Focal psychodynamic therapy, cognitive behaviour therapy, and optimised treatment as usual in outpatients with anorexia nervosa (ANTOP study): randomised controlled trial

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Summary

Background Psychotherapy is the treatment of choice for patients with anorexia nervosa, although evidence of efficacy is weak. The Anorexia Nervosa Treatment of OutPatients (ANTOP) study aimed to assess the efficacy and safety of two manual-based outpatient treatments for anorexia nervosa—focal psychodynamic therapy and enhanced cognitive behaviour therapy—versus optimised treatment as usual.

Methods The ANTOP study is a multicentre, randomised controlled efficacy trial in adults with anorexia nervosa. We recruited patients from ten university hospitals in Germany. Participants were randomly allocated to 10 months of treatment with either focal psychodynamic therapy, enhanced cognitive behaviour therapy, or optimised treatment as usual (including outpatient psychotherapy and structured care from a family doctor). The primary outcome was weight gain, measured as increased body-mass index (BMI) at the end of treatment. A key secondary outcome was rate of recovery (based on a combination of weight gain and eating disorder-specific psychopathology). Analysis was by intention to treat. This trial is registered at http://isrctn.org, number ISRCTN72809357.

Findings Of 727 adults screened for inclusion, 242 underwent randomisation: 80 to focal psychodynamic therapy, 80 to enhanced cognitive behaviour therapy, and 82 to optimised treatment as usual. At the end of treatment, 54 patients (22%) were lost to follow-up, and at 12-month follow-up a total of 73 (30%) had dropped out. At the end of treatment, BMI had increased in all study groups (focal psychodynamic therapy 0·73 kg/m², enhanced cognitive behaviour therapy 0·93 kg/m², optimised treatment as usual 0·69 kg/m²); no differences were noted between groups (mean difference between focal psychodynamic therapy and enhanced cognitive behaviour therapy –0·45, 95% CI –0·96 to 0·07; focal psychodynamic therapy *vs* optimised treatment as usual –0·14, –0·68 to 0·39; enhanced cognitive behaviour therapy *vs* optimised treatment as usual –0·30, –0·22 to 0·83). At 12-month follow-up, the mean gain in BMI had risen further (1·64 kg/m², 1·30 kg/m², and 1·22 kg/m², respectively), but no differences between groups were recorded (0·10, –0·56 to 0·76; 0·25, –0·45 to 0·95; 0·15, –0·54 to 0·83, respectively). No serious adverse events attributable to weight loss or trial participation were recorded.

Interpretation Optimised treatment as usual, combining psychotherapy and structured care from a family doctor, should be regarded as solid baseline treatment for adult outpatients with anorexia nervosa. Focal psychodynamic therapy proved advantageous in terms of recovery at 12-month follow-up, and enhanced cognitive behaviour therapy was more effective with respect to speed of weight gain and improvements in eating disorder psychopathology. Long-term outcome data will be helpful to further adapt and improve these novel manual-based treatment approaches.

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Introduction

Anorexia nervosa is associated with serious medical morbidity[1,2] and pronounced psychosocial comorbidity.[3] It has the highest mortality rate of all mental disorders[4,5] and relapse happens frequently.[6] The course of illness is very often chronic, particularly if left untreated.[7] Partial syndromes are also associated with adverse health outcomes. Quality of life for patients is poor, and the cost and burden placed on individuals, families,[1] and society is high.[8] The overall incidence of anorexia nervosa is at least eight people per 100 000 per year, with an average prevalence of 0·3% in girls and young women.[9] The severity, poor prognosis, and low prevalence of the disorder are reasons why large randomised controlled trials are needed and why difficulties arise in implementation of treatment studies.[10]

According to international treatment guidelines, psychotherapy is the treatment of choice for patients with anorexia, although no evidence clearly supports the efficacy of any specific form of psychotherapy.[11] Guidelines from the UK's National Institute for Health and Care Excellence (NICE) outline 75 recommendations for the treatment of anorexia nervosa.[12] 74 of these treatments have received a grade of C, meaning that good quality, directly applicable

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clinical studies are absent and that recommendations are based solely on the opinions, clinical experience, or both of respected authorities in the field. According to NICE guidelines, psychological treatment of anorexia nervosa aims to lessen risk, encourage weight gain and healthy eating, reduce other symptoms related to the eating disorder, and facilitate psychological and physical recovery. In a Cochrane review of outpatient treatment for anorexia nervosa,[13] only seven small trials were identified, two of which included children or adolescents. Findings of two of the trials implied that treatment as usual might be less effective than a specific psychotherapy. No particular treatment, however, was consistently superior to any other approach.

In adults with anorexia nervosa, some evidence shows the effectiveness of outpatient focal psychodynamic therapy and cognitive behaviour therapy.[14–16] In one trial,[17] at the end of the treatment period, a supportive therapy delivered by specialists was superior to two specific psychotherapies, with respect to a combined global outcome measure. However, long-term follow-up of this trial showed that interpersonal therapy was the most successful treatment.[18] Findings of intervention studies applying deep-brain stimulation[19] or adapting psychotherapeutic approaches for patients with chronic anorexia nervosa[20] have also showed some promising results for this cohort.

Evidence accumulated thus far does not support any one particular psychotherapeutic method for the treatment of adults with anorexia nervosa.[1,13] However, therapeutic support from a non-specialist clinician might be less successful than a specific form of psychotherapy provided by a specialist. Additionally, no evidence strongly advocates drug treatment either in the acute or maintenance phase of the illness.[21] Large, well designed psychotherapeutic trials are needed urgently. We designed the Anorexia Nervosa Treatment of OutPatients (ANTOP) study to investigate the efficacy of two manual-based, psychotherapeutic, eating disorder-specific outpatient therapies for adults with anorexia nervosa—focal psychodynamic therapy and enhanced cognitive behaviour therapy—compared with optimised treatment as usual.

See Online for appendix

Methods

Study design and participants

ANTOP was a multicentre, randomised controlled efficacy trial in adult patients with anorexia nervosa. The trial protocol, outlining details on study design, has been published elsewhere.[22] Over a 2-year period, we screened patients from outpatient departments of ten German university departments of psychosomatic medicine and psychotherapy (Bochum, Erlangen, Essen, Freiburg, Hamburg, Heidelberg, Munich, Münster, Tübingen, and Ulm) for inclusion in the study. Inclusion criteria were: adult patient (aged ≥18 years); female sex; a diagnosis of anorexia nervosa or subsyndromal anorexia nervosa (one diagnostic criterion absent), according to the diagnostic and statistical manual of mental disorders, 4th edition (DSM-IV); and a body-mass index (BMI) of 15–18·5 kg/m². Exclusion criteria were: current substance abuse; use of neuroleptic drugs; psychotic or bipolar disorder; serious unstable medical problems; and ongoing psychotherapy.

