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CHRONIC PAIN (R STAUD, SECTION EDITOR)

The Invisible Burden of Chronic Fatigue in the Community: a Narrative Review

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Abstract

Purpose of Review Unexplained fatigue is commonly reported in the general population, with varying severity. Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) sits at the extreme of the fatigue continuum, yet more individuals experience unexplained prolonged fatigue (1–6-month duration) or chronic fatigue (> 6 months) that, although debilitating, does not fulfil ME/CFS criteria. This review examines the empirical literature comparing symptoms for those with prolonged fatigue, chronic fatigue and ME/CFS.

Recent Findings Substantial overlap of self-reported psychological, physical and functional impairments exists between chronic fatigue and ME/CFS. The conversion rate from prolonged or chronic fatigue to ME/CFS is not understood. Current research has failed to uncover factors accounting for differences in fatigue trajectories, nor incorporate comprehensive, longitudinal assessments extending beyond self-reported symptoms.

Summary Distinguishing factors between prolonged fatigue, chronic fatigue and ME/CFS remain poorly understood, highlighting a need for longitudinal studies integrating biopsychosocial approaches to inform early management and targeted rehabilitation strategies.

Keywords Myalgic encephalomyelitis · Chronic fatigue syndrome · Fatigue · Autonomic · Function

Introduction

Background

Fatigue is a common experience, affecting up to 38% of adults (point prevalence) in the general community [1, 2]. Fatigue can be both a transient accompaniment of everyday challenges and a pervasive symptom in a myriad of diseases, ranging from infective, autoimmune and even malignant disorders [3–5], to psychiatric conditions such as major depression, in which psychomotor slowing and fatigue are diagnostic features [6]. In these conditions, symptomatic complaints of both physical fatigue (i.e. difficulty achieving motor tasks) and mental fatigue (i.e. difficulty achieving cognitive tasks) are reported. Fatigue is therefore a complex symptom, incorporating perceptions of weakness and slowness, as well as increased effort to achieve normal physical and mental performance.

In the primary care setting, fatigue is the most common presentation of unexplained illness yet due to its non-specific nature and variance in symptom duration and severity, fatigue can be challenging to assess, diagnose and treat [5]. It has also been reported that in almost 50% of patients presenting with

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fatigue, the final diagnosis will be medically unexplained "tiredness or exhaustion", which nevertheless can persist for months and in some cases, for several years [1, 7, 8].

Medically unexplained, debilitating fatigue that persists for 1 to 6 months is defined as prolonged fatigue [9]. If the fatigue persists for more than 6 months, is not improved by rest, is often exacerbated by mental or physical strain and is accompanied by at least four additional constitutional symptoms including sore throat, neurocognitive dysfunction, tender lymph nodes, muscle pain, multi-joint pain, headaches, unrefreshing sleep and post-exertional malaise, it is termed myalgic encephalomyelitis/chronic fatigue syndrome [ME/CFS; 9]. Although other more recent diagnostic criteria for ME/CFS exist, the Fukuda criteria are the most commonly used and extensively validated [for recent review, see 10]. Further, the fundamental elements remain consistent across criteria [10]. Finally, if the fatigue persists for greater than 6 months but does not meet the criteria for ME/CFS, it is referred to as chronic fatigue.

Approximately, 18% of the population is estimated to have prolonged fatigue [7]. Limiting cases to only those with unexplained fatigue for greater than 6 months, Steele, Dobbins [8] reported a prevalence of 2%, which is considerably higher than the 0.2% who met diagnostic criteria for ME/CFS after careful exclusion of alternative medical or psychiatric explanations for the symptoms.

Chronic fatigue and ME/CFS carry substantial social and economic costs, with impairment in function, medical costs and burden of care costing an estimated £14,060 per person per annum for ME/CFS and £4704 per person per annum for chronic fatigue in the UK [11]. Over 90% of the costs were accounted for by care provided by friends and family members and by lost income from employment. Costs were significantly higher for patients with dependants and for those with greater levels of functional impairment [11, 12]. The most recent economic cost estimate for ME/CFS in Australia suggested, some decades ago, a sum of greater than $59 million per annum [13]. In the USA, the estimated cost related to chronic debilitating fatigue is greater than $9 billion per annum [14]. Clearly, the disease burden associated with chronic fatigue presents a significant economic, social and personal challenge. Yet, it is ME/CFS that has been, almost exclusively, the focus of empirical investigation into pathophysiology and treatment [15–18].

