Interventions for the Treatment and Management of Chronic Fatigue Syndrome
A Systematic Review

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Chronic fatigue syndrome (CFS) consists of a range of symptoms including fatigue, headaches, sleep disturbances, difficulties with concentration, and muscle pain. The defining characteristic has repeatedly been reported to be physical and mental fatigue.1-3 Children present with symptoms similar to those encountered in adults.4 There are reports in the literature that myalgic encephalomyelitis (ME) is a syndrome separate from CFS that is characterized by muscle weakness—more specifically, gross abnormal muscle fatigue after relatively mild activity—pain, and a disturbed nervous system.5 However, in the literature CFS is commonly referred to as being the same illness as ME, postviral fatigue syndrome (PVFS), and all similar symptom complexes. The term CFS was chosen in 1988 because it included no statement of etiology.2 For the purposes of this review CFS was taken to mean all illnesses, including ME and PVFS, with symptom complexes similar to CFS, unless otherwise stated.

See also p 1378.
The cause of CFS remains unknown although various hypotheses have been suggested, including immunological, virological, psychological, and neuroendocrine factors. Diagnosis of CFS is also difficult because there is no available laboratory test and so it is made largely from symptoms reported by the patient. Several case definitions are available, although no single definition is universally accepted. Two frequently used definitions are the UK (Oxford) criteria and the US Centers for Disease Control and Prevention (CDC) criteria. Both sets of criteria require that debilitating fatigue be present for at least 6 months, some functional impairment, and that this fatigue and impairment have not been caused by any other identifiable clinical condition. However, the case definitions differ in the number and severity of other symptoms that must be present. The London criteria, for example, are sometimes used to diagnose ME and are more stringent than the criteria for CFS.

A variety of interventions have been used in the treatment and management of CFS. Treatment tends to focus on targeting the symptoms of muscle pain, sleep disregulation, affective symptoms, and fatigue. Evaluations of the effectiveness of different approaches suggest a variety of different outcomes. While there is some lack of agreement about management strategies, there is considerable agreement on elements of these strategies, even if terminology may suggest otherwise.

Objective

The aim of this systematic review was to assess the effectiveness of all available interventions that have been evaluated for use in the treatment or management of adults and children with CFS. This report represents a collaborative effort between 2 distinct but parallel review groups who have evaluated interventions used in the treatment and management of CFS. Where necessary, review-specific differences in the 2 projects are described; otherwise, the overarching characteristics of this collaborative synthesis are presented. Detailed descriptions of the 2 individual reviews are reported elsewhere.

METHODS

Search Strategy

Nineteen specialist databases were searched, including MEDLINE, EMBASE, and PsychLIT from inception to July 2000; ERIC and Current Contents (Science Citation Index) from inception to January 2000; and the Cochrane Library through July 2000. The search was updated through October 2000 using PubMed. In addition, the Web was searched using Copernic 2000, a meta-search engine used to scan a number of individual search engines (eg, Lycos, AltaVista) at once. The bibliographies of retrieved articles were scanned for any additional references. Additional references were sought from individuals and organizations through a Web site (http://www.york.ac.uk/inst/crd/cfs.htm) dedicated for this review and through members of 2 specifically designated advisory panels. Published and unpublished studies in any language were included. Full details of the search strategies are provided in the 2 full government reports.

Inclusion Criteria

Studies including any intervention used in the treatment or management of CFS were selected for our review, as were those including adults and children with a diagnosis of CFS based on any criteria or on another syndrome having similar criteria for diagnosis as CFS, such as ME, chronic fatigue immune deficiency syndrome, or chronic Epstein-Barr virus infection. Studies including patients with a diagnosis of fibromyalgia were not selected for the review. All outcomes reported in the studies were considered relevant to reflect the wide range of medical and psychosocial outcomes used as markers of treatment response.

The studies selected for review comprised both randomized controlled trials (RCTs) and controlled trials. Studies identified in other systematic reviews were included individually if they met all of the inclusion criteria for this review. Two reviewers independently assessed all titles and abstracts identified from the literature searches for relevance. All retrieved studies were then independently assessed by 2 reviewers for possible inclusion. If these 2 reviewers could not agree, a third reviewer was consulted.

