Comparative efficacy and acceptability of psychological interventions for the treatment of adult outpatients with anorexia nervosa: a systematic review and network meta-analysis

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Summary

Background. No consistent first-option psychological interventions for adult outpatients with anorexia nervosa (AN) emerges from guidelines. A random-effect network meta-analysis (NMA) of randomised controlled trials (RCTs) about stand-alone non-pharmacological treatments was conducted. The aim of the present work is to compare stand-alone psychological interventions for adult outpatients with AN with a specific focus on weight, eating disorder symptoms and all-cause dropout rate.

Methods. We searched CENTRAL, CINAHL, MEDLINE, and PSYCINFO for published and unpublished literature until March 20th, 2020. We included RCT for the treatment of adult outpatients with acute AN, defined according to standardised criteria and assessing a stand-alone treatment. Primary outcomes were change in body mass index (BMI), change in clinical symptoms and all-cause dropout rate. Global and local inconsistencies for the NMA were measured, and CINeMA was used to assess the confidence in evidence for primary outcomes.

Findings. Overall, 16 RCTs were included in the systematic review and 13 contributed to the NMA (overall, 1047 patients, 97.4% female). Seven interventions were assessed: treatment as usual (TAU), cognitive behavioural therapy (CBT), Maudsley Anorexia Nervosa Treatment for Adults, family therapy, psychodynamic psychotherapies, and two novel forms of CBT (targeting compulsive exercise, adding cognitive remediation therapy). No intervention outperformed TAU in our primary outcomes, but all-cause dropout rate was lower for CBT than psychodynamic psychotherapies (OR 0.54, 95% CI 0.31-0.93). Heterogeneity or inconsistency emerged only for a few comparisons. Confidence in evidence was low to very low.

Interpretation. When compared with TAU, specific psychological treatments for adult outpatients with AN can be associated with modest improvements in terms of clinical course and quality of life, but no reliable evidence supports the clear superiority or inferiority of the specific treatments for AN recommended by clinical guidelines internationally. Results from our analysis are based on the best data from existing clinical studies, but these findings should not be seen as definitive or universally applicable. There is urgent need to fund new research to develop and improve therapies for adults with AN. In the meanwhile, to better understand effects of available treatments, participant-level data should be made

freely accessible to researchers to eventually identify if specific subgroups of patients are more likely to respond to specific treatments.

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Research in context

Evidence preceding this study

Treatment guidelines specify that anorexia nervosa (AN) in adults can be treated in outpatient settings with stand-alone psychological interventions including cognitive behavioral therapy (CBT), family-oriented treatments, psychodynamic treatments, and other treatments with evaluated manualised approaches such as Maudsley Anorexia Nervosa Treatment for Adults (MANTRA), and Specialist Supportive Clinical Management (SSCM). In the scientific literature we found only one recent network meta-analysis, published in 2018, which combined data from eight randomised controlled trials (RCTs) testing seven interventions for adults with AN. However, this study had major methodological limitations, as it included both in- and outpatients but omitted some relevant studies and did not select a homogeneous time point to measure outcome across the studies. In addition, the only outcome analysed was weight gain.

Added value of this study

We searched CENTRAL, CINAHL, MEDLINE, and PSYCINFO until March 20th, 2020 for RCTs administering stand-alone treatments for AN in adult outpatients and compared them using a network meta-analysis. We included thirteen RCTs in the statistical analysis, treating 1,047 subjects with AN. Primary outcomes were treatment efficacy on BMI and eating disorders symptoms (measured around one year post-randomisation to allow time for progressive weight gain and maintenance, and to detect worsening after early weight gain) and all-cause dropout rate. Overall, the methodological quality of the included studies was low. The present network meta-analysis updates and addresses the limitations of the previous one. Only jointly randomizable subjects were combined and, overall, five new RCTs were added. Among the additional RCTs, one independent study directly compared MANTRA vs CBT-

Enhanced vs SSCM in Australia, something that was recommended in order to develop more reliable evidence beyond studies from the one group in United Kingdom. This RCT directly and indirectly compared the three interventions which are indicated as the treatments of choice by National Institute for Health and Care Excellence (NICE) guidelines. Also, the present work connected a previously unevaluated treatment (focusing on exercise in addition to standard CBT) with other interventions, allowing more comparisons across the network. Authors were contacted to obtain data when not available and the project is based on an *a-priori* protocol, already published in the scientific literature.

