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Effective Treatment of Eating Disorders: Results at Multiple Sites

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We report the results of a study based on 1,428 patients with eating disorders treated at 6 clinics. These patients were consecutively referred over 18 years and used inpatient and outpatient treatment. The subjects were diagnosed with anorexia nervosa, bulimia nervosa, or an eating disorder not otherwise specified. Patients practiced a normal eating pattern with computerized feedback technology, they were supplied with external heat, their physical activity was reduced, and their social habits restored to allow them to return to their normal life. The estimated rate of remission for this therapy was 75% after a median of 12.5 months of treatment. A competing event such as the termination of insurance coverage, or failure of the treatment, interfered with outcomes in 16% of the patients, and the other patients remained in treatment. Of those who went in remission, the estimated rate of relapse was 10% over 5 years of follow-up and there was no mortality. These data replicate the outcomes reported in our previous studies and they compare favorably with the poor long-term remission rates, the high rate of relapse, and the high mortality rate reported with standard treatments for eating disorders.

Keywords: anorexia, bulimia, eating behavior, neurobiology, regulatory physiology

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We proposed that dieting is the main risk factors for loss of control over body weight (Bergh & Södersten, 1996; Ioakimidis et al., 2011; Södersten, Nergårdh, Bergh, Zandian, & Scheurink, 2008). Those who are capable of continuing their restricted diet may develop anorexia nervosa whereas others, who attempt to limit their food intake, eventually fail and overeat, often palatable food (Bruch, 1973; Polivy & Herman, 1985; Striegel-Moore, Silberstein, & Rodin, 1986). These individuals are binge eaters, and

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if they purge following their large meals, they may develop bulimia nervosa (Bruch, 1962; Garfinkel, 1974; O'Brien & Vincent, 2003; Russell, 1979; Stunkard, 1959), if not, they become overweight and, eventually, obese (Ford et al., 2010; Galhardo et al., 2012). Both anorexics and bulimics also increase their physical activity greatly (Danielsen, Bratberg, & Rø, 2012). In addition, time constraints can rapidly induce the eating behavior typical of anorexia, bulimia, and obesity (Zandian, Ioakimidis, Bergh, Brodin, & Södersten, 2009; Zandian, Ioakimidis, Bergh, & Södersten, 2009; Zandian et al., 2012), which therefore appear to be different expressions of the same disorder.

When rats and mice have restricted access to food in the presence of a running wheel, they develop symptoms remarkably similar to those of humans with anorexia (Gutiérrez, 2013). Rats and mice given food only once a day begin to increase their running activity and decrease their food intake further to the point at which they lose a great deal of body weight and can eventually die (Routtenberg & Kuznesof, 1967), very much as human anorexics. The reduction of food intake and enhancement of physical activity in female rats cause them to cease their ovarian cycling (Watanabe, Hara, & Ogawa, 1992), just as the cessation of the menstrual cycle in anorexic women (Støving, Hangaard, & Hagen, 2001). In both the rodent and the human condition, there is a profound disruption in the hypothalamus-pituitary-adrenal-axis (Burden, White, Dean, & Martin, 1993; Lawson & Klibanski, 2008; Støving et al., 2001). In addition, hormones related to food intake change, for example, leptin is suppressed and ghrelin levels are increased (Pardo et al., 2010; Rouveix et al., 2007). Hypothermia and disruption of circadian sleep patterns are also seen in both humans and rodent models of anorexia (Dwyer & Boakes, 1997; Lauer & Krieg, 2004; Luck & Wakeling, 1980, 1982; Paré, 1977; Wakeling & Russell, 1970). Finally, neuropeptide tyrosine, which is up-regulated in the brain of both the rat model of anorexia (Nergårdh et al., 2007) and anorexic patients (Goldstone, Unmehopa, Bloom, & Swaab, 2002), stimulates food intake in rats with ad libitum access to food, but inhibits food intake and stimulates physical activity to forage when food is in short supply (Nergårdh et al., 2007). Foraging for food engages evolutionarily conserved neuropeptide tyrosine receptors (Larhammar & Bergqvist, 2013).

This weight loss in the rats and mice can be prevented or reversed by keeping them warm or restricting their physical activity, thus restoring normal feeding patterns (Epling & Pierce, 1984; Gutiérrez, Vazquez, & Boakes, 2002; Lattanzio & Eikelboom, 2003). Given this perspective, one might consider treating eating disorders in humans by normalizing their food intake patterns, providing warmth to them, and restricting their physical activity.

Indeed, we have done just that. In a randomized controlled trial, we demonstrated that normalization of eating behavior with continual feedback during meals, ongoing provision of warmth, and restriction of physical activity brought 14 out of 16 patients into full remission, compared to one out of 16 in an untreated control group (Bergh, Brodin, Lindberg, & Södersten, 2002). The patients also were trained to resume their normal social interactions and with this treatment, the estimated rate of full remission among 168 patients was 75%, with 10% of those who went into remission relapsing within 5 years, and there was 0% mortality throughout treatment and follow-up (Bergh et al., 2002). These outcomes emerged despite the fact that these patients had previously failed to improve in an average of two to three standard care treatments (Bergh et al., 2002).