Data Extraction and Validity Assessment

Extraction of data from individual included studies was performed by one reviewer and checked by a second. Discrepancies were resolved by referral to the original studies and, if necessary, through arbitration by a third reviewer.

Study validity was formally assessed using a published checklist modified for this review. Each study was assigned a score based on the validity criteria fulfilled, with a maximum potential score of 20 points. Validity criteria assessed included the randomization and concealment of treatment allocation (RCTs only), adjustment for confounding factors and appropriateness of the control group (controlled studies only), baseline comparability of groups, blinding, follow-up, dropouts, objectivity of outcome assessment, analysis, sample size, and whether treatment groups were treated identically other than the named interventions. Study validity was assessed independently by 2 reviewers and disagreements were resolved through consensus.

Data Synthesis

A qualitative analysis was undertaken due to the significant heterogeneity between studies in interventions and outcomes. Outcomes and interventions were grouped to facilitate interpretation of results.

To provide an overall estimate of whether each study found a positive, negative, or no effect of the intervention, all studies were classified according to 2 separate methods: whether the study showed any effect of treatment, and whether it showed any overall effect. Studies were judged to show some effect of treatment if any of the out-
comes measured showed a significant difference between the intervention and control groups. Studies were classified as having an overall effect (positive or negative) if they showed an effect for more than 1 clinical (ie, not a physiological) outcome; if only 1 outcome was measured, studies were classified as having an overall effect if this outcome was found to show an effect. The effect was considered to be positive if the intervention group showed a greater improvement than the control group and negative if the control group showed the greater improvement. Where no differences occurred, this was classified as showing no effect.

The association between the validity score, duration of treatment, and diagnostic criteria and the effect (positive, negative, or no effect) of the intervention on outcomes, as classified above (any effect and overall effect), was investigated. Study dropouts and reasons for withdrawing from studies were discussed.

Every effort was made to negate the effects of publication bias (the tendency for studies that show certain results, usually beneficial effects, to be published). Unpublished studies were searched for by scanning reference lists of included studies, by asking the advisory panels if they were aware of any unpublished work, and through the dedicated review Web site. Insufficient data were available to assess publication bias using standard methods (eg, funnel plots), and it was therefore discussed narratively.

RESULTS

Search Results

A total of 350 studies meeting relevance criteria were identified through the literature searches. Forty-four (36 RCTs; 8 controlled trials) met the inclusion criteria. Ten of the RCTs used a crossover design.

Of the 44 included primary studies, 32 were carried out with adults, 1 with children, and 2 with both adults and children; the remaining 9 did not give this information. Ages of participants (for studies reporting this information) ranged from 11 to 87 years. Overall, the percentage of women was generally higher than men (mean, 71%; range, 19%-100%). Illness duration ranged from 27 days to 34 years for the 21 studies that provided this information. The number of participants included in each trial ranged from 12 to 326, with a total of 2801 participants included in the 44 trials combined. Inclusion criteria applied by a number of the studies limited the participants to those able to travel to the study center for treatment (n=9), those who scored above or between certain levels on some measure of CFS symptoms (n=5), and those who did not have psychiatric illnesses such as depression (n=16).

Outcomes

Within the 44 included studies, a total of 38 different outcomes were used to evaluate the effectiveness of the interventions. Within those studies that assessed the same outcomes a different scale or type of measurement was usually used (around 130), making it difficult to synthesize results across studies. The outcomes assessed are shown in Table 1.

Interventions

Thirty-one different interventions were investigated in the 44 included studies and interventions were grouped into 6 different categories as outlined in the following section.

Study Results

The results of each trial, grouped according to intervention category, are presented in Table 2. Trials were classified as having a positive, negative, or no effect, under the classifications of overall effect and any effect.

Of the 44 included trials, 29 (66%) showed some beneficial effect of the intervention, 18 (41%) showed an overall beneficial effect of the intervention, and 1 (2%) reported some negative intervention effect. The results from 3 studies (evaluating massage therapy,11 growth hormone,12 and galanthamine hydrobromide13) should be treated with extreme caution as they were based on within-group comparisons rather than comparisons between groups (ie, these studies presented their results as changes from baseline to postintervention in each group, rather than comparing postintervention findings or changes from preintervention with postintervention between control and intervention groups).

