THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Zipfel S, Wild B, Groß G, et al, on behalf of the ANTOP study group. Focal psychodynamic therapy, cognitive behaviour therapy, and optimised treatment as usual in outpatients with anorexia nervosa (ANTOP study): randomised controlled trial. *Lancet* 2013; published online Oct 16. http://dx.doi.org/10.1016/S0140-6736(13)61746-8.

Amendments to the study protocol of the ANTOP study (published in *Trials*, Wild et al., 2009)

1) In the original study design, we planned to use the last observation carried forward (LOCF) method to impute missing values. However, in recent years, the use of the LOCF method has come under increasing criticism. We, therefore, decided to change our strategy for handling missing data (before closing the study database), but not before first conducting an additional sensitivity analysis using LOCF to compare various study results based on different imputation strategies. The decision to make a change in the main strategy of missing imputation was anchored in the statistical analysis plan we developed before we began to examine the data.

The ANTOP schedule of measurements fulfills the precondition for using the mixed effects models for repeated measures (MMRM) (i.e., the inclusion of one additional measurement occasion between baseline and end of treatment allows time trends to be modeled). Since a series of studies found that MMRM was more robust against biases from missing data than LOCF, we decided to use MMRM as our primary imputation method.

2) In 2009, we applied for funding for a one-year follow-up to our initial ANTOP study. The German Ministry of Research and Education provided the funding for this one-year follow-up. As a primary hypothesis, we expected that both specific psychotherapeutic outpatient interventions FPT and CBT-E, would show significantly better outcomes in regard to gains in BMI at the one-year follow-up when compared with treatment as usual (TAU-O).

3) A complete blinding of the participants was not feasible due to the fact that a third of the patients were randomized to the TAU-O condition and, consequently, were not treated at the respective centers. As in any psychotherapy trial, psychotherapists were also not masked to group assignments. We instead masked the assessors, who measured the primary outcome and conducted the diagnostic interviews. At the centers, two independent, trained observers assessed patients: one non-blinded assessor assessed the information connected to a treatment arm and another blinded assessor measured BMI and conducted the diagnostic interviews. We deemed this procedure to be appropriate because specific questions asked at the various measurement points were related to specific treatment arms. For instance, at T1 and T2, only the patients in the TAU-O group were asked detailed questions regarding outpatient psychotherapy they received during the course of the trial from facilities outside the respective study centers.

Treatment Provided (additional information)

Ten university departments well balanced in regard to their emphasis in cognitive behavior or psychodynamic psychotherapy in eating disorders (five and five) comprised our baseline sample. In total, N=45 therapists participated in the trial (age: M=36.4yrs.; 28 – 52 yrs.), 26 postgraduate psychologists, and 19 residents and fellows in psychosomatic medicine or psychiatry, all of whom were experienced in treating eating disorders. Each therapist underwent initial training in the respective AN-specific psychotherapy (FPT, CBT-E). HS, WH and HCF provided the initial structured training for FPT and CF carried out the initial CBT-E instruction. Over the course of the study, HS and HCF, and GG and MdZ, respectively, conducted annual refresher sessions on FPT and CBT-E (for FPT, see Schauenburg et al.[26] ; for CBT-E, see Fairburn et al.,[25] personal copies - manual published in English and German). All therapists were certified before starting therapies.

We audio taped each treatment session. Supervisors at the individual centers, experienced in treating eating disorders and the corresponding treatment orientation, monitored every fourth session. Each therapist had to fill in a structured protocol of each supervision session, which included the number and purpose of the session, a brief summary, and aspects to improve the therapists' ability to adhere to the manual. On a visual analog scale (VAS) of 1 to 10, 1 being not very helpful, 10 being very helpful, FPT and CBT therapists rated their supervision session as helpful, 7·49 vs. 7·79, respectively (n.s. different).

To avoid contamination between the therapy arms, therapists offered only one treatment, FPT or CBT-E. They had to have been trained and practicing in their respective method for at least three years. AN patients who had completed treatment were defined a priori as having received two thirds of the therapy sessions (>26 sessions). One family or partner session was offered at the beginning of FPT and CBT-E treatment. No additional meetings were offered beyond the established 40 sessions and the therapists delivered all treatments face-to-face. Patients in the FPT and CBT-E arm also received written standardized information about healthy food and nutrition.

We standardized FPT and CBT-E treatments by providing therapists with therapy-specific guidance manuals. Both of the manuals used the same frequency and time structure for the treatment sessions. Therapy comprised 40 sessions over a period of ten months for both treatment groups. Patients were scheduled for two therapy sessions per week during the first two months. Over the subsequent four months, participants received one session per week. In the final four months of therapy, the session frequency was reduced to one bi-weekly session.

