Title: The MOSAIC study - comparison of the Maudsley Model of Treatment for Adults with Anorexia Nervosa (MANTRA) with Specialist Supportive Clinical Management (SSCM) in outpatients with broadly defined anorexia nervosa: a randomized controlled trial.

Date of Submission of Revised Version: 26.01.2015
Abstract

**Objective:** Anorexia nervosa (AN) in adults has poor outcomes and treatment evidence is limited. This study evaluated the efficacy and acceptability of a novel, targeted psychological therapy for AN (Maudsley Model of Anorexia Nervosa Treatment for Adults; MANTRA) compared to Specialist Supportive Clinical Management (SSCM).

**Method:** 142 out-patients with broadly defined AN (body mass index (BMI) $\leq 18.5$ kg/m$^2$) were randomly allocated to receive either 20 to 30 weekly sessions (depending on clinical severity) plus add-ons (4 follow-up sessions, optional sessions with dietician and with carers) of MANTRA (n=72) or SSCM (n=70). Assessments were administered blind to treatment condition at baseline, 6 months and 12 months after randomization. The primary outcome was BMI at 12 months. Secondary outcomes included eating disorders symptomatology, other psychopathology, neuro- and social cognition and acceptability. Additional service utilization was also assessed. Outcomes were analyzed using linear mixed models.

**Results:** Both treatments resulted in significant improvements in BMI and reductions in ED symptomatology, distress levels and clinical impairment over time with no statistically significant difference between groups at either 6 or 12 months. Improvements in neuro- and social-cognitive measures over time were less consistent. One SSCM patient died during treatment. Compared to SSCM, MANTRA patients rated their treatment as significantly more acceptable and credible at 12 months. There was no significant difference between groups in additional service consumption.
**Conclusions:** Both treatments appear to have value as first line out-patient interventions for patients with broadly defined AN. Longer term outcomes remain to be evaluated.

**Key words:** anorexia nervosa, psychological treatment, randomized controlled trial.

**Public Health Significance Statements**

This study shows that both MANTRA and SSCM have promise as first line out-patient treatments of AN in adults. MANTRA, a novel, targeted treatment based on experimental medicine principles, may have advantages in terms of overall acceptability and credibility, and weight outcomes in more severely ill patients.
Introduction:

Anorexia nervosa (AN) in adults, is one of the most difficult psychiatric disorders to treat and study (Fairburn et al., 2013; Halmi et al., 2005), because of its high risk of death or disability and poor motivation for change (Arceus, Mitchell, Wales & Nielsen, 2011; Treasure, Claudino, & Zucker, 2010). Psychological therapies are the first-line treatment, yet outcomes are poor, drop-out high and the evidence-base limited (DeJong, Broadbent, & Schmidt, 2012; Watson & Bulik, 2013). A recent landmark randomized controlled trial (RCT) of psychological therapies in adult AN outpatients found comparable outcomes with focal psychodynamic therapy, enhanced cognitive behavioral therapy (CBT-E) and optimized treatment as usual (TAU) (Zipfel et al., 2014), confirming the absence of a leading treatment.

There is widespread agreement that new interventions are needed for adults with AN and that to improve outcomes such interventions should be theory-based, and targeted to specific characteristics and maintaining factors of the disorder (Agras et al., 2004; NICE, 2004). Such a focus on ‘experimental therapeutics’ allows interventions to be used ‘as probes of disease mechanisms as well as tests of efficacy (Insel & Gogtay, 2014; Holmes, Craske & Graybiel, 2014). With this in mind, we designed a novel manual-based out-patient treatment specifically for adults with AN (MANTRA, Maudsley Model of Anorexia Nervosa Treatment for Adults) (Schmidt & Treasure, 2006; Schmidt, Wade, & Treasure, 2014). The development, model, underpinning experimental and clinical research and content of this treatment have been described elsewhere (Schmidt & Treasure, 2006; Schmidt et al., 2014; Wade, Treasure & Schmidt, 2011; Schmidt et al., 2012; Treasure & Schmidt, 2014). MANTRA has
shown promise in pilot studies (Wade et al., 2011; Schmidt et al., 2012) and the present study is the first large-scale evaluation of this treatment.

One key question in any psychotherapy trial is which comparison therapy to use. Arguably, in a potentially lethal disorder such as AN use of a waiting list, or of a minimalist psychological placebo/attention control intervention is ethically and practically problematic. Use of TAU as a comparison is also not straightforward, unless this is standardized. We therefore decided to use Specialist Supportive Clinical Management (SSCM), a manualized form of TAU, which has a key focus on improving patients’ nutritional health as a prerequisite for recovery. It is delivered in a patient-centered, supportive and authoritative manner by experts, familiar with managing AN and associated risks. SSCM was designed as a credible and ethical control treatment in an RCT in adult out-patients with AN (McIntosh et al., 2005; McIntosh et al., 2006). In this study, at end of treatment SSCM was superior in the intention to treat (ITT) analysis to one of the active therapies it was compared against (interpersonal therapy (IPT)). In the completer analysis, it was superior to both IPT and CBT, although in the longer term these effects diminished (Carter et al., 2011). Since then, SSCM has been used in one further trial in adults with longstanding AN (Touyz et al., 2013). Here, it was as effective as CBT at end of treatment, but somewhat worse than CBT at follow-up.

The aim of the present study (MOSAIC trial) was to evaluate the efficacy of MANTRA compared to SSCM in a multi-center two-arm superiority RCT of adult outpatients with AN. The main hypothesis was that MANTRA would be superior to SSCM in terms of weight gain and other outcomes at 6 and 12 months.
Method:

Full details of the MOSAIC trial design and methodology have been described elsewhere (Schmidt et al., 2013).

