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THERAPEUTICAL INTERVENTIONS FOR MYALGIC ENCEPHALOMYELITIS/CHRONIC FATIGUE SYNDROME; A REVIEW OF PHASE IV CLINICAL TRIALS

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Background: *Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a disabling and complex illness with multifactorial etiology. Current clinical trials were examined to understand the characteristics of ME/CFS as well as possible therapeutical interventions.* ***Aim:*** *To identify features of clinical trials related to ME/CFS registered at ClinicalTrials.gov, specifically, the therapeutical interventions used to manage the syndrome in phase IV.* ***Method:*** *Analysis of all clinical trials registered at ClinicalTrials.gov for ME/CFS. Those clinical trials that employed a targeted therapy were included. The analysis identified a selection of clinical trials examining a targeted therapy for ME/CFS, providing a platform for further exploration of potential treatments.* ***Results:*** *By November 19th, 2022, 151 clinical trials related to ME/CFS had been found. Interventional studies were the most prevalent type. However, the trials were restricted to specific continents and were not extensively conducted in pediatric patients. Micronutrients were the most commonly used intervention. Phase IV studies had fewer clinical trials with limited interventional measures. Only three out of nine studies completed pharmacological interventional studies, and of these, sodium oxybate was being used most frequently.* ***Conclusion:*** *Among the clinical trials identified through this paper, there were few related to ME/CFS treatment. The interventions in the completed phase IV studies involved drugs that mainly interacted with the CNS, and more rarely that had an effect on blood vessels and blood perfusion. The limited number of phase IV clinical trials meant that the results were inconclusive.*

Keywords: *Myalgic encephalomyelitis; pain; clinical trials; chronic fatigue syndrome; therapeutics.*

INTRODUCTION

Myalgic encephalomyelitis (ME), which is also known as chronic fatigue syndrome (CFS), is a complex and chronic illness that results in long-term debilitation, lasting for at least six months and frequently persisting for several years[1–3]. Myalgic encephalomyelitis (ME) typically manifests in individuals between the ages of 20 and 45, and it is more prevalent in women, with a female-to-male ratio of 3:1[4]. The etiology of ME/CFS is not yet fully understood, and it is believed to involve a complex interplay of genetic, environmental, and immunological factors[5]. Several genetic factors have been implicated in the development of ME/CFS. Studies have found that certain gene polymorphisms, such as those involved in the regulation of the immune system and the production of energy in the body, may increase the risk of developing the illness[6&7]. In addition, environmental factors such as viral infections, exposure to toxins, and psychological stress have also been associated with the onset of ME/CFS[8&9]. Immune dysfunction is a hallmark of ME/CFS, and a dysregulated immune response has been implicated in the pathophysiology of the illness. Studies have found evidence of chronic activation of the immune system, including

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elevated levels of proinflammatory cytokines[10]. Furthermore, abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis, which regulates the body's stress response, have been observed in ME/CFS patients[11]. These abnormalities may contribute to the fatigue and cognitive impairment observed in the illness.

The key features of ME/CFS include functional limitations, extreme fatigue that significantly impacts daily life, difficulties with sleeping, flu-like symptoms, impaired memory or focus, discomfort in the muscles and bones, and dysfunction in both cognitive and autonomic processes, as well as experiencing pain in multiple joints.[12&13]. This disorder significantly impairs the patients' ability to carry out their crucial daily activities[14]. The symptoms experienced by patients are prolonged fatigue, cognitive problems, chronic pain, autonomic dysfunction, and flu-like symptoms. All of these factors greatly diminish their quality of life[15-18]. At present, the US FDA has not approved any specific treatments for managing the syndrome. As a result, supportive care such as pain relief medication is typically administered[3&18]. A number of clinical trials have been conducted with the aim of managing patients' prognosis, providing relief for symptoms, and facilitating the restoration of functions that have been impaired by ME. Interestingly, this condition has no specific treatment and there are limited pharmacological options for managing the symptoms.

This paper explores the fundamental concepts of ME, focusing on its characteristics and the therapeutical interventions of clinical trials registered at clinicaltrails.gov. The U.S. National Library of Medicine publishes the data, which are collected from 221 countries around the world in both privately and publicly funded clinical studies[19].

