Component Summary (MSC) and Physical Component Summary (PCS) and the Weissman Social Adjustment Scale (WSAS)

12-item Short Form Health Survey Mental Component Summary

There was no evidence of a difference between the effect of CBT-SEAN versus SSCM-SE on HRQoL as measured with the SF-12 MSC at the end of treatment (MD 1.30, 95% CI −3.68 to 6.28; 63 participants; very low-certainty evidence; Analysis 1.14), at six months' follow-up (MD 2.00, 95% CI −2.57 to 6.57; 63 participants; very low-certainty evidence; Analysis 1.15), or at 12 months' follow-up (MD 1.00, 95% CI −4.14 to 6.14; 63 participants; very low-certainty evidence; Analysis 1.16).

12-item Short Form Health Survey Physical Component Summary

There was no evidence of a difference between the effect of CBT-SEAN versus SSCM-SE on HRQoL as measured with the SF-12 PSC at the end of treatment (MD 0.30, 95% CI −4.44 to 5.04; 63 participants; very low-certainty evidence; Analysis 1.17), at six months' follow-up (MD 3.20, 95% CI −0.17 to 6.57; 63 participants; very low-certainty evidence; Analysis 1.18), or at 12 months' follow-up (MD 2.80, 95% CI −0.91 to 6.51; 63 participants; very low-certainty evidence; Analysis 1.19).

Weissman Social Adjustment Scale

There was no evidence of a difference between the effect of CBT-SEAN versus SSCM-SE on HRQoL as measured with the WSAS at the end of treatment (MD −2.00, 95% CI −6.27 to 2.72; 63 participants; very low-certainty evidence; Analysis 1.20).

In one trial, CBT-SEAN was more effective than SSCM-SE for improving HRQoL as measured with the WSAS at six months' follow-up (MD −4.50, 95% CI −7.88 to −1.12; 63 participants; very low-certainty evidence; Analysis 1.21) and at 12 months' follow-up (MD −4.60, 95% CI −9.07 to −0.13; 63 participants; very low-certainty evidence; Analysis 1.22), but the evidence was very uncertain.

Participant satisfaction: ratings on any recognised and validated questionnaire or interview

Touyz 2013 measured participant satisfaction using the Helping Relationship Questionnaire at the end of treatment. There was no evidence of a difference between CBT-SEAN and SSCM-SE in terms of participant satisfaction (MD −0.20, 95% CI −4.87 to 4.47; 63 participants; very low-certainty evidence; Analysis 1.23).

Proportion of study dropouts or non-completers due to an adverse event or experience

Touyz 2013 provided no data to compare the effects of the interventions on adverse events.

Comparison 2: specific psychological therapy versus non-specific psychological therapy

No trials evaluated a specific psychological therapy versus non-specific psychological therapy.

Comparison 3: specific psychological therapy versus no treatment or waiting list

No trials evaluated a specific psychological therapy versus no treatment or waiting list.

Comparison 4: specific psychological therapy versus antipsychotic treatment

No trials evaluated a specific psychological therapy versus antipsychotic treatment.

Comparison 5: specific psychological therapy versus antipsychotic treatment plus psychological therapy

No trials evaluated a specific psychological therapy versus antipsychotic treatment.

Comparison 6: specific psychological therapy versus antidepressant treatment

No trials evaluated a specific psychological therapy versus antidepressant treatment.

Comparison 7: specific psychological therapy versus antidepressant treatment plus psychological therapy

No trials evaluated a specific psychological therapy versus antidepressant treatment plus psychological therapy.

Comparison 8: specific psychological therapy versus dietary counselling/advice-only treatment

No trials evaluated a specific psychological therapy versus dietary counselling/advice-only treatment.

Comparison 9: specific psychological therapy versus treatment as usual

No trials evaluated a specific psychological therapy versus treatment as usual.

Subgroup analyses

There were no data available to conduct our planned subgroup analyses.