We medically assessed patients at baseline and did a comprehensive diagnostic assessment, which included measuring weight and height and undertaking structured diagnostic interviews specific to psychiatry and eating disorders. We obtained written informed consent from every participant at the baseline visit. Independent research ethics committees at every participating centre approved the study.

Randomisation and masking

The independent coordination centre for clinical trials (Marburg, Germany) did centralised randomisation. Patients were randomly assigned to 10 months of treatment with either focal psychodynamic therapy, enhanced cognitive behaviour therapy, or optimised treatment as usual in a 1:1:1 ratio. We used the Rosenberg and Lachin covariate-adaptive randomisation procedure[23] based on Nordle and Brantmark's design.[24] This procedure combines elements of the minimisation approach (to optimally allocate a treatment to a particular patient based on his or her prognostic factor combination) with the biased-coin technique to avoid a deterministic treatment allocation. We stratified randomisation by centre and duration of anorexia nervosa (≤6 years *vs* >6 years). After patients were randomised into groups, the independent centre faxed trial sites the treatment allocation. Complete masking of participants was not feasible because a third of patients were allocated optimised treatment as usual and, therefore, were not treated at the respective centres. More information about the masking procedure is provided in the appendix (p 2).

Procedures

Patients allocated to either focal psychodynamic therapy or enhanced cognitive behaviour therapy received an individual outpatient intervention based on standardised treatment manuals.[25,26] To avoid contamination between treatment arms, the two approaches were provided by different therapists, who were all skilled at the underlying therapeutic approach (panel 1). Therapists received initial 2-day training from experts (focal psychodynamic therapy: WH, HS, H-CF; enhanced cognitive behaviour therapy: C Fairburn), followed by annual training updates (focal psychodynamic therapy: WH, HS, H-CF; enhanced cognitive behaviour therapy: GG, MdZ). At every fourth session, experienced local supervisors oversaw the therapists' work. Panel 1 outlines the essentials of the three treatment manuals. Information about adherence control and treatment fidelity is provided in the appendix (p 4).

We did the study according to International Conference on Harmonisation Good Clinical Practice guidelines. We incorporated quality-control methods including case-report

forms, independent data management, on-site monitoring, and documentation of adverse and severe adverse events. Data management included regular checks for consistency and plausibility, and queries if inconsistencies or missing data were noted. In addition to an initiation site visit in 2007 and a close-out visit in 2011, the independent coordination centre made three annual on-site data monitoring visits to every study centre, according to existing standard operating procedures. The main aim of the monitoring procedure was to verify patients' safety and the completeness, accuracy, and validity of the trial data, and to comply with the study protocol. Additionally, the principal investigators (SZ, WH, BW, and GG) had to report to the independent data safety and monitoring committee during annual meetings. After the study protocol was published and finally approved by the independent coordination centre, two statisticians not involved in treatment and diagnostics of the ANTOP study did biometric analyses.

Outcome measures

We took measurements at five timepoints: at a baseline assessment (before randomisation); 4 months after treatment was started; 10 months after the start of treatment (which accorded with the end of treatment); after 3 months of follow-up (short-term); and at a 12-month

Panel 1: **Treatment provided**

Overview

We developed a framework of medical care for all patients in the ANTOP study. This framework included at least five regular sessions of specialist assessment at the patient's specific study centre. To avoid and reduce medical complications during the study period, we asked all patients to see their family doctor at least once a month. Every individual study centre gave patients' family doctors written instructions on how to provide care in relation to this study. Treatment was provided face-to-face by doctors and psychologists specialising in anorexia nervosa and the respective assigned treatment method. Additionally, we implemented a rigorous system of supervision, adherence control, and treatment fidelity (appendix p 3).

Focal psychodynamic therapy

At the beginning of focal psychodynamic therapy (FPT), we identified psychodynamic foci with a standardised, operationalised, psychodynamic diagnostic interview. The psychodynamic treatment manual can be divided roughly into three treatment phases. The first phase focuses mainly on therapeutic alliance, pro-anorectic behaviour and ego-syntonic beliefs (attitudes and behaviour viewed as acceptable), and self-esteem. In the second phase of treatment, main focus is placed on relevant relationships and the association between interpersonal relationships and eating (anorectic) behaviour. The pertinent aspects of the final phase are the transfer to everyday life, anticipation of treatment termination, and parting. Before every treatment session, an independent assessor measured every patient's weight and reported it to his or her therapist.[26]

Enhanced cognitive behaviour therapy

The unpublished German version of the manual for enhanced cognitive behaviour therapy (CBT-E) used in this trial was developed in 2007 during initial training. It is based on a report written by Fairburn before publication of his manual.[25] Therapists in enhanced cognitive behaviour therapy have used Fairburn's manual since its publication. The cognitive behaviour treatment plan consists of several modules, of which motivation (starting well), nutrition, creating a formulation, and relapse prevention (ending well) are essential. Other modules target cognitive restructuring, mood regulation, social skills, shape concern, and self-esteem. The treatment plan represents an extension of the focused version of enhanced cognitive behaviour therapy, combined with elements of the broad version. It focuses on education of patients about being underweight and starvation and helps patients initiate and maintain regular eating and healthy weight gain. Enhancement of self-efficacy and self-monitoring are crucial elements of the entire treatment process. Therefore, therapists selected additional practice and homework worksheets, written in German, which they gave patients at the end of every session. The patients received these homework assignments (next steps) to ensure the generalisation and transfer of therapeutic changes to daily life. Further details of the two interventions are described in the treatment manuals and additional published materials.

Optimised treatment as usual

Patients assigned to optimised treatment as usual received support in accessing therapy and were given a list of established outpatient psychotherapists with experience in treating eating disorders and who work in accordance with German general psychotherapy guidelines. Patients' family doctors had an active role in treatment and monitoring. In the German health-care system, psychotherapy for patients with eating disorders—in particular, those with anorexia nervosa—is usually covered by health insurance. To further optimise the treatment as usual approach, patients' family doctors had three roles. First, they were asked to take regular weight measurements, do monthly blood tests, and make structured reports to the study centre. Second, they were advised to admit patients to hospital should they fall under a particular weight (body-mass index <14 kg/m^2). Finally, they were informed about physical and psychiatric risks in patients with anorexia nervosa and were instructed to contact the respective study centre should a patient become at risk. In the study protocol, treatment (dosage and type of therapy) in the optimised treatment as usual study group was not regulated. Patients assigned to this group had at least five contact sessions with the study centre, at which their weight, laboratory findings, eating pathology, and psychiatric comorbidity were investigated and monitored.

follow-up visit (appendix p 7). BMI measurements taken at the end of treatment and at the 12-month follow-up visit served as the ANTOP trial's primary outcome. Masked and trained assessors measured patients' height and weight at the baseline assessment. Assessors checked patients' weight at every timepoint. Patients were weighed wearing light clothing (without shoes), using a balance-beam scale that was recalibrated regularly. We calculated BMI using bodyweight in kg divided by height in m squared (kg/m²).