METHODS

Data sources, search, and extraction

The ClinicalTrials.gov database was searched, and all the clinical trials conducted on ME-related clinical trials registered from up to and including 19th November 2022 were retrieved. The data were extracted manually and downloaded from the database's registry, covering the below criteria.

Inclusion and exclusion criteria

To find relevant clinical trials related to a medical condition known as myalgic encephalomyelitis (ME), a keyword search was conducted. This condition is also referred to as chronic fatigue syndrome (CFS), so trials related to CFS were also included in the search. The database provided information on the trials, such as the type of intervention and the medication used, as well as the results. The study focused on primary outcomes, participant numbers, and trial duration, which were all obtained from the database. Only phase IV medications were considered for this study, while the first three phases were excluded.

Data categories

The information collected from each study included its present status, interventions, sponsors, phase, estimated enrollment, eligibility criteria (age), study type, study design, and location. Clinical trials for ME were identified by ClinicalTrials.gov and were conducted in various continents, including Europe, Asia, and North America (encompassing the United States, Canada, and Mexico), as well as others like Oceania, the Middle East, South and Central America, and Africa. Studies that didn't specify their location were excluded, while studies carried out in multiple locations were counted separately for each region. Interventional studies without allocation information were categorized as an unknown allocation category (N/A). Drug interventions were classified according to their drug classes, and the number of drugs within each class was determined manually from the drug's generic name.

Statistical analysis

The GraphPad Prism 9.5.1 software (GraphPad Software, Inc., San Diego, CA, USA) was utilized to express the attributes of the clinical trial variables in terms of counts and percentages for the categorical and nominal variables. This was done by employing basic descriptive statistics.

RESULTS AND DISCUSSION

Results

Analysis of the number of research registrations

A total of 151 clinical trials related to ME were found in the ClinicalTrials.gov registry.

Clinical trials' characteristics

From 151 studies, there were 58.455 subjects in total. Most studies were clinical trials with randomization, conducted in Europe or the U.S., funded by an organization/university, and already completed. The majority of the studies were carried out with subjects 18 years old and over. Only 18 (11.9%) studies included children. A detailed description of the trial characteristics, including clinical trial status, participant numbers, study type and allocation, geographical region, and funding bodies is presented in Table 1.

Table 1: Clinical trial characteristics.

Status	**Number**	**Percentage (%)**
Recruiting	26	17.2
Not yet recruiting	8	5.3
Unknown	17	11.3
Completed	77	51.0
Terminated	6	4.0
Withdrawn	4	2.6
Active, not recruiting	10	6.6
Available	1	0.7
Enrolling by invitation	2	1.3
Number Enrolled	**Number**	**Percentage (%)**
≤ 100	94	62.3
101–199	30	19.9
≥ 200	25	16.6
N/A	2	1.3
Study type and Allocation	**Number**	**Percentage (%)**
Interventional (Clinical Trial)	108	71.5
- Randomized	75	49.7
- Non-randomized	12	7.9
- N/A	21	13.9
Observational	42	27.8
Expanded Access	1	0.7
Region	**Number**	**Percentage (%)**
World	151	100.0
Africa	1	0.7
East Asia	7	4.6
Europe	64	42.4
Middle East	1	0.7
North America	61	40.4
Canada	3	2.0
United States	58	38.4
South America	1	0.7
Funding body	**Number**	**Percentage (%)**
Government, excluding U.S. Federal	9	6.0
Industry	21	13.9
National Institutes of Health	8	5.3
U.S. Federal Agency, excluding NIH	2	1.3
University/Organization	120	79.5

Drugs in phase IV

Nine studies were found in the phase IV studies, but only six studies focused on pharmacologic interventions. The drugs that were studied in the trial were the following:

