The Placebo Response in the Treatment of Chronic Fatigue Syndrome: A Systematic Review and Meta-Analysis

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Objective: The placebo response is conventionally asserted to be high in chronic fatigue syndrome (CFS) because of the latter's subjective nature and obscure pathogenesis, but no systematic review of placebo responses has been undertaken. We report such a study. Patient expectation is known to be important in the placebo response. It is also known that CFS patients attending specialist clinics often have strong physical attributions regarding causation and hence skepticism about psychological or psychiatric interventions. If so, the placebo response in CFS may be influenced by the type of intervention according to its perceived rationale. We aimed to estimate the summary placebo response in clinical trials of CFS and to determine whether intervention type influences the placebo response in CFS. **Methods:** We searched Medline, Embase, Cochrane Library, PsychInfo, and the references of the identified articles, and contacted experts for controlled trials (randomized or nonrandomized) of any intervention on CFS patients reporting the placebo response as a clinical improvement in physical or general outcomes. Data were extracted from the articles and validity assessment conducted by one reviewer and checked by a second. Meta-analysis and metaregression were performed. **Results:** The pooled placebo response was 19.6% (95% confidence interval, 15.4–23.7), lower than predicted and lower than in some other medical conditions. The meta-regression revealed that intervention type significantly contributed to the heterogeneity of placebo response ($p = .03$). **Conclusion:** In contrast with the conventional wisdom, the placebo response in CFS is low. Psychological-psychiatric interventions were shown to have a lower placebo response, perhaps linked to patient expectations. **Key words:** chronic fatigue syndrome, placebo response, expectation, systematic review, meta-analysis, meta-regression.

CFS = chronic fatigue syndrome; **CCT** = controlled clinical trial; **CBT** = cognitive-behavioral therapy; **CI** = confidence interval; **GET** = graded exercise therapy.

INTRODUCTION

The placebo has been defined as "any therapeutic procedure which has an effect on a patient, symptom, syndrome or disease, but which is objectively without specific activity for the condition being treated" (1). Similarly, the placebo effect can be described as "any effect attributable to a pill, potion, or procedure, but not to its pharmacodynamic or specific properties" (2). In order to quantify the placebo effect in clinical trials, we used the term *placebo response*, operationally defined as the proportion of responders in a placebo arm.

The placebo response has been classically considered as the rough proportion of one third in many illnesses after the publication of a review article by Henry K. Beecher in 1955 (35.2%) (3). The response rates computed in recent meta-analyses seem to be in a reasonable accordance with this classic one third. A systematic review of the clinical trials for major depression has estimated the placebo response as 29.7% (4). A similar approach to the treatment of duodenal ulcer suggests a healing rate of 44.2% in trials with a frequency of placebo administration four times a day and 36.2% in trials with administration twice a day (5). Other examples are 29.0% in the acute treatment of migraine (6) and 26.8% in the treatment of reflux esophagitis (7).

Several psychological and biological explanations for the placebo effect have been proposed. Two psychological theories have been widely invoked: the classic conditioning theory and the expectation theory (8). The former suggests that the placebo effect is a conditioned response because of repeated associations between a conditioned stimulus (a placebo event such as the color or shape of an active drug) and an unconditioned stimulus (the active element capable of eliciting therapeutic responses) (9–11).

According to the expectation theory, the patient's expectation and belief of a positive result—or negative when we deal with the nocebo phenomenon—triggers the placebo response (12–15). In studies with alcohol or caffeine, subjects experience effects according to what they expect from the substance given (14,16). Expectation is also associated with the nocebo phenomenon, in which patients who expect distressing side effects before taking a medication are more likely to develop them (17). A systematic review confirmed the importance of expectation in the placebo effect and recommended its sensible use in health care (18). Researchers have long argued either for one or for the other theory (11,12). However, it is possible and even more convincing to reconcile both theories: some recent refinements of the Pavlovian theory suggest that what is learned in Pavlovian conditioning is in fact an expectation (19).

Chronic fatigue syndrome (CFS) is characterized by severe physical and mental fatigue. The fatigue cannot be explained by any other medical condition, and the minimum duration required is 6 months (20). This main symptom is usually accompanied by other symptoms such as muscle pain, joint pain, sleep disturbance, impaired memory, mood disturbance, and headache.

Placebos seem to work best in highly subjective symptoms usually lacking identifiable physiologic correlates, in chronic conditions with a fluctuating nature often influenced by patients' selective attention, and in affective disorders (21,22). These symptoms or conditions include chronic pain, fatigue, arthritis, headache, allergies, insomnia, asthma, chronic digestive disorders, depression, and anxiety (21). Almost all the symptoms of CFS described could be categorized in one of the

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listed conditions or symptoms. The fatigue observed in CFS is essentially a subjective and fluctuating symptom lacking objective, physiological abnormalities, ostensibly a perfect soil where placebos may yield an enhanced effect.

It is therefore not surprising that many believe that the placebo effect is unusually high in CFS. For example, in 1997, a draft of clinical practice guidelines, citing several existing studies until that date, suggested "at least 30% to 50% of people with CFS typically demonstrate improvement in the nonspecific (or 'placebo') treatment arm of controlled trials" (23). A number of nonsystematic reviews also report a strong or significant placebo effect based on the results of several controlled trials (24,25). However, there has been no systematic approach to confirming this claim. We hypothesized the placebo response in the treatment of CFS to be higher than or as high as in other medical conditions.

