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Diagnosis and Treatment of Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome

Executive Summary

This systematic review was commissioned by the Office of Disease Prevention at the National Institutes of Health (NIH), sponsored by the NIH Office of Research on Women's Health, and cosponsored by the Trans-NIH Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Research Working Group to inform the NIH 2014 Pathways to Prevention Workshop, an evidence-based methodology workshop. The purpose of the workshop is to develop a research agenda. Accordingly, this review evaluates and summarizes research on methods for diagnosis of ME/CFS and the benefits and harms of treatments, and identifies gaps and limitations of current studies and needs for future research in these areas.

Background

ME/CFS is a condition characterized by chronic and disabling fatigue, as well as various additional manifestations, including neurological and cognitive changes, motor impairment, pain, sleep disturbance, and altered immune and autonomic responses.[1-4] Experts consider postexertional malaise and impairment of memory or concentration as critical components.[5-7] Consistent with the NIH Workshop, this review uses the combined term ME/CFS to describe the condition.

The etiology of ME/CFS is not known, and there is uncertainty whether the condition reflects a single pathologically discrete syndrome, whether ME and CFS are subsets of the same illness, and whether ME/CFS is a nonspecific condition shared by other disease entities. Numerous studies have attempted to

Evidence-based Practice Program

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

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identify risk factors for developing ME/CFS, but none are definitive.

The diagnosis of ME/CFS relies on the use of clinical criteria to distinguish it from other conditions that may also present with fatigue. There are currently eight published case definitions with clinical criteria.[1-3,8-12] All include persistent fatigue not attributable to a known underlying medical condition, as well as additional clinical signs and symptoms. Depending on the case definition, prevalence rates of ME/CFS in the United States range from 0.3 percent to 2.5 percent.[13-15] Currently, no medications have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of ME/CFS, but several have been used "off label." In practice, there are wide variations in the clinical management of patients, and many patients receive a multifaceted approach to treatment.

Scope of Review

This review includes studies of adults with symptoms related to ME/CFS. Outcomes from treatment trials include improved function, fatigue, quality of life, and involvement in daily activities. Included studies were conducted in clinical settings relevant to health care practices in the United States. Scientists from the NIH and Agency for Healthcare Research and Quality (AHRQ) and a panel of experts and patients worked with the systematic review investigators to consider the context and studies related to the Key Questions that guided the review. These are—

Key Question 1. What methods are available to clinicians to diagnose ME/CFS, and what conditions are required to be ruled out or excluded before assigning a diagnosis of ME/CFS?

(a) What are the accuracy and concordance of methods used to diagnose ME/CFS?

(b) How does the use of these methods vary by patient subgroups?

(c) What harms are associated with diagnosing ME/CFS?

Key Question 2. What are the (a) benefits and (b) harms of therapeutic interventions for patients with ME/CFS, and how do they vary by patient subgroups?

(c) What are the characteristics of responders and nonresponders to interventions?

Methods

This systematic review follows established methods of AHRQ's Effective Health Care Program.[16] A research librarian conducted electronic database searches identifying articles published between 1988 and September 2014. Searches were supplemented by references identified from additional sources, including suggestions from panel members and reviewers of the draft report. Criteria for including studies were developed based on relevance to the Key Questions. Two investigators independently reviewed all potential articles for eligibility, and discrepancies were resolved through discussion and consensus, with a third investigator making the final decision as needed. Only English-language articles were included.

For questions regarding diagnostic methods, studies were included that compared case definitions, outlined in the Results section under Diagnosis (e.g., Fukuda/Centers for Disease Control and Prevention [CDC], Canadian, International), and provided measures of agreement, or tested the ability of the method to identify ME/CFS patients using one of the case definitions as a reference. Studies of potential harms from diagnosis were also included, such as psychological harms, labeling, risk from diagnostic tests, and misdiagnosis.

For questions regarding treatment, studies were included that enrolled patients diagnosed with ME, CFS, or both by fulfilling criteria from at least one case definition. We included randomized controlled trials of at least 12 weeks in duration that compared medications, complementary and alternative medicine approaches, counseling and behavior therapies, and exercise therapies versus no treatment or other types of treatment. For completeness, additional trials of medications that were designed for shorter durations of treatment were separately summarized. Treatment outcomes included improved function, fatigue, quality of life, and involvement in daily activities. Studies of the results of laboratory tests or studies focusing on individual symptoms were not included.