Outcomes were assessed by researchers blind to group allocation at baseline, 6 months and 12 months after randomization. The randomization was conducted independently by the King’s Clinical Trials Unit and employed minimization with stratifiers: (1) body mass index (BMI) below or above 15 kg/m², (2) AN-subtype (restricting or binge/purge) and (3) previous ED inpatient admission. Ethical approval for the trial was obtained from Central London Research Ethics Committee (REC) 4, Royal Free Hospital, London, National Health Service (NHS) REC Reference: 10/H0714/9.

The trial is registered with Current Controlled Trials: ISRCTN67720902 (URL: www.controlled-trials.com/ISRCTN67720902).

Participants

Patients were recruited from four catchment-area based NHS specialist ED services in the UK. These were: South London and Maudsley NHS Foundation Trust (SLaM); North East London Foundation Trust Eating Disorders Service (NELFT); Barnet, Enfield & Haringey Mental Health NHS Trust (BEH); Oxford Health NHS Foundation Trust. Consecutive out-patients referred to these services by their general practitioner were offered participation if they were aged between 18 and 60 years, had a DSM-IV-TR [2000] diagnosis of AN or Eating Disorder Not Otherwise Specified (EDNOS) and a BMI of 18.5 kg/m² or below. Our definition of EDNOS was based
on that by Thomas, Vartanian & Brownell (2009) and includes people who fulfill all criteria of AN, except the weight criterion; those who fulfil all criteria for AN but still have menses; those without a fat phobia; and those with partial AN (defined as having features of AN but missing at least two of the four diagnostic criteria). We thus included patients across the spectrum of illness severity (ranging from mild to severe), to reflect a typical adult outpatient population presenting to specialist services. Exclusion criteria were: life-threatening AN requiring immediate inpatient treatment as defined in the UK NICE guidelines for eating disorders (National Institute for Clinical and Health Care Excellence, 2004); insufficient knowledge of English to understand the treatment; learning disability; severe mental or physical illness which needs treatment in its own right (for example, psychosis or diabetes mellitus); substance dependence or pregnancy. We did not exclude patients on antidepressants, provided they were on a stable dose, for at least four weeks.

Care was taken to introduce the study to potential participants in a standardized way and to maintain equipoise between both treatments and present them as equal. A recruitment DVD demonstrating this was produced to train clinicians and researchers in the recruitment process. After complete description of the study to potential participants, written informed consent was obtained.

Treatments

Commonalities between treatments

In both treatments, patients received 20 once-weekly individual therapy sessions and four monthly follow-up sessions. In patients with BMI ≤15 kg/m², weekly treatment was extended to 30 sessions. In both treatments two additional sessions with a close
other were offered. In addition, participants had access to dietitian sessions (usually 4-5) as needed, as is usual practice in the UK. Monitoring of physical risk is part of both treatments. Therapy sessions are approximately 50 minutes, however in SSCM, from the middle stage of treatment, sessions may be reduced to 30 minutes at the therapist’s discretion (McIntosh et al., 2005).

**MANTRA**

MANTRA is an empirically-based cognitive-interpersonal treatment, which proposes that four broad factors, linked to underlying obsessional and anxious/avoidant personality traits, are central to the maintenance of AN. These are (1) a thinking style characterized by inflexibility, excessive attention to detail, and fear of making mistakes; (2) impairments in the socio-emotional domain (e.g. difficulties in emotion recognition and Theory of Mind, avoidance of emotional experience and expression); (3) positive beliefs about how AN helps the person manage their life and (4) unhelpful responses of close others, such as overinvolvement, accommodation to or enabling of symptoms, criticism and hostility (Schmidt & Treasure, 2006; Treasure & Schmidt 2014). These maintenance factors are targeted in treatment with the aim of facilitating wider changes in eating disorder symptomatology and weight. Treatment is centred around a patient-manual (Schmidt et al., unpublished). There are several core (e.g. formulation) and some optional modules (e.g. module on building a ‘non-anorexic’ identity designed specifically for patients with very long-standing illness). Treatment is formulation-based and has a clear structure and hierarchy of therapeutic procedures. Individual tailoring of treatment arises from flexibility as to how components of MANTRA are combined and how much emphasis they are given (including e.g. optional modules).
The therapeutic style is that of motivational interviewing (i.e. patient-centered and using reflection strategically to facilitate change). Further details are given elsewhere (Schmidt et al., 2012; Schmidt et al., 2013; Schmidt et al., 2014).

**SSCM**

This treatment was designed as an active comparison treatment in a clinical trial to be delivered by therapists with expertise in the treatment of ED and to provide a standardized form of usual out-patient treatment (McIntosh et al., 2005; McIntosh et al., 2006). It combines clinical management i.e. giving information, advice, and encouragement with a supportive therapeutic style, designed to build a positive therapeutic relationship and to foster change. Therapy content includes assessment, identification of and regular review of target symptoms, psychoeducation, monitoring of physical status, establishing a goal weight range and nutritional education and advice. The aim is to help patients make a link between their clinical symptoms and their abnormal eating behavior and weight, and to support patients in a gradual return to normal eating and weight. Additional therapy content is determined by the patient. Further details are described in McIntosh et al. (2006). A therapist manual (McIntosh et al., unpublished) is available with detailed psycho-educational handouts for patients. These are used flexibly and as deemed appropriate for a particular patient by the therapist.

**Therapists**

Twenty-eight experienced ED therapists delivered the treatments. All attended two initial training days on MANTRA and two on SSCM and further ‘booster’ training
days were held at intervals to avoid therapeutic ‘drift’. Therapists were expected to see patients in both conditions, to control for therapist effects. Regular weekly trial supervision was provided by experienced supervisors in each team and separately for the two treatment conditions, to avoid contamination across therapies. Patients were allocated to therapists based on availability. To ensure competent and uniform treatment delivery, psychotherapy sessions were audiotaped to be able to assess adherence. Formal fidelity analyses of these tapes will be reported separately. As a further fidelity check qualitative interviews of therapists and patients were carried out (Waterman-Collins et al., 2014; Lose et al., 2014). These suggested that these treatments were delivered as designed.