Implications of all the available evidence

Overall, when compared with treatment as usual, there is no evidence supporting the superiority of the three outpatient treatments of acute AN that are recommended by NICE guidelines. Results from our analysis are based on the best data from existing clinical studies, but these findings should not be seen as definitive or universally applicable, as they are more exploratory than confirmatory. The small sample size of the included studies and the wide confidence intervals seem especially critical in the context of AN, where the importance of patient features, such as age, chronicity, and symptom severity are key for treatment outcomes. To better understand effects of available treatments, participant-level data should be made freely accessible to researchers to eventually identify if specific subgroups of patients are more likely to respond to specific treatments. A personalised medicine approach (i.e., matching treatments to biological and psychiatric presentation) and the use of novel adjunctive interventions, are warranted. There is urgent need to fund new research to develop and improve therapies for adults with AN.

Introduction

Anorexia nervosa (AN) is an eating disorder characterised by mental and behavioral symptoms leading to significantly low body weight, associated with a disturbance in the experience of body shape and/or weight, and a significant impairment in physical, social, vocational and psychological functioning.[1] Age of onset of AN typically occurs in adolescence or emerging adulthood,[2] and frequently has a chronic course,[3] associated with physical, psychological and social morbidity and the highest mortality among psychiatric disorders.[4,5] Several treatments for AN have been tested for inpatients and outpatients, but so far no best option has clearly emerged.[6]

International guidelines generally converge on indicating stand-alone outpatient psychological treatments (over pharmacological treatments alone) as a first-line option in adults with AN, but provide inconsistent recommendations when it comes to specific interventions.[7] For example, while Australian[8] guidelines state that any specialist therapist-led and manual-based approach is recommended for AN in adults,[7] ideally within a multidisciplinary approach, guidelines in The Netherlands and the United Kingdom (UK) provide more specific recommendations indicating first- and second-line psychological treatments.[7] Specifically, the 2017 UK National Institute for Health and Care Excellence (NICE) guidelines indicate Specialist Supportive Clinical Management (SSCM), Maudsley Anorexia Treatment for Adults (MANTRA), and Cognitive behavioral therapy for eating disorders (CBT-ED) as first-line treatment of AN in adults, with focal psychodynamic therapy (FPT) as a second-line treatments.[9] The methods used to make recommendations is not homogeneous across countries, and includes a mixture of evidence synthesis and expert opinion.[7]

Network meta-analysis (NMA) is the best statistical tool we have to select the most appropriate treatment from a number of options, because it allows for estimation of comparative efficacy and ranking interventions even if they have not been investigated head to head in randomised controlled trials.[10] NMAs are increasingly acknowledged as the best statistical approach to influence clinical practice, as they can compare different interventions using estimates from both direct and indirect comparisons.[11-13] A recent NMA has attempted to identify the best treatment for adults with AN,[6] showing that nothing works better than SSCM, exclusively reporting on weight outcome. However, this NMA has some important methodological flaws that undermine the validity of its findings and, since its publication, new studies have been published. The aim of the present work is to compare stand-alone psychological interventions

for adult outpatients with AN with a specific focus on weight, eating disorder symptoms and all-cause dropout rate.

Methods

We systematically searched CENTRAL, CINAHL, MEDLINE, and PSYCINFO from inception until March 20th, 2020 using the following search terms "(anorexia and (random* or rct or trial or treatment or intervention) and adult)". Full details on the search and study selection process are reported in the Appendix (page 3-4). Two authors (TW, MS) independently screened the papers and extracted data. Inclusion criteria were: i) being an RCT, ii) treating adult outpatients with acute AN (relapse prevention RCTs were not considered), defined according to DSM or ICD (any version), iii) assessing a stand-alone treatment. We followed the PRISMA extension for network meta-analyses.[14] When data were not reported, authors were contacted with the request to share them.[15] Risk of Bias was assessed using the Risk of Bias Tool as a reference.[16] Confidence in the evidence for the primary outcomes was assessed within the CINeMA framework.[17]