Behavioral Results

All 3 RCTs evaluating graded exercise therapy (GET) found an overall beneficial effect of the intervention compared with the control groups. These fairly large RCTs all scored highly on the validity assessment (scoring 17 or more out of a possible 20).14-16 One of these studies also looked at the combined effects of GET and fluoxetine but found no additional benefits.15 The studies did not report any adverse

<table>
<thead>
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<th>Table 1. Outcomes Investigated</th>
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<tr>
<td><strong>Outcome Category</strong></td>
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<td>Psychological outcomes</td>
</tr>
<tr>
<td>Physical outcomes</td>
</tr>
<tr>
<td>Quality of life and health status outcomes</td>
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<td>Physiological outcomes</td>
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<td>Resource use</td>
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## Table 2. Summary of Study Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Study Type</th>
<th>Diagnostic Criteria</th>
<th>Duration of Follow-up†</th>
<th>No. of Participants</th>
<th>Outcomes Investigated</th>
<th>Any Effect‡</th>
<th>Overall Effect§</th>
<th>Validity Score</th>
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<td>CDC 1988</td>
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<td>CDC 1988/ London (ME)</td>
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<td>58</td>
<td>PH; PS; QOL</td>
<td>+</td>
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effects of GET, although 2 studies did report study withdrawals that may have been related to the intervention.14,15

Three17-19 of the 4 RCTs17-21 comparing cognitive behavioral therapy (CBT) to control conditions found a positive overall effect of the intervention and these studies also scored highly on validity assessment. One of these studies also included a support group as an additional control and found that CBT was significantly more effective than either of the control conditions, but that there was no difference between the 2 control groups.19 Another of these RCTs followed up patients for 5 years after the intervention;20 at 5-year follow-up, improvements remained for some of the outcomes evaluated (eg, global improvement and proportion of participants completely recovered) but no differences were reported between the groups for the other outcomes measured (physical functioning, fatigue, general health, symptoms, relapses, or the proportion of participants that no longer met CFS criteria). The fourth RCT, which also included immunologic therapy,21 and one controlled trial22 did not find overall beneficial effects of CBT. However, the study that included an immunologic therapy found no effect of either dialyzable leukocyte extract (DLE) or CBT when used alone, but did find a beneficial effect on 1 of the outcomes investigated in the group receiving both interventions. The duration of the intervention in both of these studies was much shorter than in the 3 RCTs that did report overall beneficial effects (9 and 16 weeks vs 26, 52, and 35 weeks, respectively). The CBT used in the controlled trial differed from that used in the four RCTs, focusing more on limiting activities rather than trying to increase activity, and so it is questionable as to whether it should be classified as CBT. This study was methodologically poor, scoring only 1 out of a possible 20 on the validity assessment. One RCT compared CBT with counselling and found that both interventions had a similar effect for patients with CFS.23 This study included participants from general practice, of whom a small subset had CFS. Only the results for the CFS patients are included in the review. The studies evaluating CBT did not report any adverse effects of the intervention, although in 1 RCT 2 participants dropped out of the CBT group because they felt that a deterioration in their symptoms was due to the intervention.17 A second RCT showed very high dropout rates in all 3 intervention groups; the rates were highest in the CBT group but reasons for dropouts were not reported.19

### Immunological Results

Five RCTs assessed the effects of immunoglobulin; of these, 2 showed an overall beneficial effect24,25 (1 was conducted with children25) and 2 showed some positive effects26,27 although in 1 of the studies this was for physiological outcomes only.26 The largest of these 5 RCTs reported no effect of the intervention.28 Two small RCTs evaluated interferon; 1 of these found an overall beneficial effect29 and the other showed some positive effects, although these were in relation to immunological outcomes only.30 The methodological quality of both of these studies was fairly poor. One RCT evaluated ampligen and found an overall beneficial effect31 and some positive effects were reported in a small controlled trial of staphylococcus toxoid.32 A small RCT of the antihistamine terfenadine (oral) reported no beneficial effects.33 An RCT of immunological therapy (DLE) and CBT found no effect of DLE on its own but found a beneficial effect on 1 of the outcomes investigated in the group receiving both DLE and CBT.21