Decades of dedicated research into the pathophysiology of ME/CFS have so far failed to produce convincing evidence of an underlying biological cause, such as a persistent infection or immunological, endocrine, microbial or metabolic dysfunction and have also excluded simplistic notions of depression or a primary sleep disorder [as reviewed in 19]. Similarly, an array of randomised controlled trials seeking curative outcomes from anti-viral, immunological, hormonal, antidepressant and many other therapies has failed to show any benefit over placebo or have failed the test of independent replication [20••]. By broadening the scope of investigation from a narrow focus on ME/CFS to incorporate those with unexplained prolonged or chronic fatigue, better insights may be gained into the enigmatic nature of fatigue in general and thus advance targeted strategies for early intervention and management.

This short narrative review examines the current literature characterising individuals with prolonged or chronic fatigue, compared to those who meet the criteria for ME/CFS. Key challenges and gaps in the current literature will also be highlighted.

Method

A literature search was conducted using the databases PubMed, PsychInfo and Scopus, last completed in June 2018. Only articles published after 1994 were included in the search, to allow for the identification of patients with ME/CFS using the Fukuda, Straus [9] or any of the subsequently published diagnostic criteria. Search terms included ("prolonged fatigue" OR "chronic fatigue") AND ("community" OR "sub-clinical" OR "sub-threshold" OR "general population"). Reference lists of relevant papers were also searched for any additional articles. Due to substantial variation in the criteria used for defining and/or measuring prolonged fatigue, chronic fatigue and ME/CFS, a broad inclusion criterion was used. Articles were included if they described the symptomatology of individuals with unexplained prolonged fatigue or chronic fatigue, compared to participants with ME/CFS.

Results

Twelve articles met the search criteria specifically three articles including cases with either prolonged or chronic fatigue, four examining chronic fatigue and prolonged fatigue and five focusing on chronic fatigue. The sample characteristics, fatigue criteria utilised and symptomatology comparisons between participants with prolonged fatigue, chronic fatigue and ME/CFS are summarised in Table 1.

Characterising Chronic Fatigue in the Community

To date, very few studies have been conducted with a specific focus to characterise the symptomatology of individuals with chronic fatigue, and even less attention has been directed towards prolonged fatigue. The limited studies that have exclusively focused on a prolonged fatigue population have investigated prevalence rates and sociodemographic and psychiatric correlates in primary care settings [21–23]. These papers

Table 1 Summary of studies comparing prolonged fatigue, chronic fatigue and myalgic encephalomyelitis/chronic fatigue syndrome