Within the review team, a group of experts discussed and defined *a-priori* two levels for treatment definitions, in order to account for the theoretical common backgrounds behind groups of interventions on one hand (primary nodes), and the specificity of the clinical application of each individual intervention on the other hand (secondary nodes). We identified seven primary nodes: treatment as usual (TAU), CBT, MANTRA, family therapy, psychodynamic-oriented psychotherapies, a novel psychotherapy targeting compulsive exercise (CBT-Leap) and another novel intervention comparing cognitive remediation therapy (CRT) followed by CBT (CRT-CBT). Ten secondary nodes were TAU, SSCM, interventions mainly focused on dietary education (previously combined with TAU in primary nodes), CBT, CBT-Enhanced (previously combined with CBT in primary nodes), MANTRA, family therapy, psychodynamic-oriented psychotherapies, CBT-Leap and CRT-CBT. Only outpatient interventions were included, because healthcare for inpatients with AN is different from outpatients (inpatients programs are usually multidisciplinary and high intensity, while outpatient treatments generally involve once or twice a week sessions with a therapist of a single discipline, providing care in the least restrictive setting) and also because including both would have violated the transitivity assumption for the NMA.[18] Full

information about the methods of the NMA are reported in the protocol (also in PROSPERO, CRD42017064429).[19] The changes to the published protocol are listed in the online Appendix (page 46).

Outcomes

Primary nodes were used to analyse three clinically relevant outcomes: the two primary outcomes as reported in the published protocol[19] (namely change in BMI and change in eating disorder symptoms - both measured one year post-randomisation) and one secondary outcome (all-cause dropout rate measured three months post-randomisation). The decision to have two different timepoints for these outcomes was taken *a priori* and based on the authors' clinical experience: in outpatient setting, three months can be enough to measure dropout, however at least one year is needed to properly assess weight gain. The secondary nodes were used to assess the same outcomes at different time points: at study endpoint and at longest duration of follow-up. We could not analyse the secondary outcomes as described in the protocol,[19] because we did not manage to get access to the individual patient data (as originally planned) or the outcome data were not reported in the study (nor available from the study authors).

Data Analysis

We conducted a NMA within the frequentist framework by using the netmeta package, RStudio Version 1.2.1335 and STATA 16.1.[20,21] For continuous outcomes, mean difference (MD), when the unit of measure of the outcome was identical, or standardised mean difference (SMD), when the unit of measure was different across studies, were calculated; for binary outcomes, odds ratio (OR) was used. A common heterogeneity (tau^2) across all comparisons was assumed. Global inconsistency was assessed considering a full design-by-treatment model.[22] Local inconsistency was measured with a loop specific approach to assess the agreement between direct and indirect estimates for each outcome.[23] A hierarchy of the treatments among included interventions, based on cumulative ranking curve (SUCRA) and the mean ranks, was calculated for each outcome at each time-point.[24] Publication bias was measured for primary outcomes by visual inspection of funnel plot and Egger's test.[25]

Data sharing

With the publication of this Article, the full dataset will be freely available online in Mendeley Data, a secure online repository for research data, which allows archiving of any file type and assigns a permanent and unique digital object identifier (DOI) so that the files can be easily referenced (DOI to be added).

Role of the funding source

The funder of this study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit for publication. All authors have access to the data, and AC was responsible for the decision to submit for publication.

Results

Out of 14,003 studies assessed at title/abstract level, 270 full texts were retrieved for further scrutiny and ultimately 13 RCTs [15,26-38] were included in the NMA. Moreover, three additional RCTs [39-41] were included in the systematic review but could not be analysed in the NMA, because they were separated from the main network, as none of their pharmacological treatment arms was connected with any other non-pharmacological intervention in the main network (Figure 1). Characteristics of the 13 RCTs included in the NMA are reported in Table 1, and details on included interventions with their classification into respective nodes are available in Table 2. Six RCTs were set in the UK, four in Australia, one in the USA, New Zealand, and Germany each. AN was defined according to DSM-IV criteria in nine RCTs, to DSM-III-R in two RCTs, to DSM-5 and ICD-10 in one RCT each. Mean age of participants was 25.30 years (SD 4.03), 97.4% were female and mean BMI was 16.17 (SD 0.69) kg/m^2, ranging from 15 to 17.5. Duration of treatment ranged between 12 and 52 weeks.