By contrast, long-term outcome of traditional treatment of eating disorders is poor; the dropout rate is high, fewer than 50% of the patients go into remission and those who do remain symptomatic with persistent psychopathology on discharge, the majority is reported to relapse within a year, and many patients lapse into chronicity (Anckarsäter et al., 2012; Bulik, Berkman, Brownley, Sedway, & Lohr, 2007; DeJong, Broadbent, & Schmidt, 2012; Pham-Scottez et al., 2012; Von Holle et al., 2008; Wentz, Gillberg, Anckarsäter, Gillberg, & Råstam, 2009; Zerwas et al., 2013). Indeed, the rate of recovery for anorexia and bulimia is remarkably low at 10 to 11%, 10 years after onset of the disorder (Von Holle et al., 2008). Moreover, when patients with eating disorders were assessed 5 years after their initial examination, it was not possible to see any effect of standard psychiatric therapies (Ben-Tovim, 2003). Finally, although some studies report no mortality (e.g., van Elburg et al., 2012), mortality rates for standard care of anorexics are more often quite high, ranging from 6.2 to 17.8% (Arcelus, Mitchell, Wales, & Nielsen, 2011; Franko et al., 2013; Rosling, Sparén, Norring, & von Knorring, 2011; Selby et al., 2010). Mortality among bulimic patients is somewhat lower (Suokas et al., 2013).

As part of traditional treatment, many patients with eating disorders are given multiple psychoactive drugs, despite the fact that their lack of efficacy is clear, both in regard to treating their disordered eating patterns (Kaye, Wierenga, Bailer, Simmons, & Bischoff-Grethe, 2013; McKnight & Park, 2010; Powers & Bruty, 2009), and for treating their psychiatric symptoms (Kaye et al., 2013; Zhu & Walsh, 2002). Indeed, no psychoactive drug has been shown to have a clinically significant beneficial effect for patients with eating disorders (Kaye et al., 2013; Pederson, Roerig, & Mitchell, 2003; Zhu & Walsh, 2002). In fact, some psychoactive drugs can actually induce disordered eating behavior (Ioakimidis et al., 2011).

However, despite these differences in outcome our randomized study may not have been convincing because the number of subjects, although based on an appropriate power calculation, was relatively small (Ioannidis, 2005). Moreover, the study was performed only in a single clinic, raising the possibility that these outcomes may have been specific to that clinic, due to the presence of a particularly talented therapist, or to a uniquely compliant patient population. In other words, the therapy itself may not have been critical for these outcomes. To address these issues, we now report the results of a large number of patients treated with this therapy in multiple locations around the world by multiple therapists.

Method

Patients and Diagnosis

We followed the outcomes of 1,428 consecutively referred patients who entered treatment from 1993 through 2011 in one of three Swedish clinics (Alingsås, Danderyd, and Huddinge), a Dutch clinic (Amsterdam), an Australian clinic (Melbourne), and an American clinic (San Diego, CA). Patients have been referred to the clinics by physicians for 18 years, although in the last 3 years, they also had the possibility of self-referral, with about 70%

of the patients now using that means to enter therapy. The staff includes behavioral therapists, dieticians, nurses, physicians, and psychiatrists. Patients have an initial meeting in which the treatment is described to them, followed by an interview with questions regarding their eating behavior, alcohol and drug use, as well as physical and social activity. The patients are given a physical examination, which includes blood tests to determine their physiological status, and they are asked about any previous psychiatric problems. The patients also complete a 24-hr dietary history, the Eating Disorder Inventory (EDI–2; Garner, 1991), the Comprehensive Psychopathological Self-Rating Scale (Svanborg & Åsberg, 1994), and a quality of life questionnaire (Ware & Kosinski, 2003). In addition, the patients eat a meal without feedback information (see later in the article) to determine their speed of eating, the amount of food eaten, and their development of satiety over the course of a meal. After the results of the eating evaluation were reviewed, the patients were diagnosed using the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., American Psychiatric Association, 1995). The length of time over which the clinics have operated, the number of patients at each clinic, and their diagnoses are in Table 1. The treatment has been available longer in the clinic in Huddinge at the Karolinska Institute where it was developed than in the other clinics. Because it was a child- and adolescent-psychiatric clinic, most of the patients in Amsterdam were young anorexics.

There were 251 patients who were classified as severely ill and treated initially as inpatients. They had a body mass index (weight/height squared, kg/m^2) ≤ 13.5, and/or a body temperature of ≤ 36 °C, bradycardia (< 40 bpm), prolonged QTc-time, at risk of cardiac arrhythmia, dehydration 5 to 10%, $< 90/60$ mmHg (hypotension), hypokalemia (≤ 3.2 nmol/L), binge-eating, vomiting several times each day, and suicidal tendencies.

Anorexics were younger and had been ill for a shorter period of time than either bulimics or patients with an eating disorder not otherwise specified. All patients had high levels of depression, anxiety, as well as obsession, and most of them had been treated previously in other clinics (see Table 2).

Intervention

The Mandometer intervention has been described previously (Bergh et al., 2002; Bergh, Eklund, Eriksson, Lindberg, & Södersten, 1996; Court, Bergh, & Södersten, 2008; Södersten, Bergh, & Zandian, 2006a; 2006b; Södersten et al., 2008; Zandian, Ioakimidis, Bergh, & Södersten, 2007). Briefly, the patients normalize their eating pattern with mealtime feedback provided by a scale that rests under a dinner plate, connected to a small computer. By consulting a small monitor next to their plate, patients are able to compare their rate of eating in real time to that of a typical person eating that meal. The patients also develop normal feelings of satiety using the same strategy. Initially, a behavioral therapist assists the patients, but the patients get used to the procedure rapidly and can then practice eating without the support of a therapist, including practicing at home. In addition, the patients are provided with warmth, using warm rooms (temperature can be set at ≤ 40 °C), or thermal blankets (Topcam CF201, Tristar, Tilburg, The Netherlands), or jackets (556A, Venture, Melbourne, Australia), to calm them and to avoid the use of calories for thermoregulation. Their physical activity is restricted for that same purpose, and great deal of time is spent convincing and coaxing the patients to start resuming their normal social interactions. Approximately 30% of the patients were taking psychoactive drugs on admission and these are gradually withdrawn over the first months of treatment. The treatment is named Mandometer after the device that is used to teach the patients how to eat.