Two investigators extracted data from each included study, and they independently rated the quality of the methods of each study based on predefined criteria. Results of some of the treatment trials were statistically combined using meta-analysis. The overall strength of evidence was assessed for each Key Question and outcome in accordance with established methods. Experts in ME/CFS, individuals representing interest groups, and the expert and patient members of the panel were invited to review the draft

report. The draft report was also posted for public comment during September and October 2014.

Results

Diagnosis

Thirty-six observational studies of methods to diagnose ME/CFS were included. Most studies enrolled predominantly female patients, had small sample sizes, and were conducted in the United States and Western Europe.

Key Question 1. What methods are available to clinicians to diagnose ME/CFS, and what conditions are required to be ruled out or excluded before assigning a diagnosis of ME/CFS?

Eight case definitions that include clinical criteria have been developed to identify patients with ME/CFS and are used by clinicians to distinguish ME/CFS from other conditions that also present with fatigue (Table A).[1-3,8-12] One study considered the comparison based on age variance and is discussed under Key Question 1b.[17] Although most case definitions require that other conditions be excluded prior to assigning a diagnosis of ME/CFS, no studies compared strategies for ruling out alternative diagnoses. The Oxford (Sharpe, 1991) case definition incorporates the smallest number of symptoms (new onset of fatigue with impairment of physical and mental function), suggesting less specificity for ME/CFS.[12]

Table A. Case definitions

Symptoms	London ME[8]	Canadian ME/CFS[1]	Revised Canadian ME/CFS[10]	International ME[2]	CDC – CFS, Holmes[9]	Oxford CFS[12]	CDC – CFS, Fukuda[3]	CDC – CFS, Reeves[11]
General physical	X	X	X		X	X	X	X
Neurological;								
neurocognitive	X	X	X	X	X	X	X	X
Postexertional malaise	X	X	X	X	X		X	X
Neuroendocrine; immune		X	X	X	X		X	X
Other system involvement				X				

CDC = Centers for Disease Control and Prevention; CFS = chronic fatigue syndrome; ME = myalgic encephalomyelitis.

Key Question 1a. What are the accuracy and concordance of methods used to diagnose ME/CFS?

Diagnostic methods were evaluated in eight descriptive studies comparing case definitions, although the accuracy of each method could not be determined because there is no established reference standard. Patients diagnosed using clinical criteria for ME or ME/CFS had more severe symptoms or impairment than those diagnosed using criteria for CFS alone. The Oxford CFS (Sharpe, 1991) and the London ME (Dowsett, 1994) case definitions were not compared in studies, leaving uncertainty as to whether these represent similar or discordant representations of ME/CFS.[5,14,18-22]

Three studies that compared CFS patients diagnosed using the CDC (Holmes, 1988, or Fukuda, 1994) case definitions versus patients with other diseases identified differences in reported symptoms using various self-reported symptom scales.[18,23,24] These results suggest that some scales could be reasonable candidates for further evaluation as diagnostic tests (Fatigue Impact Scale, Chalder Fatigue Scale, Hospital Anxiety and Depression scale, and certain subscales or combinations of the 36-Item Short Form survey [SF-36] with the Zung Depression Scale). However, these measures have not yet been evaluated for this purpose. No studies evaluated whether diagnostic methods could adequately identify clinical subgroups of patients.

Eleven studies evaluated other types of methods to diagnose ME/CFS, but results were inconclusive. These included studies using self-reported symptom scales (the artificial neural network test, the Schedule of Fatigue and Anergia for CFS scale, subscales of the SF-36, and other scales) and various serum biomarkers.[25-36] The artificial neural network test was able to differentiate ME/CFS patients from healthy controls; however, no studies evaluated this method or other methods using an adequate sample size and spectrum of patients. No studies demonstrated an accurate and reliable method for identifying patients or subgroups of patients with ME/CFS in comparison with other patients, with diagnostic uncertainty as to whether they have ME/CFS or another condition in which fatigue is a prominent symptom.