Another aspect of CFS may provide a further window of opportunity into investigating the placebo effect, and more specifically the role of expectation. CFS is a controversial condition, never more so than in the debates about etiology. To put it at its simplest, a large number of sufferers seen in specialist settings or self-help groups have a firm conviction that their illness is of physical origin (26). For the purposes of this article, the accuracy of such beliefs is irrelevant. It is enough to know they exist and are often strongly held. There is an ongoing debate among professionals about whether this perception is accurate, but we do not intend to say who is right here. The other side of the coin is that, in accepting an organic explanation for their condition—which might be viruses, toxins, infections, allergies and so on—some sufferers equally vehemently reject psychological causation and with it psychological treatments. It is this that gives us an opportunity to test the role of expectation in the placebo response. Thus, interventions based on the assumption of physical causality were hypothesized to have a high placebo effect and those based on the psychological assumption a low effect.

METHODS

Search Strategy

The search strategy aimed to retrieve articles describing clinical trials of any intervention for patients with CFS through the major databases from their inception to August 2002. An extensive systematic review on the treatment of CFS including a highly comprehensive search was available, and studies published until July 2000 were taken from this review (27). Consequently, our search was limited to the period between January 2000 and August 2002 using Medline, Embase, Cochrane Library, and PsychInfo. A similar search strategy—containing *chronic fatigue syndrome*, its 17 synonyms, and *fibromyalgia*—was adopted (Appendix I). The search was updated through December 2002 using PubMed. The bibliographies of the identified studies were searched for additional citations and several experts in the field contacted to retrieve unpublished trials.

Study Selection

To be included in this review, articles were required to meet the following criteria.

1. Type of studies: randomized controlled trials and controlled clinical trials (CCTs)—ie, nonrandomized controlled trials—with a placebo arm according to the definition adopted in the introduction (1).

2. Participants: adults and children with a diagnosis of CFS based on any criteria or another syndrome having similar diagnostic criteria such as myalgic encephalomyelitis, chronic fatigue immune deficiency syndrome, or chronic mononucleosis.

3. Interventions: any.

4. Outcomes: physical (eg, fatigue, energy, pain, sleep, and functional status) or general (eg, quality of life, well-being, clinical improvement, and overall symptom measure) outcomes measuring placebo response as a binary variable, eg, "improved or not" and "responded or not." More stringent criteria on outcomes would have compromised the generalizability of the review results.

5. Languages: any.

Data Extraction

Data extraction was focused on the review objectives. The following items were extracted by one reviewer (H.J.C.) and checked by a second (S.W.).

1. Author and year of publication.
2. Study design.
3. Intervention details: content and type.
4. Duration of follow-up: in crossover trials, the actual period of each evaluation was computed rather than the whole duration of the study.
5. Placebo details: content, presentation form, and administration route.
6. Baseline characteristics of placebo arm participants: age, sex, duration of illness, and baseline illness severity or functioning.
7. Diagnostic criteria.
8. Source of participant recruitment.
9. Number of participants in placebo arm.
10. Drop-outs.
11. Outcomes.
12. Criteria of improvement and instruments used to measure it.

We classified the type of intervention according to the study hypothesis: high, medium, and low. Interventions based on infectious or immunological assumptions were hypothesized to have a high placebo response and those based on psychological or psychiatric assumptions a low response. Alternative therapies are also popular in CFS patients, and we therefore hypothesized they also would elicit a positive expectancy among CFS patients, and a high placebo response. Finally, other interventions either with an obscure or neutral theoretical background were hypothesized to have a medium placebo response. The former included galanthamine, sulbutiamine, and oral nicotinamide adenine dinucleotide. The latter included hormones, so-called *neuroendocrinological agents* acting locally on the central nervous system and systemically on the whole body.

When two interventions were tested with a factorial design and consequently there were four arms, the group with the ineffective procedures was selected as the placebo arm. Among the tested interventions, the one expected to elicit a higher placebo response was considered to represent the trial. For example, the trial testing dialyzable leukocyte extract (immunological agent) and cognitive-behavioral therapy (CBT; psychological intervention) simultaneously was considered to be of a high intervention type (28).

Validity Assessment

Validity assessment of the included studies was conducted according to an available guideline (29) but modified given the objectives of this review. The following criteria were adopted: method of randomization; allocation concealment; participant blinding; investigator blinding; baseline comparability of groups; completeness of follow-up; handling of dropouts and intention-to-treat analysis; objectivity of outcome assessment; appropriateness of statistical analysis; sample size calculation; whether the groups were treated identically other than the intervention of interest; and description of placebo type, placebo group, and placebo response. The scoring was 0 for not stated or poor, 1 for adequate, and 2 for good. Participant and investigator blinding was scored as 0 for not stated or no and 1 for yes. In this way, the highest possible score for each study was 22 points. For a CCT, the first two criteria were substituted by appropriateness of control and control for confounding because there was no randomization.

Data Synthesis

All statistical procedures were performed using Stata (Stata Corp., College Station, TX) (30). First, for each study, we calculated the placebo response by dividing the number of placebo responders by the number of participants assigned to the placebo arm (rather than the number of study completers). If outcome data were provided only on study completers, we assumed that noncompleters had not responded. In order to obtain a pooled placebo response in the treatment of CFS, a meta-analysis was conducted using a random effects model because of the study result heterogeneity. According to the study hypothesis, a preplanned subgroup analysis by intervention type was conducted (31). Subsequently, meta-regression was performed to investigate further the potential sources of heterogeneity, specifying the method for estimating the between-study variance as restricted maximum likelihood (32).