Sensitivity analyses

There were no data available to conduct our planned sensitivity analyses.

Reporting bias

As we were unable to obtain unpublished data from Zipfel 2014, our findings are limited to a single trial.

DISCUSSION

Summary of main results

See Summary of findings 1.

Two trials met the inclusion criteria of this review (Touyz 2013; Zipfel 2014); however, only Touyz 2013 provided data for participants with SEAN (n = 63).

Touyz 2013 compared CBT-SEAN with SSCM-SE. There was no evidence of benefit favouring either therapy in the primary outcomes of clinical improvement (weight restoration to within normal weight range) or treatment non-completion. The only differences observed in the secondary outcomes favoured CBT-SEAN (clinical response measured by EDE global score at 12 months' follow-up, EDHRQoL measured by the EDQOL at six months' follow-up, and generic HRQoL measured by the WSAS at six and 12 months' follow-up). It should be noted the evidence for all outcomes is very uncertain. Therefore, we cannot judge the effectiveness of either treatment in the trial or determine whether one treatment is superior to the other.

Overall completeness and applicability of evidence

There were insufficient data to determine whether any specific psychological therapy was more effective or safer than any other therapy or no treatment in people with SEAN. The evidence identified in this review was limited to one trial that observed little or no difference in effectiveness between two specific psychological therapies. The trial did not specifically assess the effects of the intervention in people with SEAN who were unresponsive to previous treatments.

There were no data on people who did not complete therapy due to an adverse event or experience. Further, Touyz 2013 did not specify whether participants would have similarly benefited from psychological therapies not modified for SEAN (i.e. SSCM or CBT-AN versus SSCM-SE or CBT-SEAN), and the adaptions in the CBT-SEAN intervention were based on evidence from a single relapse prevention trial.

Although the duration of illness and level of adaptive function in the participants in Touyz 2013 were indicative of SEAN, there was no information on treatment experience. According to some experts, a defining feature of SEAN is non-response to optimal evidence-based care (Wonderlich 2020), and it is unclear if the participants in Touyz 2013 met this criterion. As there may be greater benefits for commencing treatment earlier in the course of illness for younger people with earlier onset compared to adults with later onset (Radunz 2020), the evidence would be enhanced by trials that include subgroup analyses based on age of illness onset.

To improve the evidence base, there is a need for trials that replicate the methods of Touyz 2013 and trials that investigate the other eight comparisons of interest for this review.

Quality of the evidence

The certainty of the evidence assessed by the GRADE approach was very low for all outcomes, as findings were limited to one trial of 63 participants. We downgraded the certainty of the evidence by one level due to study limitations (high risk of performance and detection bias) and by two levels due to imprecision (single study of 63 participants, wide 95% CIs).

Although there are several defining features of SEAN, Touyz 2013 defined the disorder by duration alone. However, there is no consensus on the standard definition, and trials in younger participants have found that only duration is predictive of outcomes (Radunz 2020).

Potential biases in the review process

Several authors of this review were also authors of the only trial included in the quantitative analysis (Touyz 2013). For this reason independent review authors extracted data from this trial. It is also possible that we missed unpublished trials or trials not published in the databases we searched.

Agreements and disagreements with other studies or reviews

Hay and colleagues conducted a review on the treatment for SEAN, but identified no eligible published studies (Hay 2012b). When developing a guideline on eating disorders, the UK National Institute of Care Excellence (NICE) conducted a review of the evidence on treatment for SEAN (NICE 2017); it also included Touyz 2013, and reached the same conclusions as this review.

AUTHORS' CONCLUSIONS

Implications for practice

This review includes the results of one trial of cognitive behavioural therapy (CBT) compared to specialist supportive clinical management (SSCM), both modified for severe and enduring anorexia nervosa (SEAN). There was very low-certainty evidence of little or no difference between these two specific psychological therapies. The results of four analyses showed better results for CBT; however, since the total number of analyses was 26, these differences may be due to type 1 error. Attrition was low and did not differ between arms, suggesting both therapies are acceptable. No data were available from a trial of active therapy compared to treatment as usual. Therefore, the results of this review do not provide adequate evidence to demonstrate the effectiveness of any treatment in this population, or to determine whether any treatment is superior to any other.