Article	Sample characteristics	Fatigue criteria	PF vs CF or ME/CFS	CF vs healthy control	CF vs ME/CFS
De Gucht et al., 2016	563 patients recruited from primary health care centres in the Netherlands, CF = 192, ME/CFS = 192	CF = fatigue for 1–24 months and did not meet CDC 1994 criteria according to self-report questionnaire. ME/CFS = met CDC 1994 criteria according to self-report questionnaire			CF < ME/CFS scores: duration and severity of fatigue, somatic complaints, unemployment rate, medical visits. CF > ME/CFS scores: physical activity, physical functioning (using the Short Form Health Survey; SF-12), "all or nothing" behaviour. CF = ME/CFS scores: age, gender, educational level, social support, anxiety and depression (using subscales from the Brief Symptom Inventory).
Addington et al., 2001	1741 general household in USA, CF = 242	CF = unexplained fatigue for > 2 weeks and consulted health professional/took medication/functionally impaired		CF > HC: aged 25–44 years, female, self-reported lifetime Dx of depression. CF = HC: ethnicity, education, marital status.	
Sulheim et al., 2015	159 adolescents referred by hospitals and primary care practitioners, CF = 120, control = 39	CF = unexplained, disabling fatigue for > 3 months		CF < HC: processing speed, working memory, cognitive inhibition response time, verbal learning, executive function. CF = HC: cognitive flexibility, delayed recall.	CF = ME/CFS: processing speed, working memory, cognitive inhibition response time, verbal learning, executive function, cognitive flexibility, delayed recall.
Jason et al., 1999	18,675 general population in USA, PF = 1435, CF = 304, ME/CFS-like = 408	Prolonged fatigue = unexplained, disabling fatigue for 1–6 months. CF = unexplained, disabling fatigue for > 6 months and did not meet CDC 1994 criteria	Did not make comparisons of PF and CF or ME/CFS	CF > HC: ethnic minority, female, separated, ever married, divorced have children, less educated, lower occupation status, fatigue severity.	CF < ME/CFS: sore throat, painful glands, muscle aches and pains, worse after exercising, new headaches, joint pain, unrefreshing sleep, concentration/memory problems interfering.
Solomon et al., 2003	7162 from the adult population in USA, PF = 516, CF = 1129, ME/CFS = 43	Prolonged fatigue = unexplained fatigue for 1–6 months. CF = unexplained fatigue for > 6 months and did not meet CDC 1994 criteria. ME/CFS = met CDC 1994 criteria according to clinical examination	PF > CF and ME/CFS: employment, hours spent on meaningful activity. PF = CF and ME/CFS: hours spent on other activities	CF < HC scores: employment, hours spent on meaningful activity, fatigue. CF = HC: time spent on chores	CF > ME/CFS scores: employment, hours spent on work and other activities. CF = ME/CFS: time spent on chores
van't Leven et al., 2009	9062 community residents in the Netherlands, PF = 267, CF = 997, ME/CFS-like = 89	Prolonged fatigue = unexplained fatigue for 1–6 months. CF = unexplained fatigue for > 6 months and did not meet CDC 1994 criteria. ME/CFS-like = met CDC 1994 criteria but not medically confirmed	Did not make comparisons of PF and CF or ME/CFS	CF > HC: female, use of analgesics, anti-depressives, smoking, alcohol consumption, overweight. CF < HC: older age, physical activity	
Martin et al., 2007	2412 general population in Germany, SF = 146, PF = 46, CF = 147	Short fatigue = fatigue for < 3 months. Prolonged fatigue = fatigue for 3–6 months. CF = fatigue for > 6 months	Did not make comparisons of PF and CF or ME/CFS	CF > HC: female, older, not single, lower educational degree, lower income, somatoform symptoms. CF < HC: quality of life	
Buchwald et al., 1995	2132 members of health maintenance organisation in USA, CF = 71, ME/CFS = 3, control = 74	CF = unusual, unexplained, disabling fatigue for > 6 months and did not meet CDC 1994 criteria. ME/CFS = met CDC 1994 criteria		CF > HC: muscular weakness, muscular pain, sleep disturbances, enlarged/tender lymph, mental health problems, psychological distress, neuropsychological complaints. CF < HC: general health, vitality, physical function, body pain, emotional functioning, role function, social function (subscales of the Medical Outcomes Study Short Form	

Table 1 (continued)

