EXPERT REVIEWS

Diagnostic and treatment challenges of chronic fatigue syndrome: role of immediate-release methylphenidate

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José Ramón Valdizán Usón† and María Ángeles Idiazábal Alecha

†*Author for correspondence*
Servicio de Neurofisiología Clínica, Hospital Universitario Miguel Servet, Paseo Isabel la Católica 1–3, E-50009 Zaragoza, Spain
Tel.: +34 976 765 500
Fax: +34 976 566 234
jrvaldizan@auna.com

Chronic fatigue syndrome (CFS) is a distinct entity belonging to the group of persistent fatigue that can be challenging to diagnose and to treat. It is characterized by a combination of prolonged fatigue, other nonspecific somatic manifestations and neuropsychological symptoms, including difficulties with concentration, short-term memory, and thinking as well as impaired attention and slowed processing speed. Neurostimulants increasing dopamine and norepinephrine activity, such as bupropion, dextroamphetamine and recently immediate-release methylphenidate have been advocated to improve neurocognitive deficits. The use of immediate-release methylphenidate in CFS has been shown in one small study. Using the positive results of this study and the well-known beneficial effects of the drug on a range of similar cognitive symptoms in attention-deficit/hyperactivity disorder, this perspective addresses CFS and other related disorders and provides a discussion on the potential promising role of methylphenidate in the therapeutic armamentarium of CFS.

KEYWORDS: chronic fatigue syndrome • fibromyalgia • immediate-release methylphenidate

Fatigue is a common symptom in the community, with up to half of the general population reporting unusual fatigue, usually of limited duration, in large surveys [1,2]. Fatigue is also reported by at least 20% of patients seeking medical care in primary care settings [3–5]. In most cases, the fatigue is transient and is explained by prevailing circumstances, relieved by rest and is of little cause for concern. Fatigue can, however, be chronic and debilitating. Chronic fatigue syndrome (CFS) is a complex illness defined by unexplained disabling fatigue and a combination of nonspecific accompanying symptoms. Similar disorders have been described for at least 200 years and have been variously named neurasthenia, myalgic encephalomyelitis, Akureyri disease, post-viral fatigue and chronic mononucleosis [6].

CFS is characterized by profound disabling fatigue lasting at least 6 months and accompanied by numerous rheumatological, infectious and neuropsychiatric symptoms [7]. As the name implies, CFS is a symptom-based or clinical diagnosis without distinguishing physical examination or routine laboratory or imaging findings. Infectious, immunological, neuroendocrinological, sleep and psychiatric mechanisms have been investigated. However, a unifying etiology for CFS has yet to emerge. Regardless of the pathogenesis, persons with CFS, like those with other chronic diseases, have a substantially impaired functional status that results in significant personal morbidity and healthcare burden [8].

The disease affects 400,000–900,000 adults in the USA [9,10]. It has been estimated that there is a 37% decline in household productivity and a 54% reduction in labor force productivity among people with CFS. The annual total value of lost productivity in the USA was US$9.1 billion, which represents approximately $20,000 per person with CFS or approximately one half of the household and labor force productivity of the average person with this syndrome [11]. Despite the public health burden imposed by CFS, effective diagnostic, treatment and prevention strategies are not available because the etiology, risk factors and pathophysiology of the disease remain unknown.

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Box 1. Case definition for chronic fatigue syndrome [12].

A case of chronic fatigue syndrome must fulfill both major criteria and the following minor criteria: ≥6 of the 11 symptom criteria and ≥2 of the 3 physical criteria; or ≥8 of the 11 symptom criteria.

Major criteria

1. New onset of persistent or relapsing, debilitating fatigue or easy fatigability in a person who has no previous history of similar symptoms that does not resolve with bed rest, and that is severe enough to reduce or impair average daily activity below 50% of the patient's premorbid activity level for a period of at least 6 months.
2. Other clinical conditions that may produce similar symptoms must be excluded by thorough evaluation, based on history, physical examination and appropriate laboratory findings.