Figure 2 reports the networks and effect estimate of the primary outcomes, comparing CBT, FBT, Leap-CBT, MANTRA, and psychodynamic-oriented psychotherapies with TAU. In terms of head-to-head comparisons, no differences were found between individual interventions, with the only exception of CBT which had fewer all-cause dropouts than psychodynamic-oriented psychotherapies (OR 0.54, 95% CI 0.31-0.93) (Table 3). The analyses with secondary nodes showed that this effect was driven by CBT-Enhanced (OR 0.45, 95% CI 0.23-0.87) (see Appendix, page 19).

Examination of secondary outcomes did not show any difference between specific treatments with just few exceptions. Specifically, considering BMI change at the longest follow-up, psychodynamic-oriented psychotherapies outperformed TAU with both primary (SMD 0.31, 95% CI 0.05-0.57) and secondary nodes (SMD 0.34, 95% CI 0.1-0.59). Considering secondary nodes, among NICE first-line treatments, only CBT-E was not inferior to psychodynamic-oriented psychotherapies. Both psychodynamic-oriented psychotherapies and CBT-E were superior to other NICE-recommended treatments: versus SSCM (SMD 0.76, 95% CI 0.29-1.23 and 0.54, 95% CI 0.15-0.92, respectively) and versus MANTRA (SMD 0.83, 95% CI 0.35-1.31 and 0.61, 95% CI 0.21-1.01, respectively). MANTRA was also inferior to TAU (SMD -0.48, 95% CI -0.97-0.00). CBT did not outperform any comparator.

In sensitivity analyses excluding RCTs with high risk of bias, no treatment was better than TAU in terms of BMI, but CBT-E was better than MANTRA (secondary nodes, MD 0.68, 95% CI: 0.08-1.28). CBT-E had less all-cause drop-out than psychodynamic-oriented psychotherapies (primary nodes, OR 0.46, 95% CI: 0.26-0.82), and the effect was driven by CBT-E (secondary nodes, OR 0.43, 95% CI: 0.22-0.84).

High heterogeneity emerged for three out of fourteen outcomes, with I^2 ranging between 51.8% and 61.3% (Appendix, page 23). Global inconsistency was statistically significant only for one outcome (BMI change, p=0.04) and local inconsistency was significant for seven comparisons in primary and secondary outcomes, mainly involving CBT and MANTRA (with p values ranging between 0.05 and 0.01) (Appendix, page 24-27).

Overall, risk of bias was low in six RCTs, unclear in four, and high in three RCTs (Appendix, pages 6-7). CINeMA assessment showed that confidence in estimates was low to very low for the majority of primary and secondary outcomes (Appendix, pages 31-39). Comparison adjusted funnel plots and Egger's test suggested presence of publication bias for symptoms (but not for BMI) at 52 weeks (Appendix, pages 28-30). In the Appendix we reported all results about network and forest plots with SUCRA tables (pages 8-17), and league tables with direct and mixed estimates (pages 18-22).

Discussion

This NMA included data from thirteen RCTs (1,047 patients), showing that no best outpatient psychosocial treatment is supported by evidence for adults with AN. First line treatments recommended

in the NICE guidelines[9] did not significantly differ from TAU in terms of BMI, clinical symptoms and dropout rate after up to 52 weeks post-randomisation. These results do not fully support recent guidelines for the treatment of AN in adults. The lack of a strong evidence-base for psychological interventions that can have a specific effect on adults with AN is an important clinical problem.[42]