Masked assessors measured secondary outcomes of general psychopathology and eating disorder-specific psychopathology (appendix p 5). They used a self-assessment test—the eating disorder inventory-2 (EDI-2)—to investigate eating disorder pathology. We used the structured clinical interview for DSM-IV axis I mental disorders (SCID-I) to measure psychiatric comorbidity. Furthermore, we used the full structured interview for anorexic and bulimic syndromes (SIAB-EX) to measure in detail the symptomatology of anorexia nervosa and bulimia nervosa. In addition to receiving certified SCID-I training, the authors of the SIAB-EX interview held a 2-day workshop to train assessors how to do expert ratings, before patient recruitment began. Annual 1-day workshops were held throughout the study period to ensure the high quality of data assessment.

Masked assessors also applied the psychiatric status rating (PSR) scale based on the patient's SIAB-EX interview (appendix p 5). The PSR scale is used to measure the general severity of the anorexic disorder. PSR scores range from 1 (patient has no symptoms of anorexia nervosa) to 6 (patient has severe symptoms of anorexia nervosa that require admission). A score of 5 indicates that all DSM-IV criteria for anorexia nervosa have been fulfilled. At baseline, all patients had a PSR score of 4 (subsyndromal anorexia nervosa) or 5 (full syndromal anorexia nervosa). To ascertain a strictly defined rating of outcome at the end of treatment and at the 12-month follow-up visit, we established a global outcome score based on the following combinations of PSR scores and BMI: recovery (scored as 3) was defined as a PSR score of 1 or 2 and BMI greater than 17·5 kg/m²; full syndrome anorexia nervosa (scored as 1) was a PSR score of 5 or 6 and BMI of 17·5 kg/m² or lower; and partial syndrome anorexia nervosa (scored as 2) included all other cases.

We recorded service dosage in terms of the number of outpatient psychotherapy sessions accessed (including the studied interventions of focal psychodynamic therapy and enhanced cognitive behaviour therapy) and use of any inpatient or day-patient treatment. Additionally, we asked patients assigned to both focal psychodynamic therapy and enhanced cognitive behaviour therapy groups to give brief feedback about the helpfulness of the sessions (gauged on a visual analogue scale from 0 to 10) and the length of treatment (too short, adequate, or too long).

Statistical analysis

Our primary hypothesis had two parts. The first part stated that the outpatient intervention of focal psychodynamic therapy would have a better outcome with respect to BMI at the end of treatment compared with optimised treatment as usual. The second part stated that, compared with optimised treatment as usual, the outpatient intervention of enhanced cognitive behaviour therapy would have a better outcome with respect to BMI at the end of treatment.[22] Before we began to obtain data, we also proposed the same hypotheses for the 12-month follow-up visit. Additionally, we expected that both at the end of treatment and at the 12-month follow-up visit, recovery rates defined in terms of a combined outcome (in accordance with DSM-IV) would be higher for treatments specific for anorexia nervosa (ie, focal psychodynamic therapy and enhanced cognitive behaviour therapy) than for optimised treatment as usual.

On the basis of the results of two smaller randomised controlled trials, in which the effects of focal psychodynamic therapy and enhanced cognitive behaviour therapy were assessed in outpatients with anorexia nervosa,[13,14] we assumed that the different interventions would result in an improvement in BMI of 1·0 kg/m² compared with optimised treatment as usual (assumed SD 1·7; effect size 0·59). Because the hypothesis for the primary efficacy endpoint entails two statistical tests—namely, focal psychodynamic therapy versus optimised treatment as usual, and enhanced cognitive behaviour therapy versus optimised treatment as usual—the nominal α for the primary hypothesis was set to 2·5% (two-sided) to restrict the type 1 error to 5%. For a two-sided *t* test with 2·5% significance and 80% power, we needed a sample size of 55 patients per group, resulting in a study sample size of 165. We increased the sample size to 242 patients to allow for a dropout rate of at least 30%. The independent coordination centre approved the statistical analysis plan before outcome data were examined.

We analysed the primary outcome by intention to treat, which included all patients who underwent randomisation, at the end of treatment and at the 12-month follow-up visit. We imputed missing data with a longitudinal approach (mixed model for repeated measures [MMRM]). The ANTOP schedule of measurements provided a precondition for using MMRM—ie, one additional measurement timepoint between baseline and end of treatment—so time trends could be modelled. We decided to use MMRM as the first imputation method because findings of a series of studies showed that MMRM is more robust to biases from missing data than is the last-observation-carried-forward method.[27] This decision was noted in the statistical analysis plan before data were examined. We also applied the mean-other imputation method. With this approach, missing values are replaced with the mean of the other group to provide a conservative approach (in our trial, this process was done to avoid erroneous decisions in favour of focal

psychodynamic therapy or enhanced cognitive behaviour therapy; appendix p 8). As an additional sensitivity measure, we did a complete case analysis (appendix p 9) that included all patients who had BMI values at all measurement timepoints. We also did a per-protocol analysis that included all patients who received at least 27 therapy sessions, had a BMI measurement taken either at the end of treatment or at the 12-month follow-up visit, were not pregnant during the trial or at 12-month follow-up, and were not admitted to hospital for more than 4 weeks during the trial.

For the primary outcome analysis, we compared both treatment groups (focal psychodynamic therapy and enhanced cognitive behaviour therapy) with the optimised treatment as usual group. The primary outcome—BMI at the end of treatment—was analysed with a mixed modelling approach. We entered the grand mean, treatment effects, and the binary stratification variable (duration of anorexia nervosa, ≤6 years *vs* >6 years) as fixed effects. Because trial sides were not chosen at random, we decided before data analysis started to model the centre effect as a fixed effect. Baseline BMI was entered as a covariate. The mathematical equation for our modelling approach is described elsewhere.[22] We tested the main hypothesis (primary outcome) by doing a series of pairwise comparisons. To investigate secondary hypotheses, we did exploratory analyses with a similar approach. In all analyses, we entered the variable of centre as a control variable. We analysed the global outcome with the MMRM approach, and this variable was treated as continuous. For the moderator analysis of anorexia nervosa subtypes, we divided the study sample into two groups and did the MMRM analysis for each group separately. We set the significance level to 5% for exploratory analyses. We used SAS versions 9.1 and 9.2 for statistical analyses.