Minor criteria

- Symptom criteria:

To fulfill a symptom criterion, a symptom must have begun at or after the time of onset of increased fatigability, and must have persisted or recurred over a period of at least 6 months (individual symptoms may or may not have occurred simultaneously). Symptoms include:

1. Mild fever (oral temperature between 37.5C and 38.6C, if measured by the patient) or chills
2. Sore throat
3. Painful lymph nodes in the anterior or posterior cervical or axillary distribution
4. Unexplained generalized muscle weakness
5. Muscle discomfort or myalgia
6. Prolonged (24 h) generalized fatigue after levels of exercise that would have been easily tolerated in the premorbid state
7. Generalized headaches (of a type, severity or pattern that is different from headaches the patient may have had in the premorbid state)
8. Migratory arthralgia without joint swelling or redness.
9. Neuropsychological complaints (≥1 of the following: photophobia, transient visual scotomata, forgetfulness, excessive irritability, confusion, difficulty thinking, inability to concentrate or depression)
10. Sleep disturbance (hypersomnia or insomnia)
11. Description of the main symptom complex as initially developing over a few hours to a few days (this is not a true symptom, but may be considered as equivalent to the above symptoms in meeting the requirements of the case definition)

- Physical criteria:

Physical criteria must be documented by a physician on at least two occasions, at least 1 month apart

1. Low-grade fever: oral temperature between 37.6°C and 38.6°C, or rectal temperature between 37.8°C and 38.8°C (See 'Symptom criterion 1')
2. Nonexudative pharyngitis
3. Palpable or tender anterior or posterior cervical or axillary lymph nodes (lymph nodes greater than 2 cm in diameter suggest other causes)

The aim of the present perspective is to present comprehensive information on case definition of CFS, symptom overlap with other disorders, such as fibromyalgia and attention-deficit/hyperactivity disorder (ADHD) and hypothetical considerations of the use of immediate-release methylphenidate in the treatment of CFS based on promising positive results obtained in one small study.

Case definition

The complexities of CFS and the methodological problems associated with its study indicated the need for a comprehensive, systematic, and integrated approach to the evaluation, classification, and study of persons with this condition and other fatiguing illnesses. A working definition for CFS designed to improve the comparability and reproducibility of clinical research and epidemiologic studies, and to provide a rational basis for evaluating patients who have chronic fatigue of undetermined cause was first proposed by Holmes and colleagues in 1988 [12], in which the implication of Epstein-Barr virus infection (the chronic Epstein-Barr virus syndrome) as a causative agent was removed. Major and minor criteria required to fulfill the case definition for CFS are summarized in Box 1. Moreover, the name 'chronic fatigue syndrome' suggested in this first formal case definition in 1988 was retained in subsequent Australian [13] and British case definitions [14].

In this case definition of CFS, clinical conditions that may produce similar symptoms that must be excluded by thorough evaluation, based on history, physical examination and appropriate laboratory findings included: malignancy; autoimmune disease; localized infection (e.g., occult abscess); chronic or subacute bacterial (e.g., endocarditis, Lyme disease or tuberculosis), fungal (e.g., histoplasmosis, blastomycosis or coccidioidomycosis) and parasitic disease (e.g., toxoplasmosis, amebiasis, giardiasis or helminthic infestation); disease related to HIV infection; chronic psychiatric disease, either newly diagnosed or by history (e.g., endogenous depression, hysterical personality disorder, anxiety neurosis, schizophrenia, or chronic use of major tranquilizers, lithium or antidepressive medications); chronic inflammatory disease (e.g., sarcoidosis, Wegener granulomatosis or chronic hepatitis); neuromuscular disease (e.g., multiple sclerosis or myasthenia gravis); endocrine disease (e.g., hypothyroidism, Addison disease, Cushing's syndrome or diabetes mellitus); drug dependency or abuse (e.g., alcohol, controlled prescription drugs or illicit drugs); side effects of a chronic medication or other toxic agent (e.g., a chemical solvent, pesticide or heavy metal); or other known or defined chronic pulmonary, cardiac, gastrointestinal, hepatic, renal or hematological disease.

Specific laboratory tests or clinical measurements are not required to satisfy the definition of CFS, but the recommended evaluation includes serial weight measurements (weight change of >10% in the absence of dieting suggests other diagnoses); serial morning and afternoon temperature measurements;

complete blood count and differential; serum electrolytes; glucose; creatinine or blood urea nitrogen; calcium or phosphorus; total bilirubin, alkaline phosphatase, serum aspartate aminotransferase or serum alanine aminotransferase; creatine phosphokinase or aldolase; urinalysis; posteroanterior and lateral chest roentgenograms; detailed personal and family psychiatric history; erythrocyte sedimentation rate; antinuclear antibody; TSH level; HIV antibody measurement; and intermediate-strength purified protein derivative skin test with controls. If any of the results from these tests are abnormal, the physician should search for other conditions that may cause such a result. If no such conditions are detected by a reasonable evaluation, this criterion is satisfied.