In the meta-regression, the dependent variable was the rate of placebo response. The independent variables were the characteristics of each trial defined before the data extraction. They were either categorical or continuous variables: intervention type (low, medium, or high), placebo type (behavioral, oral, or injected), double-blindness (yes or no), participants' mean age, proportion of women, sample size, follow-up duration, publication year, illness duration at baseline, and validity score. Intervention type and placebo type were tested as ordered categories. The rationale to assume an order is self-evident for the former. For the latter, we assumed the described order because usually the more invasive the route of placebo administration, the greater the placebo effect (5). Strictness of criteria for placebo response, a binary variable (strict or loose), was added to this list after the data extraction because of the perceived heterogeneity of measurement systems (Table 1), indicating more caution in the categorization procedure and interpretation of the results. When a trial had set a more elaborate criterion to designate the response, eg, an increase of 10 points or more in the Karnofsky scale rather than improved or much improved, it was categorized as strict. Separate regressions were conducted for each independent variable. We calculated coefficients that reflect the percent increase in placebo response for each unit increase of the independent variable and the 95% confidence interval (CI) for the coefficient. The *p*-values for continuous and ordered categorical variables are from tests for trend, which are more powerful than a test of global heterogeneity (31). The assumptions for the regression models—normal distribution of residuals and homoscedasticity—were tested with residual versus fitted plots and the Cook-Weisberg test. Publication bias was not assessed because of the limited meaning of this procedure, because researchers do not depend on the magnitude of placebo response to publish their studies or not.

RESULTS

The search for 2000 to 2002 yielded 782 references, out of which 28 were initially selected, checking their abstracts for the predetermined relevance criteria (33–60). Studies dealing only with fibromyalgia were excluded. Four unpublished studies (61–64) were identified by contacting several experts in the field of CFS. All of them came to be published later on. Among 28 references of the new search, 6 (33–38) had already been included in the review by Whiting et al. (27). Consequently, the initial selection included 22 from the new search (39–60), 4 from CFS experts (61–64), 1 from the update using PubMed (65), and 45 from the review by Whiting et al. (28,33–38,66–103), yielding 72 in total. Out of these 72

TABLE 1. Summary of 29 Trials Included

Author (Reference) and Intervention	Intervention Type and Follow-Up in Weeks	Placebo Type	*N* of Participants (Dropouts)	Placebo Response in % (95% CI)	Instrument and Strictness of Response Criteria	Validity
Deale 1997 (72) CBT	Low 26	Behavioral	30 (4)	16.7 (3.3 to 30.0)	SF-36 physical functioning Strict	20
Fulcher 1997 (77) GET	Low 12	Behavioral	33 (1)	27.3 (12.1 to 42.5)	CGI Loose	18
Hickie 2000 (34) Moclobemide	Low 6	Oral	43 (6)	32.6 (18.6 to 46.6)	Self-reported improvement Loose	21
Powell 2001 (35) GET	Low 52	Behavioral	34 (2)	5.9 (−2.0 to 13.8)	SF-36 physical functioning Strict	19
Prins 2001(36) CBT	Low 61	Behavioral	94 (33)	8.5 (2.9 to 14.1)	CIS fatigue Strict	18
Sharpe 1996 (93) CBT	Low 52	Behavioral	30 (0)	23.3 (8.2 to 38.5)	Karnofsky Scale Strict	17
Vercoulen 1996 (100) Fluoxetine	Low 12	Oral	53 (2)	9.4 (1.6 to 17.3)	Self-reported improvement Loose	14
Wearden 1998 (103) Fluoxetine + GET	Low 26	Oral	34 (5)	5.9 (−2.0 to 13.8)	Chalder Fatigue Questionnaire Strict	19
Blacker 2002 (61) Galanthamine	Medium 16	Oral	82 (22)	16.5 (8.5 to 24.5)	CGI Loose	19
Cleare 1999 (70) Hydrocortisone	Medium 4	Oral	32 (0)	6.3 (−2.1 to 14.6)	CGI Loose	20
Forsyth 1999 (75) Oral NADH	Medium 4	Oral	26 (2)	7.7 (−2.6 to 17.9)	Symptom scoring system Strict	14
McKenzie 1998 (83) Hydrocortisone	Medium 12	Oral	38 (3)	50.0 (34.1 to 65.9)	Wellness Scale Loose	16
Rowe 2001 (38) Fludrocortisone	Medium 11	Oral	50 (8)	10.0 (1.7 to 18.3)	Wellness Scale Strict	20
Andersson 1998 (66) Staphylococcus toxoid	High 12	Injected	14 (3)	21.4 (−0.1 to 42.9)	CGI Loose	10

TABLE 1. *Continued*

Author (Reference) and Intervention	Intervention Type and Follow-Up in Weeks	Placebo Type	*N* of Participants (Dropouts)	Placebo Response in % (95% CI)	Instrument and Strictness of Response Criteria	Validity
Awdry 1996 (67)	High	Oral	32 (1)	15.6 (3.0 to 28.2)	Self-rated symptom charts	8
Homeopathy	52				Loose	
Behan 1990 (68)	High	Oral	24 (0)	16.7 (1.8 to 31.6)	Improvement evaluated by doctor	18
Essential fatty acid	13				Loose	
Brouwers 2002 (62)	High	Oral	26 (1)	15.4 (1.5 to 29.3)	Self reported improvement	20
Polynutrient	12				Loose	
Cox 1991 (71)	High	Injected	17 (0)	17.6 (−0.5 to 35.8)	Self-reported improvement	17
Magnesium	7				Loose	
DuBois 1986 (73)	High	Injected	19	31.6 (10.7 to 52.5)	Self-rated improvement	12
Gamma-globulin	9				Loose	
Lloyd 1990 (80)	High	Injected	26 (0)	11.5 (−0.7 to 23.8)	Symptom severity and functioning by doctor	14
Immunoglobulin	26				Strict	
Lloyd 1993 (28)	High	Injected	23 (1)	30.4 (11.6 to 49.2)	Symptom and functional status scales	14
DLE + CBT	30				Strict	
Ockerman 2000 (49)	High	Oral	22 (0)	22.7 (5.2 to 40.2)	Self-rated improvement	13
Pollen extract	13				Loose	
Rowe 1997 (90)	High	Injected	35 (1)	42.9 (26.5 to 59.3)	Functional score assessed by doctor	18
Gamma-globulin	26				Strict	
Stewart 1987 (96)	High	Oral	12 (2)	16.7 (−4.4 to 37.8)	Self-rated tiredness	7
Supplements	3				Loose	
Strauss 1988 (97)	High	Injected + oral	27 (3)	37.0 (18.8 to 55.3)	Wellness Scale	17
Acyclovir	5				Loose	
Teitelbaum 2001 (56)	High	Oral	34 (2)	35.3 (19.2 to 51.4)	Self-reported improvement	17
Multidrug and supplement	14				Loose	
Warren 1999 (102)	High	Oral	26 (5)	46.2 (27.0 to 65.3)	Self-observation of improvement	17
Essential fatty acid	13				Loose	
Weatherly-Jones 2002 (64)	High	Oral	50 (7)	24.0 (12.2 to 35.8)	Multidimensional Fatigue Inventory	19
Homeopathy	30				Strict	
Zachrisson 2002 (65)	High	Injected	50 (1)	18.0 (7.4 to 28.7)	CGI	19
Staphylococcus toxoid	26				Loose	
Pooled result				19.6 (15.4 to 23.7)		