Key Question 1b. How does the use of these methods vary by patient subgroups?

Three studies described how methods for diagnosis may differ for patient subgroups.[17,33,34] One study reported that older patients were more impaired, but it did not consider how symptom evaluation might vary with age. Two studies found that cardiopulmonary exercise tests were different for ME/CFS patients and for healthy controls, and that certain subscales of the SF-36 were associated with slow recovery after exercise. No studies evaluated differences in the performance of case definitions among patients with specific sets of symptoms (autonomic/neuroendocrine, neurological/neurocognitive, immunological/infectious).

Key Question 1c. What harms are associated with diagnosing ME/CFS?

Fourteen studies evaluated harms of the diagnostic process or diagnosis of ME/CFS, including the perceived harms (or benefits) of receiving a diagnosis of ME/CFS, as well as missed/alternative diagnoses.[13,37-49] Five studies found that patients with CFS feel stigmatized by their diagnosis in terms of financial stability, work opportunities, perceived judgments on their characters, social isolation, and interactions with the health care system.[38,39,41-43] Two studies indicated that medical trainees and mental health practitioners make judgments about a patient's condition based on the name it carries (ME, CFS, or other) and what treatment is being given.[37,44] A substantial burden of misdiagnosis was found in the ME/CFS population.[13,37,40,45,46,48]

Treatment

Thirty-five randomized trials of the benefits and harms of treatments for ME/CFS were included. Most had fair- or poor-quality research methods, enrolled predominantly female patients from ME/CFS specialty clinics based on the CDC (Fukuda, 1994) or Oxford (Sharpe, 1991) case definitions, had small sample sizes, and were conducted in the United States and Western Europe.

Key Question 2. What are the (a) benefits and (b) harms of therapeutic interventions for patients with ME/CFS, and how do they vary by patient subgroups?

Nine trials compared medical treatment of ME/CFS with placebo, although none of these medications have been approved by FDA for this indication.[50-58] Results are summarized in Table B. Studies primarily included patients meeting CDC case definitions for ME/CFS (Fukuda, 1994, and/or Holmes, 1988), which identify less debilitated patients than those meeting ME case definitions. The immune modulator rintatolimod improved some measures of exercise performance compared with placebo in two trials (low strength of evidence), while trials of galantamine, hydrocortisone, immunoglobulin G, valganciclovir, isoprinosine, and fluoxetine were inconclusive (insufficient evidence). Additional trials with durations less than 12 weeks indicated no differences versus placebo for acyclovir[59] and improved scores for physical health and function with rituximab,[60] although both studies enrolled 30 or fewer participants and the clinical implications of these results are not clear.

Harms of medications included suppression of adrenal glucocorticoid responsiveness, increased appetite, weight gain, and difficulty sleeping with hydrocortisone; flulike syndrome, chills, vasodilation, dyspnea, and dry skin with rintatolimod; headaches with immunoglobulin G; discontinuation of treatment with fluoxetine; and nephrotoxicity with acyclovir.

Table B. Trials of medications

Treatment	Number of Trials (Participants)	Results (Treatment vs. Placebo)*
Galantamine (acetyl-cholinesterase inhibitor)	1 (423)	No differences. (Insufficient evidence)
Hydrocortisone (corticosteroid)	1 (68)	No differences. (Insufficient evidence)
Hydrocortisone + fludrocortisone (corticosteroid)	1 (80)	No differences. (Insufficient evidence)
Immunoglobulin G (antibody)	1 (28)	Better scores on social functioning scale for placebo group; no difference on physical functioning scale. (Insufficient evidence)
Rintatolimod (immune modulator)	2 (324)	Increased activities of daily living. Improved exercise duration, exercise work, and cardiopulmonary exercise tolerance. (Low strength of evidence)
Valganciclovir (antiviral agent)	1 (30)	Decreased fatigue scores; no differences in overall function. (Insufficient evidence)
Isoprinosine (immune modulator)	1 (15)	No differences. (Insufficient evidence)
Fluoxetine (selective serotonin reuptake inhibitor)	1 (68)	No differences. (Insufficient evidence)
Acyclovir (antiviral)†	1 (30)	No differences. (Insufficient evidence)
Rituximab (monoclonal antibody)†	1 (27)	Improved physical health and function scores, but not other outcomes. (Insufficient evidence)

*Statistically significant differences between treatment and placebo groups.