Solriamfetol

Solriamfetol is a selective norepinephrine-dopamine reuptake inhibitor with US FDA approval for the treatment of excessive sleepiness during the day with narcolepsy or obstructive sleep apnea[20]. It binds with dopamine reuptake transporter and norepinephrine reuptake transporter at the presynaptic neuron, leading to an increase in dopamine and norepinephrine levels in the brain[21]. The mechanism of solriamfetol's effect on ME/CFS was not published but it might involve the dopamine imbalance in ME/CFS pathology. A dopamine dysfunction has been found in CFS, especially in childhood chronic fatigue syndrome (CCFS)[22]. Therefore, it is assumed that dopamine-modulating drugs could result in the clinical improvement of ME/CFS fatigue and cognitive symptoms because of the disease pathology[23]. Solriamfetol is a promising wake-promoting agent that has been shown to improve fatigue, cognitive function, and other symptoms in patients with ME/CFS. The use of Solriamfetol in clinical practice may provide a much-needed treatment option for patients with this debilitating condition. However, further studies are needed to assess the long-term safety and efficacy of Solriamfetol, particularly with regards to its potential for abuse and dependence.

Sodium Oxybate

Sodium oxybate is a central nervous system (CNS) depressant for excessive daytime sleepiness associated with narcolepsy treatment[24&25]. Sodium oxybate is the salt form of gamma-hydroxybutyrate (GHB) – an endogenous GABA metabolite. Its mechanism of action is related to its property as a neurotransmitter, which acts as GABA, binds to GABA-B receptors and leads to GABA-B receptor agonist activity[26&27]. In addition, it can improve deep sleep by increasing the time spent in Stages N2 and N3 while reducing stages N1/Wake/REM shift[28]. With this property of improving deep sleep, it was reported to reduce the sleep disturbances in ME/CFS, lessening fatigue[24]. Particularly, it was the intervention found in three out of nine (33%) phase IV trials. Overall, Sodium oxybate works by decreasing the activity of certain cells in the brain, helping to reduce excessive daytime sleepiness. It is usually taken orally and can help regulate sleep patterns. Solriamfetol has been shown to be generally safe and well-tolerated in clinical trials[29]. The most common adverse effects reported in clinical trials include headache, nausea, and decreased appetite[30].

Lisdexamfetamine dimesylate

Lisdexamfetamine dimesylate is a long-acting amphetamine prodrug for attention-deficit hyperactivity disorder (ADHD) in both adults and children[31]. The mechanism of lisdexamfetamine on ADHD symptom improvement is not clear. Lisdexamfetamine dimesylate is a prodrug that is converted to dextroamphetamine in the body[32]. Dextroamphetamine is a central nervous system stimulant that increases the levels of dopamine and norepinephrine in the brain[33]. It is believed that the dysregulation of these neurotransmitters may play a role in the pathophysiology of ME/CFS[34]. Therefore, Lisdexamfetamine dimesylate may have a beneficial effect in patients with ME/CFS by improving fatigue, cognitive impairment, and other symptoms.

However, it has been hypothesized that it inhibits dopamine and norepinephrine reuptake, leading to the enhancement of dopamine and norepinephrine release from the presynaptic neuron to the extra neuronal space[35]. In one of the clinical trials, Lisdexamfetamine dimesylate was used and up-titrated from 30 to 70 mg in week 4 when no significant adverse effects were observed in the subjects.

Sildenafil

Sildenafil is phosphodiesterase 5 (PDE-5) inhibitor and it is used to treat pulmonary hypertension and erectile dysfunction. Sildenafil selectively and competitively binds to PDE-5 – an enzyme found in high concentrations in the smooth muscle of the corpus cavernosum and pulmonary arteries. The inhibition of PDE-5 decreases the degradation of cyclic guanosine

monophosphate (cGMP), resulting in cGMP prolongation and concentration elevation, which leads to vasodilation[36&37]. With this mechanism, sildenafil became a drug of interest in fatigue treatment as it increases blood flow. The effects of sildenafil were studied for ME/CFS with regard to fatigue alteration, functional status changes, and improvement of impaired cerebral blood flow, which are the pathology and symptoms of ME/CFS[38]. Therefore, while sildenafil may have some potential benefits in certain contexts, it is not a recommended treatment for chronic fatigue syndrome.