CGI = Clinical Global Impressions; CIS = Checklist Individual Strength; DLE = dialyzable leukocyte extract, NADH = nicotinamide adenine dinucleotide; SF-36 = 36-item Medical Outcomes Study Short-Form.

studies, 29 met all the inclusion criteria (28,34–36,38,49,56,61,62, 64–68,70–73,75,77,80,83,90,93,96,97,100,102,103).

The characteristics of the included trials are shown in Table 1, and more details are shown in Appendix II. Only one was a CCT (66). Out of 28 randomized controlled trials, 6 had a crossover design (49,70,73,75,96,97). In only two trials were the participants recruited from primary care (71,61). Six trials did not provide information on setting (49,68,73,80,83,96), but four of these recruited patients with poor baseline functioning or relatively severe illness (49,68,80,83), and one of them included only the patients with chronic mononucleosis syndrome (73). The others recruited the participants from secondary care, tertiary care, patient organizations, or advertisements. Very few trials accurately recorded patient attributions, but the sample source suggested they were typical of specialist samples—they were actually from specialist clinics, had poor baseline functioning or had a specific label denoting a physical cause—and were likely to have in general a bias toward physical attributions.

Eight trials had interventions related to a low placebo effect (34–36,72,77,93,100,103), 5 had medium effect interventions (38,61,70,75,83), and 16 had high effect interventions (28,49,56,62,64–68,71,73,80,90,96,97,102). Five had used behavioral placebos such as relaxation or standardized medical care and hence were not double-blind (35,36,72,77,93), 16 had oral placebo (34,38,49,56,61,62,64,67,68,70,75,83,96,100,102,103), and 8 had injected placebo (28,65,66,71,73,80,90,97). The total number of placebo arm participants was 1016 (median = 32; range = 12–94). Among the participants with known gender—only 27 trials provided the data—70.3% were female. The pro-

portion of women in each trial ranged between 49.0% and 100%. Placebo response in each trial ranged between 5.9% and 50.0%. The weighted mean age of participants in 27 trials with the data available was 38.3 years. The weighted mean duration of illness in 26 trials with the data available was 61.6 months. The median of follow-up duration was 13 weeks (range = 3–61). The publication year varied from 1986 to 2004. Information about baseline illness severity or functioning was available in 22 trials (28,34–36,38,56,62,64–67,70–72,75,77,90,93,97,100,102,103), but the modes of reporting varied substantially across trials (Appendix 2). For this reason, this component of the trials could not be investigated further for heterogeneity. Overall, baseline functioning was poor, with the proportion of patients on sick leave or illness benefits ranging from 8% to 67%.

Many trials had more than two categories—eg, much improved, improved, unchanged, worse, or much worse—but all of them ended up categorizing the subjects into response or no response, and almost all of them reported only the data concerning the binary division. As the initial selection criteria, the outcome was computed only as binary. Twenty-two trials presented general outcomes (28,34,38,49,56,61,62,65–68,70,71,73,75,77, 80,83,96,97,100,102) and seven trials physical outcomes (35,36,64,72,90,93,103). Study validity varied across the included trials. With 22 the maximum score, the validity ranged between 7 and 21 (median = 17).

Meta-analysis using a random effects model showed the pooled placebo response of 19.6% (95% CI, 15.4–23.7). The test for heterogeneity was highly significant ($p < .001$). Subgroup analysis by intervention type revealed some reduction of the heterogeneity, especially in the high effect intervention category ($p = .05$; Table 2). However, heterogeneity remained significant in all categories. The subgroup analysis also revealed a trend of increased placebo response across the subgroups. Low effect group and medium effect group had a placebo response of 14.0% (95% CI, 8.0% to 19.9%) and 16.5% (5.7% to 27.4%), respectively. As expected, the high effect group presented the highest placebo response (24.0%, 18.9% to 29.1%). Meta-regression produced the following equation:

$$\text{Mean placebo response} = 0.137 + 0.050 \times \text{Intervention type}$$

(Intervention type was 0 = low, 1 = medium or 2 = high)

The coefficient of 0.050 (95% CI, 0.003–0.097) means there was an average increase of 5.0% in placebo response moving from one category to the next. Intervention type was significantly contributing to the heterogeneity of placebo response ($p = .03$). We conducted meta-regression for the other potential sources of heterogeneity (Table 3). Strictness of criteria revealed a marginally significant contribution to heterogeneity ($p = .08$), but none of the remaining variables did. Regression diagnostics revealed that the assumptions of regression models were met sufficiently.