Implications for research

There is very limited evidence on the benefits of psychological therapies for people with SEAN. There is a need for more trials of people with SEAN, or anorexia nervosa trials that stratify randomisation by duration of illness and publish separate data for participants with an illness duration of three years or more. However, trials in people with anorexia nervosa of any duration would not evaluate therapies developed specifically for SEAN. Trials should also report general outcomes of interest, such as clinical improvement: we were unable to include some trials in our review because they assessed unique outcomes. Future trials should seek large samples across many settings to ensure sufficient sample size.

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1. Sign-off Editor (final editorial decision): Tari Turner, Cochrane Australia, School of Public Health and Preventive Medicine, Monash University
2. Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Sam Hinsley, Cochrane Central Editorial Service
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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Touyz 2013

Study characteristics	
Methods	**Study design:** multicentre parallel-group RCT.

Touyz 2013 *(Continued)*

	Study dates: recruitment July 2007–November 2010
Participants	**Diagnosis:** DSM-5 anorexia nervosa of minimum 7 years' duration; BMI range 11.8–18.5 kg/m^2 **Method of diagnosis:** Eating Disorder Examination interview **Age:** all participants: range 20–62 years; CBT-SEAN: mean 34.6 (SD 9) years; SSCM-SE: mean 32.3 (SD 10) years **Sex:** 100% women **Location:** NSW Australia, UK **Comorbidities:** 22 participants (35%) had a mood disorder or dysthymia, 20 (31.7%) had generalised anxiety disorder, 16 (25.4%) had social phobia, 6 (9.5%) had obsessive-compulsive disorder, and 1 had current substance dependence. Exclusion criteria included a current manic episode or psychosis, current alcohol or substance abuse or dependence, significant current medical or neurological illness (including seizure disorder), except nutrition-related alterations that impact on weight. **Adjunctive therapy:** exclusion criteria included unwillingness to suspend treatment for the duration of participation in the study and current psychotherapy. **Adjunctive medication**: 26 (43%) on psychotropic medication
Interventions	**Intervention 1:** CBT-SEAN 1. **Duration:** 30 sessions over 8 months 2. **Treatment protocol:** weekly sessions 3. **Therapist/face-to-face contact:** face-to-face **Intervention 2:** CBT-SEAN 1. **Duration:** 30 sessions over 8 months 2. **Treatment protocol:** weekly sessions 3. **Therapist/face-to-face contact:** face-to-face
Outcomes	**Time points of assessment:** pre- and post-treatment, 6 months, 12 months **Primary outcomes** 1. Quality of life (SF12 MCS and EDQoL) 2. Depression (BDI) 3. Social adjustment (WSAS) **Secondary outcomes** 1. BMI (kg/m^2) 2. EDE global and subscale scores 3. ANSCQ 4. End of treatment healthcare utilisation: frequency and intensity of use of primary care physician services, emergency department treatment services, other medical services, and specialist appointments over the preceding 6-month period
Notes	**Study Name**: There is no published study name. **Funding:** the Australian National Health and Research Council (PG 457419; Dr Touyz, Dr Le Grange, Dr Lacey, and Dr Hay), South West London and St George's NHS Trust (Dr Lacey), the Butterfly Foundation (Dr Touyz), and the University of Western Sydney (Dr Hay). **Trial registration:** Australian New Zealand Clinical Trials Registry no. 12607000440426.