Ruconest

Ruconest is being used for the treatment of hereditary angioedema (HAE) attacks in adults and adolescents[39]. It works by increasing the level of C1 esterase inhibitor protein in the blood. This protein is crucial in regulating the blood complement system, which is involved in the immune response, including infection and inflammation[40]. Essentially, Ruconest is a synthetic copy of the C1 esterase inhibitor protein and its mechanism of action is to supplement the level of this important protein[16]. The low concentration of C1 esterase inhibitor protein because of HAE results in excessive activity in the complement and immune system, resulting in symptoms of angioedema[41]. With regard to ME/CFS, it can develop after certain infections. It has been reported that post-infectious ME/CFS involves the autoimmune mechanism[42]. Thus, ruconest is being studied in post-SARS-CoV-2 infectious ME/CFS[43].

Table 2: Summary of drugs in phase IV.

Interventions	Phase	Participants (n)	Time frame	Reason
Solriamfetol	IV	44	8 weeks	Evaluate solriamfetol's effectiveness in treating fatigue symptoms in adults with CFS
Sodium oxybate	IV	13	4 weeks	Determine whether the drug reduces the impact of sleep disruption in CFS on daytime function
Sodium oxybate	IV	17	6 weeks	Test the drug's efficacy in patients with CFS alone, without fibromyalgia
Sodium oxybate	IV	65	16 weeks	Evaluate how sodium oxybate affects fatigue and investigate the interdependence of sleep quality and fatigue in CFS
Lisdexamfetamine Dimesylate	IV	26	6 weeks	Assess how effective lisdexamfetamine dimesylate (LDX) is for treating executive functioning deficits in adults with CFS
Sildenafil	IV	12	6 weeks	Improve fatigue, functional status and impaired cerebral blood flow in CFS patients
Ruconest	IV	40	19 weeks	Assess how ruconest can improve neurological symptoms in Post-SARS-CoV-2 infections

Pharmacological classes

Table 3: Summary of drugs used, pharmacological class and mechanisms.

Drug	Pharmacological classes	Neurological mechanisms
Solriamfetol	Dopamine/norepinephrine reuptake inhibitor	Dual reuptake inhibition activity at dopamine and norepinephrine transporters
Sodium oxybate	GABA-B receptor agonist	Increases dopamine levels and increases serotonin turnover
Lisdexamfetamine Dimesylate	Central nervous system stimulants	Increases dopamine and noradrenaline efflux in prefrontal cortex
Sildenafil	Phosphodiesterase 5 (PDE5) inhibitors	Increases sympathetic activity
Ruconest	Recombinant human C1-inhibitor	Improves neurological symptoms

Discussion

This paper aimed to review the therapeutical interventions used to manage ME/CFS in phase IV clinical trials. Myalgic encephalomyelitis, sometimes called chronic fatigue syndrome, is a neurological condition that impacts how people do their usual activities. It can persist for several years, and in some cases it causes severe disability, causing problems with physical activity, social interaction, and communication[44&45]. The neurological symptoms of ME include central fatigue, mental exhaustion, brain dysfunctions, psychomotor slowness, disrupted sleep, altered pain and sensory perception, cognitive disorders, and severe dysautonomia[46–48].

Various mechanisms may contribute to the debilitating symptoms of ME/CFS, including underlying pathogenesis that cause body-wide molecular and cellular changes maintained by stable alternative states[49&50]. These underlying causes could include infection, toxins, trauma, and other environmental factors. These triggers set off a chain reaction of events that disrupt the body's normal homeostatic state, resulting in the wide array of symptoms associated with ME/CFS. This paper has also revealed that the pharmacological treatment of ME is limited to some continents and not extensively studied in pediatrics. The clinical trials carried out on this disease were majorly conducted with adults, which is logical as the disease peak is seen in patients aged 20–45 years old.