Outcomes

Patients are considered to be in remission when they no longer meet the criteria for an eating disorder, when their body weight, eating behavior, feelings of satiety, physiological status, level of depression, anxiety, and obsession are normal, when they are able to state that food and body weight are no longer a problem, and when they are back at school or work. Bulimic patients must in addition have stopped bingeing and purging for at least 3 months. Meeting five of these criteria was regarded as "partial remission" starting in 2009. A normal body weight is a body mass index of 19 to 24 for women and 20 to 25 for men. Normalization of depression, anxiety, and obsession symptoms is reflected in values less than six on the Comprehensive Psychopathological Self-Rating Scale (Svanborg & Åsberg, 1994).

Follow-Up

After remission, patients were followed for 1, 2, 3, 6, 9, 12, 18, 24, 36, 48, and 60 months by a trained behavioral therapist. The follow-up appointment, which lasted for 2 hr in the first

Table 1
Number of Patients and Diagnoses

Clinic	Treatment[a]	*N*	Female (%)	Anorexia nervosa *n* (%)	Bulimia nervosa *n* (%)	EDNOS *n* (%)
Alingsås	2	77	99	18 (23)	15 (20)	44 (57)
Amsterdam	5	98	96	80 (82)	7 (7)	11 (11)
Danderyd	7	205	96	57 (28)	24 (12)	124 (60)
Huddinge	18	918	97	345 (38)	175 (19)	398 (43)
Melbourne	5	76	97	46 (60)	12 (16)	18 (24)
San Diego	7	54	96	25 (46)	13 (24)	16 (30)
Total		1,428	97	571 (40)	246 (17)	611 (43)

Note. EDNOS = eating disorder not otherwise specified.
[a] Given in years.

Table 2
Some Characteristics of the Patients at Admission

Variable	Anorexia nervosa[a] *Mdn* (Quartile range)	Bulimia nervosa[b] *Mdn* (Quartile range)	EDNOS[c] *Mdn* (Quartile range)
Age[d]	17.5 (15.3–20.9)	22.6 (19.2–28.2)	20.5 (16.9–26.7)
Duration of disorder[d]	3.2 (1.6–6.6)	7.4 (4.0–13.3)	5.5 (2.5–11.3)
No. of previous treatments:			
0	25%	16%	24%
1	34%	29%	29%
> 1	41%	55%	47%
BMI, kg/m^2	14.9 (13.8–16.1)	21.5 (19.6–23.5)	18.5 (17.3–21.2)
Depression	11.5 (10.0–14.5)	11.5 (10.0–14.5)	12.0 (10.0–14.0)
Obsession	9.5 (9.5–14.5)	11.5 (9.5–14.5)	12.0 (10.0–14.0)
Anxiety	11.5 (9.5–14.0)	12.0 (9.5–15.0)	12.0 (10.0–14.0)

Note. EDNOS = eating disorder not otherwise specified; BMI = body mass index.
[a] $n = 571$. [b] $n = 246$. [c] $n = 611$. [d] Given in years.

year and 2.5 hr the following years, was a semistructured interview employing the same method and most of the forms used in the initial eating examination (Garner, 1991; Svanborg & Åsberg, 1994; Ware & Kosinski, 2003). Patients also ate a meal using the Mandometer without feedback to make sure that their eating behavior and feelings of satiety were normal. If, at any time a patient lost at least 4 kg, or developed signs of binge-eating/purging, the eating examination was repeated, and if the criteria for an eating disorder were fulfilled, the patient was considered to have relapsed.

Statistical Analyses

Medians and quartile ranges are presented unless stated otherwise. The 95% confidence intervals are shown in Figures 1A and 3A, but omitted in the other figures to facilitate consideration of the data. Time to remission and relapse was evaluated using survival analysis (Tableman & Jong Sung, 2004). The effect of severity of illness, previous treatments, diagnosis, and body mass index on survival curves was evaluated using the log rank and likelihood ratio tests (Gray, 2011; Machin, Cheung, & Parmar, 2006). STATISTICA (StatSoft, Tulsa, OK) was used for the statistical analyses.

Data from patients who were still in treatment or who dropped out for unknown reasons were censored. The effect of a "competing event," which interfered with the possibility of going into remission, was analyzed using cause-specific hazard functions and corresponding cumulative incidence estimators (Gray, 2011). Competing events included instances when patients withdrew because they felt that they were not improving, when they were diagnosed with an unrelated illness, or when they withdrew because of financial constraints. That is to say, incidents that were either related (treatment failure) or unrelated (e.g., insurers did not pay) to the therapy could prevent the patient from completing the treatment and were therefore considered competing events.

Survival Analysis

Survival analysis was applied to a process that extends over time. All patients were included in the analysis, that is, those who just entered treatment, who were in treatment, withdrew, failed, or dropped-out of treatment, and those who went into remission. The number of patients at each point in time of the analysis is therefore variable.