However, the 1988 CFS working case definition did not effectively distinguish CFS from other types of unexplained fatigue [12]. For this reason, an international panel of CFS research experts convened in 1994 to draft a definition of the syndrome that would be useful both to researchers studying the illness and to clinicians diagnosing it [15]. The core of the revised case definition for CFS developed by the Centers for Disease Control and Prevention (CDC) is a set of uniformly applicable guidelines for the clinical and research evaluation of CFS and the other forms of fatigue. In the revised definition (Box 2), CFS is treated as a subset of chronic fatigue, a broader category defined as unexplained fatigue lasting 6 months or more. Chronic fatigue, in turn, is treated as a subset of prolonged fatigue, which is defined as fatigue lasting 1 month or longer. The expectation is that scientists will devise epidemiological studies of populations with prolonged fatigue and chronic fatigue, and search within those populations for illness patterns consistent with CFS.

A notable feature of the CDC case definition is that many nonpsychotic psychiatric disorders are not exclusionary for the diagnosis of CFS. In addition, CFS is defined on the basis of expert consensus and its diagnosis is made on the basis of symptom criteria.

Conversely, a minimum battery of laboratory screening tests should be performed. Routinely performing other screening tests for all patients has no known value. However, further tests may be indicated on an individual basis to confirm or exclude another diagnosis, such as multiple sclerosis. In these cases, additional tests should be performed according to accepted clinical standards. The use of tests to diagnose CFS (as opposed to excluding other diagnostic possibilities) should be done only in the setting of protocol-based research. In this respect, the International Chronic Fatigue Syndrome Study Group had identified ambiguities associated with exclusionary and comorbid conditions of the 1994 case definition [15], and proposed standardized internationally applicable instruments used to measure symptoms, fatigue intensity and associated disability [16]. Evaluations included psychiatric illness (Composite International Diagnostic Instrument [CIDI], Strictures Clinical Interview for DMS-IV Axis I [SCID]),

Box 2. 1994 revision of the Centers for Disease Control and Prevention case definition for chronic fatigue syndrome [15].

- In order to receive a diagnosis of chronic fatigue syndrome, a patient must satisfy two criteria:
  1. Have severe chronic fatigue of 6 months or longer duration with other known medical conditions excluded by clinical diagnosis
  2. Concurrently have four or more of the following symptoms:
     - Substantial impairment in short-term memory or concentration
     - Sore throat
     - Tender lymph nodes
     - Muscle pain
     - Multi-joint pain without swelling or redness
     - Headaches of a new type, pattern or severity
     - Un-refreshing sleep
     - Post-exertional malaise lasting >24 h
- The symptoms must have persisted or recurred during ≥6 consecutive months of illness and must not have predated the fatigue.
- Conditions that exclude a diagnosis of chronic fatigue syndrome:
  1. Any active medical condition that may explain the presence of chronic fatigue, such as untreated hypothyroidism, sleep apnea and narcolepsy, and iatrogenic conditions such as side effects of medication;
  2. Some diagnosable illnesses may relapse or may not have completely resolved during treatment. If the persistence of such a condition could explain the presence of chronic fatigue, and if it cannot be clearly established that the original condition has completely resolved with treatment, then such patients should not be classified as having chronic fatigue syndrome (e.g., some types of malignancies and chronic cases of hepatitis B or C virus infection);
  3. Any past or current diagnosis of a major depressive disorder with psychotic or melancholic features:
     - Bipolar affective disorders
     - Schizophrenia of any subtype
     - Delusional disorders of any subtype
     - Dementias of any subtype
     - Anorexia nervosa
     - Bulimia nervosa
  4. Alcohol or other substance abuse, occurring within 2 years of the onset of chronic fatigue and any time afterwards;
  5. Severe obesity as defined by a BMI ≥ 45 kg/m^2 (the range of 45 kg/m^2 was selected because it clearly falls within the range of severe obesity).
- Any unexplained abnormality detected on examination or other testing that strongly suggests an exclusionary condition must be resolved before attempting further classification.

measurement of fatigue (Checklist Individual Strength [CIS], Chalder Fatigue Scale, Krupp Fatigue Severity Scale), functional disability (Medical Outcomes Survey Short Form-36 [MOS SF-36], Sickness Impact Profile, Activity record [ACTRE]), accompanying symptoms (Somatic and Psychological Health Reports [SPHERE], CDC Symptom Checklist), sleep disturbances (Sleep Assessment Questionnaire [SAQ]), characterization of pain (McGill Pain Questionnaire [MPQ]) and neurocognitive functioning using new emerging technology (e.g., functional neuroimaging) to complement and eventually replace traditional neurocognitive function tests. The intent of the proposal of the International Chronic Fatigue Syndrome Study Group is to guide systematic and reproducible application of the current case definition so that case ascertainment will be more uniform across research study sites [16]. The fact that such tests are investigational and do not aid in diagnosis or management should be explained to the patient.