Management of significant deterioration or failure to improve

Patients who deteriorated significantly whilst receiving out-patient therapy were offered in-patient treatment if they fulfilled criteria for admission (NICE, 2004). Those who failed to improve with out-patient treatment were offered day-care.

Assessment

Outcome measures

Outcome measures were collected pre-randomization (baseline), and at 6 and 12 months post randomization. The primary outcome was BMI at 12 months.

ED psychopathology was assessed with the Eating Disorders Examination (EDE) Interview (Fairburn, Cooper & O’Connor, 2008). For the small number of patients unwilling/unable to complete the EDE interview at follow-up, the questionnaire form
of this assessment (EDE-Q) was used instead. The EDE-Q has been found to have similar validity to the EDE interview (Fairburn & Beglin, 1994).

General psychopathology was assessed using two measures. We used the Depression, Anxiety and Stress Scale - 21 (DASS-21) (Lovibond & Lovibond, 1995), a 21-item self-report measure that assesses mood state over the past seven days using a 4-point Likert scale. The total score can be used as a measure of general distress. High scores indicate higher symptomatology. This measure has good reliability and validity (Brown, Chorpita, Korotitsch, & Barlow, 1997). We also used the Obsessive Compulsive Inventory-Revised (OCI) (Foa, Huppert, Leiberg, Langner, Kichic, Hajcak, & Salkovskis, 2002). This 18 item questionnaire uses a 5 point forced choice severity scale and provides a single global score (max score=72). The measure has excellent psychometric properties.

Psychosocial Impairment was assessed using the Clinical Impairment Assessment (CIA) (Bohn & Fairburn, 2008), a self-report measure of impairment resulting from the individual’s ED. This is a 16- item questionnaire which generates a single global score to signify level of impairment. Each item is rated on a 4 point scale (max score=48). The CIA has high levels of internal consistency, construct and discriminant validity, test-retest reliability, and sensitivity to change.

Treatment credibility and acceptability were assessed with visual analogue scales (VAS), rated on a 0 to 10 scale, at 6 and 12 months. These were designed for the purpose of the study.
Neurocognition and social cognition were assessed using measures of set-shifting (Wisconsin Card Sorting Task (Psychological Assessment Resources, 2003), Brixton Spatial Anticipation Task, (Burgess & Shallice, 1997)), central coherence (Rey-Osterrieth Complex Figure Test (Osterrieth, 1944; Rey, 1941)) and Theory of Mind (‘Reading the Mind in Film’ task (Golan, Baron-Cohen, Hill, Golan, 2006)). Scoring details are given elsewhere (Renwick et al., 2014). Additional potential mediator variables were measured (Schmidt et al., 2013), but will be reported elsewhere.

**Sample Size Calculation**

The sample size calculation was based on a mean weight gain of 7.3 kg (standard error 0.96 kg) observed in an unpublished series of nine pilot patients treated with MANTRA. The mean weight gain for SSCM was previously estimated as 4 kg (McIntosh et al. (2005)). We derived a conservative estimate of the group difference by a low estimate of the weight gain under MANTRA (mean – 0.8 × standard error = 6.5 kg) minus the weight gain estimate for SSCM; giving a difference of 2.5 kg. We calculated that a sample size of 55 participants per group would have 90% power to detect a difference in mean weight gain of 2.5 kg assuming a common weight gain standard deviation of 4 kg (as per an unpublished series of 9 MANTRA patients) and using an independent samples t-test with a significance level of 0.05. Correcting for 20% attrition, a total of 138 patients was needed.

**Statistical Analyses**

All statistical analyses were based on the intention-to-treat principle and were carried out by statisticians blind to treatment allocation using Stata 12 (StataCorp, 2011).
All outcomes were analysed using linear mixed models. The dependent variable was the outcome at the respective time point and the (fixed) explanatory variable of interest was trial arm. Further covariates for inclusion in the model were chosen \textit{a priori} on the basis that such variables were known to predict outcome (within trial arms). Specifically we conditioned on baseline values of the variable under investigation and the randomization stratifiers BMI, AN-subtype and previous ED inpatient admission (Pocock, Assmann, Enos, & Kasten, 2002). In addition the model contained random effects for therapists in the two randomization groups to allow for correlation in outcomes due to treatment being facilitated by the same therapist. The variance of these random effects was allowed to vary between trial arms by including an interaction between therapist and treatment.

Outcome variables contained some missing values. We empirically assessed whether a number of baseline variables were predictive of missing values in outcome and also checked whether non-adherence to treatment (coded “1”=completed at least 15 therapy sessions, “0”=did not complete intervention) was predictive of loss to follow-up; out of these only non-adherence was found to be an empirical predictor (see Results). To allow this process to be predictive of missingness, multiple imputation (MI) using chained equations was implemented (Stata command ice, (Royston, 2004)). The imputation step of the procedure used treatment arm, baseline value, randomization stratifiers, outcome at other time points, adherence and therapist dummy variables to predict missing post-randomization outcome values. Here the benefit of MI lies in its ability to incorporate post-randomization variables that are not part of the analysis model (treatment non-adherence) in the imputation step and so enable an analysis that is valid under a more realistic missing at random (MAR)
assumption (Sterne et al., 2009). To minimise Monte-Carlo error, fifty imputations were used. Subgroup analyses were used to assess the estimated treatment effects amongst those with a baseline BMI below 17.5kg/m² and amongst treatment completers.

Results:

Participant Flow and Baseline Characteristics

One hundred and forty-two participants were recruited between June 2010 and November 2012 (SLaM: n= 85; NELFT: n=10; BEH: n= 20; Oxford Health: n=27). Demographic and clinical characteristics are summarised in Table 1. The two treatment arms were reasonably balanced on all baseline characteristics.