In patients with anorexia nervosa, food restriction and purging behaviour can lead to life-threatening starvation that requires inpatient medical monitoring. Because severe weight loss is central to the psychopathology of anorexia nervosa, intermittent inpatient treatment of up to 4 weeks as a crisis intervention was not judged a serious adverse event. All other life-threatening or fatal events were defined as serious adverse events, and these had to be reported immediately to the principal investigator. Additionally, we set up an independent safety and data monitoring board. This board consisted of internationally renowned experts in the area of eating disorder research and treatment, and in data and safety monitoring. Further details about medical complications in the ANTOP trial have been published elsewhere.[22] This trial is registered at http://isrctn.org, number ISRCTN72809357.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had access to the data, and SZ, WH, BW, GG, H-CF, and KEG were responsible for submitting the manuscript. SZ made the final decision to submit the paper for publication.

Results

Between May, 2007, and June, 2009, we screened 727 patients for eligibility; 242 underwent randomisation after baseline assessment (figure 1). The number of patients enrolled per study centre was between 12 and 35. Table 1 shows baseline characteristics. We did not record any differences between groups with respect to demographic characteristics, BMI, illness duration, subtype of anorexia nervosa, and affective disorders. However, a comorbid anxiety disorder was more frequent in patients allocated either enhanced cognitive behaviour therapy or optimised treatment as usual, compared with focal psychodynamic therapy (table 1). Overall, mean BMI at baseline was 16·7 kg/m² (SD 1·0) and mean weight was

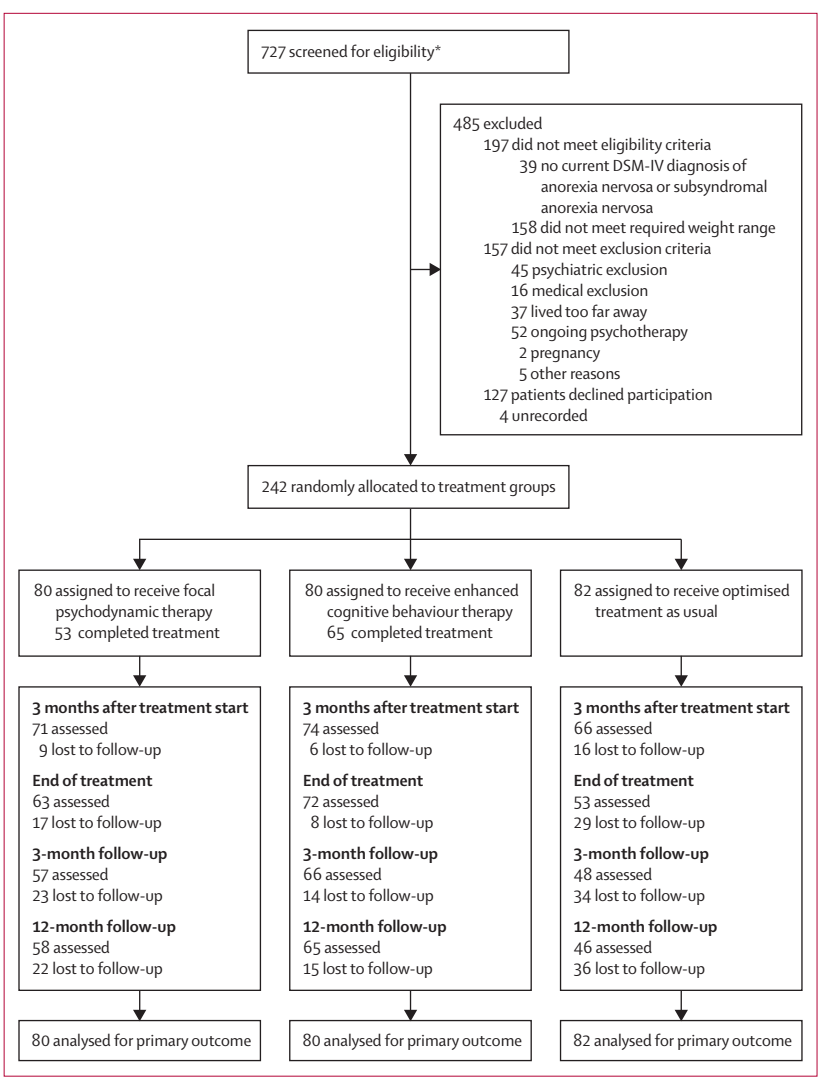

Figure 1: **Trial profile**
*Six male patients were excluded before screening because of predefined inclusion criteria.

46·5 kg (SD 4·2). 94 (39%) patients had anorexia nervosa for longer than 6 years. A restrictive subtype of anorexia nervosa was present in 131 (53%) patients, and 96 (40%) had at least one additional SCID-I diagnosis of a co-morbid mental disorder.

After 10 months of treatment (at the end of treatment), 54 (22%) of 242 patients were lost to follow-up, and 73 (30%) had dropped out by 12-month follow-up. At both these timepoints, rates of loss-to-follow-up differed significantly between study groups, with the highest rate noted in the optimised treatment as usual group. We did a sensitivity analysis to detect any possible selection bias attributable to different dropout rates at the end of treatment and at 12-month follow-up; BMI at baseline, difference in BMI between baseline and the end of treatment, anorexia nervosa subtype, and comorbid diagnosis of a mental disorder were not related to the dropout rate.

Table 2 shows outcome data after 4 months of treatment, at the end of treatment, at 3-month follow-up, and at 12-month follow-up. Figure 2 depicts the course of weight gain during treatment and at follow-up. At the end of treatment, patients in all study groups showed substantial weight gains from baseline (focal psychodynamic therapy, 0·73 kg/m²; enhanced cognitive behaviour therapy, 0·93 kg/m²; optimised treatment as usual, 0·69 kg/m²). We recorded no differences in BMI between study groups at the end of treatment in the adjusted models (table 2), using the MMRM algorithm to replace missing values. At 12-month follow-up, mean BMI values for patients from all study groups had risen further (focal psychodynamic therapy, 1·64 kg/m²; enhanced cognitive behaviour therapy, 1·30 kg/m²; optimised treatment as usual, 1·22 kg/m²). Again, we did not note a significant difference in BMI between study groups (table 2). A sensitivity analysis using the mean-other imputation method showed the same result pattern as with the MMRM approach (appendix, p 8). Complete case analysis (appendix, p 9) and per-protocol analysis (data not shown) did not show any different results.