In clinical practice, no tests can be recommended for the specific purpose of diagnosing CFS. Tests should be directed toward confirming or excluding other possible clinical conditions (e.g., serological tests for Epstein-Barr virus, enteroviruses, retroviruses, human herpesvirus 6, and *Candida albicans*); tests of immunologic function, including cell population and function studies; and imaging studies, including MRI scans and radionuclide scans, such as SPECT and PET).

Two widely used definitions of CFS (from the CDC [15] and from Oxford [14]) have been developed as operational criteria for research. There are two important differences between these definitions (Box 3). The British criteria insist on the presence of mental fatigue; the American criteria include a requirement for several physical symptoms, reflecting the belief that CFS has an underlying immunological or infective pathology [16].

The Canadian Expert Consensus Panel has published the first clinical case definition for the disease known as myalgic encephalomyelitis/CFS (ME/CFS) [17]. In sharp contrast to the CDC's 1994 definition [15], this new clinical case definition makes it compulsory that in order to be diagnosed with ME/CFS, a patient must become symptomatically ill after exercise and must also have neurological, neurocognitive, neuroendocrine, dysautonomic, circulatory and immune manifestations (Box 4). In short, symptoms other than fatigue must be present for a patient to meet the criteria.

On the other hand, the Canadian diagnostic protocol also includes a list of active disease processes that explain most of the major symptoms of fatigue, sleep disturbance, pain, and cognitive dysfunction; the diagnoses of which are essential to be excluded. In addition, comorbid entities may occur in the setting of ME/CFS. Moreover, general considerations in applying the clinical case definition to the individual patient should take into account the following considerations: assessment of the patient's total illness, variability and coherence of symptoms, severity of symptoms and symptom severity hierarchy, and separate secondary symptoms and aggravations.

Box 3. Diagnostic criteria for chronic fatigue syndrome.

Diagnostic criteria

- Centers for Disease Control, 1994 [15]:
  - Clinically evaluated, medically unexplained fatigue of at least 6 months duration that is:
    - Of new onset
    - Not a result of ongoing exertion
    - Not substantially alleviated by rest
    - A substantial reduction in previous levels of activity
  - The occurrence of four or more of the following symptoms:
    - Subjective memory impairment
    - Tender lymph nodes
    - Muscle pain
    - Headache
    - Nonrefreshing sleep
    - Post-exertional malaise (>24 h)
- Oxford UK definition, 1991 [14]:
  - Severe, disabling fatigue of at least 6 months duration that:
    - Affects both physical and mental functioning
    - Was present for more than 50% of the time
  - Other symptoms, particularly myalgia and sleep and mood disturbance, may be present

Exclusion criteria

- Centers for Disease Control, 1994 [15]:
  - Active, unresolved or suspected disease likely to cause fatigue
  - Psychotic, melancholic or bipolar depression (but not uncomplicated major depression)
  - Psychotic disorders
  - Dementia
  - Anorexia or bulimia nervosa
  - Alcohol misuse or other substance misuse
  - Severe obesity
- Oxford UK definition, 1991 [14]:
  - Active, unresolved or suspected disease likely to cause fatigue
  - Psychotic, melancholic or bipolar depression (but not uncomplicated major depression)
  - Psychotic disorders
  - Dementia
  - Anorexia or bulimia nervosa

Overlapping conditions

The boundary between chronic fatigue and CFS is quite arbitrary. By common consent, the term chronic fatigue is used for an illness characterized by fatigue as the main symptom lasting for more than 6 months and CFS when criteria for a case definition are met. However, the symptoms of chronic fatigue, as well as CFS itself, often co-occur with other disorders, particularly fibromyalgia, a syndrome of characteristic exaggerated tenderness at 18 specified tender points and chronic diffuse body

Box 4. Clinical working case definition of myalgic encephalomyelitis/chronic fatigue syndrome [17].

A patient with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) will meet the criteria for fatigue, post-exertional malaise and/or fatigue, sleep dysfunction and pain; have two or more neurological/cognitive manifestations and one or more symptoms from two of the categories of autonomic, neuroendocrine and immune manifestations; and adhere to item 7.

