In 2012, van Elburg et al. published a paper claiming that Mandometer treatment is slightly less effective than treatment as usual[1]. Their paper has many problems which Bergh et al. pointed out in a manuscript submitted to the journal that published van Elburg et al.´s paper. The manuscript was rejected without review. Bergh et al. published some of the problems with van Elburg et al.´s paper in 2013[2], but the manuscript, that was rejected, is published here to provide the full details of the problems with van Elburg et al.´s paper.

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Comparison of Mandometer Treatment and Treatment as Usual for Anorexia Nervosa; Standards of Evidence

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Abstract

Objective: To examine the basis for the recent conclusion by van Elburg et al.[1] that the effect of Mandometer treatment for anorexia nervosa is not superior to that of treatment as usual.

Method: Examination of the methods used and the reported results in that study.

Results: Criteria for patient inclusion and exclusion were not mentioned, patients were not randomly assigned to treatments, treatment failures were differentially excluded from the results, statistical methods were unsuitable, and treatment as usual resulted in much higher remission rates than expected, while Mandometer treatment outcomes were comparable to previous results.

Discussion: The study by van Elburg et al.[1] does not allow conclusions to be drawn regarding the effectiveness of Mandometer treatment versus treatment as usual. Their treatment should be better described and compared with Mandometer treatment in a randomized controlled study.

Keywords: Mandometer treatment; treatment as usual; randomized controlled study; anorexia nervosa

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Recently, van Elburg et al.[1] published a report entitled: *Mandometer treatment not superior to treatment as usual for anorexia nervosa*. We would like to clarify some methodological issues in that report, including the absence of randomization and inclusion/exclusion criteria, the presence of statistical distortions, as well as the disregard of the criteria for compliance, and the uniquely high probability of positive outcomes for treatment as usual (TAU), relative to previous studies. We discuss these issues and then suggest how their report should be interpreted.

Treatment as Usual (TAU)

In their introduction, van Elburg et al.[1] mention that TAU for anorexia nervosa (AN) has met with limited success. Even if patients respond to the treatment, relapse is quite common, and more often than not, the illness runs a chronic course. In agreement with many previous reports, they concluded that TAU leads to "disappointing" results, with only 10% of the patients experiencing a long-term remission.[2] Short-term positive outcomes are somewhat better, with almost 50% reporting some kind of remission before the relapses which are frequent among patients subjected to TAU.[2-4] They also indicated that family therapy "has had the most consistent effect in adolescent patients with AN". However, while family therapy is somewhat effective for the least severely affected AN patients, there is no evidence that it is more effective than other types of TAU.[5,6]

Mandometer treatment (MT)

As van Elburg et al.[1] point out, a randomized controlled trial demonstrated that Mandometer treatment (MT) has a strong effect, with 75% patients going into full remission and only 7% patients who were treated to remission relapsing over a five-year follow-up period, resulting in a long-term remission rate of 68%.[7] However, van Elburg et al.[1] are wrong in dismissing the MT randomized controlled trial[7] as a "small" study. This mistake is a common one, based on misunderstanding of the relationship between sample size and the import of an effect (see ref[8] for a discussion of this issue with respect to MT). Suffice it to say that a statistically significant effect is not more valid if it is based on a large, rather than small sample. Moreover, if there is a strong effect, such as was the case with MT on AN, a sample size larger than the power calculation demands should not be used.[7,8] Therefore, the trial evaluating MT was properly sized. It should also be noted that data from 291 eating disorder patients who were treated with MT have now been reported, with a similar outcome.[7,9-12]

Inclusion criteria and randomization

Nothing is mentioned about inclusion and exclusion criteria in their study, with the exception that the patients were 12-18 years old. No power calculation was apparently done and there is no description of how the patients entered the study. *Importantly, the patients were not randomly assigned to groups, undoubtedly the most critical aspect of a proper*

comparison between different clinical approaches.[13] Non-randomized studies are not considered for publication in major medical journals and they are not included in assessments of the evidentiary basis for effective treatments. Also, the study was biased by their design; the fact that van Elburg et al.[1] included twice as many patients in TAU (n=51) than in MT (n=25) obviates their conclusions, as group size differentially impacts the variance of the data.[13]

Statistical analysis and patient selection

Another major problem with their study design was produced by the differential elimination of subjects from the study. Six of 51 patients in TAU and one of 25 patients in MT "resigned" from treatment within two months and they were excluded from the analysis. Another five TAU patients and two MT patients "dropped-out," but were included in the analysis. While 11 of 51 TAU patients (23%) compared to three of 25 MT patients (12%) resigned or dropped-out, no explanation for this difference was provided. Van Elburg et al.[1] also did not give a reason why these patients did not comply with the study protocol. However, it seems likely that treatment failed in these cases, because van Elburg et al.[1] reported that the five patients who dropped-out of TAU had a very high score on a "motivation for treatment" questionnaire. Although van Elburg et al,[1] did not report the scores of the six patients who "resigned" from TAU, these patients were probably motivated as well, since they initiated TAU. Hence, TAU failed in 11 patients, who were apparently motivated for this treatment.