Touyz 2013 *(Continued)*

Conflicts of interest: Dr Touyz and Dr Hay received royalties from Hogrefe and Huber, McGraw Hill Education, and Blackwell
Scientific Publications; Dr Le Grange received royalties from Guilford Press and Routledge and is codirector of the Training Institute for Child and Adolescent Eating Disorders, LLC.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were individually randomized using Ephron's biased coin approach stratified within sites based on subtype of illness [AN restricting type (ANR) versus AN binge-purging type (ANBP)] and current use of psychiatric medication."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed by a biostatistician in the Data and Coordinating Centre (DCC, The University of Chicago), independent from either intervention site."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and therapists were not blinded when completing self-reported primary outcome measures.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessment was not blinded for most outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	50/63 (80%) assessed at final assessment.
Selective reporting (reporting bias)	Low risk	All participants were included in data analyses.
Other bias	Low risk	We identified no other risk of bias.

Zipfel 2014

Study characteristics

Methods	**Study design:** multicentre parallel-group RCT. Power calculations were reported. **Study dates:** recruitment May 2007–June 2009
Participants	**Diagnosis:** DSM-IV anorexia nervosa (full or all but one criterion met); BMI 15.0 to < 18.5 kg/m^2 **Method of diagnosis:** Psychiatric Status Rating scale based on the patient's SIAB-EX interview **Age:** all participants ≥ 18 years; FPT: mean 28.0 (SD 8.6) years; CBT-E: mean 27.4 (SD 7.9) years; optimised TAU: mean 27.7 (SD 8.1) years **Sex:** 100% women **Location:** German clinics **Comorbidities:** 58 (24%) participants had a mood disorder, 59 (24%) participants had an anxiety disorder, and 5 (2%) had a somatoform disorder. Exclusion criteria were current substance abuse, use of

Zipfel 2014 *(Continued)*

	psychotropic medications, psychotic or bipolar disorder, serious unstable medical problems, and ongoing psychotherapy. **Adjunctive therapy:** exclusion criteria included unwillingness to suspend treatment for the duration of participation in the study and current psychotherapy. **Adjunctive medication**: neuroleptic medication use was an exclusion criterion
Interventions	**Intervention 1:** FPT 1. **Duration:** 40 sessions over 10 months 2. **Treatment protocol:** twice weekly for 2 months, weekly for 4 months, every 2 weeks for 4 months 3. **Therapist/face-to-face contact:** face-to-face **Intervention 2:** CBT-E 1. **Duration:** 40 sessions over 10 months 2. **Treatment protocol:** twice weekly for 2 months, weekly for 4 months, every 2 weeks for 4 months 3. **Therapist/face-to-face contact:** face-to-face **Intervention 3:** optimised TAU 1. **Duration:** flexible number of sessions over 10 months (similar number and intensity of sessions as for FPT and CBT-E) 2. **Treatment protocol:** flexible 3. **Therapist/face-to-face contact:** face-to-face
Outcomes	**Time points of assessment:** pretreatment, 4 months, 10 months, 12 months **Primary outcomes** 1. BMI **Secondary outcomes** 1. Eating Disorder Inventory version 2 score 2. SIAB-EX 3. DSM-IV Axis 1 comorbidities 4. Health service use: number of therapy sessions any hospitalisations 5. Participant ratings of therapy helpfulness
Notes	**Study name:** the ANTOP study. **Funding:** the trial was funded by the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung; BMBF), and the German Eating Disorders Diagnostic and Treatment Network (EDNET). **Trial registration:** doi.org/10.1186/ISRCTN72809357 **Conflicts of interest:** none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation procedure described in detail and referenced as the Rosenberg and Lachin co-variate adaptive method.
Allocation concealment (selection bias)	Low risk	Centralised randomisation done at an independent co-ordination centre.

Zipfel 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Complete masking of participants was not feasible because one-third of participants were allocated optimised treatment as usual and so were not treated at the respective centres.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were assessed by mask assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was low (70% completed assessment at 1 year of follow-up) and complete data analysis was conducted on the primary outcome.
Selective reporting (reporting bias)	Low risk	There was a published protocol and the prespecified outcomes matched the reported outcomes.
Other bias	Low risk	Both interventions were provided by trained therapists and all sessions audio-taped and every ninth audiotape audited by monitors. Financial support was declared (the German federal Ministry of Education and Research). Therapists were experienced in the treatment of eating disorders and participated in training for the manuals with supervision at every fourth session. Therapists were psychologists or medical doctors with ≥ 3 years' psychotherapy training in the method used.