1. Fatigue:
   The patient must have a significant degree of new onset, unexplained, persistent or recurrent physical and mental fatigue that substantially reduces activity level.
2. Post-exertional malaise and/or fatigue:
   There is an inappropriate loss of physical and mental stamina, rapid muscular and cognitive fatigability, post-exertional malaise and/or fatigue and/or pain, and a tendency for other associated symptoms within the patient's cluster of symptoms to worsen. There is a pathologically slow recovery period usually 24 h or longer.
3. Sleep dysfunction*:
   There is un-refreshed sleep or sleep quantity or rhythm disturbances such as reversed or chaotic diurnal sleep rhythms.
4. Pain:*
   There is a significant degree of myalgia. Pain can be experienced in the muscles and/or joints, and is often widespread and migratory in nature. Often there are significant headaches of new type, pattern or severity.
5. Neurological/cognitive manifestations:
   Two or more of the following difficulties should be present: confusion, impairment of concentration and short-term memory consolidation, disorientation, difficulty with information processing, categorizing and word retrieval, and perceptual and sensory disturbances; for example, spatial instability and disorientation, and inability to focus vision. Ataxia, muscle weakness and fasciculations are common. There may be overload1 phenomena: cognitive, sensory (e.g., photophobia and hypersensitivity to noise) and/or emotional overload, which may lead to crash-2 periods and/or anxiety.
6. At least one symptom from two of the following categories:
   - Autonomic manifestations:
     Orthostatic intolerance neurally mediated hypotension, postural orthostatic tachycardia syndrome, delayed postural hypotension; lightheadedness; extreme pallor; nausea and irritable bowel syndrome; urinary frequency and bladder dysfunction; palpitations with or without cardiac arrhythmias; or exertional dyspnea.
   - Neuroendocrine manifestations:
     Loss of thermostatic stability subnormal body temperature and marked diurnal fluctuation, sweating episodes, recurrent feelings of feverishness and cold extremities; intolerance of extremes of heat and cold; marked weight change, anorexia or abnormal appetite; or loss of adaptability and worsening of symptoms with stress.
   - Immune manifestations:
     Tender lymph nodes, recurrent sore throat, recurrent flu-like symptoms, general malaise, or new sensitivities to food, medications and/or chemicals.
7. The illness persists for at least 6 months. It usually has a distinct onset, although it may be gradual‡. Preliminary diagnosis may be possible earlier. A persistence of 3 months is appropriate for children.

To be included, the symptoms must have begun or have been significantly altered after the onset of this illness. It is unlikely that a patient will suffer from all symptoms in criteria 5 and 6. The disturbances tend to form symptom clusters that may fluctuate and change over time. Children often have numerous prominent symptoms but their order of severity tends to vary from day to day.

*There are a small number of patients who have no pain or sleep dysfunction, but no other diagnosis fits except ME/CFS. A diagnosis of ME/CFS can be entertained when this group has an infectious illness type onset.
‡Some patients have been unhealthy for other reasons prior to the onset of ME/CFS and lack detectable triggers at onset and/or have more gradual or insidious onset.

pain accompanied by other somatic symptoms, including poor sleep, fatigue and stiffness, in the absence of disease [18–20]. Despite the contrasting definitions of the two disorders, 20–70% of patients with fibromyalgia also meet the criteria for CFS and, conversely, 35–70% of those with CFS-like illness have concurrent fibromyalgia [8]. In fact, a syndrome may be delineated by means of a criterion that reflects a cutoff point on a continuum of symptoms and dysfunctions. Thus ME/CFS and fibromyalgia syndrome can be differentiated on the basis of symptom balance in what many believe are variants of the same or similar disease pathogeneses. By criterial definition, pain is the major feature of fibromyalgia whereas post-exertional malaise and fatigue are the major symptoms of ME/CFS. However, the latter often involves significant cognitive dysfunction and pain, and overlap situations are common where both pain and fatigue are of similar prominence. Some patients with fibromyalgia have complex symptomatology that is often indistinguishable from ME/CFS. Indeed many patients are diagnosed with both ME/CFS and fibromyalgia. Approximately 75% of ME/CFS patients also meet the criteria for fibromyalgia syndrome [18].

The diagnosis of fibromyalgia is based on the 1990 American College of Rheumatology criteria. Following these criteria, patients with fibromyalgia present with 11 of 18 positive tender points and with widespread pain [21]. Validity of both the definition for CFS and fibromyalgia has been shown [21,22]. The

overlap in case definition, reported symptoms, patient characteristics and treatments for these functional somatic syndromes has led some researchers to suggest that these conditions are arbitrarily classified and should be considered as manifestations of the same biomedical and psychosocial processes [23–25].