Article	Sample characteristics	Fatigue criteria	PF vs CF or ME/CFS	CF vs healthy control	CF vs ME/CFS
				General Health Survey; SF-36). CF = HC: age, sex, ethnicity, employment.	
Darbishire et al., 2003	141 patients recommended by general practitioners in the UK, CF = 97, ME/CFS = 44	CF = presented to GP with unexplained fatigue for > 6 months and did not meet CDC 1994 criteria. ME/CFS = met CDC 1994 criteria			CF < ME/CFS scores: depression, psychiatric referral history, fatigue symptoms, functional impairment, self-help group membership, GP consultations, unemployment, psychotropic medication prescription, believed that fatigue will last longer, dizziness, headaches, pain, sore joints, breathlessness. CF = ME/CFS scores: duration of fatigue, perceived control, anxiety, attribution of illness to physical causes.
Evengard et al., 2003	640 outpatients at fatigue clinic in Sweden, CF = 216, ME/CFS = 269	CF = unexplained fatigue and did not meet CDC 1994 criteria. ME/CFS = met CDC 1994 criteria			CF < ME/CFS: somatic complaints, self-reported functional impairment and absence from work. CF > ME/CFS: psychiatric comorbidity, depression, believed stress as starter. CF = ME/CFS: socioeconomic status, marital status, sick leave.
Buchwald et al., 1996	431 patients at chronic fatigue clinic in USA, CF = 246, ME/CFS = 185	CF = unexplained fatigue that did not meet CDC 1988 criteria. ME/CFS = met CDC 1988 criteria		CF < HC scores: physical function, general health, vitality, body pain, role function, emotional function, social function, mental health (subscales of the SF-36). CF = HC: age, sex, ethnicity, employment.	CF > ME/CFS scores: physical functioning, role functioning, body pain (subscales of the SF-36). CF = ME/CFS scores: general health, vitality, emotional function, social function, or mental health (subscales of the SF-36).
Skapinakis et al., 2003	10,108 general household in UK, CF = 970	CF = unexplained fatigue for > 6 months		CF > HC: female, with children, recent stressful life event, perceived lack of social support, self-rating of health as poor, psychiatric comorbidity, consulted GP more. CF < HC: adults living with parents and single.	
Taylor et al., 2002	18,675 general population in USA, CF = 51, control = 78	CF = randomly selected from those who met the CDC 1994 criteria but were not medically confirmed for ME/CFS (not unexplained, not separating ME/CFS)		CF > HC: divorce, older, functional interference, disability income, fatigue severity.	
Taylor et al., 2003	18,675 general population in USA, CF = 227, control = 74	CF = met CDC 1994 criteria but not medically confirmed (not unexplained, not separating ME/CFS)		CF > HC: have children, lower SES, female, older age, divorced/widowed/separated, ethnic minority, current psychiatric Dx, lifetime psychiatric Dx. C > CF: working full time, never married.	

PF prolonged fatigue, *CF* chronic fatigue, *ME/CFS* myalgic encephalomyelitis/chronic fatigue syndrome

are outside the scope of the current review because they have not compared the symptomatology of participants with prolonged fatigue to patients with ME/CFS.

Summarising the results detailed in Table 1, only four studies [1, 24–26] made distinctions between prolonged fatigue and chronic fatigue, and of these, only Solomon and Nisenbaum [26] compared the groups. Participants with prolonged fatigue were more likely to be employed and spend more hours on meaningful activity than those with chronic fatigue, as well as those with ME/CFS. There were no differences between those with prolonged fatigue, chronic fatigue and ME/CFS for hours spent on other activities such as schooling, hobbies and volunteer work [26]. Prolonged fatigue likely represents a more heterogeneous illness category due to the relatively short duration of fatigue and potentially undiagnosed aetiology of the fatigue. The fatigue may ultimately self-resolve with adequate time and/or medical intervention, or after more extensive investigation, it may be determined to be a symptom of another condition such as a chronic viral infection, anaemia or other chronic disease [4].

In respect to chronic fatigue, patients were characterised by higher scores on self-report measures of psychological distress [27, 28] and physical health [27–29] and higher scores on measures of functional impairment across physical, social and mental domains [27–29], compared to healthy control subjects. Sulheim and Fagermoen [30] also demonstrated neurocognitive impairments, including reduced processing speed, poorer working memory, a reduction in cognitive inhibition, poorer verbal learning and executive function but not cognitive flexibility or delayed recall, compared to healthy control subjects.

In many ways, the *nature* of the symptoms reported by those with chronic fatigue is very similar to those reported by individuals with ME/CFS, including significant impairment in physical and mental functioning. In particular, most studies found that subjects reported similar levels of psychological distress (e.g., SF-36, Anxiety and Depression Rating Scale) and cognitive performance [27, 30; but also see Darbishire et al., 2003, 31, 32•]. However, patients with ME/CFS did report greater *severity* of symptoms on some measures. Specifically, physical health was generally rated lower in people with ME/CFS compared to those with chronic fatigue, particularly for somatic complaints such as sore joints, headaches and body pain [24, 31–33]. This is not surprising given that the presence of several of these somatic symptoms is a contributing factor towards a diagnosis of ME/CFS [9]. Functionality is also more severely impaired for patients with ME/CFS compared to subjects with chronic fatigue, demonstrated by self-reported impairment on disability scales, as well as reduced rates of employment and increased frequency of medical consultations [27, 31–33]. Although some symptoms reported by patients with ME/CFS are more severe than those reported by sufferers of chronic fatigue, it is very apparent that chronic fatigue is a debilitating condition in its own right and overlaps substantively with ME/CFS.