†Trial less than 12 weeks in duration

Seven trials compared complementary and alternative medicine approaches versus usual care, placebo, or alternative therapies (Table C) in ME/CFS patients diagnosed by the Oxford (Sharpe, 1991) or CDC (Fukuda, 1994) case definitions.[61-67] Therapies included dietary supplements, distant healing, homeopathy, melatonin, and phototherapy. Although studies of homeopathy, pollen extracts, and L-carnitine preparations reported benefit for some outcomes, these findings are inconclusive because of methodological limitations and small sample sizes (insufficient evidence). Harms were not reported in the studies.

Table C. Trials of complementary and alternative medicine therapies

Treatment	Number of Trials (Participants)	Results (Treatment vs. Control)*
Acclydine vs. placebo	1 (57)	No differences. (Insufficient evidence)
Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination	1 (89)	Lower fatigue scores with acetyl-L-carnitine, but more improvement from baseline with propionyl-L-carnitine and the combination. Better global improvement with propionyl-L-carnitine and acetyl-L-carnitine compared with the combination. (Insufficient evidence)
Pollen extract vs. placebo	1 (22)	Improved fatigue and quality-of-life scores. (Insufficient evidence)
Low sugar/low yeast diet vs. healthy eating	1 (39)	No differences. (Insufficient evidence)
Distant healing vs. no treatment	1 (409)	No differences. (Insufficient evidence)
Homeopathy vs. placebo	1 (89)	Improved fatigue scores for placebo. (Insufficient evidence)
Melatonin vs. phototherapy	1 (30)	No differences. (Insufficient evidence)
Home orthostatic training vs. sham home orthostatic training	1 (36)	No differences. (Insufficient evidence)

*Statistically significant differences between treatment and control groups.

Fourteen trials compared counseling or behavioral therapy versus usual care, no treatment, or other types of counseling or behavioral therapy (Table D) in ME/CFS patients diagnosed primarily by the Oxford (Sharpe, 1991) or CDC (Fukuda, 1994) case definitions.[68-89] Results were mixed for most outcomes, but when considering all studies comparing any type of counseling with a control, counseling improved fatigue (7 of 11 trials showed positive effect), measures of functioning (4 of 11 trials showed positive effect; 2 of 11 showed mixed results on different measures), quality of life (2 of 4 trials showed positive effect), and global improvement (2 of 2 trials showed positive effect). Treatment effectiveness may not be generalizable to all patients because no study used a case definition that selected for more disabled patients (i.e., case definition for ME). Harms of counseling and behavioral therapies were rarely reported by the studies, but when they were reported, harms were fewer with counseling compared with usual care, support, or adaptive pacing.

Table D. Trials of counseling or behavioral therapy

Treatment	Number of Trials (Participants)	Results (Treatment vs. Control)*
Counseling and behavioral therapy vs. no treatment, support, relaxation, or adaptive pacing	13 (1,648)	Higher function scores; weighted mean difference, 7.73 (95% CI, 3.58 to 11.87; 8 trials). (Low strength of evidence) Improved fatigue in 7 trials; no differences in 4 trials. (Low strength of evidence) Improved quality of life in 2 trials; no differences in 2 trials. (Low strength of evidence) More hours worked per week (mean 36 vs. 24; $p<0.04$) in 1 trial; no differences in 1 trial. (Low strength of evidence) Improvement on work and social adjustment scales in 2 trials. (Low strength of evidence) Better global improvement in 2 trials. (Moderate strength of evidence)
Face-to-face vs. telephone cognitive behavioral therapy	1 (43)	Better clinical global improvement with face-to-face therapy; no differences in overall function. (Insufficient evidence)

*Statistically significant differences between treatment and control groups.
CI = confidence interval.