Some severe adverse effects were noted in participants in the immunological intervention groups. Seven people withdrew from immunoglobulin therapy: 2 due to severe constitutional symptoms,28 1 due to a skin eruption,28 1 due to mild but transient liver failure,27 and 1 due to phlebitis occurring with the first infusion;32 the adverse effects that caused the other 2 participants to withdraw were not reported.26 It should be noted that immunoglobulins and DLE are blood products and there are known risks associated with their use, such as the possible transfer of infectious diseases. Three participants withdrew from α-interferon therapy due to adverse effects; 2 had neutropenia and 1 had palpitations.30

### Pharmacological Results

An overall beneficial effect of hydrocortisone was found in 1 RCT30 and some...
beneficial effects were reported in another.35 One RCT showed an overall beneficial effect of oral NADH (reduced nicotinamide adenine dinucleotide),36 and 1 controlled trial of selegiline reported some positive effects but found no overall effect.37 Randomized controlled trials of moclobemide,38 sulbutiamine,39 growth hormone,12 galanthamine hydrobromide,40 2 RCTs of fludrocortisone,41,42 and 2 of antidepressants53,54 found no effects of the interventions. A further RCT that assessed the combined effects of GET and fluoxetine found no effect of fluoxetine either on its own or in combination with GET.13 A negative effect for 1 of the outcomes investigated was found in an RCT of acyclovir.45

Adverse effects serious enough to cause people to withdraw from the study occurred with fludrocortisone,42 moclobemide,38 sulbutiamine,39 galanthamine hydrobromide,40 and antidepressants.43,44 In the galanthamine hydrobromide study, the dosage had to be reduced in 30% of participants due to adverse effects, mainly nausea. Three people withdrew from acyclovir treatment due to reversible renal failure.45

Supplements
Two good-quality RCTs of essential fatty acids reported some beneficial effects of the intervention46,47 and 1 also found an overall beneficial effect.48 Magnesium supplements were found to have an overall beneficial effect in 1 good-quality RCT.49 One poor-quality RCT and 1 controlled trial evaluated general supplements; the RCT found a positive effect49 and the controlled trial reported no effect.50 One small RCT of liver extract reported no beneficial effects.51 The study of magnesium supplements reported that 2 participants left the intervention group after experiencing a generalized rash52 and the other studies did not report adverse effects.

Complementary/Alternative Medical Therapy
Alternative therapies were evaluated in 2 RCTs and 1 controlled trial.11,32,33 In 1 poor-quality RCT, participants given homeopathic remedies reported some beneficial effects of the intervention but the results were not analysed statistically.52 An overall beneficial effect of massage therapy was found in 1 small RCT.11 A poor-quality controlled trial of osteopathy53 found overall beneficial effects. There were no reports of adverse effects from the interventions in any of these studies.

Other Interventions
An overall beneficial effect was also found in 2 controlled trials of 2 different multitreatment approaches, one of which included CBT54 and the other which was based on providing information and advice.55 However, the methodological quality of both these studies was very poor. A third controlled trial of social support that evaluated a buddy/mentor program found a beneficial effect for 1 of the 7 outcomes investigated; this study also scored poorly in the validity assessment and only included 12 participants.56 These trials did not report any adverse effects from the intervention.

Validity Assessment
The 36 RCTs included in this review were of reasonable quality, with 30 (83%) scoring 10 points or more (out of 20) on the validity criteria. However, the controlled trials were of much poorer quality: the highest score achieved was 11 out of 20, and only 2 of the 8 trials (25%) scored 10 points or more. No single intervention type scored more highly on the validity criteria than any other, although trials of GET, essential fatty acid supplements, and CBT all scored highly with the exception of the 1 study of CBT and DLE that scored 13.

The validity score for each RCT was plotted against the percentage of RCTs showing at least that score to investigate whether there was any association between validity score and study result. This was done separately for studies that showed any effect of treatment, and for the overall treatment effect. The graph suggested that a positive effect was more likely to be reported by the studies of better quality; this was found for studies that showed an overall effect from treatment and for those that showed any beneficial effect from treatment. The graph for the overall treatment effect is shown in the FIGURE.

Duration of Intervention and Follow-up
The duration of intervention and follow-up varied between studies and within intervention types. In most trials, the duration of intervention and follow-up was the same. Thirteen of the 44 trials followed up participants for several weeks or months after the intervention had ceased. These trials showed a mixture of no effect, some positive effects, and an overall positive effect. There are insufficient numbers of trials with longer follow-up to investigate whether there is any association between study outcome and a longer follow-up period.