Pathophysiology

Despite extensive research, the etiology of CFS remains unclear [26]. A large number of investigations have documented abnormalities in different domains, such as brain structure and function, neuroendocrine responses, sleep architecture, immune function or exercise capacity, although the scientific literature related to current theories about the etiology and pathogenesis of CFS have been focused on what appear to be the four most significant aspects in the development and perpetuation of this disease: the role of infectious agents as well as immunological, neuroendocrine and psychiatric factors [27–29]. However, it has been suggested that CFS is a condition of complex and multifactorial etiology. The heritability of CFS has also been proposed. Recently, new research has linked CFS with genes that have roles in the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system, specifically genes involved in the body's response to stress [30–33].

It has been recognized that cognitive problems are some of the most disabling and disruptive symptoms of CFS. Patients with CFS typically complain of difficulties with concentration, short-term memory and thinking, as well as impaired attention, slowed processing speed and poor learning of information. These impairments could account for the poorer performance of subjects with CFS on complex attention and information processing tasks. Moreover, mood disorders are frequent clinical manifestations in patients with CFS. In fact, coexisting psychological distress or psychiatric disorders may also contribute to neurocognitive dysfunction [8]. Neuropsychological evidence has accumulated to suggest that depression alone does not account for the cognitive problems experienced by individuals with CFS and that these problems may be related to CNS dysregulation [34]. To date, no specific pattern of cerebral abnormalities has been found that uniquely characterizes patients with CFS [35]. In addition, abnormalities of HPA axis activity, in at least some patients, have been suggested, including an interaction between the HPA axis and serotonin and other neurotransmitters systems in the brain [36]. However, it seems likely that HPA axis disturbance in CFS is heterogeneous and multifactorial.

Pharmacological treatment of neurocognitive symptoms

Because of the unclear etiology, diagnostic uncertainty based on the fact that many patients are not diagnosed according to an established case definition, and the heterogeneity of the CFS population, there are no firmly established treatment recommendations for CFS. In an updated systematic review of interventions for the treatment, management and rehabilitation of patients with ME/CFS, Chambers *et al.* concluded that there is a need for research to define the characteristics of patients who would benefit from specific interventions and to develop clinically relevant objective outcome measures [37]. In the framework of a multidisciplinary team approach to the management of CFS based on nonpharmacological and pharmacological interventions, cognitive–behavioral therapy and graded exercise therapy have shown to be positive in terms of effectiveness and are now considered as evidence-based treatments [38,39], although cognitive–behavioral therapy is expensive and requires special skills. The NICE (clinical guideline 53) recommends the following [101]:

- To develop an individualized management plan.
- To provide care in ways suitable for the individual (this may include providing some tests or treatments at home, or support and advice by telephone or email).
- To offer advice on managing activity, rest periods, sleep patterns, diet, equipment to maintain independence and advice on fitness (not simply "go to the gym" or "exercise more").
- To offer cognitive–behavioral therapy and/or graded exercise therapy to people with mild or moderate CFS/myalgic encephalomyelitis, as there is the clearest evidence of benefit for these approaches.

Neurocognitive symptoms in patients with CFS are well characterized and the current research shows that slowed processing speed and efficiency, impaired working memory and poor learning of information are the most prominent features [40–45]. On the other hand, reduced attentional capacity results in impaired performance on effortful tasks requiring planned or self ordered generation of responses from memory [44]. Mental fatigue has been considered an important component of CFS-related cognitive dysfunction [46]. Fibromyalgia patients often have memory and cognitive complaints, as well as impaired control of attention, perhaps due to chronic pain [47]. These cognitive impairments in both patients with CFS and fibromyalgia syndrome, particularly in those with coexisting mood disorders, may disrupt activities of daily living and reduce patient's quality of life.

Stimulant medications have been used to counter fatigue, excessive daytime sleepiness and in patients with ADHD who share cognitive disturbances with CFS patients [48]. Pharmacotherapy of fibromyalgia syndrome also includes stimulants to address issues of sleep disturbance, fatigue or concomitant psychiatric disorders [49]. When pooling individual patient data from six double-blind, randomized clinical trials comparing the norepinephrine–dopamine reuptake inhibitor bupropion with selective serotonin reuptake inhibitors for the treatment of major depressive disorder that also included outcome measures for both hypersomnia and fatigue, bupropion resulted in a greater resolution of sleepiness and fatigue than with selective serotonin reuptake inhibitors [50]. The association of bupropion at high dosage with paroxetine led to a rapid relief of symptoms

related to CFS [51]. Dextroamphetamine has also been successfully used in CFS [52], although this drug is likely to raise concerns about side effects and potential for abuse.