Several specific factors could explain the negative findings of the present study. TAU has been administered by mental health professionals who were working and have been trained in the same settings where the experimental interventions have been administered (and developed in some cases). Hence, common theoretical and educational background between clinicians administering different treatments, in practice, could have contaminated TAU with elements of experimental interventions. In other words, some interventions might be superior to TAU in peripheral rather than specialist settings where TAU is not delivered by an "highly experienced" professional. Also, despite different interventions with different and specific protocols (i.e., MANTRA, CBT), several shared components exist among most treatments; namely their multidisciplinary nature with inclusion of at least a GP in addition to a psychotherapist, the focus on behavioral and nutritional indications, medical monitoring, and regular weighing and eating. Furthermore, it has been shown that an excess of significance bias affects the psychotherapy field.[43] In an umbrella review it has been shown that almost half of around 250 meta-analyses of RCTs of psychotherapies report significant effect sizes, that virtually all favor experimental interventions, but that 93% of such positive results are affected by a number of different biases, including high heterogeneity, publication bias, small sample size, small study effect, and excess of significance bias, among others.[43] According to the results of the present work, the superiority of specific psychotherapies over others, at least in adults with a long duration of illness, appears questionable in the eating disorders field. Pooling data from all RCTs without individual-patient data level did not allow us to examine the role of specific individual characteristics, such as depressive symptoms, personality traits, BMI, psychiatric comorbidities and family history of mental illness, previous treatments, or duration of illness. Such clinical features certainly could play a role in differential response rates across specific treatments, possibly being an important area of future investigation. Finally, therapeutic alliance could have played a relevant role particularly more so in less behavioral interventions where therapeutic alliance only weakly moderates treatment outcome (in adults in particular).[44]

It is worth noting that the present work differs from previous meta-analyses[45] and network meta-analyses,[6] because we followed the most recent methodological recommendations about evidence synthesis for the evaluation of treatments of AN, which suggest to avoid comparisons between outpatient and inpatient treatments, assess clinical outcomes at similar time-points, and keep adolescents separate from adults.[46] This NMA has some limitations that should be taken into account when interpreting our findings. First, some methodological issues may have affected treatment estimates. For instance, there were differences in treatment dose (i.e. number of outpatient sessions offered to patients) across different studies included in the systematic review, or the earlier RCTs reporting on psychodynamic-oriented psychotherapies had lower quality, suggesting potentially biased and inflated results. Second, while we attempted to match meaningful post-randomisation points for comparison, we note that there was significant variability between studies and greater uniformity is required in future studies. In particular, it is important to plan a 12-month post-randomisation assessment in order to properly monitor weight gain. It would also be helpful if all trials included information related to inpatient days, a separate reporting of reasons for all-cause drop-out, a clear description of the interventions included in TAU and the costs over the course of outpatient treatment so that health economic comparisons can be made between different interventions. A third limitation was that our reference treatment for monotherapies was TAU, which is not a monotherapy, as it can involve many different components delivered by many different people, and was poorly described in most studies. Fourth, classification of the treatment categories was largely based on their label, but as a larger body of studies amasses, it would be of interest to categorise treatments according to the main procedures and specific components utilised in the therapies.[47] Fifth, the present analysis has focused only on adults with AN. Different findings might have emerged if studies of adolescents had been included as adults with AN might all have been affected from long duration of illness which might have flattened efficacy across different treatments. In the current investigation we omitted treatment studies including adolescents, given that RCTs in this group generally focussed on Family Based Therapy and hence were not overlapping with adult treatments and did not allow for direct comparisons in a network meta-analysis. The small sample size of the majority of included studies (only two of them had more than 50 participants per arm), the limited number of studies (some of the analyses were based only on a single study, as reported in Figure 2) and the mean age ranging between around 18 and 32 years old are other potential limitations of our analysis (however, a recent meta-analysis showed

that duration of illness does not predict treatment outcome in eating disorders).[48] Finally, due to the lack of available data, we could not conduct an individual-patient network meta-analysis, as originally intended by protocol.[19]

In conclusion, no clear evidence is currently supporting the superiority or inferiority of any specific manualised psychotherapeutic intervention indicated as first line treatment in international clinical guidelines over TAU after one year. However, results from our analysis are more exploratory than confirmatory. It appears that currently available outpatient treatments for AN are associated with modest improvements, and even a modest improvement may greatly improve the clinical course and quality of life for an individual with AN. The lack of interventions that are clearly better than TAU, though, suggests an urgent need to improve our outpatient therapies for adults with AN. Large collaborative multi-centre RCTs, investigating both novel psychological treatment and biological interventions (e.g. given the association between AN and metabolism-related genes)[49] should be funded and they should ideally include the investigation of moderators of treatment and compare the overall characteristics of clinical samples across the inpatient and outpatient contexts to review difference in aspects such as age, symptom severity, length of treatment and others. To this end, principal investigators of past and future RCTs should make data freely available to allow individual patients data (network) meta-analyses, which might reveal whether subgroups of patients benefit the most from specific interventions.[50] If differences are identified, such a finding could be critical for evaluating the suitability and prospect of the out-patient pathway, with important implications for routine clinical practice. We also need to learn much more about non-specific therapist effects and their contribution to outcome and how they may impact different types of therapy.[49]