ANSCQ: Anorexia Nervosa Stages of Change Questionnaire; BDI: Beck Depression Inventory; BMI: body mass index; CBT-E: enhanced cognitive behavioural therapy; CBT-SEAN: cognitive behavioural therapy for severe and enduring anorexia nervosa; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; EDE: Eating Disorder Examination; EDQoL: eating disorder quality of life; FPT: focal psychoanalytic psychotherapy; RCT: randomised controlled trial; SF12 MCS: 12-item Short Form Health Survey Mental Component Summary; SIAB-EX: Structured Interview for Anorexic and Bulimic Syndromes for expert rating; SSCM-SE: specialist supportive clinical management for severe and enduring anorexia nervosa; TAU: treatment as usual; WSAS: Weissman Social Adjustment Scale.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Agras 2014	Participants did not have SEAN (mean duration of illness 13.5 years).
Brockmeyer 2014	The intervention, comparator, and the outcomes assessed did not meet the inclusion criteria for this review.
Brockmeyer 2021	The intervention, comparator, and the outcomes assessed did not meet the inclusion criteria for this review.
Byrne 2017	Randomisation was not stratified by participant duration of illness and thus data could not be collected for those with SEAN.
Crisp 1991	No details of the randomisation process, so we cannot assume that randomisation was stratified by illness duration.
Dalle Grave 2013	Randomisation not stratified by illness duration.
Dingemans 2014	Randomisation not stratified by illness duration.

Study	Reason for exclusion
Geist 2000	Unclear if participants met SEAN criteria. We contacted the study authors but received no reply.
Godart 2012	Participants did not meet SEAN criteria.
Hall 1987	Study did not focus on SEAN as defined by this review (≥ 3 years' illness duration). Whilst some patients may have fulfilled criteria as mentioned in the text (up to 72 months illness duration), randomisation was not stratified by duration of illness.
Lock 2010	Participants did not fulfil SEAN criteria as defined by this review (≥ 3 years' illness duration).
Lock 2013	Randomisation not stratified according to duration of illness.
McIntosh 2005	Participants did not have SEAN.
Parling 2016	Randomisation not stratified by illness duration.
Schmidt 2012	Randomisation not stratified by illness duration.
Schmidt 2015	Randomisation not stratified by illness duration.
Stein 2013	Randomisation not stratified by illness duration.
Steinglass 2014	Randomisation not stratified by illness duration.
Weiss 2013	Randomisation not stratified by illness duration.

SEAN: severe and enduring anorexia nervosa.

HISTORY

Protocol first published: Issue 3, 2015

CONTRIBUTIONS OF AUTHORS

JZ: study selection, preparation of Figure 1, data extraction (primary author responsible for data extraction where PH was an author), contact with study authors, drafting of final review.
PH: drafting of protocol; search strategy development; study selection; data extraction, entry, analyses, and interpretation; drafting of final review.
YY: data entry (for the trial in which PH was an author), checking of data entry, editing of final review.
DG (content expert): drafting of protocol, data interpretation, drafting of final review.
JL (content expert): drafting of protocol, data interpretation, drafting of final review.
SL: data interpretation, drafting of final review.
CS: drafting of protocol, data interpretation, drafting of final review.
ST (content expert): drafting of protocol, data interpretation, drafting of final review.

DECLARATIONS OF INTEREST

JZ has no conflicts of interest to declare.