A "Life Table" Approach to Survival Analysis

A simplified "life table" procedure was used to estimate the probability of going into remission over consecutive 3-month intervals. The number of patients decreases over time as patients go into remission and because not all of them have been in treatment long enough. The results are presented to provide information on the actual numbers of patients at various points in time. Note, however, that "survival" is a continuous process.

Patients withdrawn for reasons unrelated to the treatment were censored at the time when they were no longer in treatment. Failure of insurers to pay for treatment in San Diego provided an example and explained why 50% of the patients were censored in this clinic (see Table 3). Patients withdrawn for reasons related to the treatment, that is, the treatment failed, were retained in the analysis, "burdening" the denominator in the calculation at all times, thus yielding a conservative estimate of the rate of remission.

Consider the results in Alingsås (Table 1[1] in the supplementary file online). Out of the 77 patients who started treatment, 17 had not been treated for 3 months, their average time in treatment was set to be 1.5 months. The number of patients treated over the first 3 months was therefore 77 - 17/2 = 68.5 and because one patient went into remission the probability of going into remission within the first 3 months was 1/68.5 = 0.015 and the probability to proceed to the next 3 months of treatment ("survive") was 1 − 0.015 = 0.985. The number of patients over these 3 months of treatment was 77 − 17 − 1 = 59; three went into remission, and nine were censored. The

[1] The numerical details used for the calculations of outcome in Alingsås in the Method section are in Supplement Table 1. The same numerical details for the other clinics are in Supplement Tables 2 through 6, but the cumulative number and proportion of patients not in remission have been omitted.

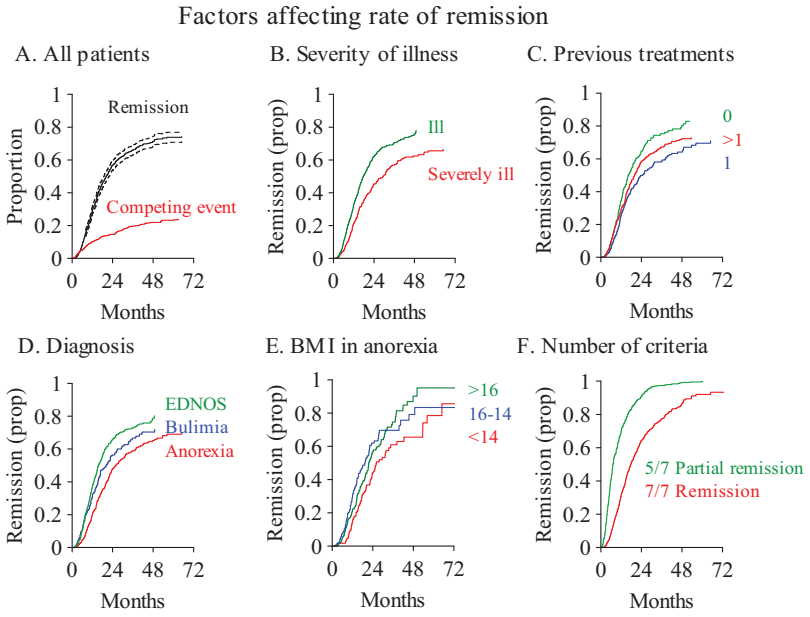

Figure 1. Factors affecting the rate of remission in 1,428 patients with eating disorders. (A) Proportion of all patients going into remission. 95% confidence intervals (CI) indicated by dotted lines. Competing events (red line) prevented some of the patients from going into remission. (B) Effect of severity of illness: 251 patients were classified as severely ill and 486 were classified as ill. (C) Effect of previous treatments: 328 patients had received no previous treatment, 442 patients had received one previous treatment, and 558 patients had received more than one previous treatment. (D) Effect of diagnosis: 611 patients were diagnosed with an eating disorder not otherwise specified (EDNOS), 246 were diagnosed with bulimia nervosa, and 571 patients were diagnosed with anorexia nervosa. (E) Effect of body mass index (BMI) in 571 patients with anorexia nervosa: 182 patients had a BMI less than 14, 238 had a BMI between 14 and 16, and 151 patients had a BMI of more than 16. (E) Effect of criteria of remission: 737 patients fulfilled seven out of seven criteria and 378 fulfilled five out of seven criteria for remission. Outcome was not differentially influenced by competing events in B-F and these have not been included in the figures. Confidence intervals have been omitted to facilitate visual inspection of the data in B-F.

probability of going into remission in this time interval was: 3/(59 – 9/2) = 0.055 and the probability to proceed to the next 3 months was 1 − 0.055 = 0.945. The cumulative probability to remain in treatment over the first 6 months was 0.985*0.945 = 0.931 and the cumulative probability of going into remission was 1 − 0.931 = 0.069. Probabilities were calculated in the same manner keeping the 11 failures in the denominator over all time intervals yielding an estimated probability of going into remission within 21 months of 0.461.

Table 3
Summary of Outcome in Each Clinic

Clinic	Patients				
	n	Censored	Remission	Withdrawal	Failure
Alingsås	77	44	19	3	11
Amsterdam	98	74	24	0	0
Danderyd	205	40	141	9	15
Huddinge	918	243	490	91	94
Melbourne	76	34	38	1	3
San Diego	54	27	25	1	1
Total	1,428	462	737	105	124

Ethical Considerations and Certification of Clinics

All patients or their parents gave written consent to participate in this study. The Central Ethical Review Board of Stockholm approved these procedures and we were in compliance with the ethical and legal considerations relevant to each country. The Swedish clinics were ISO–9001 and ISO–14001 certified by the Swedish Company for Quality, and they were accredited by the Swedish Board for Accreditation and Conformity Assessment. The clinic in the United States was accredited by the Commission on Accreditation of Rehabilitation Facilities. The Dutch clinic was part of the Academic Medical Center in Amsterdam, which was accredited by Joint Commission International. The Australian clinic was accredited by the Australian Council on Health Care Standards, ISO–9001 certified, and certified as a Day Procedure Centre by the Department of Health of the State of Victoria. Mandometer has been approved as a medical device by the Therapeutic Goods Administration

of Australia and has also been approved for the treatment of eating disorders by the U.S. Food and Drug Administration.