Exploratory data analyses were done to investigate the proportion of patients with full and partial anorexia nervosa syndrome at baseline and those showing full recovery at the end of treatment and at 12-month follow-up (figure 3). Study groups did not differ in terms of global outcome between baseline and the end of treatment. At 12-month follow-up, however, patients assigned focal psychodynamic therapy had a significantly higher recovery rate compared with optimised treatment as usual (full recovery, 35% *vs* 13%; p=0·036). Table 3 shows BMI-related within-group effect sizes and table 4 provides additional information for the 12-month follow-up outcome.

Because fewer patients allocated focal psychodynamic therapy had comorbid anxiety disorders at baseline, compared with the other treatment groups, we did a sensitivity analysis to investigate whether an anxiety disorder at baseline could have affected the BMI outcome at the end of treatment or at 12-month follow-up. Results of the MMRM analysis showed no such association. Further subgroup analyses were done of patients with baseline BMI less than 17·5 kg/m², which accords with the weight criterion for full syndrome anorexia nervosa. In this subgroup, at the end of treatment, mean BMI in patients assigned focal psychodynamic therapy was lower than in those allocated enhanced cognitive behaviour therapy (16·9 kg/m² *vs* 17·5 kg/m²; p=0·038). Analysis of anorexia nervosa subtypes (restrictive *vs* binge-purge) showed no differences in treatment response between these two intervention groups.

Eating disorder psychopathology with respect to self-rating (EDI-2) did not differ over the course of treatment and follow-up (table 2). However, with the expert interview (SIAB-EX), patients with anorexia nervosa who were assigned enhanced cognitive behaviour therapy had the lowest SIAB-EX scores at the end of treatment (table 2). At 12-month follow-up, however, this difference was no longer detectable.

No serious adverse events attributable to weight loss or trial participation were reported during the study.

	Focal psychodynamic therapy (n=80)	Enhanced cognitive behaviour therapy (n=80)	Optimised treatment as usual (n=82)
Demographic characteristics			
Mean (SD) age at entry (years)	28·0 (8·6)	27·4 (7·9)	27·7 (8·1)
Marital status			
Single, never married	65 (81%)	66 (83%)	66 (81%)
Married, or living as such	12 (15%)	7 (9%)	13 (16%)
Separated or divorced	3 (4%)	5 (6%)	3 (4%)
Unknown	0	2 (3%)	0
Clinical characteristics			
Mean (SD) weight (kg)	46·37 (4·3)	46·33 (3·9)	46·71 (4·4)
Mean (SD) body-mass index (kg/m²)	16·57 (1·0)	16·82 (1·0)	16·75 (1·0)
Body-mass index			
<17·5 kg/m²	62 (78%)	53 (66%)	56 (68%)
17·5 to ≤18·5 kg/m²	18 (23%)	27 (34%)	26 (32%)
Duration of illness			
≤6 years	49 (61%)	49 (61%)	50 (61%)
>6 years	31 (39%)	31 (39%)	32 (39%)
Anorexia nervosa subtypes			
Binge-purge	34 (43%)	38 (48%)	39 (48%)
Restrictive	46 (58%)	42 (53%)	43 (52%)
Comorbidities			
Affective disorder	14 (18%)	25 (31%)	19 (23%)
Anxiety disorder	11 (14%)	20 (25%)	28 (34%)
Somatoform disorder	1 (1%)	3 (4%)	1 (1%)
Substance abuse	0	0	0
Mean (SD) total score on the eating disorder inventory	256 (54·6)	271 (53·4)	275 (51·7)
Mean (SD) total score on the structured inventory for anorexic and bulimic syndromes	1·0 (0·3)	1·1 (0·3)	1·1 (0·3)

Data are mean (SD) or number of patients (%).

Table 1: **Baseline characteristics**

Between baseline and 12-month follow-up, 13 (23%) of 57 patients assigned focal psychodynamic therapy (with available data), 20 (34%) of 58 allocated enhanced cognitive behaviour therapy, and 21 (41%) of 51 assigned optimised treatment as usual received additional inpatient treatment. The proportion receiving treatment differed significantly between the focal psychodynamic therapy group and the optimised treatment as usual group (p=0·044), whereas other group comparisons did not differ by much. Between baseline and the end of treatment, two patients assigned focal psychodynamic therapy, three allocated enhanced cognitive behaviour therapy, and five assigned optimised treatment as usual had inpatient treatment due to weight loss for 28 days or less; inpatient treatment for longer than 28 days was given to five patients assigned focal psychodynamic therapy, eight allocated enhanced cognitive behaviour therapy, and nine assigned optimised treatment as usual. The mean duration of admissions that arose between baseline and the end of treatment was 6·8 days (SD 22·9) for focal psychodynamic therapy, 12·6 days (36·9) for enhanced cognitive behaviour therapy, and 12·5 days (30·6) for optimised treatment as usual (p=0·49). For admissions between baseline and 12-month follow-up, mean duration was 19·0 days (SD 52·7) for focal psychodynamic therapy, 29·4 days (55·3) for enhanced cognitive behaviour therapy, and 29·3 days (54·2) for optimised treatment as usual (p=0·52). However, the distributions of days in hospital were skewed such that a few patients had a comparably long duration and more patients had short durations.

The overall dosage of outpatient psychotherapy sessions did not differ from baseline to 12-month follow-up between treatment groups (focal psychodynamic therapy, mean 39·9 sessions, 95% CI 33·8–46·5; enhanced cognitive behaviour therapy, 44·8, 38·4–50·8; optimised treatment as usual, 41·6, 35·1–48·1; p=0·503). At the end of treatment, 110 (81%) of 135 participants who were assessed from the focal psychodynamic therapy and enhanced cognitive behaviour therapy groups gave full or partial feedback about their treatment. On a scale of 0 (therapy was not at all helpful) to 10 (therapy was very helpful), mean values were reported of 7·3 (SD 2·6) for focal psychodynamic therapy and 7·6 (2·3) for enhanced