Methylphenidate is a mild CNS stimulant. The mode of action in humans is still uncertain. There is evidence that the drug inhibits dopamine reuptake from the synaptic cleft by binding the dopamine transporter. This is in contrast with the primary action of amphetamine, a stimulant also used in the treatment of ADHD, which causes the release of newly synthesized cytosolic dopamine from the nerve terminal. This difference may contribute to the higher abuse potential of amphetamine than methylphenidate. Experimental data provided evidence of a regional specificity of methylphenidate in inhibiting dopamine reuptake particularly in the prefrontal cortex, limbic regions and striatum. In humans, the highest density for methylphenidate binding was shown to be the striatum. However, while it would appear that the primary action of the drug is on dopamine reuptake, there is evidence that methylphenidate also inhibits norepinephrine reuptake with only a very slight effect on serotonin reuptake at pharmacologically relevant doses [53].

Pharmacokinetic studies have shown that methylphenidate is almost completely absorbed and primarily metabolized by de-esterification to ritalinic acid. In humans, peak plasma concentrations occur 1–3 h after an oral dose with a plasma half-life of 1.5–2.5 h. In the currently available preparations, methylphenidate contains a racemic mixture of the *d*- and *l*-isomers. Methylphenidate in the extended-release formulation (duration of action: 8 h) is more slowly but as extensively absorbed as in the regular immediate-release tablets. Methylphenidate is indicated in the treatment of ADHD in children over 6 years of age and adolescents as an integral part of a total treatment program which typically includes other remedial measures (e.g., psychological, educational and social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate-to-severe distractibility, short attention span, hyperactivity, emotional liability and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Minor neurological signs, learning disability and abnormal EEG may or may not be present, and a diagnosis of CNS dysfunction may or may not be warranted. Daily dosage above 60 mg is not recommended. Doses of 1 mg/kg/day are recommended for adults.

Methylphenidate is the most frequently prescribed medication for the treatment of ADHD. In a review of the cognitive effects of immediate-release methylphenidate in children with ADHD in which a total of 40 relevant placebo-controlled studies were evaluated [54], 63.5% of the studies identified some improvement in cognitive function following the administration of the drug. Studies administering more than one dose of methylphenidate generally found that the higher dose produced a significant response on cognitive measures. Methylphenidate reliably improved saccadic eye movement, planning/cognitive flexibility, attention/vigilance, inhibitory control and working memory.

The short pharmacokinetic and pharmacodynamic half-life of the standard immediate-release formulation of methylphenidate, requiring administration three times a day, worsening of attention and behavior in case of delayed or missing doses, adverse effect on sleep quality due to late administration of the afternoon dose, and peaks and troughs as a result of the short half-life have been the main reasons for development of the sustained-release formulation. In this respect, osmotic-controlled release oral delivery system (OROS) methylphenidate, which employs the advanced longitudinally compressed tablet multilayer formulation, is designed to maintain efficacy through 12 h with once daily administration [55]. The effectiveness of OROS methylphenidate has been assessed in short- and long-term studies [56–58]. This type of formulation is also more effective [59].

Methylphenidate has also emerged as a useful treatment for the target ADHD symptoms of inattention, hyperactivity and impulsivity observed in children with pervasive developmental disorders [60]. In a study in which the components of working memory in ADHD were investigated, methylphenidate enhanced the ability to manipulate both auditory-verbal and visual-spatial information [61]. Moreover, methylphenidate has been used to ameliorate opioid-induced somnolence, to augment the analgesic effects of opioids, to treat depression, and to improve cognitive function in patients with cancer [62,63], as well in acute poststroke rehabilitation [64] and for the treatment of fatigue in patients with HIV [65].

The effect of immediate-release methylphenidate was assessed during a 4-week treatment period in 60 patients who fulfilled the 1994 CDC criteria for CFS and had concentration difficulties. The effectiveness of methylphenidate 2 × 10 mg/day compared with placebo was evaluated in a double-blind placebo-controlled crossover study [66]. Methylphenidate showed a significant effect on both outcome measures (Visual Analog Scale score and Checklist Individual Strength). Other accompanying symptoms, such as joint pain, sleeping disturbances and post-exertional malaise also improved significantly with methylphenidate treatment compared with baseline. This study shows that standard immediate-release methylphenidate was useful to relieve fatigue and concentration disturbances in a clinical series of patients who met the CDC case definition of CFS. Conversely, a recent study in adult patients who presented primarily with symptoms of ADHD, predominately inattentive type and also reported unexplained fatigue, widespread musculoskeletal pain or a pre-existing diagnosis of CFS or fibromyalgia syndrome, the use of methylphenidate attenuated the core ADHD symptoms of inattention, distractibility, hyperactivity and impulsivity but, unexpectedly, some patients also reported amelioration of pain and fatigue symptoms [67].