Results

The outcome is described in all patients; an account of the outcome at the different clinics is in the Supplementary Tables.

Remission

We calculated that 75% of the patients went into remission after a median of 12.5 months (quartile range 8–19.5) of treatment (Figure 1A), a competing event prevented 16% of patients from going into remission after a median of 10 months (quartile range 4.5 to 22), that is, the two events took place approximately simultaneously. The other patients remained in treatment.

We accepted into therapy 251 individuals who were severely ill and initially had to be treated as inpatients for a median period of 1.5 months (range 0.1–7): 150 anorexics, 33 bulimics, and 68 patients with an eating disorder not otherwise specified. These severely ill patients and those who had been previously treated unsuccessfully in standard care eating disorder treatment facilities, took longer to go into remission ($p < .001$; Figures 1 B and 1C), but there was no difference between patients who had been treated once previously and those who had been treated several times before (Figure 1C).

Patients with an eating disorder not otherwise specified went into remission first, bulimic patients second, and anorexic patients last ($p < .001$; Figure 1D). The lower the body mass index of anorexic patients at admission, the longer their time to remission ($p < .001$; Figure 1E). Patients were in partial remission after a median of 7 months (quartile range 4–14) of treatment, that is, in about 55% of the time to full remission (Figure 1F). Competing events were neither taken into consideration in the analysis of the effect of body mass index on the time to remission among anorexic patients nor in comparing the time to reach partial and full remission.

Competing Events

Failure of insurers to pay for the therapy interfered early with treatment in the U.S. clinic, resulting in a low rate of remission (Figure 2A). However, psychiatric symptoms (median and range) measured by the Comprehensive Psychopathological Self-Rating Scale (Svanborg & Åsberg, 1994) in those patients still decreased from admission to discharge. In particular, there were improvements in depression: initially 14 (6–24), improved to 8.5 (1.5–24; $p = .01$), anxiety: initially 13.5 (4–26), improved to 9.3 (2.5–26; $p = .023$), and obsession, improved from 13 (5.5–20) to 9 (1–20; $p = .012$) in the 13 patients who were unable to continue treatment due to a lapse in insurance coverage. These patients remained in treatment over a median of only 2 months (range 0.5–7), hence the abrupt increase in a competing event that deprived the patients of the chance of going into remission (Figure 2A). However, the treatment offered in that clinic failed in only one patient. Censoring the data from the patients who were unable to comply because of a competing event unrelated to the treatment resulted in a high rate of remission for the other patients (Figure 2B).

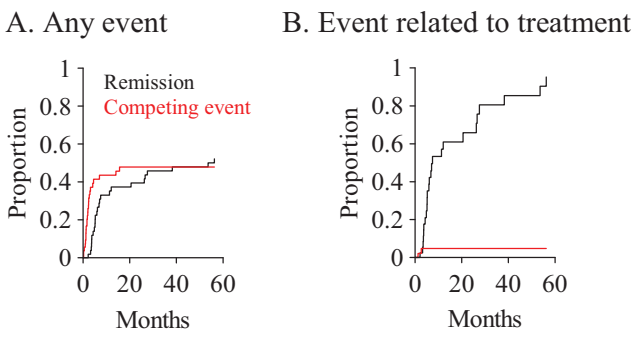

Figure 2. Effect of competing events on remission in 54 patients with an eating disorder treated in San Diego, California. (A) Low rate of remission taking any competing event into consideration. Note the early onset of competing events. (B) High rate of remission taking only competing events related to the treatment into consideration.

Relapse and Recovery

There was an estimated rate of relapse of about 10% (Figure 3A) after a median of 24 months (range 6–60) of follow-up. Moreover, there were no patient deaths during treatment or follow-up. The most common diagnosis at relapse was an eating disorder not otherwise specified (75%). One patient diagnosed with anorexia at admission relapsed into bulimia, but no bulimic patient relapsed into anorexia. At least 80% of those who went into remission came to their follow-up appointments, with anorexic patients more likely to do so than the other patients ($p = .018$; Figure 3B).

Discussion

Treatment of 1,428 patients in multiple sites yielded an estimated 75% rate of remission after an average of 12.5 months of treatment, along with a 10% rate of relapse over 5 years of follow-up, outcomes that are similar to those previously reported in 168 patients who were treated at a single facility (Bergh et al., 2002). Using partial remission as a measure of outcome showed that patients improved within on average 7 months of treatment. None of the patients reported here died either in treatment or during their follow-up, despite the severity of the symptoms in a significant portion of the patients. These data indicate that the Mandometer therapy for eating disorders is not a statistical anomaly, does not depend exclusively on the quality of an individual therapist, or on the quality of an individual clinic, nor does it depend on the treatment of a unique patient population. Although there were differences in outcome among the clinics (see Supplementary file), these may be caused by events that are unrelated to the treatment, such as failure of insurers to pay as noted in the U.S. clinic. Additional competing events, such as failure to offer inpatient treatment to severely ill patients and insufficient resources for training of staff, can detract from the success when a treatment is implemented in a new environment. Competing events vary both nationally and internationally and treatment outcome should therefore be expected to vary. For this reason and because it was neither possible nor desirable to assign patients randomly to the different clinics in this study, statistical analysis of the difference in outcome is not suitable.