Participant flow through the study is shown in Figure 1.

All 142 participants were included in the primary outcome analysis.

Treatment Uptake, Attendance and Acceptability

Figure 1 shows treatment uptake and attendance. There was some suggestion that the median number of individual therapy sessions attended differed between groups (p=0.05). As in SSCM, from the middle stage of treatment, individual therapy sessions could be reduced to 30 minutes at the therapist’s discretion, we also calculated the mean duration of sessions for each treatment. In MANTRA (where this information was available for n=54 (75%) of participants) the mean session duration was 53.1 (4.3) mins, whereas in SSCM (where this information was available for n=40 (57%) of participants) the mean session length was 47.4 (6.8) mins. This difference was significant (t(92)=4.88, p<0.001). As in other studies, treatment
completion was defined a priori as attending ≥15 therapy sessions, i.e. receiving more than 75% of weekly sessions (Zipfel et al., 2014). Seventy-five percent of MANTRA and 59% of SSCM participants completed treatment. One SSCM patient who had a very severe chronic illness with multiple previous treatments, died suddenly during treatment.

Non-completion of treatment was predictive of loss to follow-up at 12 months. 45.2% of non-completing participants compared to 10.5% of completers had missing primary outcome data at 12 month follow-up (p<0.001). Web-table 1 gives details.

There were no significant differences in acceptability and credibility ratings between MANTRA and SSCM at 6 months (Acceptability: MANTRA=8.5 (2.0), SSSCM= 8.0 (2.2) [t(100)=1.33, p=0.18], Credibility: MANTRA=6.4 (3.1), SSSCM= 5.8 (2.7) [t(100)=1.1, p=0.29]). However, at 12 months MANTRA received significantly higher acceptability and credibility ratings than SSCM (Acceptability: MANTRA=8.6 (1.8), SSSCM= 7.8 (2.3) [t(91)=2.01, p=0.047] Credibility: MANTRA=6.8 (3.1), SSSCM= 5.5 (2.7) [t(91)=2.24, p=0.027]).

Groups did not differ in proportions of participants who had additional sessions with a dietician (MANTRA 33/72 (45.83%); SSCM 31/70 (44.29%), χ²(1)=0.03, p=0.85), nor in proportions of participants who had sessions with a carer (MANTRA 30/61 (49.18%); SSCM 31/61 (50.81%), χ²(1)=0.00, p=1.00). The median total number of treatment sessions (individual therapy plus dietician sessions plus sessions with a carer) was n=23 for MANTRA and n=20 for SSCM (p=0.063).
Additional Service Utilization

Information on additional service utilization during the study period was available for 67/72 (93.1%) MANTRA and 64/70 (91.4%) SSCM patients. Eight MANTRA patients (11.9%) had additional psychiatric treatment. Five had ED in-patient or day-care treatment (range 1-217 days). One of these and three others had brief general psychiatric treatment (e.g. for suicidality or alcohol problems).

Ten SSCM patients (15.6%) had additional psychiatric treatment. Eight had ED in-patient or day-care (2-198 days), one of these and two others also had a general psychiatric admission for depression and suicidality. The difference in proportions of patients with additional treatment was not significant ($\chi^2(1)=0.38, p=0.54$).

Treatment Outcomes

No baseline variables were found to be predictive of later missingness. However non-completion of treatment predicted missingness in that 45.2% of those who were non-compliant had missing outcome data, whereas this proportion was only 10.5% for treatment completers. Table 2 shows estimated group differences at 6 and 12 months. Table 3 shows the corresponding estimated means and standard errors, accounting for the fact that adherence predicts missingness (using multiple imputation) and allowing for therapist effects.

Mean BMI did not differ significantly between groups at either 6 ($p=0.39$) or 12 months ($p=0.34$; primary outcome; see Figure 2). Mean EDE Global score also did not differ significantly at either 6 ($p=0.62$) or 12 months ($p=0.30$), nor did any of the
other secondary outcomes. All associated standardised effect sizes were estimated to be small (Cohen’s d ≤ 0.30).

Web-Table 2 shows estimated mean outcome change by group and post-randomization time point. There was a significant improvement in BMI in both groups after commencing treatment, with mean BMI in the MANTRA group estimated to increase from baseline to month 6 by 1.06 (95% CI 0.55 to 1.57) and from baseline to month 12 by 1.83 (95% CI 1.12 to 2.54). Respective figures in SSCM were 0.80 (0.31 to 1.29) and 1.44 (95% CI 0.73 to 2.15). In both groups, there was also significant change for EDE Global and subscale scores, DASS-21 and CIA scores between baseline and 6 months and baseline and 12 months, whereas OCI-R and neuro- and social cognitive measures changed less consistently or not at all.

**Recovery Rates**

Our definitions of recovery and partial recovery were based on those previously used in other studies (Fairburn et al., 2013) and were as follows: recovered: BMI>18.5 kg/m² and EDE Global Score <2.77; partially recovered: BMI≤17.5 kg/m² and EDE≤2.77 or BMI between >17.5 kg/m² and ≤18.5 kg/m² or BMI>18.5 kg/m² and EDE>2.77; not recovered: BMI≤ 17.5 kg/m² and EDE>2.77. Recovery rates by group were comparable in those for whom this information was available: Baseline: SSCM: recovered: 0/70; partially recovered: 33/70 (47.14%), not recovered: 37/70 (52.86%). MANTRA: recovered: 0/72, partially recovered: 39/72 (54.17%), not recovered: n=33/72 (45.82%). 6-months: SSCM: recovered: 7/55 (12.73 %), partially recovered: 32/55 (58.18 %), not recovered: 16/55 (29.09 %). MANTRA: recovered: 7/63 (11.11 %), partially recovered: 41/63 (65.08 %), not recovered: 15/63
(23.81 %). 12-months: SSCM: recovered: 8/49 (16.33 %), partially recovered: 32/49 (65.31 %), not recovered: 9/49 (18.37 %). MANTRA: recovered: 13/58 (22.41 %), partially recovered: 36/58 (62.07 %), not recovered: 9/58 (15.52 %).