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Contributors

AC and MS had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. AC, TDW and CJ conceived and designed the study. MS, EGO, JC and FDC selected the articles and extracted the data. AC, MS and CDG analysed the data. AC, MS, TDW, SB, CF, US, JT, AF and SZ interpreted the data. AC, MS and TDW wrote the first draft of the manuscript. All authors contributed to critical revision of the report for important intellectual content. All authors read and met the ICMJE criteria for authorship and agree with the results and conclusions of this Article.

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Table 1. Characteristics of included studies.

Author	Country	Diagnosis	Female %	Authors' treatment definition	Sample size	Mean age (SD)	Mean BMI (SD)	Treatment duration
Ball, 2004 [38]	Australia	DSM-IV	100	Cognitive behavioral therapy	13	18.45 (2.57)	16.06 (1.58)	52 wks
				Behavioral family therapy	12	17.58 (3.37)	16.45 (0.85)	
Byrne, 2017[15]	Australia	DSM-IV	96	Maudsley Anorexia Nervosa Treatment for Adults	41	25.95 (9.00)	16.86 (1.02)	25-40 wks
				Cognitive Behavioral Therapy -Enhanced	39	24.18 (8.00)	16.48 (1.46)	
				Specialist Supportive Clinical Management	40	28.44 (10.94)	16.54 (1.22)	
Crisp, 1991[28]	UK	DSM-III-R	100	Individual/group psychotherapy on transference/counter-transference (2 arms merged)	40	20.45 (3.85)	15.74 (NA)	12-52 wks
				Referred back to general practitioner or local consultant	20	21.9 (4.50)	15.45 (NA)	
Dare, 2001[29]	UK	DSM-IV	98	A time-limited form of psychoanalytic therapy + psychodynamic therapy (2 arms merged)	43	26.95 (7.00)	15.54 (1.63)	28-52 wks
				Family therapy	22	26.6 (7.60)	15.18 (1.50)	
				Usual practice of an eating disorders service	19	24.3 (4.5)	15.32 (1.65)	
Hall, 1987[27]	UK	DSM-III-R	100	Psychodynamic therapy.	15	19.55 (NA)	15.68 (NA)	12-24 wks
				Discussed diet, mood, and daily behaviors with experienced dietician	15	19.57 (NA)	15.01 (NA)	
Hay, 2018[35]	Australia	DSM-5	95	Cognitive Behavioral Therapy	38	28.6 (10.3)	NA	32-40 wks
				LEAP-CBT (compuLsive Exercise Activity theraPy)	40	26.1 (7.9)	NA	
Lock, 2013[26]	USA	DSM-IV	89	Cognitive Behavioral Therapy	23	22.7 (5.9)	17.5 (1.2)	24 wks
				Cognitive Remediation Therapy followed by Cognitive Behavioral Therapy	23			
McIntosh, 2005[30]	New Zealand	DSM-IV	100	Nonspecific supportive clinical management	16	17 to 40	17.3 (1.1)	20 wks
				Cognitive Behavioral Therapy	19			
				Interpersonal psychotherapy	21			
Schmidt, 2012[31]	UK	DSM-IV	93	Specialist supportive clinical management	37	27.5 (8.70)	16.4 (1.3)	20 wks
				Maudsley Anorexia Nervosa Treatment for Adults	34	25.6 (6.90)	16.3 (1.3)	
Schmidt, 2015[32,33]	UK	DSM-IV	98	Specialist supportive clinical management	70	25.9 (7.1)	16.6 (1.3)	20-30 wks
				Maudsley Anorexia Treatment for Adults	72	27.5 (8.1)	16.6 (1.2)	
Touyz, 2013[34]	Australia	DSM-IV	100	Specialist supportive clinical management	32	32.3 (10.0)	16.1 (1.4)	36 wks
				Cognitive Behavioral Therapy (weight gain/recovery from core features of eating disorders were not treatment priorities)	31	34.6 (9.0)	16.3 (1.3)	
Treasure, 1995[36]	UK	ICD-10	unclear	Cognitive-analytic therapy	14	24.7 (5)	15.6 (2.1)	20 wks