CONCLUSION

In contrast with the initial hypothesis, the pooled placebo response was substantially lower than the usually reported one third response in other medical conditions. Among the potential sources of heterogeneity we investigated, only the intervention type had a statistically significant contribution to the heterogeneity of placebo response across the trials ($p = .03$). The second hypothesis was confirmed. Psychological-psychiatric interventions were shown to have a low placebo response, whereas neutral interventions had a medium placebo response. Finally, infectious-immunological and alternative-complementary interventions were shown to have a high placebo response.

This is the first systematic review on the placebo response in the treatment of CFS. It included 29 trials of a variety of interventions in CFS with a wide range of trial level characteristics. The review was hypothesis-driven rather than purely descriptive.

The major limitation of the review was the heterogeneity of the outcome measurement systems across the trials. Different scales and instruments were used to define and measure the endpoint, clinical improvement. Because of this concern, we categorized the trials according to the strictness of response criteria and investigated its contribution to the heterogeneity. The meta-regression showed a marginal effect for strictness of response criteria ($p = .08$), with studies with very strict criteria having lower placebo response rates. Given this observation, one might also expect an association between study validity and placebo response, which was, however, clearly nonsignificant ($p = .77$). Unfortunately, it is not clear whether this nonsignificance is actually caused by the nonassociation or the widely commented limitations of the validity assessment (104). Five trials were not double-blind, which may have led to bias in the assessment of response, but the meta-regression showed that this did not contribute to heterogeneity ($p = .31$).

Another possible limitation which could be pointed out is the meaningfulness of a pooled result from a meta-analysis with high heterogeneity. We did not intend to produce a summary placebo response for clinical purposes, but instead a

TABLE 2. Subgroup Analysis by Intervention Type

	Pooled Placebo Response*	95% CI	Test for Heterogeneity	Risk Ratio
Low ($N = 8$)	14.0%	8.0 to 19.9	p=.004	1
Medium ($N = 5$)	16.5%	5.7 to 27.4	p<.001	1.18
High ($N = 16$)	24.0%	18.9 to 29.1	p=.05	1.71

* Using random effects model.

TABLE 3. Metaregression With Placebo Response as Dependent Variable

Independent Variable	*N* of Studies With Data	Unit of Increase	Coefficient in %	95% CI in %	*p*-Value
Intervention type	29	1 category (out of 3)	5.0	0.3 to 9.7	.03
Placebo type	29	1 category (out of 3)	5.3	−1.3 to 11.9	.12
Double-blindness	29	1 category (out of 2)	5.9	−5.4 to 17.1	.31
Strictness of response criteria*	29	1 category (out of 2)	7.6	−1.0 to 16.2	.08
Mean age	27	1 yr	−0.2	−1.0 to 0.6	.67
Proportion of women	27	1%	0.2	−0.1 to 0.6	.27
Sample size	29	1 person	−0.1	−0.3 to 0.1	.24
Follow-up duration	29	1 wk	−0.2	−0.4 to 0.1	.22
Publication year	29	1 yr	−0.4	−1.4 to 0.6	.40
Illness duration	26	1 mo	−0.01	−0.2 to 0.1	.88
Validity	29	1 point	−0.2	−1.5 to 1.1	.77

* Previously unplanned analysis.

comparison with pooled placebo responses from the other meta-analyses also with high heterogeneity. This comparison of like with like enabled us to conclude that contrary to the received wisdom, the summary placebo response in CFS was actually lower compared with the comparison disorders. In this sense, the result of this meta-analysis seems to be meaningful.

Finally, caution is needed to interpret the findings, because a relatively large number of regression parameters were estimated against a small number of observations ($N = 29$). This means that the parameters we estimated are imprecise. Had the power of this study been higher, the independent variables with a marginal effect size such as strictness of response criteria and placebo type could have been significant predictors. However, this limitation does not seem to invalidate the meaningfulness of the significant association of intervention type, the main exposure variable of the meta-regression.

Why might the placebo response have been lower than expected in CFS compared with other medical conditions? First, the low placebo response could be a result of low expectation of CFS patients in relation to the interventions in general, because CFS is widely understood to be difficult to treat (27). Our finding that the type of intervention had an effect on placebo response concords with this explanation—the treatments we anticipated would lead to the lowest expectations of recovery in sufferers also had the lowest placebo responses. Second, the frequently observed lack of a shared belief system between CFS patients and medical professionals could be an explanation for the finding. The therapeutic relationship between patients and clinicians seems to be one of the determinants of the placebo effect (105). In clinical practice, these differences over attribution and illness models, so frequently observed between medical specialists and CFS patients, can impede the development of a collaborative therapeutic relationship, and this difficulty may extend to clinical trials, lowering the placebo response. Finally, the low placebo response could relate to the natural history of CFS. By definition, it is a chronic condition with duration of at least 6 months. Many of the sufferers entered into trials have illnesses that have lasted many years, and the disorder has a poor prognosis. Researchers have suggested that the response rate in the placebo arm of a clinical trial—*placebo response* as operationally defined—may include not only the pure placebo effect but also the other components such as spontaneous improvement, regression to the mean, measurement bias, and unidentified parallel interventions (106,107). A controversial meta-analysis of the trials comparing placebo with no treatment—an attempt to distinguish the placebo effect from the other components—has found little evidence that placebos had powerful clinical effects, and this seems to accord with the thesis (108). Given this context, our finding may be partly explained by the low rate of spontaneous remission in CFS.

As mentioned, CFS patients in specialist settings frequently have strong physical attributions and are skeptical about psychological and psychiatric treatments. Concurrently, expectation is the key component of the placebo effect. The present review provides some evidence to link these two established research findings. Psychological-psychiatric interventions showed a lower placebo response, possibly because of patients' lower expectations.