Subgroup analyses

The sample was restricted to those with baseline BMI below 17.5 kg/m² because our pilot study (Schmidt et al., 2012) suggested that MANTRA may be more advantageous in more underweight patients (MANTRA: n=56; SSCM: n=49). The magnitudes of the group differences in BMI increased at both post-randomization time points. At 6 months, the group difference was 0.57 kg/m² ($z=1.70, p=0.09, 95\% \text{ CI } -0.09 \text{ to } 1.22$) or 1.23 kg ($z=1.26, p=0.21, 95\% \text{ CI } -0.69 \text{ to } 3.14$) in favor of MANTRA. The predicted change in BMI was 1.25 kg/m² (or 3.08 kg) for those offered MANTRA and 0.68 kg/m² (or 1.85 kg) for those allocated to SSCM. At 12 months, the BMI difference was 0.70 kg/m² ($z=1.55, p=0.12, 95\% \text{ CI } -0.19 \text{ to } 1.58$) or 1.51 kg ($z=1.21, p=0.23, 95\% \text{ CI } -0.94 \text{ to } 3.95$) in favor of MANTRA. The predicted BMI changes were 1.98 kg/m² (or 5.03 kg) and 1.28 kg/m² (or 3.52 kg) for those in the MANTRA and SSCM groups respectively.

To evaluate effect of treatment receipt, another subgroup analysis included only treatment completers (MANTRA n=54, SSCM n=41). In the completers the BMI difference at 6 months was 0.33 kg/m² ($z=1.08, p=0.28, 95\% \text{ CI } -0.27 \text{ to } 0.94$) or 0.65 kg ($z=0.71, p=0.48, 95\% \text{ CI } -1.13 \text{ to } 2.43$) and at 12 months was 0.34 kg/m² ($z=0.83, p=0.41, 95\% \text{ CI } -0.46 \text{ to } 1.13$) or 0.66 kg ($z=0.59, p=0.56, 95\% \text{ CI } -1.54 \text{ to } 2.87$), all in favor of MANTRA.
**Discussion:**

Participants in both groups improved significantly in BMI, ED psychopathology, affective symptoms and psychosocial impairment at both 6 and 12 months post-randomization, with neuro- and social-cognitive change less consistent. However, our main hypothesis was not confirmed as there were no statistically significant differences in outcomes between the two treatments.

As per our study design, MANTRA therapy sessions were significantly longer than SSCM sessions. In addition, patients receiving MANTRA attended more of their scheduled individual therapy sessions than those receiving SSCM. Utilization of therapy add-ons (dietician and carer sessions) and of services outside the study treatments were similar in both groups.

On patients’ self-report of treatment acceptability and credibility, MANTRA was rated significantly more favourably on both compared to SSCM at 12 months.

Subgroup analyses found a trend for more underweight patients receiving MANTRA to show greater BMI increase at 6 months ($p=0.09$) and 12 months ($p=0.12$).

These findings deserve comment: Firstly, whilst there were some improvements in both groups on neuro- and social cognitive measures, these were less clear-cut than changes in the other outcome measures. This may be explained by the fact that our outpatient sample had a broad range of severity and many patients were not particularly impaired on neuro- and social-cognitive measures (Renwick et al., 2014), which has previously been highlighted elsewhere (Schmidt et al., 2012; Tchanturia et al., 2011). Whilst MANTRA explicitly targets patients’ thinking and socio-emotional
style, including e.g. cognitive inflexibility, lack of bigger picture thinking and fear/avoidance of emotions and relationships, these features go much beyond narrowly defined neuro- or social-cognitive impairments. As such the lack of consistent or differential improvement on neuro- and social cognitive variables is not surprising.

Secondly, MANTRA patients received a somewhat higher dose of treatment. Group differences in treatment dose were in part ‘design driven’ (i.e. shorter SSCM sessions) and in part ‘patient-driven’ (MANTRA patients attended more of their scheduled therapy sessions). It is possible that some SSCM patients opted not to attend their full contingent of scheduled therapy sessions because they were only offered shorter sessions during the second half of treatment.

Thirdly, trends for MANTRA to produce better BMI outcomes in more severely ill patients are encouraging. Whether these result from differential treatment dose effects (including the availability of a treatment manual for reference beyond the scheduled sessions), greater acceptability of this treatment per se or specific content targeted towards AN maintenance factors remains to be seen.

Fourthly, one death occurred in our trial, in an SSCM patient with longstanding severe AN. The highly elevated mortality risk in chronically ill, low-weight AN, has been documented (e.g. Arcelus et al., 2011) and previous AN outpatient trials have reported deaths (McIntosh et al., 2005; Dare et al., 2001).
Our findings also need to be put into context of the wider AN treatment literature. Overall, participant retention in the MOSAIC trial was excellent with 83% and 73% of MANTRA and SSCM participants respectively providing BMI and EDE data at 12 months. In comparison, in the German landmark trial\(^7\) between 59% (TAU) and 83% (CBT-E) participants provided data at 13 month post-randomization. Treatment completion rates (MANTRA: 75%; SSCM: 59%) also compare well against those of similar recent studies (54 to 91%) (Fairburn et al., 2013; Zipfel et al., 2014; McIntosh et al., 2005; Dare, Eisler, Russell, Treasure, & Dodge, 2001; Wildes, Marcus, Cheng, McCabe, & Gaskill, 2014; Lock et al., 2013).