PH receives sessional fees and lecture fees from the Australian Medical Council, Therapeutic Guidelines publication, and New South Wales Health Education and Training Institute (former Institute of Psychiatry) and royalties from Hogrefe and Huber, McGraw Hill Education, and Blackwell Scientific Publications. She has received research grants from the National Health and Medical Research Council (NHMRC) (2010 to 2013) and Australian Research Council (ARC) (2010 to 2011). She has received honoraria from Takeda (formerly Shire) Pharmaceuticals for education of psychiatrists and commissioned reports in relation to binge eating disorder and been a consultant to Takeda Pharmaceuticals on binge eating disorder. She was a Chief Investigator on a trial included in this review (Touyz 2013), with the funding PG457419 from the Australian National Health and Research Council and by the South-West London and St. George's NHS Trust, the Butterfly-Foundation, and the University of Western Sydney.

YY is employed as a private practice dietitian working in eating disorders and in receipt of an Australian Government (Research Training Program) Stipend Scholarship.

DLG received funding from the National Institute of Mental Health (US), NHMRC, and private foundations. He receives royalties from Routledge and Guilford Press, and is co-director of the raining Institute for Child and Adolescent Eating Disorders, LLC. He was a Chief Investigator on a trial included in this review (Touyz 2013), with the funding PG457419 from the Australian National Health and Research Council and by the South-West London and St. George's NHS Trust, the Butterfly-Foundation, and the University of Western Sydney.

JL has received funding from National Health and Medical Research Council (NHMRC). He was a Chief Investigator on a trial included in this review (Touyz 2013), with the funding PG457419 from the Australian National Health and Research Council and by the South-West London and St. George's NHS Trust, the Butterfly-Foundation, and the University of Western Sydney.

SL has no conflicts of interest to declare.

CS has no conflicts of interest to declare.

ST is Editor of the Journal of Eating Disorders. He has received honoraria from Takeda for speaking engagements and commissioned reports as well as travelling grants for educational purposes. He was the recipient of a research grant and is Chair of the Australian Clinical Advisory Board on binge eating disorder. He also receives royalties from Hogrefe and Huber, Taylor and Francis, and Mc Graw Hill for books/book chapters. He is a consultant to Weight Watchers. He is a mental health adviser to the Commonwealth of Australia Department of Veteran Affairs and a member of the Technical Committee on Eating Disorders of the Commonwealth Department of Health. He was Principal Investigator on a trial included in this review (Touyz 2013), with the funding PG457419 from the Australian National Health and Research Council and by the South-West London and St. George's NHS Trust, the Butterfly-Foundation, and the University of Western Sydney.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

See Hay 2015b (review protocol).

We revised the wording of the primary outcome 'acceptability: to be measured by proportion of dropouts', changing it to 'treatment non-completion: proportion of participants who did not complete treatment'. This was to more clearly reflect the adverse quality of this outcome.

Dr James Zhu and Ms Yive Yang were was added as review authors and assisted in updating the review. In particular, they aided with the search, study selection, data extraction, data entry, and analyses. We adjusted the author order to comply with new Cochrane policies. Additionally, because several years have passed since publication of the protocol in 2015, some original authors no longer had capacity to assist with the updating of searches and quality appraisal of newly identified trials. Dr Rishi Sud and Dr Angelica Claudino were authors of the protocol but chose not to participate in the preparation of this review. Angelica Claudino had the Latin languages required for a LILACS search and thus a LILACS search was not undertaken for the review.

We removed the second objective (to assess the effects of specific psychological therapy in people with severe and enduring anorexia nervosa who are resistant to treatment) on the recommendation of peer reviewers, who considered it should be included as a subgroup analysis.

We updated the text in the Background.

On the advice of the Cochrane methods peer reviewer, we changed the effect measure from standardised mean difference to mean difference, as our analyses included only one study and there was no need to pool results from different scales.

INDEX TERMS

Medical Subject Headings (MeSH)

*Anorexia Nervosa [therapy]; *Antipsychotic Agents; *Cognitive Behavioral Therapy; *Drug-Related Side Effects and Adverse Reactions; Fear

MeSH check words

Adult; Child, Preschool; Humans