	Focal psychodynamic therapy		Enhanced cognitive behaviour therapy		Optimised treatment as usual		Focal psychodynamic therapy *vs* enhanced cognitive behaviour therapy			Focal psychodynamic therapy *vs* optimised treatment as usual			Enhanced cognitive behaviour therapy *vs* optimised treatment as usual		
	Ls-mean (SE)	95% CI	Ls-mean (SE)	95% CI	Ls-mean (SE)	95% CI	Ls-m diff (95% CI)	p	Effect size	Ls-m diff (95% CI)	p	Effect size	Ls-m diff (95% CI)	p	Effect size
Body-mass index															
After 4 months of treatment	16·94 (0·14)	16·67–17·21	17·08 (0·13)	16·81–17·34	16·96 (0·14)	16·68–17·23	−0·14 (−0·51 to 0·23)	0·46	−0·12	−0·01 (−0·39 to 0·36)	0·94	−0·01	0·12 (−0·25 to 0·50)	0·52	0·11
After 10 months of treatment (end of treatment)	17·30 (0·19)	16·92–17·67	17·75 (0·18)	17·39–18·11	17·44 (0·20)	17·05–17·83	−0·45 (−0·96 to 0·07)	0·09	−0·29	−0·14 (−0·68 to 0·39)	0·60	−0·09	0·3 (−0·22 to 0·83)	0·26	0·20
At 3-month follow-up	17·63 (0·22)	17·20–18·05	17·74 (0·21)	17·33–18·15	17·74 (0·23)	17·29–18·19	−0·11 (−0·70 to 0·47)	0·70	−0·07	−0·11 (−0·73 to 0·51)	0·72	−0·07	0 (−0·60 to 0·60)	1·00	0·00
At 12-month follow-up	18·20 (0·24)	17·72–18·69	18·10 (0·23)	17·64–18·56	17·95 (0·26)	17·44–18·47	0·10 (−0·56 to 0·76)	0·76	0·05	0·25 (−0·45 to 0·95)	0·48	0·13	0·15 (−0·54 to 0·83)	0·67	0·08
EDI, total score															
After 4 months of treatment	295 (4·46)	286–304	295 (4·32)	287–304	293 (4·57)	284–302	−0·27 (−12·30 to 11·77)	0·97	−0·01	1·81 (−10·68 to 14·30)	0·78	0·05	2·08 (−10·08 to 14·24)	0·74	0·06
After 10 months of treatment (end of treatment)	272 (6·18)	260–284	270 (5·83)	259–282	277 (6·46)	264–289	1·67 (−14·92 to 18·26)	0·84	0·03	−4·98 (−22·53 to 12·58)	0·58	−0·10	−6·64 (−23·63 to 10·34)	0·44	−0·14
At 3-month follow-up	269 (6·41)	257–282	270 (6·03)	258–282	274 (6·76)	260–287	−0·89 (−18·10 to 16·32)	0·92	−0·02	−4·41 (−22·71 to 13·90)	0·64	−0·09	−3·52 (−21·23 to 14·19)	0·70	−0·07
At 12-month follow-up	257 (6·76)	244–271	263 (6·47)	251–276	260 (7·22)	246–275	−6·17 (−24·49 to 12·15)	0·51	−0·12	−2·98 (−22·42 to 16·47)	0·76	−0·06	3·19 (−15·79 to 22·17)	0·74	0·06
SIAB-EX, total score															
After 10 months of treatment (end of treatment)	0·86 (0·05)	0·77–0·95	0·77 (0·04)	0·68–0·85	0·89 (0·05)	0·80–0·98	0·09 (−0·03 to 0·21)	0·14	0·26	−0·03 (−0·16 to 0·09)	0·61	−0·09	−0·12 (−0·25 to −0·00)	0·05	−0·35
At 12-month follow-up	0·72 (0·05)	0·61–0·82	0·73 (0·05)	0·63–0·83	0·71 (0·06)	0·59–0·82	−0·01 (−0·15 to 0·13)	0·88	−0·03	0·01 (−0·15 to 0·16)	0·92	0·02	0·02 (−0·13 to 0·17)	0·81	0·05

Differences between groups were tested using the final adjusted models; missing values were replaced by the mixed model for repeated measures algorithm. 95% CIs are given for estimated least square means (Ls-mean) for every treatment group and for least square mean differences (Ls-m diff) between treatment groups. EDI=eating disorder inventory. SIAB-EX=structured inventory of anorexic and bulimic syndromes, expert version.

Table 2: **Adjusted mean scores for body-mass index and eating disorder pathology, by treatment group**

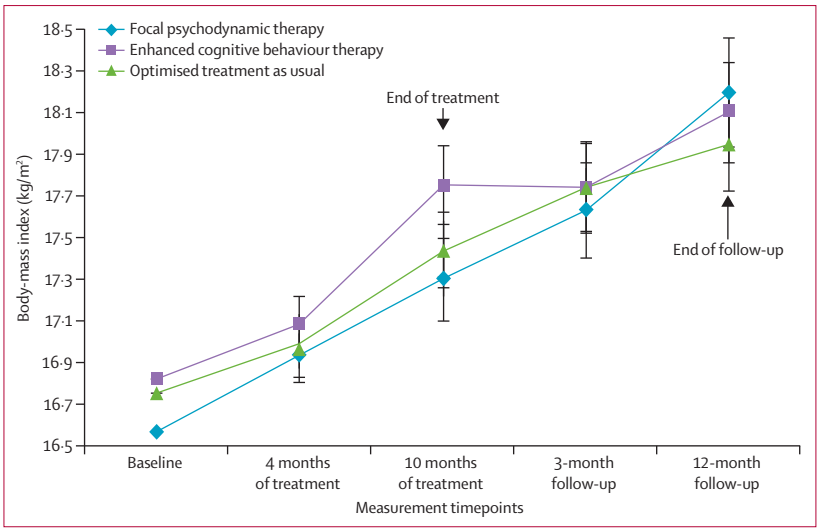

Figure 2: **Course of weight gain during treatment and follow-up, by treatment group**
Data are least square means (Ls-mean). Error bars show SE.