Discussion

Missing Evidence

The course of illness from prolonged or chronic fatigue potentially to a diagnosis of ME/CFS is not well understood. Little progress has also been made in uncovering risk profiles, early and late perpetuators, as well as the factors accounting for potential differences in the trajectories of fatigue. Given that the definitional separation of ME/CFS from prolonged and chronic fatigue was not originally intended to create distinct clinical entities but to facilitate comparative study [9], it follows that a careful study of these groups may benefit our understanding of the aetiology and progression of ME/CFS.

While it is generally acknowledged that efforts need to be directed towards discovery of objective markers and biological concomitants of the disorder, much of the available evidence in the area is still reliant on self-report measures of symptoms. This is problematic, given the well-documented discrepancies between subjectively reported and objective performance measures in patient populations generally [34–36] and in patients with ME/CFS in particular [37–39]. For a more accurate understanding of chronic fatigue, there is a need for research in this area to move towards utilising more biological and behavioural assessments, in combination with self-report measures.

In recent years, a growing body of solid evidence supports a role for autonomic dysfunction in ME/CFS [40–44]. ME/CFS is characterised by neural hyper-vigilance, sympathetic hyper-responsivity and a marked loss of parasympathetic, vagus nerve activity that persists even during sleep. Measures of beat-to-beat heart rate variability provide well-established reliable indices of autonomic functioning, which have been repeatedly found to be the best independent predictor of core symptoms of unrefreshing sleep, daytime fatigue and cognitive impairment [45, 46]. Additional autonomic dysfunctions have been noted in patients with ME/CFS, such as increased heart rate with the head in the tilt position and an increased prevalence of postural orthostatic tachycardia syndrome [for a review, see 43].

It would be of value to know if the identified biological correlates in ME/CFS are linked to the aetiology of the disorder and thus detectable early and across the fatigue continuum, or whether these emerge as a secondary response to suffering from a debilitating condition over longer periods. In particular, as physical activity in patients with ME/CFS is often severely restricted, cardiovascular and autonomic disturbances may develop as a consequence of inactivity [47, 48]. For example, symptoms of orthostatic intolerance have been replicated in

healthy individuals who have also undergone dramatic reductions in physical activity [49]. Such symptoms may evolve because of the severity and duration of the illness and act as a perpetuator of impairment, offering a window of opportunity for early intervention in patients with chronic fatigue conditions.

As no curative treatment exists, current "best practice" management of ME/CFS focuses on symptom and functional improvement [50, 51]. Both cognitive behavioural therapy and graded exercise therapy have empirical support for symptom reduction in patients with ME/CFS [17, 18], yet these interventions typically show only moderate effect sizes with the average success rate rarely exceeding 30% [18, 52, 53]. With such limited response rates in long-term sufferers, these "best practice" techniques might be more useful in the early rehabilitation of those with chronic fatigue, potentially reducing the progression to a more severe condition.

Towards a Better Understanding of Fatigue

Moving forward, research into fatigue in the community would benefit from broadening its focus to include longitudinal designs that can improve current understanding of who may progress to ME/CFS, and who will recover from their fatigue. A thorough evaluation of the benefits of targeted early intervention in rehabilitating those suffering from debilitating fatigue is also long overdue. Cairns and Hotopf [54] reviewed studies investigating the prognosis of patients with chronic fatigue and ME/CFS. They identified factors associated with recovery and positive ME/CFS outcomes, such as lower baseline fatigue, a perception of symptom control and illness attribution (specifically, not attributing one's illness to physical causes). However, these studies did not include behavioural or biological assessments and mostly described recovery outcomes rather than tracking potential protective and risk factors over time.

In contrast, such efforts have been made in post-infective models of chronic fatigue. This not only offers a more homogeneous group of patients but also enables prospective, longitudinal examination of the evolution of ME/CFS followed from exposure to a documented infective trigger until recovery occurred or to a variant time period of 6 to 24 months [55–59]. These cohort studies have empirically verified the existence of a post-infective fatigue syndrome (PIFS), with up to 12% of patients with persistent fatigue fulfilling diagnostic criteria for ME/CFS at 6 months after infection. The development of PIFS was most consistently predicted by the severity of symptoms during the acute illness rather than by demographic, psychological/psychiatric or microbiological factors. Moreover, two of these studies noted a connection between the intensitiy of initial immune activation and prolonged recovery including post-infective fatigue [58, 60].