BMI outcomes from the present study compare well with those of the recent German trial (Zipfel et al., 2014) where patients had similar baseline characteristics, but received 40 psychotherapy sessions. The degree of improvement in the current trial is somewhat better than that in our single-centre pilot RCT of these treatments (Schmidt et al., 2012), suggesting that both MANTRA and SSCM can be disseminated with relatively brief training of therapists.

Two other RCTs have used SSCM (McIntosh et al., 2005; Touyz et al., 2013). Comparison of our data against these trials is difficult, because of differences in patient populations, with one focusing on milder, less chronic (McIntosh et al., 2005) and the other on very chronic patients (Touyz et al., 2013).

The MOSAIC trial is the first RCT of AN treatment to include qualitative feedback from both patients and therapists. As is recommended, we published this prior to outcome evaluation (Waterman-Collins et al., 2014; Lose et al., 2014). Process data
from therapists identified major differences in focus, procedures and strengths between the two treatments (Waterman-Collins et al., 2014). Data from patients echo this, and also highlight the importance of the therapeutic relationship (Lose et al., 2014). We also examined written qualitative feedback on their experience of therapy from all study participants at 12 months (Zainal, unpublished data). Significantly more MANTRA compared to SSCM patients provided positive feedback. Taken together with acceptability and credibility ratings these qualitative findings suggest that MANTRA is preferred by patients and thus and provides a strong alternative to SSCM. Importantly, greater acceptability of MANTRA may translate into greater willingness to have further treatment if needed or into better longer-term outcomes.

The study has considerable strengths. It is one of the largest RCTs of first line psychological treatments for adult outpatients with AN worldwide. It had excellent participant retention, treatment completion and acceptability rates and very good outcomes compared to other similar studies. The trial therefore adds to our limited knowledge regarding the effective treatment of this population. This study is also the first large-scale AN trial to report neuro- and social cognitive outcomes. Furthermore, it incorporates a process evaluation, offering insight into patient and therapist perceptions of the two treatments. Trial interventions were delivered by therapists with different backgrounds and levels of experience, reflecting real life clinical practice. The trial also included patients across a broad range of clinical severity.

The study also has several limitations. First, it would probably have been better to offer individual therapy sessions of similar length in both treatments as this would have made reasons for any differences in attendance and acceptability easier to
understand. Second, although large, the study is still not large enough to perform definitive mediation and moderation analyses of the maintenance factors targeted by MANTRA and thereby illuminate mechanisms of action. However, MOSAIC trial data can be combined with those from our pilot RCT (Schmidt et al., 2012) to do so. Third, a further limitation, common to all psychotherapy trials is that neither patients nor therapists were blind to treatment allocation. MANTRA was developed in one of the participating sites, by investigators involved in the current trial. Despite our best efforts not to bias patients or therapists towards or against either of the study treatments, we cannot rule out the presence of subtle allegiance effects to MANTRA in at least one of the centres (where this treatment was developed). These allegiance effects may have manifested e.g. in patients’ perception of greater acceptability and credibility of this treatment. Ultimately, independent replication of the study is needed, and this is currently in progress in Australia in a multi-centre RCT comparing MANTRA, SSCM and CBT-E (Byrne, personal communication). Fourth, we have not as yet completed a formal therapist fidelity analysis. A final limitation is the short duration of follow-up. Further follow up is necessary to measure the longer-term effects of these two treatments on different outcomes. This is especially important given suggestions that SSCM effects may ‘wash out’ over time (Carter et al., 2011). We are currently collecting 2-year follow-up data of MOSAIC patients.

In conclusion, findings from this trial suggest that both treatments have promise as first line out-patient treatments of AN in adults, with MANTRA, a novel, targeted treatment based on experimental medicine principles, having advantages in terms of overall acceptability and credibility, and possibly also BMI outcomes in more severely ill patients.
In considering which of these treatments to choose for their patients, clinicians need to bear in mind the ‘three-legged stool’ principle of evidence-based medicine (Lilenfeld, 2014; Sackett, Rosenberg, Gray, Haynes, & Richardson, 1996). This suggests that best available research evidence, clinical expertise and patient preference need to all be considered in selecting interventions.

Future studies may want to assess the utility of these treatments against other psychological therapies for AN. As mentioned above, comparison of MANTRA and SSCM with CBT-E is already in progress. It would also be useful to establish the relative efficacy of these treatments for different groups of patients, defined by illness severity or duration (e.g. first episode cases versus more established cases). In adolescents or young adults with AN, it may be of interest to evaluate MANTRA as an adjunct to family therapy. Finally, with the emergence of novel brain-directed treatments, such as neuromodulation and neurofeedback treatments (McClelland, Bozhilova, Campbell, & Schmidt, 2013; McClelland, Bozhilova, Nestler, Campbell, Jacob, Johnson-Sabine, & Schmidt, 2013; Bartholdy, Musiat, Campbell & Schmidt, 2013), attention-bias modification (Renwick, Campbell & Schmidt, 2013), exposure treatment (Koskina, Campbell & Schmidt, 2013) and novel medication strategies (Maguire, O'Dell, Touyz, & Russell, 2013) it may be of interest to see whether the combination of these with psychological treatments such as MANTRA or SSCM leads to improved outcomes in adults with AN.
References:


McClelland, J., Bozhilova, N., Nestler, S., Campbell, I.C., Jacob, S., Johnson-Sabine, E., & Schmidt, U. (2013). Improvements in symptoms following neuronavigated repetitive transcranial magnetic stimulation (rTMS) in severe and enduring anorexia


StataCorp (2011). *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP.