At the clinical practice level, the finding of the overall low placebo response emphasizes the need to enhance the nonspecific effects in the current treatment of CFS. Contextual factors such as a collaborative therapeutic relationship should be maximized in the management of CFS, hence increasing the overall effect of an active treatment, which consists of an active component and a nonspecific component—the placebo effect. The role of contextual factors may be even more critical for CBT, graded exercise therapy (GET), and antidepressants, because at least CBT and GET are validated treatments for CFS (27) and antidepressants effective for comorbid depression in both physical and psychological disorders (109). It is of course both intriguing and paradoxical to note the disconnection between expectations of improvement and the actual effectiveness of interventions such as CBT and GET—an area worthy of closer study, perhaps using observation methods. Whatever explanation is favored, the clinical implication is the need to provide existing evidence supportive of CBT and GET in a language accessible to patients, and if antidepressants are to be used, to make it clear that this is a treatment for depression rather than CFS itself. These strate-

gies may assist in eliciting positive expectations in patients and hence improving outcomes.

APPENDIX I. Search Strategy

1. exp Chronic Fatigue Syndrome/ or chronic fatigue syndrome.mp.
2. exp NEURASTHENIA/ or neurasthenia.mp.
3. exp FIBROMYALGIA/ or fibromyalgia.mp.
4. myalgic encephalomyelitis.mp.
5. akureyri disease.mp.
6. chronic epstein barr virus.mp.
7. cfids.mp.
8. (chronic fatigue and immune dysfunction syndrome).mp.
9. chronic mononucleosis.mp.
10. chronic mononucleosis like syndrome.mp.
11. chronic mononucleosis syndrome.mp.
12. chronic mononucleosis-like syndrome.mp.
13. effort syndrome.mp.
14. iceland$ disease.mp.
15. low natural killer cell syndrome.mp.
16. neuromyasthenia.mp.
17. post viral fatigue syndrome.mp.
18. postviral fatigue syndrome.mp.
19. post-viral fatigue syndrome.mp.
20. post viral syndrome.mp.
21. postviral syndrome.mp.
22. exp Postviral Fatigue Syndrome/
23. post-viral syndrome.mp.
24. post infectious fatigue.mp.
25. postinfectious fatigue.mp.
26. post-infectious fatigue.mp.
27. chronic postviral fatigue syndrome.mp.
28. chronic post viral fatigue syndrome.mp.
29. chronic post-viral fatigue syndrome.mp.
30. raggedy ann$ syndrome.mp.
31. raggedy anne.mp.
32. royal free disease$.mp.
33. royal free epidemic$.mp.
34. royal free hospital disease$.mp.
35. tapanui disease$.mp.
36. yuppie flu.mp.
37. yuppy flu.mp.
38. chronic infectious mononucleosis like syndrome.mp.
39. chronic infectious mononucleosis-like syndrome.mp.
40. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41. exp Randomized Controlled Trial/ or randomized controlled trial.mp.
42. randomised controlled trial.mp.
43. exp Controlled Study/ or controlled trial.mp.
44. controlled clinical trial.mp.
45. exp Clinical Trial/ or clinical trial.mp.
46. random$.mp.
47. ((doubl$ or singl$) and blind$).mp.
48. crossover.mp.
49. clin$ trial$.mp.
50. (control$ and (trial$ or stud$)).mp.
51. ((singl$ or doubl$ or tripl$ or trebl$) and (blind$ or mask$)).mp.
52. placebo$.mp.
53. exp Methodology/ or research design.mp.
54. exp Comparative Study/ or comparative study.mp.
55. 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54
56. 40 and 55

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APPENDIX 2. Data Extraction Table[a]