Adherence Control and Treatment Fidelity

Four full–length sessions were recorded and analyzed at the PI centers (Tübingen, Germany for CBT-E and Heidelberg, Germany for FPT: The sessions recorded were 9, 18, 27, 36 – one in the early, twice in the mid-term and one in the later phases of each intervention). Based on the audio tapes, therapists received a prompt, but brief, structured email of feedback regarding their adherence to the therapy manual. Additionally, 20% of the audio tapes were selected for a structured adherence control check conducted by two clinically experienced PhD-level researchers. Based on a 13-item checklist for FPT and an 11-item checklist for CBT-E, the average overall adherence assessed via a rater intraclass correlation coefficient was as follows: FPT adherence scale: .74 and CBT-E adherence scale: .82.

Outcome Measures

Outcome Measure	**Reference**
The structured interview for anorexic and bulimic disorders for DSM-IV and ICD-10 (SIAB-EX)	Fichter. M., Quadflieg, N. (2001). The structured interview for anorexic and bulimic disorders for DSM-IV and ICD-10 (SIAB-EX): reliability and validity. *Eur Psychiatry, 16*(1), 38-48.
Eating Disorder Inventory-2 (EDI-2)	Paul, T., Thiel, A. (2004). Eating Disorder Inventory-2 - German Version. Göttingen, Germany: Hogrefe.
Operationalized Psychodynamic Diagnostics (OPD-2)	Kaechele, H. (2009). Operationalized Psychodynamic Diagnostics OPD-2. Manual of Diagnosis and Treatment Planning. *Psychotherapy Research, 19*(1), 125-7.
Psychiatric status ratings scale (PSR)	Herzog, D.B., Sacks, N.R., Keller, M.B., Lavori, P.W., von Ranson, K.B., Gray, H.M. (1993). Patterns and predictors of recovery in anorexia nervosa and bulimia nervosa. *J Am Acad Child Adolesc Psychiatry, 32*(4), 835-42.
Structured Clinical Interview for DSM Disorders (SCID-I)	Wittchen, H-U., Wunderlich, U., Gruschwitz, S., Zaudig, M. (1997). SCID-I. Structured Clinical Interview for DSM Disorders - German Version. Göttingen, Germany: Hogrefe.

Additional References for the Methods section (in alphabetic order)

1. Legenbauer, T., Vocks, S. (2005). Manual der kognitiven Verhaltenstherapie bei Anorexie und Bulimie. Berlin, Heidelberg: Springer.

2. Littell, R.C., Milliken, G.A., Stroup, W.W., Wolfinger, R.D., Schabenberger, O. (2006). SAS for mixed models. Cary, NC.

3. Mallinckrodt, C.H., Sanger, T.M., Dube, S., et al. (2003). Assessing and interpreting treatment effects in longitudinal clinical trials with missing data. *Biol Psychiatry, 53,* 754-760.

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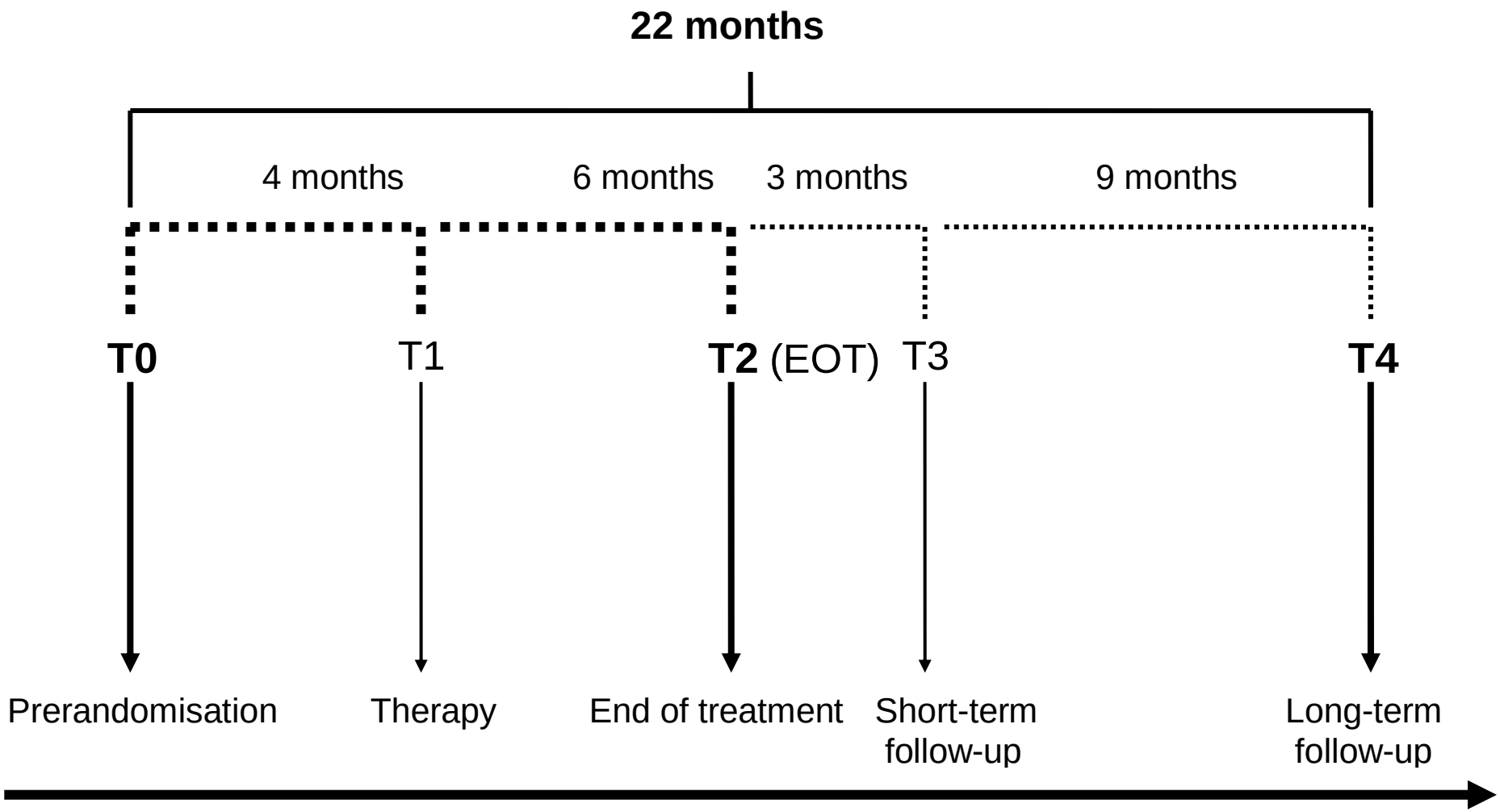
6. Siddiqui, O., Hung, H.M., O'Neill, R. (2009). MMRM vs. LOCF: a comprehensive comparison based on simulation study and 25 NDA datasets. *J Biopharm Stat, 19,* 227-246.