Table 1: Baseline Characteristics of the Sample

<table>
<thead>
<tr>
<th>Demographic details</th>
<th>Whole Group</th>
<th>SSCM</th>
<th>MANTRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years: Mean (SD)</td>
<td>142 26.7 (7.7)</td>
<td>70 25.9 (7.1)</td>
<td>72 27.5 (8.1)</td>
</tr>
<tr>
<td>Males: Females, n</td>
<td>142 3:139</td>
<td>70 3:67</td>
<td>72 0:72</td>
</tr>
<tr>
<td>Years in Education, Mean (SD)</td>
<td>125 15.8 (2.3)</td>
<td>62 15.5 (2.5)</td>
<td>63 16.1 (2.1)</td>
</tr>
<tr>
<td>In relationship, n (%)</td>
<td>138 50 (35.2 %)</td>
<td>66 29 (41.4)</td>
<td>72 21 (29.2)</td>
</tr>
</tbody>
</table>

Clinical details

<table>
<thead>
<tr>
<th>Diagnosis, n (%)</th>
<th>Whole Group</th>
<th>SSCM</th>
<th>MANTRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>AN-R</td>
<td>142 63 (44.4)</td>
<td>70 28 (40)</td>
<td>72 35 (48.6)</td>
</tr>
<tr>
<td>AN-BP</td>
<td>44 (31.0)</td>
<td>22 (31.4)</td>
<td>22 (30.6)</td>
</tr>
<tr>
<td>EDNOS</td>
<td>35 (24.6)</td>
<td>20 (28.6)</td>
<td>15 (20.8)</td>
</tr>
<tr>
<td>BMI, kg/m², Mean (SD)</td>
<td>142 16.6 (1.2)</td>
<td>70 16.6 (1.3)</td>
<td>72 16.6 (1.2)</td>
</tr>
<tr>
<td>Weight, kg, Mean (SD)</td>
<td>142 45.1 (4.9)</td>
<td>70 45.4 (5.4)</td>
<td>72 44.8 (4.5)</td>
</tr>
<tr>
<td>Age at onset, years, Mean (SD)</td>
<td>132 17.7 (6.5)</td>
<td>65 18.1 (6.6)</td>
<td>67 17.3 (6.5)</td>
</tr>
<tr>
<td>Duration of Illness, years, mean (SD)</td>
<td>134 8.3 (7.3)</td>
<td>67 7.2 (6.5)</td>
<td>67 9.3 (7.9)</td>
</tr>
<tr>
<td>Previous ED treatment, n (%)</td>
<td>140 80 (56.3)</td>
<td>70 39 (55.7)</td>
<td>70 41 (56.9)</td>
</tr>
<tr>
<td>EDE, Mean (SD)</td>
<td>142 3.3 (1.3)</td>
<td>70 3.5 (1.3)</td>
<td>72 3.1 (1.3)</td>
</tr>
<tr>
<td>DASS21, Mean (SD)</td>
<td>138 30.5 (12.7)</td>
<td>69 31.4 (13.8)</td>
<td>69 29.6 (11.5)</td>
</tr>
<tr>
<td>OCI-R, Mean (SD)</td>
<td>139 23.6 (13.7)</td>
<td>69 24.9 (15.1)</td>
<td>70 22.3 (12.2)</td>
</tr>
<tr>
<td>CIA, mean (SD)</td>
<td>141 32.6 (8.9)</td>
<td>70 33.0 (8.9)</td>
<td>71 32.1 (9.0)</td>
</tr>
<tr>
<td>Current antidepressant medication, n (%)</td>
<td>140 55 (38.7)</td>
<td>70 26 (37.1)</td>
<td>70 29 (40.3)</td>
</tr>
</tbody>
</table>

SSCM: Specialist Supportive Clinical Management; MANTRA: Maudsley Model of Anorexia Nervosa Treatment for Adults; AN-R, anorexia nervosa restricting type; AN-BP, anorexia nervosa binge eating/purging type; EDNOS, eating disorder not otherwise specified; BMI, body mass index; EDE, eating disorder examination; DASS21, depression anxiety stress scale; OCI-R, Obsessive Compulsive Inventory-Revised; CIA, clinical impairment assessment.
Figure 1: CONSORT Flow Diagram

Assessed for eligibility (n=319)
- Not meeting inclusion criteria (n=48)
  - Outside of age limit (n=2)
  - BMI > 18.5 (n=34)
  - No current DSMIV diagnosis of AN or EDNOS-AN (n=12)
- Met exclusion criteria (n=33)
  - Alcohol / drug dependence (n=4)
  - Severe mental illness (n=8)
  - Learning disability (n=1)
  - Received MANTRA in past year (n=3)
  - Receiving treatment elsewhere (n=3)
  - Pregnancy (n=1)
  - Severe Physical Risk (n=13)
- Declined to participate (n=73)
- Other reasons (n=23)

Randomized (n=142)

Allocated to SSCM (n=70)
- Received allocated intervention: n=68
- Did not receive allocated intervention: n=2 (1 patient received MANTRA, 1 patient received Cognitive Analytical Therapy)

Allocated to MANTRA (n=72)
- Received allocated intervention: n=71
- Did not receive allocated intervention: n=1 (received mixture of CBT and MANTRA)

Treatment sessions attended
- Missing: n=3 (4.3%)
- Did not start treatment: n=6 (8.6%)
- 1-4 sessions: n=3 (4.3%)
- 5-9 sessions: n=12 (17.1%)
- 10-14 sessions: n=5 (7.1%)
- 15-19 sessions: n=12 (17.1%)
- 20-24 sessions: n=22 (31.4%)
- >25 sessions: n=7 (10%)
- Median no of sessions attended: 18 (0-32)

Completed EDE interview:
- Baseline: n = 70/70 (100%)
- 6 months: n = 55/70 (79%)
- 12 months: n = 51/70 (73%)

Completed BMI assessment:
- Baseline: n = 70/70 (100%)
- 6 months: n = 55/70 (79%)
- 12 months: n = 51/70 (73%)