Intervention duration ranged from 2 weeks to 1 year, with an average duration of 16 weeks. Studies with a longer treatment duration (>3 months) were more likely to report any positive effect and an overall positive effect from the intervention. However, the association between treatment duration and trial outcome was found not to be significant for any effect of treatment ($\chi^2$, 4.78; $P = .19$) or for the overall treatment effect ($\chi^2$, 7.35; $P = .06$).
INTERVENTIONS FOR CHRONIC FATIGUE SYNDROME

Diagnostic Criteria

Eight studies used the Oxford criteria to identify people with CFS.14-16,18,44,47,52,57 11 studies used the CDC 1988 criteria,2,19,24,32,36,61 and 5 studies used the Australian criteria.21,27,28,38,48 One study used both the 1988 and the 1994 CDC criteria to diagnose participants, and was classified as using 1994 CDC criteria because these are stricter than the earlier criteria.41 One study used both the Oxford and 1994 CDC criteria.34 One study used the 1994 CDC criteria to diagnose a subset of patients from patients diagnosed using a more general diagnostic criteria.23 Eight studies used other diagnostic criteria to diagnose people with postviral syndrome,46 chronic fatigue immunodeficiency syndrome,11 ME,49 chronic mononucleosis syndrome,25 chronic postinfectious fatigue,30 postinfectious fatigue syndrome,53 chronic fatigue syndrome (diagnostic criteria not described further),39 and a main complaint of fatigue.60 In 1 study the author’s own criteria were used.30 One study included patients with a diagnosis of CFS based on the 1988 CDC criteria who also met the London Criteria for ME.53 The association between method of diagnosis and study outcome was investigated graphically and using a χ² test. The association was not significant for any effect of treatment (χ², 1.06; P=.90) or for the overall treatment effect (χ², 4.91; P=.30).

Study Withdrawals

The overall drop out rate from all the included studies was 15% (412/2801 participants): 13% (328/2469) in the RCTs and 25% (84/332) in the controlled trials. The highest dropout rates were in the behavioral interventions. Cognitive behavioral therapy trials had a dropout rate of 19% (114/589). This high dropout rate was due largely to the high dropout rates in 1 of the RCTs of CBT.19 This trial had significantly higher dropout rates in the CBT group (40%) than in the support group (32%) or control group (20%; χ², 8.27; P=.02). The other RCTs of CBT had lower dropout rates (range, 2%-17%). Trials of GET also had a high dropout rate of 18% (68/370). The pharmacological therapy RCTs had a dropout rate of 11% (99/869), with 4 of the 12 trials reporting more withdrawals from the intervention groups. Randomized controlled trials of the remaining 4 intervention categories all showed relatively low dropout rates of less than 8%.

Publication Bias

Due to heterogeneity of outcomes and interventions it was not possible to assess the extent of publication bias using funnel plots. However, every effort was made to trace unpublished studies (see “Methods” section). None of the trials found an overall negative effect from the intervention, suggesting that there may be bias toward publication of trials showing a positive effect.

COMMENT

Most of the interventions have only been evaluated in 1 or 2 studies, which may limit the generalizability of the findings. Another factor that may limit the applicability of the findings is the inclusion criteria specified in some trials. For example, in some studies participants were only eligible if they could physically get to the clinic, which implies a certain level of fitness. Those people who were unable to walk or to get out of bed were automatically excluded and so it is not possible to assess whether the interventions investigated would be effective, ineffective, or even hazardous for a more severely disabled group of people. In many of the trials, very limited information was given about participants who were ineligible or even about the baseline functioning of many of those who were included. Therefore, it is difficult to extrapolate how the findings might transfer to other people with CFS. It would have been useful with regard to the generalizability of the trial results if more studies had given details of participants’ baseline functioning in a standardized way. Some form of classification system that assesses the severity of the illness would be helpful for future trials.

This review reported many different outcomes measured using a variety of different scales, making it inappropriate to pool the data for specific interventions investigated in more than 1 trial and also making it difficult to compare the findings in a qualitative synthesis. Trial authors rarely included detailed information about the scales and measurements used to assess outcomes. Consequently, it is not clear whether a positive result based on 1 scale to measure disability (for example) is as good as, better than, or worse than a positive result on a different scale. It is also unclear what is represented in clinical terms by the divisions on each of the scales, whether these are similar, and how many of these scales or measures have been validated.