				Educational behavioral treatment	16	25.3 (7)	15.0 (1.0)	
Zipfel, 2014[37]	Germany	DSM-IV	100	Focal psychodynamic therapy	80	28.0 (8.6)	16.57 (1.0)	40 wks
				Cognitive Behavioral Therapy - Enhanced	80	27.4 (7.9)	16.82 (1.0)	
				Optimised treatment as usual	82	27.7 (8.1)	16.75 (1.0)	

Legend. BMI, Body Mass Index; DSM, Diagnostic and Statistical Manual; ICD, International Classification of Diseases; NA, not available; RCT, randomised controlled trial; SD, standard deviation; UK, United Kingdom; USA, United States of America.

Table 2. Description of interventions included in the network meta-analysis and definitions of nodes in the network (at arm level)

Author	Complete authors' intervention definition	Primary node	Secondary node
Ball, 2004[38]	CBT: based on Garner and Bemis (1982) and modified to address maladaptive core beliefs often associated with feelings of failure and inadequacy	CBT	CBT
	Behavioral Family Therapy: behavioral interventions described by Robin and Foster (1989)	FBT	FBT
Byrne, 2017[15]	Maudsley Anorexia Nervosa Treatment for Adults (MANTRA): formulation-based treatment accompanied by a patient workbook	MANTRA	MANTRA
	CBT-E: based on the trans-diagnostic maintenance model of eating disorders (Fairburn, 2008)	CBT	CBT-E
	SSCM: mimic outpatient treatment that could be offered in usual clinical practice (normalisation of eating and restoration of weight, psychoeducation)	TAU	SSCM
Crisp, 1991[28]	Individual or group psychotherapy focusing on transference and countertransference issues: 2 arms merged	PSD-O	PSD-O
	Referred back to their GP or local consultant	TAU	TAU
Dare, 2001[29]	A time-limited form of cognitive analytic therapy or psychodynamic therapy: 2 arms merged	PSD-O	PSD-O
	Family therapy	FBT	FBT
	Usual practice of an eating disorder service	TAU	TAU
Hall, 1987[27]	Psychodynamic therapy	PSD-O	PSD-O
	Discussed diet, mood, and daily behaviors with experienced dietician	TAU	DIET
Hay, 2018[35]	CBT: restoring weight and normal eating habits by challenging underlying beliefs and thoughts through cognitive restructuring and behavior change.	CBT	CBT
	CBT + LEAP	Leap-CBT	Leap-CBT
Lock, 2013[26]	CBT	CBT	CBT
	Cognitive remediation therapy (8 sessions) + CBT (16 sessions)	CTR-CBT	CTR-CBT
McIntosh, 2005[30]	Specialist supportive clinical management	TAU	SSCM
	CBT	CBT	CBT
	Interpersonal psychotherapy	PSD-O	PSD-O
Schmidt, 2012[31]	Specialist supportive clinical management	TAU	SSCM
	MANTRA	MANTRA	MANTRA
Schmidt, 2015[32,33]	Specialist supportive clinical management	TAU	SSCM
	MANTRA	MANTRA	MANTRA
Touyz, 2013[34] *	Specialist supportive clinical management	TAU	SSCM
	CBT (weight gain/recovery from core features of eating disorders were not treatment priorities)	CBT	CBT
Treasure, 1995[36]	Cognitive-analytic therapy	PSD-O	PSD-O
	Educational behavioral treatment: monitor daily intake using a diary, goals to increase the amount and range of food eaten were set each week	TAU	DIET

