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Review Article

An Integrative Review of Chronic Fatigue Syndrome (CFS): Clinical Insights and Therapeutic Approaches in Unani and Modern Medicine

*Rafat Afzal [1], Saif Ali Siddiqui [2]

[1] Assistant Professor, Department of Ilaj-Bit-Tadbeer, Inamdar Unani Medical College and Hospital, Kalaburagi, Karnataka (India).

[2] Assistant Professor, Department of Ilaj-Bit-Tadbeer, Markaz Unani Medical College and Hospital, Kozhikode, Kerala, India.

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*For Correspondence:

Dr. Rafat Afzal, Assistant Professor, Dept. of Ilaj bit Tadbeer, Inamdar Unani Medical College & Hospital, Gulbarga, Karnataka

Abstract

Excruciating fatigue that lasts for at least six months is a defining feature of the complicated illness known as chronic fatigue syndrome (CFS). With a prevalence of 0.4% to 2.5% worldwide, CFS is becoming more common. CFS impacts more women than men. In wealthy nations, it is considered a common condition. Although CFS has no recognized cure, symptoms can be controlled and managed. Daily normal activities are significantly hampered by chronic fatigue. An imbalance of brain neurotransmitters, mitochondrial dysfunction, reduced oxidative phosphorylation, disruption of the hypothalamic-pituitary-adrenal (HPA) axis, and decreased ATP synthesis are all essential components of the pathophysiology of CFS. The current study aims to identify the herbs used as medicine for chronic fatigue syndrome (CFS) and to examine the current treatment strategies for it. The phytochemicals found in the Unani medicinal plants discussed in this article make them highly effective in treating the symptoms of chronic fatigue syndrome. The current treatment approach for chronic fatigue syndrome is also briefly covered in this review article. It includes cognitive-behavioral therapy (CBT), graded exercise therapy (GET), immunoglobulin use, psychodynamic counseling, and isometric exercises that are very helpful in reducing the symptoms of CFS. Conventional treatments for CFS include corticosteroids, immunomodulatory drugs, and antidepressants. Various Unani medicinal plants are examined in this article, along with their pharmacological characteristics, potential uses, and available therapies for mitigating the symptoms of chronic fatigue syndrome.

Keywords: chronic fatigue syndrome, brain neurotransmitters, mitochondrial dysfunction, reduced oxidative phosphorylation

Introduction

Chronic fatigue syndrome is defined by the Centers for Disease Control and Prevention (CDC) as a chronic, multi-systemic, debilitating, and complicated illness. Deep exhaustion that persists for longer than six months and is not alleviated by rest, together with a diminished capacity to carry out pre-illness activities, are characteristics of chronic fatigue syndrome (CFS). CFS is characterized by post-exertional malaise (PEM), a condition in which symptoms might get worse after exerting oneself physically, mentally, and emotionally. Sleep difficulties are also a problem for CFS patients. Cognitive impairment, discomfort, and orthostatic intolerance are other prevalent symptoms. A variety of rheumatological, viral, and neuropsychiatric symptoms are associated with CFS.1

Chronic Fatigue Syndrome (CFS) Day is observed globally on May 12th each year. It's a day dedicated to raising awareness of a disease that affects millions of people worldwide yet is often overlooked and misunderstood. Chronic Fatigue Syndrome, also known as myalgic encephalomyelitis (ME/CFS), is a complicated illness characterized by extreme fatigue that may not subside with rest, along with other symptoms, including mental challenges, joint and muscle pain, and sleep disturbances.

Extensive surveys have shown that up to half of the general population reports feeling tired, making it a common symptom in the community. At least 20% of people who seek medical attention also report feeling tired. This weariness is usually self-limiting, transient, and understandable in the context of the situation at hand. Debilitating and persistent fatigue, however, is experienced by a tiny minority of people. When this weariness cannot be explained by a medical disease, such as hypothyroidism or anemia, it may be a sign of chronic fatigue syndrome (CFS).2

Unani Perspective on Fatigue (Iya)

In Unani medicine, fatigue is referred to as **Iya (Takaan)**, a condition marked by general tiredness and lack of energy, often accompanied by physical and mental exhaustion. Fatigue is categorized into three main types:

Types of Iya [3,4,5]

Iya-e-Quroohi

In this type, Fatigue resembling soreness or a wound in the skin, often with tingling sensations Caused by *Akhlat-e-Raddiya* and *Mawad-e-Fasida*.

Iya-e-Tamaddudi

This type of fatigue includes Sensation of heaviness or crushing, accompanied by heat and tension in muscles, making movement unpleasant and caused by *reeh* in muscles.

Iya-e-Warmi

In this type of fatigue, there is an increase in body temperature, swelling of organs, redness, and sensitivity to touch and movement. Symptoms worsen with prolonged standing or walking.

Additional Subtypes

Iya-e-Qazofi

This includes sensation of dryness and constipation due to excessive exertion. It can be triggered by fast pace activity, sexual activity, or inadequate rest.