This analysis included the treatment of seriously ill patients who would typically not be accepted into most eating disorder facilities for treatment and the results suggest that the therapy also can be

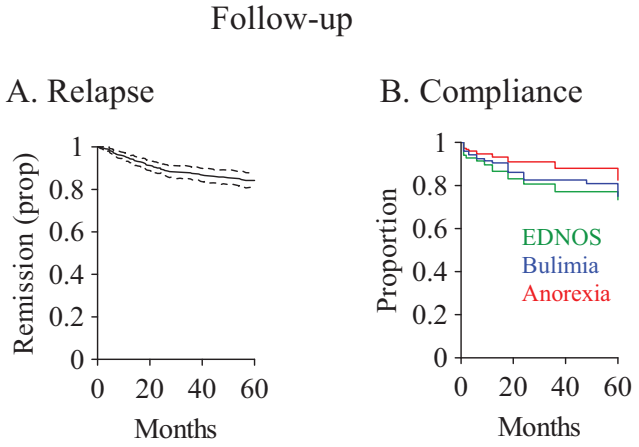

Figure 3. Relapse and compliance over 5 years of follow-up in 737 patients with eating disorders treated to remission. (A) Proportion of patients remaining in remission. 95% confidence intervals (CI) indicated by dotted lines. (B) Proportion of patients coming to follow-up appointments. Three hundred forty-five patients were in remission from an eating disorder not otherwise specified (EDNOS), 125 from bulimia nervosa, and 267 patients were in remission from anorexia nervosa. Confidence intervals have been omitted to facilitate visual inspection of the data.

successful with this population. The low rate of relapse and the high degree of compliance with the follow-up program suggest that a large majority of the patients treated to remission with Mandometer therapy have recovered. It is noteworthy, however, that patients who had been treated for anorexia came to their follow-up appointments more often than the other patients and may need their follow-up visits to prevent relapse.

Recently, Mandometer treatment in the clinic in Amsterdam was compared with a standard of care for anorexia nervosa in a clinic in Utrecht (van Elburg et al., 2012). However, the assignment to treatment groups was not randomized, 14 out of 54 patients dropped out of standard care, and five patients did not fulfill the body weight criterion for anorexia at admission. Thus, 19 (35%) of the patients assigned to the standard care group were either inappropriately included or inappropriately excluded in the analysis. In comparison, only three out of 25 patients (12%), dropped out of Mandometer treatment. And although 76% of the anorexics who entered the trial had already been unsuccessfully treated in standard care, or had failed in the current trial, a surprising 71 to 85% success rate was reported for another round of standard care. This figure is more than twice as high as the previously reported remission rate for the same treatment by the same clinicians (The Netherlands Organization for Health Research & Development, 2013), and is a higher remission rate than any other eating disorders clinic has reported. The outcomes with Mandometer treatment, 63 to 75% success rate, however, were similar to what has been previously reported (Bergh et al., 2002) and to the 64% success rate reported here, using different measures of outcome.

Cause–Effect Relationship Among Eating Disorders and Psychiatric Symptoms

The psychiatric symptoms seen in anorexics have been suggested to be a result of food deprivation, rather than its cause (Bergh et al., 1996; 2002; Bergh & Södersten, 1996; Epling, Pierce, & Stefan, 1983; Södersten et al., 2006a; 2006b, 2008; Zandian et al., 2007). However, anorexia and bulimia are generally thought to be symptoms of a complex psychiatric disorder in which the disordered eating behaviors are a subset of psychiatric symptoms that may include anxiety, obsessions, compulsions, depression, mania, and self-injurious behavior. Due to this the treatments that constitute standard care involve strategies to deal with an underlying complex mental disorder, which if resolved, would eliminate the disordered eating behavior (Kaye et al., 2013).

There is certainly no agreement on how to treat the psychiatric symptoms associated with eating disorders, and in fact, standard psychiatric care for anorexia and bulimia is anything but standardized. Table 4 lists dozens of such treatments currently in use for the treatment of eating disorders. What is remarkable is how their use persists despite their lack of efficacy and we evaluate here the various types of data that address these issues.

The failure of psychotherapy argues against an underlying mental health disorder. The poor long-term remission rate for patients with eating disorders using interventions aimed at treating their psychiatric symptoms (reviewed in the Introduction) suggests that that these symptoms are not the cause of their eating disorder.

The failure of pharmacotherapy argues against an underlying mental health disorder. The failure of psychoactive medication, which may be effective in alleviating psychiatric symptoms in other groups of patients, in treating eating disorders (reviewed in the Introduction), provides additional evidence that psychiatric disease does not cause eating disorders.