Author and Year	Intervention (Type and Content)	Follow-Up in Weeks	Placebo (Content, Route)	Participants Details (Age, Sex, Illness Duration)	Baseline Illness Severity or Functioning	Source of Participant Recruitment	Diagnostic Criteria	Number of Placebo Recipients (Dropouts)	Clinical Improvement (%)	Instrument Measuring Improvement	Strictness of Instrument	Validity Score
Deale 1997 RCT	LOW CBT	26	Relaxation sessions Behavioral	38 ± 11 20 F, 10 M 4.6 ± 3.3 yr	CFQ mean fatigue score 19.5 ± 2.6, WSAS mean score 6.1 ± 1.4, 23 (77%) unemployed, 20 (67%) on disability benefit	Specialist CFS clinics	Oxford	30 (4)	5 (16.7)	Increase ≥50 or an end score ≥83 in SF-36 physical functioning scale	Strict	20
Fulcher 1997 RCT	LOW GET	12	Flexibility training Behavioral	*37.2 ± 10.7* *49 F, 17 M* *2.7 y*	CFQ mean fatigue score 30.5 ± 5.6	Chronic fatigue clinic in a general hospital department of psychiatry	Oxford	33 (1)	9 (27.3)	Much or very much improved in self-rated CGI	Loose	18
Hickie 2000 RCT	LOW Moclobemide	6	Tablet Oral	44.9 ± 12.8 24 F, 19 M 90.9 ± 74.0 wk	Karnofsky mean score 75.9 ± 4.5	Infectious diseases and immunology outpatient clinics in university hospital	Australia	43 (6)	14 (32.6)	Improvement in self-rated global outcome scale	Loose	21
Powell 2001 RCT	LOW GET	52	Standardized medical care Behavioral	34 ± 10.5 24 F, 10 M 48.6 ± 38.5 mo	11 (32%) working, 15 (44%) on disability benefit	Specialist CFS clinic and infectious diseases clinic	Oxford	34 (2)	2 (5.9)	Increase ≥10 or an end score ≥25 in SF-36 physical functioning scale	Strict	19
Prins 2001 RCT	LOW CBT	61	Participation in support group Behavioral	37.1 ± 10.6 6.6 ± 6.4 yr 71 F, 19 M	Karnofsky mean score 71.2 ± 7.5, 16 (18%) generally passive in activity pattern	Outpatient clinics of internal medicine in university hospitals	CDC 1994	94 (33)	8 (8.5)	Score change >1.64 and an end score <36 in CIS fatigue	Strict	18
Sharpe 1996 RCT	LOW CBT	52	Medical care Behavioral	38 ± 11.8 23 F, 7 M 29.7 ± 24.1 mo	15 (50%) not working, mean fatigue severity 7.9 ± 1.9 (0–10 scale) 7.9 ± 1.9 (0–10 scale)	Hospital infectious diseases outpatient clinic	Oxford	30 (0)	7 (23.3)	Improvement from baseline ≥10 points in Karnofsky scale	Strict	17
Vercoulen 1996 RCT	LOW Fluoxetine	12	Capsule Oral	38.1 37 F, 14 M 6 yr	11 (22%) working, 2 (4%) unemployed, 24 (47%) on disablement benefit or sick leave	Department of General Internal Medicine of the University Medical Center Nijmegen	Oxford	53 (2)	5 (9.4)	Self-reported change as recovered, improved, unchanged or worse	Loose	14
Wearden 1998 RCT	LOW Fluoxetine + GET	26	Capsule Oral	37.6 ± 10.7 21 F, 13 M 22.0 ± 36.8 mo	28 (82%) changed occupation and 7 (21%) members of self-help group	University department of medicine outpatient clinic	Oxford	34 (5)	2 (5.9)	Below case level on CFQ	Strict	19
Blacker 2004 RCT	MEDIUM Galanthamine	16	Tablet Oral	37.6 ± 9.76 51 F, 31 M	NS	Primary and tertiary care	CDC 1994	82 (22)	16.5% (≅14 patients)	Much or very much improved in CGI by doctor	Loose	19

Author and Year	Intervention (Type and Content)	Follow-Up in Weeks	Placebo (Content, Route)	Participants Details (Age, Sex, Illness Duration)	Baseline Illness Severity or Functioning	Source of Participant Recruitment	Diagnostic Criteria	Number of Placebo Recipients (Dropouts)	Clinical Improvement (%)	Instrument Measuring Improvement	Strictness of Instrument	Validity Score
Cleare 1999 RCT crossover	MEDIUM Hydrocortisone	4	Opaque white capsules Oral	35.3 20 F, 12 M 36 mo	CFQ mean fatigue score 25.1 (23.7–26.5), WSAS mean score 5.1	Specialist CFS clinics	Oxford and CDC 1994	32 (0)	2 (6.3)	Much or very much improved in CGI by doctor	Loose	20
Forsyth 1999 RCT crossover	MEDIUM Oral NADH	4	Tablet Oral	39.6 17 F, 9 M 7.2 yr	NS	Referred by a variety of physicians, self-referred or from Division of Allergy-Immunology	CDC 1994	26 (2)	2 (7.7)	10% improvement in symptom scoring system developed by authors	Strict	14
McKenzie 1998 RCT	MEDIUM Hydrocortisone	12	Tablet Oral	38.3 ± 7.5 27 F, 8 M 59.9 ± 31.7 mo	24 (69%) able to work only part-time or not at all	NS	CDC 1988	38 (3)	19 (50.0)	Improvement in mean wellness scores	Loose	16
Rowe 2001 RCT	MEDIUM Fludrocortisone	11	Capsule Oral	37.3 ± 9.3 33 F, 17 M 6.0 ± 4.9 yr	Mean percentage functional score 25.9 ± 20.5%	Registry of participants in other CFS studies at NIH and advertisement	CDC 1994	50 (8)	5 (10.0)	At least 15-point improvement in wellness score	Strict	20
Andersson 1998 CCT	HIGH Staphylococcus toxoid	12	Sterile water injection Subcutaneous	47.0 ± 7.3 14 F, 0 M 12.9 yr	*18 (75%) moderately ill, 5 (21%) markedly, 1 (4%) severely ill by CGI*	Care centers, other hospitals and psychiatric units	CDC 1994	14 (3)	3 (21.4)	Improvement in CGI by doctor	Loose	10
Awdry 1996 RCT	HIGH Homeopathy	52	Inert powder or tablet Oral	41.1 21 F, 10 M 5.3 yr	10 (31%) working, 12 (38%) unemployed, 7 (22%) on sick leave	Volunteers having read about trial in literature produced by Action for ME and the ME association	Oxford	32 (1)	5 (15.6)	Improved in self-rating charts of fatigue, disability, mood disturbance, myalgia and sleep disturbance	Loose	8
Behan 1990 RCT	HIGH Essential fatty acid	13	Capsule with linoleic acid in liquid paraffin Oral	*40.0* *36 F, 27 M* *1–3 yr*	Illness severity expressed in mean total score of symptoms 1.8 (0–3 scale)	NS (all cases were severe and followed a definite viral infection)	NS	24 (0)	4 (16.7)	Overall condition evaluated by doctor as improved, unchanged or worse	Loose	18
Brouwers 2002 RCT	HIGH Polynutrient with high antioxidative capacity	12	125-ml packages Oral	38.9 ± 10.9 17 F, 9 M 4.5 yr	NS	Department of General Internal Medicine of the University Medical Center Nijmegen	CDC 1994	26 (1)	4 (15.4)	Self reported improvement as recovered, improved, unchanged or worse	Loose	20
Cox 1991 RCT	HIGH Magnesium	7	Injectable water Intramuscular	37.1 12 F, 5 M 6–18 mo	Mean NHP score 261.1 ± 91.6	Referred by general practitioners	CDC 1988	17 (0)	3 (17.6)	Self-report of benefit from treatment	Loose	17
DuBois 1986	HIGH	9	Bacteriostatic water	NS	Included patients with chronic mononucleosis syndrome	NS	NS	19 (?)	32% of 63 injections (≅6 patients)	Self-rating yes/no question	Loose	12

