New Drug Review

A Systematic Review of Drug Therapies for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis

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ABSTRACT

Purpose: The pathogenesis of chronic fatigue syndrome or myalgic encephalomyelitis (CFS/ME) is complex and remains poorly understood. Evidence regarding the use of drug therapies in CFS/ME is currently limited and conflicting. The aim of this systematic review was to examine the existing evidence on the efficacy of drug therapies and determine whether any can be recommended for patients with CFS/ME.

Methods: MEDLINE, EMBASE, and PubMed databases were searched from the start of their records to March 2016 to identify relevant studies. Randomized controlled trials focusing solely on drug therapy to alleviate and/or eliminate chronic fatigue symptoms were included in the review. Any trials that considered graded exercise therapy, cognitive behavior therapy, adaptive pacing, or any other nonpharmaceutical treatment plans were excluded. The inclusion criteria were examined to ensure that study participants met specific CFS/ME diagnostic criteria. Study size, intervention, and end point outcome domains were summarized.

Findings: A total of 1039 studies were identified with the search terms; 26 studies met all the criteria and were considered suitable for review. Three different diagnostic criteria were identified: the Holmes criteria, International Consensus Criteria, and the Fukuda criteria. Primary outcomes were identified as fatigue, pain, mood, neurocognitive dysfunction and sleep quality, symptom severity, functional status, and well-being or overall health status. Twenty pharmaceutical classes were trialed. Ten medications were shown to be slightly to moderately effective in their respective study groups ($P < 0.05$).

Implications: These findings indicate that no universal pharmaceutical treatment can be recommended. The unknown etiology of CFS/ME, and complications arising from its heterogeneous nature, contributes to the lack of clear evidence for pharmaceutical interventions. However, patients report using a large number and variety of medications. This finding highlights the need for trials with clearly defined CFS/ME cohorts. Trials based on more specific criteria such as the International Consensus Criteria are recommended to identify specific subgroups of patients in whom treatments may be beneficial. (*Clin Ther.* 2016;38:1263–1271)

Key words: chronic fatigue syndrome, clinical evidence, drug therapy, myalgic encephalomyelitis, pharmaceutical therapy, treatment.

INTRODUCTION

Chronic fatigue syndrome or myalgic encephalomyelitis (CFS/ME) is a complex and debilitating disorder with an unknown etiology. Patients experience a substantial loss in quality of life, with severe disruption to daily activities.[1] This disorder is heterogeneous in nature, with patients experiencing varied symptoms, at different severities, frequencies, and duration. Patients also report relapse and remission of their symptoms.[2] Consequently,

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there are no universally acceptable approaches to treating and managing the syndrome, and patients are often prone to self-adjusting their medication regimens to try and enhance the treatment response.[3]

The unknown etiology and inconsistent presentation have hindered the formation and implementation of standardized diagnostic criteria.[4,5] The lack of standardization has resulted in CFS/ME becoming an umbrella term.[6] Patients who experience general chronic fatigue but do not meet the other criteria, or experience fatigue as a result of an underlying condition, can be misdiagnosed with CFS/ME. Alternatively, those who may have CFS/ME are often misdiagnosed as having another illness due to lack of recognition.[7] Progress toward establishing a well-defined diagnostic criterion was made in 1994 with the publication of the Fukuda criteria.[8,9] To meet these criteria, debilitating fatigue must be present for at least 6 months that substantially interferes with daily activities. In addition, ≥4 of the following symptoms must be present: postexertional malaise, difficulties with short-term memory or concentration, unrefreshing sleep, sore throat, muscle pain, joint pain, headaches, and tender lymph nodes. Although widely applied, the Fukuda criteria have been considered too broad,[1] capturing a widely heterogeneous patient population.

In 2003, the Canadian Consensus[1] definition was released that included the core requirements of the Fukuda criteria (chronic fatigue and postexertional malaise), with the additional requirements of symptoms specific to the neurologic, autonomic, endocrine, and immune body systems. The 2011 revision included renaming the definitions as the International Consensus Criteria (ICC) and emphasized the role of postexertional fatigue, which was labeled as postexertional neuroimmune exhaustion (PENE).[10] PENE outlines the pathologic inability of patients with CFS/ME to produce sufficient energy on demand. This scenario includes a marked, rapid physical and/or cognitive fatigability in response to exertion; postexertional symptom exacerbation; postexertional exhaustion that may be immediate or delayed; a recovery period that is prolonged, usually taking ≥24 hours; and a low threshold of physical and mental fatigability. This more specific criteria may identify a homogeneous sample compared with the Fukuda criteria.[1]

The lack of a gold standard diagnostic criteria has prevented clinical trials from being conducted in consistent CFS/ME populations, and it has also prevented the application of results in different settings. Additional complications arise when factors such as ethnicity, age, and socioeconomic demographic factors are taken into account. In many cases, trials have suffered from poor external validity. Thus, universally applicable evidence-based research and practices are limited. Pharmacologic treatment of CFS/ME and management of symptoms is a research area that has proven to be inconsistent and inconclusive.[11] Despite a lack of strong supporting evidence, however, patients with CFS/ME report using a great number and variety of medications.[12]

The aim of the present systematic review was to summarize and examine available clinical research on drug therapies in patients with CFS/ME, provide a comprehensive assessment of the effectiveness of these therapies, and identify how outcomes are being measured and whether these outcomes are appropriate.

MATERIALS AND METHODS

Ovid MEDLINE, EMBASE, and PubMed databases were searched. The Medical Subject Headings used included the following: *fatigue syndrome, chronic; myalgic encephalomyelitis; therapeutics; treatment; medication; complementary therapies; pharmaceutical preparations; drug therapy; vitamins; minerals; enzymes and coenzymes; anti-depressive agents; gastrointestinal agents* or *anti-inflammatory agents, non-steroidal; analgesic; antibacterial agents; non-prescription drugs; melatonin; symptom management; serotonin receptor agonists;* and *fatty acids, omega 3,* or *fish oil*. Search was restricted to English publications. Databases were searched from the beginning of their archives to March 2016.

Selection Criteria

Publications were included in this literature review if the trial was a randomized, placebo-controlled clinical trial, with a modern drug therapy/pharmaceutical substance as the intervention to alleviate symptoms and the subject group met specific CFS/ME criteria (Fukuda or ICC). Complementary and alternative medications were not investigated. No age or geographical restriction was placed on the patient population.

Trials were excluded if the drug therapy was combined with any other form of treatment/therapy; for example, trials including graded exercise therapy, cognitive behavior therapy, adaptive pacing, or any other nonpharmaceutical treatment plans. Trials were also excluded if participants were experiencing any other conditions (eg, CFS/ME and fibromyalgia). Publications involving patients with "unexplained