The vulnerability of women athletes argues against an underlying mental health disorder. Although women athletes are 10 times more likely than nonathletes to develop eating disorders, they do not have an elevated incidence of psychiatric disorders (Berry & Howe, 2000; Johnson, Powers, & Dick, 1999; Kirk, Kusum, & Hildy, 2001; Martinsen & Sundgot-Borgen, 2013). Rather, these individuals are often in a state of negative energy balance due to their high level of activity and their situation may well mimic that of individuals who are in a similar state due to

Table 4
Various Treatments Used by Different Clinics as Part of What Can Be Considered To Be Standard Care

Group therapy	Contract therapy
Individual therapy	Dialectical behavioral therapy
Drug therapy	Experiential therapy
Spiritual therapy	Music therapy
12-step program	Art therapy
Process therapy	Posttraumatic stress disorder therapy
Food/feelings therapy	Sexual abuse counseling
Psychoeducation	Gestalt therapy
Trauma therapy	Traumatic incident reduction therapy
Family therapy	Thought field therapy
Yoga therapy	Neural-linguistic programming
Body image therapy	Eye movement desensitization and reprocessing
Nutrition education	High risk model of threat perception therapy
Cognitive–behavioral therapy	Intensive structural therapy
Equine therapy	Danger ideation reduction therapy
Dance therapy	Light therapy
Intimacy therapy	Creative therapy

dieting. Their caloric deficit thereby places them at great risk of developing an eating disorder.

Starvation studies argue against an underlying mental health disorder. Starvation of healthy men induces a full complement of mental health symptoms seen in anorexia (Keys, Brozek, Henschel, Mickelsen, & Taylor, 1950). When individuals try to lose weight rapidly by semistarvation, they show the same psychiatric symptoms seen in both men who were being starved and in anorexics (Robinson & Winnik, 1973). Moreover, the return to normal eating patterns obviated their psychiatric symptoms.

Studies of comorbidities argue against an underlying mental health disorder. Kaye, Bulik, Thornton, Barbarich, and Masters (2004) suggested that young women who go on to develop eating disorders previously have had obsessive–compulsive disorder (OCD) that makes them vulnerable to eating disorders. However, only 7% of those individuals in their study who developed anorexia previously had OCD symptoms (Södersten & Bergh, 2006; Södersten et al., 2006a; 2006b; Zandian et al., 2007) and only 11.3% of 815 patients with an anxiety disorder, including OCD, had an eating disorder (Sallet et al., 2010). Further on, when a dimensional (rather than a categorical) approach to determining whether there are relationships between eating disorders and specific symptoms of OCD, panic, depression, and general distress showed a zero-order correlation with anorexia (Wu, 2008). Moreover, the drugs that can treat OCD are ineffective in the treatment of eating disorders (Walsh et al., 2006; Zhu & Walsh, 2002). Some have argued that the persistence of anxiety related disorders after weight gain supports the notion that these symptoms underlie the eating disorders (Kaye et al., 2004), but a more likely explanation is that these individuals have not actually recovered from the disorder.

Gender differences argue against an underlying mental health disorder. Women constitute more than 90% of eating disorder patients (Hoek & van Hoeken, 2003), but teenage males are more likely to have OCD than teenage females (Fireman, Koran, Leventhal, & Jacobson, 2001), and there are no differences in the prevalence of anxiety and anxiety-related disorders in male and female teens (Beesdo, Knappe, & Pine, 2009). Instead, young women respond differently to skipping a meal than young men. When the young men miss dinner, they respond by eating about 30% more during the next day. Young women, on the other hand, eat about 20% less the day after they missed their dinner (Zandian, Ioakimidis, Bergh, Leon, & Södersten, 2011). One can see how a reduction of food intake can lead to a further reduction in food intake, thereby making some women more vulnerable to developing an eating disorder when they engage in dieting.

Studies of the mechanism underlying increased physical activity in those with eating disorders argue against an underlying mental health disorder. Foraging strategies that include increased activity are engaged in humans when food is restricted (McCue, 2012; Noakes & Spedding, 2012), and physical hyperactivity has long been recognized as a symptom of anorexia (Gull, 1874; Södersten et al., 2008). Increased physical activity greatly worsens their physiological status, given that they are also starving. Although this behavior appears to be consistent with a psychiatric disorder involving self-injurious behavior, there is an alternative explanation for this behavior. In particular, when individuals lose body weight, their surface area through which they lose heat is not as affected, but the biomass producing heat is much diminished. Moreover, body metabolism is suppressed in individuals who are restricting their food intake (Speakman & Mitchell, 2011). Patients with eating disorders therefore feel cold continually (Gull, 1874; Luck & Wakeling, 1980, 1982) and a primitive, yet effective method of thermoregulation in such circumstances is increasing physical activity. On the other hand, if one provides warmth to either patients with eating disorders or to rats in an animal model of anorexia, one can prevent the increased physical activity (Bergh et al., 2002; Carrera et al., 2012; Gull, 1874; Gutiérrez, 2013). Rather than being a psychiatric symptom, this behavior can therefore be understood as a normal physiological response to feeling cold and/or displaced foraging for food (Södersten et al., 2008).

Commonalities with the etiology and the treatment of obesity argue against an underlying mental health disorder. Just as anorexia and bulimia are generally thought to be the consequence of a complex mental disorder, obesity is often thought to be a consequence of a character flaw (Brownell et al., 2010). However, obesity appears to have the same etiology as anorexia and bulimia. That is when individuals skip meals, restrict their food intake, or speed through their meals, gut hormones are not available to limit food intake, and consequently, these individuals go on eating (Galhardo et al., 2012). A small portion of those in this situation continue eating only little food slowly. The vast majority, however, simply gains weight. When we normalize food intake patterns for obese individuals in a manner similar to that used to treat anorexics and bulimics, their body weight is significantly reduced, and their health improves (Ford et al., 2010). Moreover, normalizing their eating patterns normalizes the levels of ghrelin and peptide tyrosine tyrosine, the gut hormones associated with the feelings of hunger and satiety (Galhardo et al., 2012).