Conclusion

The use of immediate-release methylphenidate in CFS has been shown in one small study. Using the positive results of this study and the well-known beneficial effects of the drug on a

range of similar cognitive symptoms in ADHD, the potential promising role of the drug in the therapeutic armamentarium of CFS may be hypothesized. However, further studies are needed to confirm the results obtained in this single study. The processes by which catecholamine-modulated activity in the CNS can affect clinical manifestations related to executive dysfunction of the prefrontal cortex in ADHD and other disorders including CFS and fibromyalgia syndrome are unknown.

Expert commentary

Methylphenidate is a mild psychostimulant. The drug inhibits dopamine reuptake from the synaptic cleft by binding the dopamine transporter; it also inhibits noradrenaline reuptake, and has a very slight effect on serotonin reuptake. Methylphenidate is indicated for the treatment of ADHD and there is a wide experience with the favorable effects of the drug on a constellation of behavioral and cognitive clinical manifestations experienced by patients with ADHD. Recently, treatment with immediate-release methylphenidate was administered to a clinical series of 60 patients with CFS who met case definition criteria for the diagnosis of the disease and were included in a double-blind randomized placebo-controlled crossover study [66]. The active drug was given at daily doses of 20 mg/day for 4 weeks. The main findings of the study were improvements in fatigue and concentration when the active medication was given, with statistically significant differences as compared with placebo. Unexpectedly, other accompanying symptoms, such as joint pain, sleep disturbances and post-exertional malaise were significantly better with methylphenidate treatment compared with placebo.

The results of this study open new and encouraging perspectives in the pharmacological management of patients with CFS and fibromyalgia. However, further double-blind randomized, placebo-controlled clinical trials in a larger number of patients are mandatory to confirm that immediate-release methylphenidate remains effective at both the short term and the long term in the CFS population. More importantly, research efforts are needed to elucidate which are the underlying pathophysiological mechanisms interfered by methylphenidate and responsible for the apparently beneficial effect of the drug in patients with CFS. Despite an improved recognition and understanding of CFS, treatment continues to be challenging.

Five-year view

It is now recognized that physiological and psychological factors work together to predispose an individual to CFS and to precipitate and perpetuate the illness. CFS is unlikely to be caused or maintained by a single agent. Patients experience profound disabling fatigue accompanied by numerous rheumatological, infectious and neuropsychiatric symptoms. In the absence of biological markers, working case definitions for CFS, with clear identification of major and minor criteria as well as conditions that exclude a diagnosis of CFS, not only provide a rational basis for the diagnosis and evaluation of individual patients with chronic fatigue of undetermined cause, but also have been crucial advancement tools for clinical research and epidemiological studies. CFS is defined on the basis of expert consensus and its diagnosis is made on the basis of symptom criteria. Therefore, the availability of operational case definitions for the diagnosis of CFS is a fundamental step for the design of clinical trials in homogeneous study populations to assess the efficacy and safety of medications capable of improving fatigue and cognitive dysfunction in patients with this condition. In the meantime, treatment of CFS and fibromyalgia may be variable and should be tailored to each patient according to prominent clinical complaints.

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Key issues

- Chronic fatigue syndrome (CFS) is a complex and heterogeneous disease that can be challenging to treat.
- Severe fatigue is a common complaint among patients with CFS but cognitive dysfunction can be some of the most disabling clinical manifestation of the illness.
- Methylphenidate treatment in attention-deficit/hyperactivity disorder (ADHD) is supported by a large body of evidence.
- In patients with chronic fatigue syndrome, preliminary data indicate that immediate-release methylphenidate can successfully alleviate fatigue and symptoms related to the cognitive domain, which are similar to those found in ADHD.
- Methylphenidate may have a hypothetical role in the therapeutic arsenal of CFS and fibromyalgia.

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Affiliations

- José Ramón Valdizán Usón, DEGREE
  Servicio de Neurofisiología Clínica, Hospital Universitario Miguel Servet, Paseo Isabel la Católica 1–3, E-50009 Zaragoza, Spain
  Tel.: +34 976 765 500
  Fax: +34 976 566 234
  jrvaldizan@auna.com
- María Ángeles Idiazábal Alecha, DEGREE
  Unit of Clinical Neurophysiology, Clínica Nuestra Señora del Pilar, Barcelona, Spain
  TEL
  FAX
  EMAIL