Treatment sessions attended
- Missing: n=2 (2.8%)
- Did not start treatment: n=4 (5.5%)
- 1-4 sessions: n=2 (2.7%)
- 5-9 sessions: n=7 (9.7%)
- 10-14 sessions: n=3 (4.2%)
- 15-19 sessions: n=12 (16.7%)
- 20-24 sessions: n=31 (43.1%)
- >25 sessions: n=11 (15.2%)
- Median no. of sessions attended: 20 (0-30)

Completed EDE interview:
- Baseline: n = 72/72 (100%)
- 6 months: n = 64/72 (89%)
- 12 months: n = 60/72 (83%)

Completed BMI assessment:
- Baseline: n = 72/72 (100%)
- 6 months: n = 64/72 (89%)
- 12 months: n = 60/72 (83%)
Figure 2. Predicted mean BMI at both post-randomization time points (originating from observed mean at baseline). Covariates were fixed at mean baseline level of BMI (16.69), restrictive AN and no previous hospital admissions.
Table 2. Estimated outcome differences between treatment arms at 6 and 12 months post randomization. (Results are derived by multiple imputation.)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>6 months after randomization</th>
<th>12 months after randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimated group difference✓</td>
<td>Test</td>
</tr>
<tr>
<td>BMI (kg / m^2)</td>
<td>0.26</td>
<td>z=0.85, p=0.39</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>0.62</td>
<td>z=0.74, p=0.46</td>
</tr>
<tr>
<td>Eating Disorder Examination</td>
<td>0.10</td>
<td>z=0.50, p=0.62</td>
</tr>
<tr>
<td>EDE restraint subscale</td>
<td>0.03</td>
<td>z=0.11, p=0.91</td>
</tr>
<tr>
<td>EDE eating concern subscale</td>
<td>-0.03</td>
<td>z=-0.14, p=0.89</td>
</tr>
<tr>
<td>EDE shape concern subscale</td>
<td>0.17</td>
<td>z=0.64, p=0.52</td>
</tr>
<tr>
<td>EDE weight concern subscale</td>
<td>0.06</td>
<td>z=0.21, p=0.83</td>
</tr>
<tr>
<td>Depression, Anxiety and Stress Scale</td>
<td>-0.12</td>
<td>z=-0.05, p=0.96</td>
</tr>
<tr>
<td>Obsessive Compulsive Inventory-Revised</td>
<td>1.36</td>
<td>z=0.64, p=0.52</td>
</tr>
<tr>
<td>Clinical Impairment Assessment</td>
<td>-0.25</td>
<td>z=-0.13, p=0.90</td>
</tr>
<tr>
<td>Wisconsin Card Sorting Task; Perseverative errors (log)*</td>
<td>0.95</td>
<td>z=0.39, p=0.70</td>
</tr>
<tr>
<td>Brixton Spatial Anticipation Task; Total errors</td>
<td>0.10</td>
<td>z=0.13, p=0.90</td>
</tr>
<tr>
<td>Rey-Osterrieth Complex Figure Test; Central Coherence Index</td>
<td>0.05</td>
<td>z=0.79, p=0.43</td>
</tr>
<tr>
<td>Reading the Mind in Films Task</td>
<td>0.87</td>
<td>z=1.49, p=0.14</td>
</tr>
</tbody>
</table>

† coefficients represent estimated treatment effect of MANTRA – SSCM.
‡‡ standardised coefficients were derived by dividing estimated differences by respective baseline standard deviations
* analysed on the log-scale, estimates represent factor change
Table 3. Predicted mean outcomes (standard errors) by treatment arm and post-randomization time point*. (Results are derived by multiple imputation.)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>6 months after randomization</th>
<th>12 months after randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SSCM</td>
<td>MANTRA</td>
</tr>
<tr>
<td>BMI (kg / m²) [16.61]</td>
<td>17.41</td>
<td>0.25</td>
</tr>
<tr>
<td>Weight (kg) [45.07]</td>
<td>47.16</td>
<td>0.69</td>
</tr>
<tr>
<td>Eating Disorder Examination [3.30]</td>
<td>2.68</td>
<td>0.17</td>
</tr>
<tr>
<td>EDE restraint subscale [3.73]</td>
<td>2.74</td>
<td>0.24</td>
</tr>
<tr>
<td>EDE eating concern subscale [2.84]</td>
<td>2.28</td>
<td>0.20</td>
</tr>
<tr>
<td>EDE shape concern subscale [3.50]</td>
<td>2.99</td>
<td>0.22</td>
</tr>
<tr>
<td>EDE weight concern subscale [3.15]</td>
<td>2.62</td>
<td>0.23</td>
</tr>
<tr>
<td>Depression, Anxiety and Stress Scale [30.51]</td>
<td>24.92</td>
<td>1.85</td>
</tr>
<tr>
<td>Obsessive Compulsive Inventory-Revised [23.56]</td>
<td>20.79</td>
<td>1.66</td>
</tr>
<tr>
<td>Clinical Impairment Assessment [32.56]</td>
<td>25.65</td>
<td>1.69</td>
</tr>
<tr>
<td>Wisconsin Card Sorting Task [7.77]</td>
<td>6.35</td>
<td>0.81</td>
</tr>
<tr>
<td>Brixton Spatial Anticipation Task [12.30]</td>
<td>10.37</td>
<td>0.79</td>
</tr>
<tr>
<td>Rey-Osterrieth Complex Figure Test [1.29]</td>
<td>1.31</td>
<td>0.06</td>
</tr>
<tr>
<td>Reading the Mind in Films Task</td>
<td>13.15</td>
<td>0.62</td>
</tr>
</tbody>
</table>

* Mean outcomes were predicted for patients with sample average baseline levels (shown in [] in the left column, and from the most frequent stratifier categories (baseline BMI>15, AN-subtype=AN-restrictive, no previous admission)).