The success of a therapy in which eating behavior is normalized in patients with eating disorders argues against an underlying mental health disorder. In the initial randomized clinical trial, we found that 88% of the patients went into remission, compared to 7% of the control patients (Bergh et al., 2002). In both the study with 168 patients (Bergh et al., 2002) and the current study with 1,428 patients, the estimated rate of full remission was 75%, with only 10% of the patients relapsing within 5 years and 0% mortality. These outcomes compare favorably with standard care treatments and could be implemented easily in clinics that treat these disorders, much to the benefit of their patients.

A partially successful standard of care. Family therapy has become a standard therapy for anorexia that shares certain aspects with our treatment. In particular, this therapy treats anorexia by coaxing affected individuals to increase their food intake without psychiatric treatment. However, without an effective feedback system during meals, this approach does not improve the outcomes of most individuals with eating disorders, and only affords a small improvement in those few patients who are both very young and very mildly affected (Bergh et al., 2006; Eisler et al., 1997; 2000; Fisher, Hetrick, & Rushford, 2010; Lock & le Grange, 2005; Russell, Szmukler, Dare, & Eisler, 1987). At the same time, those patients do not reach a normal body weight, their psychiatric symptoms typically persist, and they are at an increased risk for developing bulimia (Bergh et al., 2006; Geist, Heinmaa, Stephens, Davis, & Katzman, 2000; Robin et al., 1999). Indeed, there was no difference between the groups after a long-term follow-up, very

much like the long-term outcomes from psychiatric care (Ben Tovim, 2003). Appropriately, the authors of the family therapy study concluded that their results could be "attributed to the natural outcome of the illness" rather than to the therapy (Eisler et al., 1997, p. 1025).

A Framework for Understanding Eating Disorders

When Mandometer treatment was launched 20 years ago, outcome of traditional treatments of eating disorders was poor and it has not improved significantly over the intervening years (see Introduction). A new framework is clearly necessary. As a first step, it is important to understand that: "A framework is not a detailed hypothesis or set of hypotheses; rather, it is a suggested point of view for an attack on a scientific problem" (Crick & Koch, 2003, p. 119). A good scientific framework is one that is reasonably plausible with regard to the available data and is eventually shown to be largely correct (Crick & Koch, 2003). Hence, we suggested that a reduced intake of food activates mesolimbic dopamine neurons, which are engaged in a feeling of "reward," encouraging the patients to continue eating less food. Food deprivation also activates the noradrenergic neurons of the locus coeruleus, which are engaged in attention (Bergh & Södersten, 1996). At the time, a substantial amount of experimental evidence supported this point of view. This allowed us to suggest that anorexia develops because it is initially "rewarding" to eat less food and that it is maintained by conditioning to the situations that originally provided the reward (Bergh & Södersten, 1996). Bulimia nervosa and other eating disorders can be similarly analyzed (Bergh et al., 2002). Although it is unlikely that our framework is correct in all its details, the treatment outcomes using this therapy support it. Moreover, some additional aspects of our framework have been confirmed by recent reports. For example, the dopamine reward system in the brain of anorexics appears to be engaged just as we predicted (Fladung et al., 2010). In addition, the role of noradrenergic projections from the brainstem to the forebrain in conditioning and attention has been further established in experimental animals (Bari & Aston-Jones, 2013; Södersten et al., 2008). It also has postulated that all symptoms are caused by the state of the patient and that they therefore are reversible. The evidence that this is the case is compelling (Södersten et al., 2008). Further on, the neurobiological mechanisms through which disordered eating behavior causes psychiatric symptoms have been outlined (Ioakimidis et al., 2011). Needless to say, however, our framework should be further tested and developed.

The reason for the poor outcomes of standard treatments of eating disorders is because they do not rely on neurobiologically plausible hypotheses (Bergh et al., 2002; Södersten et al., 2006a; 2006b, 2008). However, if one looks to the animal model of restricted food intake, a plausible model for eating disorders emerges. In particular, food restriction of rats increases their physical activity and further reduces their food intake, in a process that escalates to the point that the animals lose control over their body weight and can even die if the experiment is not terminated (Gutiérrez, 2013). This model also has revealed a possible explanation for the failure of pharmacological treatment, by showing that the effect of neural messengers depends on the physiological state. Thus, in the model, the role of neuropeptide tyrosine, and possibly other signaling molecules as well (Adan et al., 2011; Gietzen & Aja, 2012; LeSauter, Hoque, Weintraub, Pfaff, & Silver, 2009), is to increase foraging for food, even at the expense of eating. By contrast, when food is freely available at a low physical cost, the same messengers increase eating. This physiological complexity, and additional "nonhomeostatic" factors (Begg & Woods, 2013), appear to make pharmacological approaches to the treatment of eating disorders ineffective (Ioakimidis et al., 2011; Södersten et al., 2008).

Conclusions

The replication of the previously reported 75% rate of remission in 12.5 months of treatment and the 10% rate of relapse over 5 years of follow-up with 0% mortality in six different clinics in four countries demonstrates that the treatment is robust. Also, the use of a minimum number of exclusion criteria indicates that the treatment can be used in most patients with eating disorders, even seriously affected ones. The strict criteria for remission and the high compliance with both the treatment and the follow-up program may contribute to the favorable outcomes that have been found.

The results reported here suggest that our approach provides an effective method for managing patients with eating disorders. In the future, it would be desirable to minimize the influence of competing events, to perform a cost-effect analysis on this therapy in different countries, and to compare the effect of Mandometer treatment with that of standard care in randomized controlled trials.

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