In an initial report from our Dubbo Infection Outcomes Study (DIOS), the 13% of cases with PIFS at 6 months strictly included only those individuals who *consistently* exceeded the established threshold score of the empirically derived scale of key clinical features of prolonged fatigue states [56]. Re-analysis of the now completed longitudinal DIOS data sets has revealed an additional proportion of individuals with a relapsing pattern of fatigue (34/484 or 7%) who, while not scoring above the threshold score for clinically significant fatigue at each assessment point, evidenced a score at 6 months indicative of PIFS. This discovery suggests that there is a subgroup of patients with an intermittent or relapsing course of chronic fatigue that has so far been overlooked. Further inspection of the trajectory of the fatigue in each of the groups illustrates significant differences in the progression of the fatigue from the acute illness in these groups (Fig. 1). Notably, the "relapsing" PIFS pattern follows a quadratic trend in fatigue severity, which at 1 month, it suggests recovery; however, at 6 months, it shows levels of fatigue well above the threshold score [as previously described; 56]. Moreover, at 6 months, both the consistent and relapsing PIFS groups experienced significantly more severe symptoms, not only in terms of fatigue, but also in regard to pain, neurocognitive and mood disturbance and for symptom severity overall.

Taken together, the findings that the severity of the initial illness response acts as a pertinent risk factor for the development of persistent fatigue suggest that a dysregulation in neural stress-response pathways may be triggered by such an internal stressor. Existing vulnerabilities including genetic makeup, acquired/developmental sensitisation in stress-response systems, personality and psychosocial stressors are likely to interact with such a trigger to potentiate the risk of prolonged fatigue [44]. Moreover, the notion that a dysregulation in neural stress response pathways contributes to the pathophysiology of chronic fatigue is consistent with the body

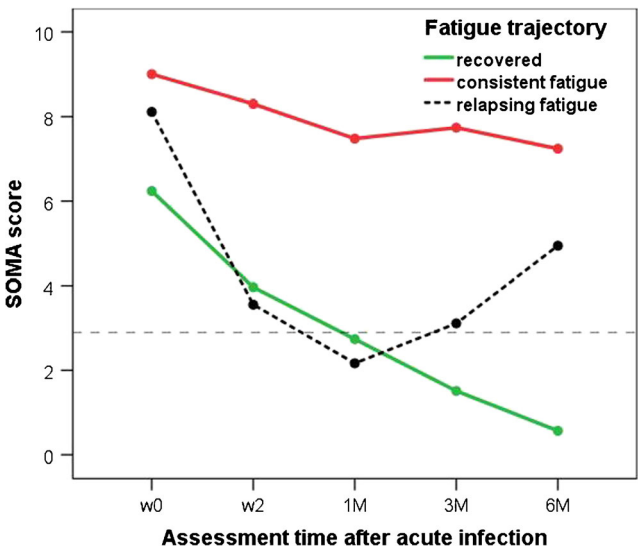

Fig. 1 Different fatigue trajectories (recovered, consistent or relapsing) identified assessing participants up to 6 months after an acute infection. The grey dotted line indicates the PIFS threshold score

of evidence relating to disturbances in autonomic signalling in ME/CFS [61]. The autonomic nervous system provides a major hard-wired connection between the body and the brain. Its complex roles, not only in maintaining homeostasis in all microenvironments, but also in adaptation, self-regulation and the modulation of motivated behaviour have been highlighted in the recent years [62–65].

Conclusion

It is only by adopting such longitudinal designs and a biopsychosocial approach to assessment that the capacity to unlock issues of vulnerability and risk will be maximised, allowing for the prediction of who will recover quickly from a period of fatigue and who will progress to ME/CFS and possibly years of disability. As very few evidence-based therapeutic options currently exist, insights gained from such study designs can help inform effective and targeted early intervention strategies to assist those with chronic fatigue before conversion to ME/CFS. In addition, this knowledge may aid in the rehabilitation of those with ME/CFS especially if underlying biological correlates are able to be identified. This would provide significant benefit to patients suffering from debilitating chronic fatigue, a group which seems to have been largely overlooked by the clinical and scientific community.

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Compliance With Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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