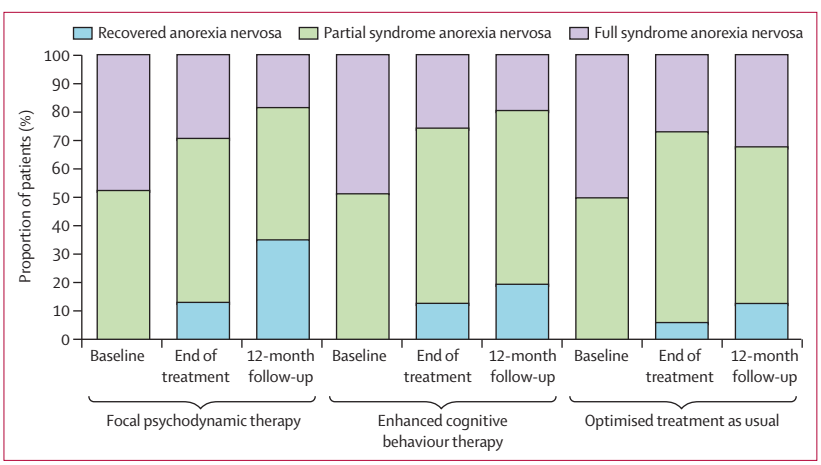

Figure 3: **Recovery rates during treatment and follow-up, by treatment group**

	Focal psychodynamic therapy		Enhanced cognitive behaviour therapy		Optimised treatment as usual	
	Effect size (95% CI)	p	Effect size (95% CI)	p	Effect size (95% CI)	p
After 4 months of treatment	0·23 (0·06–0·50)	0·12	0·37 (0·12–0·61)	0·003	0·23 (0·04–0·52)	0·10
After 10 months of treatment (end of treatment)	0·62 (0·29–0·90)	0·0003	1·00 (0·60–1·41)	<0·0001	0·71 (0·35–1·10)	0·0003
At 3-month follow-up	0·95 (0·56–1·28)	<0·0001	1·00 (0·54–1·48)	<0·0001	1·00 (0·60–1·46)	<0·0001
At 12-month follow-up	1·60 (1·10–2·00)	<0·0001	1·40 (0·87–1·87)	<0·0001	1·20 (0·74–1·77)	<0·0001

Data are effect size (95% CI), standardised by the mixed model for repeated measures.

Table 3: **Within-group changes in body-mass index from baseline, by treatment group**

cognitive behaviour therapy. 44% of patients assigned focal psychodynamic therapy found the length of treatment adequate, 52% said it was too short, and 4% judged it too long; by comparison, 40% of patients allocated enhanced cognitive behaviour therapy said the treatment length was adequate, 49% thought it was too short, and 11% judged it too long.

Discussion

Findings of the ANTOP study show that outpatient treatment of adults with anorexia nervosa by either optimised treatment as usual, focal psychodynamic therapy, or enhanced cognitive-behaviour therapy leads to relevant weight gains and a decrease in general and eating disorder-specific psychopathology during the course of treatment. These positive effects continue beyond treatment until 12-month follow-up. However, the primary hypothesis of the ANTOP study was not confirmed: no difference in weight gain was recorded by the end of treatment between the study groups. Weight gains noted in the ANTOP study accord with those reported in small single-centre studies.[16,17,20] However, with respect to the global outcome measure, patients allocated focal psychodynamic therapy had higher recovery rates compared with those assigned optimised treatment as usual at 12-month follow-up.

Under close guidance from their family doctor—eg, regular weight monitoring and essential blood testing—and with close supervision of their respective study centre, patients allocated optimised treatment as usual were able to choose their favourite treatment approach and setting (intensity, inpatient, day patient, or outpatient treatment) and their therapist, in accordance with German national treatment guidelines for anorexia nervosa.[11] Moreover, comparisons of applied dosage and intensity of treatment showed that all patients—irrespective of treatment allocation—averaged a similar number of outpatient sessions over the course of the treatment and follow-up periods (about 40 sessions). These data partly reflect an important achievement of the German health-care system: that access to psychotherapy treatment is covered by insurance. However, patients allocated optimised treatment as usual needed additional inpatient treatment more frequently (41%) than either those assigned focal psychodynamic therapy (23%) or enhanced cognitive behaviour therapy (35%). In a study in adolescent patients, similar results were noted over a 2-year period, with fewer admissions reported with family-based treatment (15%) compared with a more general approach of adolescent-focused therapy (37%).[28] Although, to date, clear consensus has not been reached with respect to the definition of outcome in anorexia nervosa,[29] analysis of recovery rates is common in psychotherapy trials.[30] Our results showed that at follow up, patients assigned focal psychodynamic therapy had significantly higher recovery rates compared with those receiving optimised treatment as usual.

Psychodynamic treatments make interpersonal relationships the major theme. Compared with cognitive behaviour therapy they are less directive, induce augmented emotional arousal, and target insight more (*vs* behaviour and cognition).[31] In view of difficulties in the field of autonomy that individuals with anorexia nervosa have, we postulate that these specific aspects of psychodynamic therapy contribute to the positive effects of treatment in this patient group. Substantial and lasting changes after interpersonal treatment for eating disorders have been shown for bulimia nervosa.[32] Findings of a New Zealand study[17,18] indicate that psychotherapy focusing on interpersonal aspects (eg, interpersonal therapy and focal psychodynamic therapy) across different eating disorders might need a prolonged timeframe to show effects, thereby producing better long-term results.[18,32] In a single-centre study comparing two manual-based treatments in anorexia nervosa outpatients,[30] significant weight gains were noted for patients in both study groups, with no differences recorded between the two approaches with respect to the amount of weight gained. However, these researchers showed that the estimated proportion of recovered anorexia nervosa patients depended strongly on the underlying definition of recovery. When applying a strict definition of recovery, as we did in our study (a combination of objective measure [weight] and eating disorder pathology based on expert assessment), recovery rates were 7–13% at 6 months and 14–19% at 12 months. Again, no differences with respect to recovery rates were noted between treatments.

Treatment acceptance is a major challenge in the management of patients with anorexia nervosa.[33] The main reason for this difficulty is typically the patient's high ambivalence and lack of acceptance of the seriousness of their illness. Thus, therapists not only have to cope with a frequently difficult therapy process but also must take responsibility for management of physical and psychiatric complications of this potentially lethal disorder. In the ANTOP study, we had a clear framework of rules for medical and psychiatric monitoring and a minimum weight limit for admission to short-term inpatient treatment (BMI <14 kg/m²). In both manual-based treatments, we included a brief nutrition guideline, and a structured session for close family and other relatives was also offered. These design aspects of the ANTOP study contributed to relatively high treatment completion rates (76% average; 70% with focal psychodynamic therapy; 81% with enhanced cognitive behaviour therapy) compared with other small-scale adult anorexia nervosa studies.[10,15] Moreover, patients allocated either focal psychodynamic therapy or enhanced cognitive behaviour therapy gave positive ratings to their treatment experience, which might have contributed further to the comparably low dropout rates.