Some studies measured employment status at baseline, but this was often not reported at the end of the intervention. It could be argued that such an outcome is more relevant to those diagnosed as having CFS than outcomes such as CD4 cell counts, and should be reported more frequently. Outcomes such as “improvement,” in which participants were asked to rate themselves as better or worse than they were before the intervention began, were frequently reported. However, the person may feel better able to cope with daily activities because they have reduced their expectations of what they should achieve, rather than because they have made any recovery as a result of the intervention. A more objective measure of the effect of any intervention would be whether participants have increased their working hours, returned to work or school, or increased their physical activities.

There is a need for standard outcome measures to be used in trials evaluating interventions for CFS so that results can be meaningfully compared across studies. A mix of validated tools for different dimensions or domains is needed to take into consideration the wide and pervasive impact of this ill-
ness on many domains. A comprehensive review of outcome measures currently used would be the first step in this process. The outcomes measures identified via the intervention studies included in this review could form the basis of such a review.

The number of different interventions assessed and the rationales given for their use is almost as large as the number of studies included in this review, possibly reflecting the uncertainty over the etiology of CFS. Immunological and pharmacological interventions were the most frequently investigated, with complementary/alternative therapies the least frequently studied.

There is little evidence from the literature concerning the appropriate duration and follow-up of interventions used in the management of CFS. However, as CFS is by definition long-term, it would seem sensible to follow up participants for an appropriate period of time. The relapsing nature of CFS suggests that follow-up should continue for at least an additional 6 to 12 months after the intervention period has ended, to confirm that any improvement observed was due to the intervention itself and not just to a naturally occurring fluctuation in the course of the illness.

Dropout rates may be important indicators of the acceptability of an intervention. Alternatively, high dropout rates may indicate that the trial protocol is too rigid to accommodate any but a very specific group of participants, which will again limit the generalizability of the findings. Where dropout rates are higher in the intervention group than in the control group it may be the case that there is something about the intervention that trial participants find unacceptable. It may be the method or frequency of administration, or adverse effects arising from the intervention. Although studies of behavioral interventions reported high dropout rates, none of these studies found any adverse effects from the intervention and so the reasons for withdrawing from these studies is not clear. Interventions that reported adverse effects severe enough to cause withdrawal from the study included immunoglobulin, α-interferon, magnesium supplements, fludrocortisone, moclobemide, sulbutiamine, galanthamine hydrobromide, antidepressants, and acyclovir. When deciding what treatments should be given to patients it is important to take adverse effects, especially those which are so severe as to cause patients to discontinue treatment, into consideration.

It is difficult to draw overall conclusions because very little information was provided on baseline functioning of participants. Different case definitions and inclusion/exclusion criteria were used across the studies, so it is difficult to compare the studies point-for-point and those patients with the most severe symptoms were excluded from many of the studies included in the review.

Overall, the interventions demonstrated mixed results in terms of effectiveness. All conclusions about effectiveness should be considered together with the methodological inadequacies of the studies. Interventions that have shown promising results include CBT and GET. Interventions that have shown some limited effects but for which overall evidence is inconclusive include immunoglobulin and hydrocortisone. Interventions for which there is insufficient evidence about effectiveness include α-interferon, ampligen, staphylococcal toxoid, terfenadine (antihistamine), oral NADH, selegiline, acyclovir, moclobemide, fludrocortisone, antidepressants (either in treating the symptoms of depression or any other outcomes), sulbutiamine, growth hormone, galanthamine hydrobromide, magnesium supplements, general supplements, liver extract, homeopathy, massage therapy, osteopathy, combination programs, and buddy/mentor programs. The large number of outcome measures used in these trials makes standardization of outcomes a priority for future research.

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CORRECTIONS


Misleading Statements: In the response letter from Bagnall et al to Goudsmit in the December 26, 2001, issue of THE JOURNAL (2001;286:3079), there were 2 misleading statements. First, the sentence that reads, “It is unclear how many of those excluded were in the treatment and control groups,” should instead have read, “It is unclear which exclusions occurred in the treatment group and which in the control group.” Second, the sentence that reads, “Finally, the reference we presented for the London criteria was provided to us by Dr Goudsmit,” was printed in error and should be retracted.