Zipfel, 2014[37]	Focal psychodynamic therapy: pro-anorectic behaviour, ego-syntonic beliefs, and self-esteem; the association between interpersonal relationships and eating; transfer to everyday life, anticipation of treatment termination, and parting	PSD-O	PSD-O
	CBT-E	CBT	CBT-E
	Optimised treatment as usual; psychotherapists with experience in eating disorders working in accordance with German general psychotherapy guidelines	TAU	TAU

Legend. CBT, cognitive behavioral therapy; CBT-E, CBT-Enhanced; CRT-CBT, Cognitive Remediation Therapy followed by CBT; DIET, dietary intervention; FBT, family-based treatment; MANTRA, Maudsley Anorexia Treatment for Adults; LEAP-CBT, compuLsive Exercise Activity theraPy; PSD-O, psychodynamic oriented psychotherapies; RCT, randomized controlled trial; SSCM, Specialist Supportive Clinical Management; TAU, treatment as usual. *: CBT-AN was modified to reflect the shift in treatment goals. Specifically, weight gain and recovery from core features of the ED were not assumed to be treatment priorities.

Table 3. League table with Body Mass Index change mean difference (grey) and symptoms change standardized mean difference (light blue) at 52 weeks (lower triangle) and drop-out odds ratio from network meta-analysis after at least three months of treatment (upper triangle).

Outcomes in Anorexia Nervosa	CBT	FBT	Leap-CBT	MANTRA	PSD-O	TAU	Acceptability OR [95% CI]
		0.44 [0.16; 1.16]	1.22 [0.50; 2.94]	1.00 [0.51; 1.96]	**0.54 [0.31; 0.93]**	0.67 [0.37; 1.19]	
BMI MD [95% CI]	-0.11 [-1.14; 0.92]		2.78 [0.74; 10]	2.27 [0.78; 6.67]	1.23 [0.48; 3.12]	1.51 [0.56; 4.17]	
Symptoms SMD [95% CI]	-0.06 [-0.59; 0.46]						
BMI MD [95% CI]	1.10 [-0.43; 2.63]	1.21 [-0.63; 3.06]		0.83 [0.27; 2.52]	0.44 [0.16; 1.26]	0.55 [0.19; 1.59]	
Symptoms SMD [95% CI]	-0.15 [-0.68; 0.38]	-0.09 [-0.84; 0.66]					
BMI MD [95% CI]	0.39 [-0.24; 1.02]	0.50 [-0.64; 1.64]	-0.71 [-2.37; 0.94]		0.54 [0.26; 1.10]	0.66 [0.41; 1.07]	
Symptoms SMD [95% CI]	0.04 [-0.31; 0.39]	0.10 [-0.47; 0.68]	0.19 [-0.45; 0.83]				
BMI MD [95% CI]	-0.23 [-0.89; 0.42]	-0.12 [-1.16; 0.91]	-1.33 [-3.00; 0.33]	-0.62 [-1.42; 0.18]		1.23 [0.67; 2.27]	
Symptoms SMD [95% CI]	0.05 [-0.28; 0.38]	0.12 [-0.39; 0.62]	0.20 [-0.42; 0.83]	0.01 [-0.38; 0.41]			
BMI MD [95% CI]	0.22 [-0.25; 0.68]	0.33 [-0.70; 1.35]	-0.88 [-2.49; 0.72]	-0.17 [-0.73; 0.39]	0.45 [-0.17; 1.07]		
Symptoms SMD [95% CI]	0.15 [-0.11; 0.42]	0.22 [-0.30; 0.73]	0.31 [-0.29; 0.90]	0.12 [-0.16; 0.39]	0.10 [-0.19; 0.39]		

Legend. CBT, cognitive behavioral therapy; FBT, family-based treatment; LEAP-CBT, compuLsive Exercise Activity theraPy; MANTRA, Maudsley Anorexia Treatment for Adults; PSD-O, psychodynamic oriented psychotherapies; TAU, treatment as usual. Lower triangle, mean difference (MD) for BMI (grey) [95% confidence interval], standardized mean difference (SMD) for symptoms

(light blue) [95% confidence interval]; upper triangle, odds ratio of drop-out [95% confidence interval]. Odds Ratio (OR) lower than 1, and positive MD or SMD favor column-defining treatment in the lower triangle, and the row-defining treatment in the upper triangle.