Previous findings show that a comorbid anxiety disorder could be associated with a poorer treatment outcome in individuals with anorexia nervosa.[34,35] In the

	Focal psychodynamic therapy (n=58)	Cognitive behaviour therapy (n=65)	Treatment as usual (n=46)	*F* or χ^2	p
Mean (SD) weight (kg)	51·3 (7·2)	51·0 (8·8)	48·6 (9·7)	1·60	0·20
Body-mass index					
≤17·5 kg/m²	18 (31%)	22 (34%)	19 (41%)	1·24	0·54
>17 5 kg/m²	40 (69%)	43 (66%)	27 (59%)		
Full criteria for anorexia nervosa*	12 (21%)	14 (22%)	13 (28%)	0·97	0·62
Comorbidities					
Affective disorder	7 (12%)	10 (15%)	4 (9%)	1·12	0·57
Anxiety disorder	5 (9%)	8 (12%)	9 (20%)	2·76	0·25
Somatoform disorder	1 (2%)	2 (3%)	0	1·46	0·48
Substance abuse	0	1 (2%)	0	1·61	0·45
Bulimia nervosa	4 (7%)	4 (6%)	3 (7%)	0·03	0·99

Data are number of patients (%), unless otherwise stated. *F* values (and corresponding p values) are derived from ANOVA tests to compare the three groups. χ^2 values (and corresponding p values) compare percentages between the three groups. *Patients with a body-mass index of ≤17·5 kg/m² and psychiatric status rating score of 5 or 6 met full criteria for anorexia nervosa.

Table 4: **Clinical characteristics at 12-month follow-up**

Panel 2: Research in context

Systematic review

We searched PubMed and the Cochrane Library for full papers published before May 3, 2013, reporting randomised controlled trials, systematic reviews, and meta-analyses, with the MeSH terms: "anorexia nervosa", "treatment", "psychotherapy", "cognitive behavior therapy", and "psychodynamic therapy". We did not apply any language restrictions. We excluded trials focused exclusively on adolescents, group interventions, and family therapy and those reporting on pure education. Our search identified five systematic reviews,[1,3,29] one meta-analysis,[13] and three additional trials that were not included in the respective reviews.[16,20,30] To date, no evidence provides solid support for a particular therapeutic approach, setting, or procedure for treatment of adults with anorexia nervosa. Thus, large, multicentre, randomised controlled trials of commonly used psychotherapies for older adolescents and adults with anorexia nervosa are needed urgently.

Interpretation

The findings of the ANTOP trial showed that multicentre outpatient studies in patients with anorexia nervosa are possible. We also showed that patients can be treated safely, many individuals with anorexia nervosa gain weight, and that a substantial proportion have striking improvements in eating disorder pathology and comorbid psychopathology. The findings of the ANTOP study provide evidence to support use of manual-based interventions; focal psychodynamic therapy proved most advantageous in terms of recovery at 12-month follow-up, and enhanced cognitive behaviour therapy was most effective in terms of the speed of weight gain and improvements in eating disorder psychopathology.

ANTOP study sample, despite the randomisation algorithm, fewer patients allocated focal psychodynamic therapy had comorbid anxiety disorders at baseline compared with those assigned enhanced cognitive behaviour therapy and optimised treatment as usual. However, results of a sensitivity analysis showed no association between anxiety disorders at baseline and BMI at the end of treatment or at 12-month follow-up.

The ANTOP study was designed as a large, multicentre, randomised controlled trial in adults with anorexia nervosa. These design features overcome the shortcomings of previous studies (panel 2) by providing a randomised controlled design, a large sample size, appropriate inclusion criteria, a detailed treatment protocol, and a clear separation of intervention conditions.[22] We judged our study a success because most patients completed treatment and reported high satisfaction scores with the treatments; the dropout rate was much lower than in previous anorexia nervosa treatment studies.[10,17]

Our trial, however, had several limitations. First, we chose gain in BMI as a simple, objective, and conservative primary outcome measure. This approach might have been too one-dimensional. To get a more comprehensive picture, we also looked at a combined secondary outcome that included core aspects of eating disorder psychopathology. Second, although the dropout rate within our overall sample was acceptable, we noted a higher dropout rate for patients assigned optimised treatment as usual compared with the other groups. Therefore, information on the course of the illness in individuals in this group is limited. We only had scant contact with patients assigned optimised treatment as usual at our centres and, thus, formed a weaker alliance with these patients. This diminished personal contact might have contributed to the dropout rate. Finally, we were restricted by funding to intermediate follow-up of 12 months. Additional long-term follow-up measurement points for outcome data (for at least 5 years after initial treatment ends) are necessary.

Although the findings of the ANTOP study suggest that adults with anorexia nervosa have a realistic chance of recovery or, at least, can achieve substantial improvement, a relevant proportion of patients still had anorexic symptoms at the end of our study. Anorexia nervosa "remains an enigma and its clinical challenge is [still] intimidating".[36] Besides strategies of prevention and early intervention, we have to refine our treatments further to fight the vicious cycles of dieting behaviour.[37]

Contributors

The principal investigators (SZ, WH, BW, and GG) designed the study and obtained funding. The ANTOP trial management group, trial steering committee, and the data monitoring and ethics committee further developed study design. The statistical analysis plan was written by the analysis strategy group and approved by the trial steering committee and the data monitoring and ethics committee before the analysis began. DS and BW did the main statistical analysis. Patient recruitment was done by SH (Bochum), MdZ (Hannover), Prof W Senf (Essen), AZ (Freiburg), BL (Hamburg), WH (Heidelberg), Prof P Henningsen (Munich), SZ (Tübingen), and JvW (Ulm). Treatment leaders for focal psychodynamic therapy were HS, H-CF, and WH, for enhanced cognitive behaviour therapy were GG, MdZ, and MT (with initial support from C Fairburn), and for optimised treatment as usual were SZ, GG, MT, KEG, H-CF, and WH. Treatment leaders designed the treatment manuals in collaboration with the principal investigators, and trained and supervised the trial therapists. The writing and publication oversight committee wrote the report. All authors commented on drafts and approved the final version.

ANTOP study group

Trial management group—SZ (chair), BW, GG, H-CF, MT, DS, KEG, MdZ, AD, SH, MB, BL, ST, JvW, AZ, CS-B, HS, and WH (co-chair); *trial steering committee*—SZ (chair) and WH (co-chair); *data monitoring and ethics committee*—U Schmidt (London, UK), H-C Deter (Berlin, Germany), S Schneider (Bochum, Germany), and A Faldum (Münster, Germany); *analysis strategy group*—BW (chair), DS, WH, KEG, GG, SZ, and CS-B; *writing and publication oversight committee*—SZ (co-chair), BW (co-chair), GG, H-CF, MT, DS, MdZ, and KEG; *trial manager*—GG.

Conflicts of interest

We declare that we have no conflicts of interest.

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