In addition, three patients who registered for TAU were excluded because of "severe co-morbidities" or age. In contrast, no patient was excluded from MT. In the randomized controlled trial that evaluated MT,[7] patients with an eating disorder not otherwise specified (EDNOS) were excluded because EDNOS outcomes are better than AN outcomes.[14,15] Patients requiring immediate medical care were also excluded because it would have been impossible to randomize such patients to the untreated control group in that study.[7] However, all eligible patients, compliers as well as non-compliers, were included in the estimation of the rate of remission of original MT study.[7]

Because it is essential for clinical studies to take all participating patients into consideration, regardless of compliance,[16] the fact that TAU had a higher level of non-compliance than MT, suggests that there was inappropriate patient selection for the data analysis in the study by van Elburg et al.[7] An intention-to-treat analysis should consider the loss of sensitivity associated with data that are lost to follow-up and by the use of prior measurement carried forward.[16]

It is difficult to understand how the data from the patients who dropped-out of treatment affected the analysis of the results. Van Elburg et al.[1] report means and standard deviations (SDs) and say that data from patients who dropped-out were carried forward to the next point of measurement. A decrease in a mean value should therefore be accompanied by an increase in the associated SD of that mean, but it is not possible to determine if this is the case, because

the SDs from TAU and MT overlap in all figures. The depression score of TAU in Fig. 5C may be an exception; this mean value is about 12 at T0, with an SD of 7. The mean falls to 7.5 at T1, yet the SD remains 7. The use of mean values relies on the assumption of an underlying continuous and symmetric distribution of interval data, but this assumption cannot be made in this case, because the means are smaller than the associated SDs in several cases, e.g., MF in Table 3. These data therefore reveal values outside the range of outcome for some variables and hence describe a data set with a skewed distribution. There is no "standard" deviation for such data, which therefore should be modeled using medians and quartile ranges. This problem can also be seen in analyses of ordinal data obtained with Likert scales, which are unsuitable for the parametric methods[17] used by van Elburg et al.[1] These considerations undermine the validity of their statistical analyses.

The study also included six patients who did not fulfill the weight criterion for AN, and therefore were diagnosed with an EDNOS. Five of these patients were subjected to TAU and one to MT. As already mentioned, outcome is better for EDNOS than for AN,[14,15] and this differential assignment to the treatment groups again distorts the outcome in favor of TAU. Remission, as shown in Fig. 2, was considered to be an increase in SD BMI above "poor", a criterion that the five EDNOS patients in TAU, but not the EDNOS patient in MT, fulfilled at the start of the study (Table 2).

Finally, the SD BMI values in Table 2 do not match those in Fig. 2, the Morgan Russell (MROAS) data for TAU have been mistaken for those with MT in Fig. 3 and these scores do not match with those in Table 3. Figure 5 only shows CPRS-S-A results but, according to the text, it also shows STAI and CDI scores. The final two paragraphs of the Results section provide statistical analyses of data that are not displayed. The lack of care in the reporting of data does not instill confidence in the quality or the analysis of the study.

Unanticipated success with TAU

Van Elburg et al.[1] reported that 83% of the TAU patients went into remission using MROAS criteria and that 71% went into remission using SD BMI criteria. These rates are about twice as high for short-term positive outcomes than previously reported with TAU.[2-4] At the same time, they report that MT had success with 75% (MROAS) and 63% (SD BMI) of the patients, data that are comparable to the 75% remission rate in the original MT report.[7]

Interpretation of the results

The design of the study by van Elburg et al.[1] has several shortcomings which should be of concern for those having an interest in the treatment of AN. The authors conclude that "outcome data of TAU and MT are comparable with or even better than outcome data of other AN studies". However, the outcomes for TAU in this study are *far* better than anyone has ever reported for TAU.[2-6] The reason for this unexpected success for their version of TAU is unclear, as this group previously reported that TAU has a short-term positive outcome of 39%,[18] i.e., a great deal less than the 71-83% success in this report.

The effectiveness of TAU claimed by van Elburg et al.[1] is also in question, because it was the first treatment for only 12 of the 45 patients who entered TAU, and MT was the first treatment for only 8 of the 24 patients who entered MT (Table 1). Hence, 33 patients who entered TAU and 16 patients who entered MT in their study had failed to improve previously with TAU. In addition, TAU failed in 11 patients during the study (resignations and drop-outs), leaving us with TAU treatment failures in 60 attempts, some of which may have been repeated attempts, among the 79 patients who registered for treatment.

Even if their patients responded to TAU, readers of the report are at a loss in understanding how remission was achieved. In their version of TAU, van Elburg et al.[1] included not only "psychomotor therapy" and "creative therapy" but "additional treatments", which were "assigned to patients according to their needs". It would be useful to know the criteria used for the assignment, and the evidentiary basis for such treatment; we are not aware of any evidence that the therapies listed by van Elburg et al.[1] are effective in treating AN.

At the same time, the outcome of MT in this study is better than that of previous reports of TAU, and comparable to previously reported outcome of MT.[7,9-12] We therefore consider their report to be a replication of the original finding of the efficacy of MT although outcome of the major intervention in MT, eating behavior,[7,9-12] is not mentioned in the report.

To help improve the outcomes in eating disorder treatment, we repeat the invitation to our colleagues to collaborate in a randomized controlled study and compare the effect of MT with that of a clearly defined version of TAU.[10] As AN is a serious disorder, it is critical that therapies with suboptimal outcomes are replaced by effective alternatives.

Conflict of interest

C Bergh and P Södersten each have 28% and M Leon has 3% of the stock in Mando Group AB.

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