7. Unnebrink, K., Windeler, J. (2001). Intention-to-treat: methods for dealing with missing values in clinical trials of progressively deteriorating diseases. *Statistics in medicine, 20*(24), 3931-46.

The ANTOP study's measurement time points



EOT=end of treatment.

Intention-to-treat analysis (n=242)

	FPT Is-means(SE)	**CBT-E** Is-means(SE)	**TAU-O** Is-means(SE)	**FPT vs· CBT-E** Is-means diff (p-value)	**FPT vs· TAU-O** Is-means diff (p-value)	**CBT-E vs· TAU-O** Is-means diff (p-value)
BMI T1	17·0 (0·11)	17·1 (0·11)	17·0 (0·11)	-0·11 (0·51)	-0·004 (0·98)	0·10 (0·53)
BMI T2	17·4 (0·15)	17·8 (0·15)	17·5 (0·15)	-0·40 (0·07)	-0·12 (0·57)	0·27 (0·21)
BMI T3	17·7 (0·16)	17·7 (0·17)	17·8 (0·16)	-0·05 (0·82)	-0·06 (0·76)	-0·01 (0·96)
BMI T4	18·2 (0·18)	18·1 (0·18)	18·0 (0·18)	0·1 (0·71)	0·14 (0·57)	0·05 (0·85)

Missing values were replaced by the mean–other imputation method. Presented here are adjusted mean scores in BMI by treatment group at the various measurement time points. FPT=focal psychodynamic psychotherapy. CBT-E=cognitive behavior therapy–enhanced. TAU-O=treatment as usual–optimised.

Complete case analysis (n=150)

	FPT Is-means(SE) (95%-CI)	**CBT-E** Is-means(SE) (95%-CI)	**TAU-O** Is-means(SE) (95%-CI)	**FPT vs. CBT-E** Is-means diff (p-value)	**FPT vs. TAU-O** Is-means diff (p-value)	**CBT-E vs. TAU-O** Is-means diff (p-value)
BMI T1	17·0 (0·14)	17·0 (0·14)	17·0 (0·17)	-0·02 (0·92)	0·04 (0·84)	0·06 (0·77)
	(16·7 - 17·3)	(16·8 - 17·3)	(16·6 - 17·3)			
BMI T2	17·4 (0·22)	17·8 (0·20)	17·4 (0·26)	-0·32 *(0·28)*	0·004 (0·99)	0·32 (0·32)
	(17·0 - 17·9)	(17·4 - 18·2)	(16·9 - 18·0)			
BMI T3	17·7 (0·25)	17·7 (0·23)	17·7 (0·30)	-0·04 (0·89)	-0·02 (0·95)	0·02 (0·95)
	(17·2 - 18·2)	(17·3 - 18·2)	(17·1 - 18·3)			
BMI T4	18·3 (0·27)	18·2 (0·25)	18·0 (0·32)	0·1 (0·75)	0·24 (0·56)	0·13 (0·76)
	(17·7 - 18·8)	(17·7 - 18·7)	(17·4 - 18·7)			

Adjusted mean scores in BMI by treatment group at the various measurement time points. Differences between groups were tested using the final adjusted models. FPT=focal psychodynamic psychotherapy. CBT-E=cognitive behavior therapy–enhanced. TAU-O=treatment as usual– optimised.