Author and Year	Intervention (Type and Content)	Follow-Up in Weeks	Placebo (Content, Route)	Participants Details (Age, Sex, Illness Duration)	Baseline Illness Severity or Functioning	Source of Participant Recruitment	Diagnostic Criteria	Number of Placebo Recipients (Dropouts)	Clinical Improvement (%)	Instrument Measuring Improvement	Strictness of Instrument	Validity Score
RCT crossover Lloyd 1990 RCT	Gamma-globulin HIGH Immunoglobulin	26	Intramuscular 10% w/v maltose Intravenous	33 ± 12 11 F, 15 M 61 ± 43 mo	QAL mean score 41 ± 1.6 Overall, the participants' baseline functioning was poor	NS	Similar to CDC 1988	26 (0)	3 (11.5)	"Response" from doctor assessment defined by major reduction in symptom severity and functional improvement	Strict	14
Lloyd 1993 RCT	HIGH DLE + CBT	30	Lyophilized normal saline TcIntramuscular	*39.6 ± 12.3* *68 F, 22 M* *5.5 yr*	Karnofsky mean score 70.5	Only "outpatient" stated	Australia	23 (1)	Up to ⅓ (≅7 patients)	Greater than 1 SD of improvement in the assessments of physical and psychological status	Strict	14
Ockerman 2000 RCT crossover	HIGH Pollen extract	13	Tablet Oral	50 19 F, 3 M NS	Mean fatigue score 7.14 (0–10 scale), only relatively serious cases included	NS	CDC 1994	22 (0) One dropped out after a placebo period.	5 (22.7)	Self-rated total well-being as worse, no change or better	Loose	13
Rowe 1997 RCT	HIGH Gamma-globulin	26	1% albumin in 10% w/v maltose solution intravenous	15.6 ± 2.0 28 F, 7 M 16.9 ± 11.4 mo	53% working, 8% on disability	Royal Children's Hospital, Melbourne	CDC 1994	35 (1)	15 (42.9)	Improvement ≥25% in mean functional score assessed by doctor	Strict	18
Stewart 1987 RCT crossover	HIGH Supplements	3	Capsule Oral	NS NS 7 yr	NS	NS	NS (patients had ME)	12 (2)	2 (16.7)	One had 36% and the other 17% decrease in self-rated tiredness	Loose	7
Strauss 1988 RCT crossover	HIGH Acyclovir	5	Intravenous solution for 7 days + tablet for 30 days	34.1 ± 1.5 19 F, 8 M 6.8 ± 1.4 yr	12 (44%) disabled, 10 (37%) working part time	NIH	CDC 1988	27 (3)	10 (37.0)	Feeling better according to wellness score	Loose	17
Teitelbaum 2001 RCT	HIGH Multidrug and supplement therapy	14	Stated only appearance was identical to medication Oral	46.7 ± 9.2 31 F, 3 M 9.7 ± 7.8 yr	Well-being score by 5 VAS 177.1 ± 57.6 (each scaled 0–100)	By word of mouth, patient support groups and media	CDC 1994	34 (2)	12 (35.3)	Patients were asked whether they felt much worse, worse, same, better or much better	Loose	17
Warren 1999	HIGH	13	Capsule	*37.1 ± 11.9*	NS	Regional infectious diseases unit	Oxford	26 (5)	12 (46.2)	Patients' own observation of response to treatment	Loose	17

Author and Year	Intervention (Type and Content)	Follow-Up in Weeks	Placebo (Content, Route)	Participants Details (Age, Sex, Illness Duration)	Baseline Illness Severity or Functioning	Source of Participant Recruitment	Diagnostic Criteria	Number of Placebo Recipients (Dropouts)	Clinical Improvement (%)	Instrument Measuring Improvement	Strictness of Instrument	Validity Score
RCT	Essential fatty acid		Oral	*29 F, 21 M* *4.0 ± 2.7 yr*								
Weatherley-Jones 2002	HIGH	30	Tablet	38.8 ± 11.2	Severe, disabling fatigue that substantially impaired functioning	Fatigue clinic and infectious diseases clinic	Oxford	50 (7)	12 (24.0)	Improvement ≥3 points in general fatigue of Multidimensional Fatigue Inventory	Strict	19
RCT2002	Homeopathy		Oral	31 F, 19 M 3.7 ± 2.4 yr								
Zachrisson 2002	HIGH	26	Sterile water	47	*17 (17%) moderately ill, 70 (70%) markedly ill, 12 (12%) severely ill by CGI*	Special unit at university hospital	CDC1994	50 (1)	9 (18%)	Improvement in CGI by nurse	Loose	19
RCT	Staphylococcus toxoid		Subcutaneous	50 F, 0 M 12 yr								

[a] The information in italic is not only of placebo recipients but of all participants.
CFQ = Chalder Fatigue Questionnaire; CIS = Checklist Individual Strength; F = female; M = male; NHP = Nottingham Health Profile; NS = not stated; VAS = Visual Analogue Scale; CGI = Clinical Global Impressions; DLE = dialyzable leukocyte extract; MOS = Medical Outcomes Study; NIH = National Institutes of Health; QAL = Validity of Life visual analogue scale; SF-36 = 36-item Medical Outcomes Study Short-Form.

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