Six trials evaluated exercise therapies, including graded exercise therapy (GET), qigong, and home orthostatic training, compared with no treatment or several other types of therapies in ME/CFS patients diagnosed primarily by the Oxford (Sharpe, 1991) or CDC (Fukuda, 1994) case definitions (Table E).[57,89-93] GET improved measures of fatigue, function, and clinical global impression of change compared with controls. Treatment effectiveness may not be generalizable to all patients because no study used a case definition that selected for more disabled patients (i.e., case definition for ME). Harms were not well reported, although in one trial patients receiving GET reported more adverse events compared with those receiving cognitive behavior therapy (CBT), adaptive pacing, or usual care; one trial reported more withdrawals of patients receiving GET, one trial had a high percentage of patients refusing repeat exercise testing, and several other trials reported more withdrawals of patients receiving GET, all compared with controls.

Table E. Trials of exercise therapy

Treatment	Number of Trials (Participants)	Results (Treatment vs. Control)*
Graded exercise therapy vs. no treatment, flexibility/relaxation therapy, or adaptive pacing	4 (619)	Better overall function scores; weighted mean difference, 10.29 (95% CI, 6.71 to 13.86; 3 trials). (Moderate strength of evidence) Decreased fatigue in 3 trials; no differences in 1 trial. (Low strength of evidence) More working 1 year after treatment (66% vs. 39%). (Insufficient evidence) Improved scores on work and social adjustment scales compared with adaptive pacing and no treatment. (Low strength of evidence) Better global improvement; changes in clinical global improvement, 1.26 (95% CI, 1.26 to 1.89; 3 trials). (Moderate strength of evidence)
Qigong exercise vs. no qigong exercise	1 (52)	Better physical function and fatigue scores. (Insufficient evidence)
Home orthostatic training vs. sham home orthostatic training	1 (36)	No differences. (Insufficient evidence)

* Statistically significant differences between treatment and control groups.
CI = confidence interval.

Four trials compared either head-to-head interventions or combinations of two interventions (Table F). GET and CBT had similar improvement in measures of function but mixed results on other outcomes.[57,73,74,76,79,89] When reported, harms of CBT appear to be less than those with GET. GET appears to improve fatigue and function when compared with fluoxetine, which was found to be ineffective.

Table F. Head-to-head and comparison trials

Treatment	Number of Trials (Participants)	Results*
Cognitive behavioral therapy vs. cognitive therapy vs. anaerobic therapy	1 (114)	Improved function with cognitive behavioral therapy or cognitive therapy vs. anaerobic therapy. (Insufficient evidence)
Graded exercise therapy ± fluoxetine vs. fluoxetine ± placebo	1 (136)	Improved functional work capacity with exercise alone or combined with fluoxetine. Improved fatigue with exercise alone or combined with fluoxetine. (Insufficient evidence)
Cognitive behavioral therapy vs. graded exercise therapy	1 (314)	No differences. (Insufficient evidence)
Cognitive behavioral therapy + graded exercise therapy vs. usual care	1 (115)	No differences. (Insufficient evidence)

* Statistically significant differences between treatment and control groups.

Key Question 2c. What are the characteristics of responders and nonresponders to interventions?

Four trials describe characteristics of patients more likely to respond to therapies for ME/CFS. Younger patients with less impairment and less focus on symptoms who are adherent to therapy (e.g., readings, sleep diaries, activity goals, relaxation) are more likely to improve on some measures of fatigue and/or function.[68,74,87,92] Avoiding overexercising and underexercising (i.e., staying within one's energy envelope) was also beneficial. This represents an insufficient body of evidence, as the results have not been duplicated and the applicability of these results to other patients is not known.

Conclusions

Eight case definitions for ME/CFS exist, and several diagnostic methods have been studied. Case definitions with criteria for ME and ME/CFS that require symptoms of postexertional malaise, neurological impairment, and autonomic dysfunction identify patients with more impairment, lower functioning, and more severe symptoms than case definitions with criteria for CFS alone. However, none of the case definitions or other diagnostic methods have been adequately tested to determine how well they differentiate patients with ME/CFS from patients with other conditions. No studies evaluated how diagnostic tests vary by patient subgroups or how to rule out related conditions before making an ME/CFS diagnosis. Studies indicated that an ME/CFS diagnosis is associated with perceived stigma, financial instability, difficulty in social interactions and relationships, and a greater chance of receiving a psychiatric diagnosis. One study identified feelings of legitimacy upon receiving the diagnosis of ME/CFS.