For the pharmacological treatment, this study concentrated on phase IV studies, which are conducted after the US FDA has approved a drug for marketing. The primary aim of phase IV trials is to gather additional information about a drug's safety, efficacy, or optimal use (U.S. National Library of Medicine, 2021). In some cases, phase IV represents a real-world scenario of drug usage[51]. In this review, all of the drugs involved with phase IV were linked to the CNS or had an effect on blood vessels and blood perfusion – the one exception was ruconest, which is an immunomodulator. Sodium oxybate was frequently used in phase IV trials. It is a CNS depressant used to treat excessive daytime sleepiness associated with narcolepsy treatment[28]. Earlier studies on sodium oxybate and ME were limited. One retrospective study used 118 participants found that sodium oxybate was able to relieve pain and fatigue in CFS and fibromyalgia (FMS) patients (Spitzer and Broadman, 2010). Lisdexamfetamine is a central nervous system stimulant approved for ADHD (Goodman, 2010). It attracted interest because a previous study in the early 2000's reported a possible relationship between ADHD and CFS/FMS. Therefore, one phase IV efficacy and safety trial was conducted. Moreover, solriamfetol is still being examined in clinical trials, which means that it has not yet been approved by the FDA. Therefore, its effects on cognition or its effectiveness in treating cognitive impairment are still unknown and not backed by scientific evidence. The published data from the above clinical trials show significant outcomes with different therapeutical interventions and targeted therapies. For instance, sodium oxybate was used frequently for patients with fatigue and muscle pain who also complained of disturbed sleep.

Conclusion

The findings from the paper suggest that there are few clinical trials on ME, with few therapeutical options. The interventions found in phase IV trials involved drugs that affected the CNS or which had an effect on blood vessels and blood perfusion. This review has also revealed that the pharmacological treatment of ME is limited to some continents. Further research should focus on finding ways to improve the efficacy of existing treatments and exploring potential novel treatments that may be more effective. Additionally, research should look into how treatments can be made more accessible in regions where they are not currently available.

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Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

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التدخلات العلاجية لالتهاب الدماغ والنخاع العضلي / متلازمة التعب المزمن ؛ مراجعة المرحلة الرابعة من التجارب السريرية

ناصر العرفي

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مقدمة: التهاب الدماغ والنخاع العضلي / متلازمة التعب المزمن (ME / CFS) هو مرض معقد له مسببات متعددة العوامل. تم فحص التجارب السريرية الحالية لفهم خصائص هذا المرض وكذلك التدخلات العلاجية الممكنة.

الهدف: تحديد سمات التجارب السريرية المتعلقة بالتهاب الدماغ والنخاع العضلي المسجلة في ClinicalTrials.gov، وبشكل أكثر تحديدًا ، التدخلات العلاجية المستخدمة لإدارة المتلازمة في المرحلة الرابعة. علاوة على ذلك ، يلخص هذا التحليل نتائج التجارب السريرية من حيث فعالية الدواء ، والإجراءات ، والتأثير على نوعية الحياة.

الطريقة: تحليل جميع التجارب السريرية المسجلة في ClinicalTrials.gov لالتهاب الدماغ والنخاع العضلي .تم تضمين تلك التجارب السريرية التي استخدمت العلاج الموجه لهذا المرض.

النتائج: حتى ١٩ نوفمبر ٢٠٢٢ ، تم العثور على ١٥١ تجربة إكلينيكية متعلة بالتهاب الدماغ والنخاع العضلي كانت الدراسات التدخلية الأكثر انتشارًا. ومع ذلك ، اقتصرت التجارب على قارات محددة ولم يتم إجراؤها على نطاق واسع في مرضى الأطفال. كانت المغذيات الدقيقة هي التدخل الأكثر استخدامًا. من ناحية أخرى ، كان لدراسات المرحلة الرابعة عدد أقل من التجارب السريرية ذات الإجراءات التدخلية المحدودة. أكملت ثلاث دراسات فقط من أصل تسع دراسات علاجات و تدخلات دوائية ، ومن بينها ، تم استخدام أوكسيبات الصوديوم بشكل متكرر.

الخلاصة: من بين التجارب السريرية التي تم تحديدها من خلال هذا البحث ، كان هناك عدد قليل من التدخلات العلاجية لعلاج التهاب الدماغ والنخاع العضلي. تضمنت الاستخدامات في دراسات المرحلة الرابعة المكتملة الأدوية التي تفاعلت بشكل أساسي مع الجهاز العصبي المركزي ، ونادرًا ما كان لها تأثير على الأوعية الدموية. كان العدد المحدود من التجارب السريرية للمرحلة الرابعة يعني أن النتائج كانت غير كافية.