Thirty-five trials of treatments included medication, complementary and alternative medicine approaches, counseling or behavioral therapy, and exercise therapy. Two trials of rintatolimod showed improvement in some measures of performance, while one trial showed improvement in fatigue, activities of daily living, and reduced use of other medications for relief of ME/CFS symptoms. Single trials enrolling only 30 participants reported improved measures of fatigue with valganciclovir and improved physical health and function scores with rituximab. The benefits of pollen extract, homeopathy, and L-carnitine preparations remain uncertain, because improvement was found in some but not other measures of the same outcome. When all counseling and behavioral therapy trials were combined, measures of fatigue and global improvement were significantly improved, although results were not consistent across all trials. GET improved measures of function, global improvement, and to a lesser degree, fatigue. Although harms were not well reported across trials, GET was associated with a higher number of reported harms and withdrawals in some trials. For all other treatments, effects are uncertain because important outcomes were not measured, the study methods were inadequate, or too few participants were enrolled to provide useful estimates. Most treatments were evaluated in only a single trial and were conducted in referral settings. Participants' baseline function and severity of symptoms were not usually reported, and it is not clear how well the results of the trials apply to clinical practice.

Limitations

The main limitation of this review is the lack of studies to address important questions, particularly regarding methods of diagnosis. Available studies generally enrolled small numbers of participants, and many treatment trials were too small to detect significant differences between groups. Most treatment trials did not describe their methods in sufficient detail to assess their quality. Studies used a variety of methods to measure outcomes, limiting comparisons across studies. While this review focused on outcomes that patients can experience, such as fatigue, a review of other types of outcomes such as postexertional malaise would provide additional evidence.

Future Research

Consensus about which case definition is appropriate to use as the gold standard will further advance the study of diagnostic methods for ME/CFS. In the absence of consensus, future studies aimed at clarifying the diagnosis of ME/CFS should consider reporting how well a diagnostic test compares with more than one of the case definitions. A national longitudinal registry of patients with a diagnosis of ME/CFS would allow for comparison of diagnostic criteria between patients and clarification of diagnoses over time. This strategy could also identify a well-characterized population for use in both diagnostic and treatment trials.

Future studies evaluating the capability of diagnostic methods for ME/CFS should include a broad range of patients with conditions that require clinical distinction from ME/CFS, such as fibromyalgia and depression. Additionally, studies should report how well a particular method distinguishes ME/CFS from other conditions using standard performance measures, such as concordance, sensitivity, and specificity.

Treatment trials should use consistent case definitions and outcome measures to improve comparisons across trials,

and should refrain from using the Oxford (Sharpe, 1991) case definition because it is less specific for ME/CFS than the other definitions are. Definitive treatment trials require larger numbers of participants based on appropriate power calculations for primary outcomes to determine efficacy, and more rigorous adherence to methodological standards such as blinding of outcome assessors, intention-to-treat analysis, and strategies to minimize patients lost to followup. Future trials should enroll more men, more racial and ethnic minorities, and broader age ranges. Given the fluctuating nature of ME/CFS, followup periods greater than 1 year would help determine effectiveness and harms over time. The development of a set of core outcome measures, including patient-centered outcomes, such as quality of life, employment, and time spent in activity, would help guide research and facilitate future analyses. Trial registries and collaborations would help consolidate and standardize data. Reporting more information about concomitant treatments and adherence to treatment would improve the applicability of study findings. Similarly, stratification of results by patient characteristics, such as age, sex, race, and intermediate outcomes, would help determine the applicability of different treatments for specific patients and situations.

Studies should report findings according to important features of ME/CFS, such as postexertional malaise, neurocognitive status, and autonomic function, to identify subgroups that may respond differently to specific treatments. Studies also need to report harms more completely to help identify patients negatively affected by certain treatments. Given the devastating impact that this condition has had on patients and families, researchers planning and developing trials should consider involving the patient and/or advocate voice so that future research is relevant and meaningful to those affected by ME/CFS.

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Full Report

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