Epidemiology

The prevalence estimates of chronic fatigue syndrome (CFS) vary depending on the definition used, the population surveyed, and the study methods employed. Current prevalence estimates for CFS range from 0.007% to 2.8% in the general adult population and from 0.006% to 3.0% in primary care or general practice settings. CFS also occurs in children and adolescents, but at a lower rate.[6] Early reports from tertiary clinics indicated that CFS primarily affected young, white, successful women.[7] Most individuals diagnosed with CFS are between 30-40 years old, with a higher prevalence among females.[8,9]

However, community surveys have shown that white individuals have a lower risk of CFS compared to Latinos, African Americans, and Native Americans. These findings suggest that the higher prevalence of CFS among whites in clinic populations is likely due to biases related to healthcare access and utilization. [10] According to the latest diagnostic criteria, CFS is characterized by substantial reduction or impairment in pre-illness activity levels, post-exertional malaise (PEM), and unrefreshing sleep, along with cognitive impairment or orthostatic intolerance.

Etiopathogenesis[11]

The etiopathogenesis of chronic fatigue syndrome (CFS) is intricate and multifaceted, reflecting a complex interplay between the brain and body. While CFS is not classified as a psychiatric illness, its chronic nature and profound impact necessitate consideration of its psychosocial dimensions. For both patients and researchers, it is crucial to distinguish between the illness's underlying causes, its triggering factors, and the subsequent pathophysiological processes that sustain it.

The pathophysiological mechanisms perpetuated by a dysregulated stress response system, which encompasses the following components:

- Immune System
- Hypothalamic-Pituitary-Adrenal (HPA) Axis
- Autonomic Nervous System
- Central Sensitization

Dysregulated Immune System

CFS has been associated with immune system abnormalities, notably reduced natural killer (NK) cell activity, which correlates with symptom severity. Patients often exhibit an atypical response to exercise, marked by diminished antioxidant defense, heightened oxidative stress, elevated complement product levels, and increased production of interleukin-10 (IL-10) and TLR4, which align with the severity of symptoms. Despite these findings, systematic reviews of immune-related studies in CFS reveal inconsistent patterns, indicating no definitive immunological signature. Additionally, in CFS patients, the binding potential (BPND) of 11C-(R)-PK11195 in regions such as the midbrain, thalamus, and amygdala correlates with cognitive impairments.

Neuroendocrine Dysregulation

Dysregulation of the HPA axis has been observed in some CFS patients, manifesting as slightly reduced cortisol levels (hypocortisolism), diminished diurnal variation in cortisol secretion, elevated serotonergic activity, and decreased HPA axis responsiveness. However, it remains unclear whether HPA axis dysfunction is a primary driver of CFS or a secondary factor that exacerbates symptoms or sustains the illness.

Dysregulated Autonomic Nervous System and Orthostatic Intolerance

There is tentative evidence linking CFS to autonomic nervous system dysfunction. Studies suggest abnormalities, including altered heart rate variability, impaired responses to tilt table tests, reduced sleep efficiency, prolonged sleep onset latency, and decreased slow-wave sleep. These findings provide a physiological basis for orthostatic intolerance, although inconsistencies in results limit definitive conclusions about causality.

Central Sensitization

Central sensitization (CS) refers to an increased sensitivity of nociceptive neurons to normal or subthreshold stimuli within the central nervous system. Clinically, this manifests as heightened pain perception (hyperalgesia) or pain triggered by non-painful stimuli (allodynia). CS is hypothesized to underlie various chronic pain conditions, including CFS. Preliminary evidence suggests a potential role for CS in CFS symptoms, although small sample sizes and conflicting interpretations have left this hypothesis open to debate.

Clinical Features[12]

Primary Symptoms of ME/CFS:

1. Required Symptoms

These are the main symptoms that must be present:

a) Reduced Activity and Persistent Fatigue

- A person is unable to do activities they could before falling ill.
- Fatigue lasts 6 months or more and: Is severe, Isn't caused by overexertion, Doesn't get better with sleep or rest.

b) Worsening Symptoms after Activity (Post-Exertional Malaise or PEM)

- Doing physical or mental tasks worsens symptoms.
- This can cause a "crash" or "collapse" where patients feel extremely unwell.
- Recovery can take days or weeks, and tasks like shopping, showering, or attending events might leave someone bed-bound or house-bound.

c) Sleep Problems

- Sleep doesn't leave the person feeling refreshed.
- They may struggle to fall asleep or stay asleep.

2. Additional Symptoms (Need at Least One)

a) Memory and Cognitive Issues (Brain Fog)

- Problems with quick thinking, memory, or focusing.
- It feels like being "stuck in a fog."

b) Problems with Upright Posture (Orthostatic Intolerance)

- Symptoms worsen when standing or sitting upright.
- May cause dizziness, light headedness, weakness, or fainting.
- Vision changes like blurriness or seeing spots may also happen.

3. Other Common Symptoms

Some individuals also experience:

- Pain: Muscle pain, joint pain (no redness or swelling), and headaches.
- Frequent sore throat or tender lymph nodes in the neck or armpits.
- Digestive issues: Like irritable bowel syndrome (IBS).
- Chills, night sweats, or sensitivity to light, noise, or smells.
- Muscle weakness, shortness of breath, or irregular heartbeat.

Diagnostic Criteria[12]

The latest diagnostic criteria for chronic fatigue syndrome (CFS), also known as Myalgic Encephalomyelitis (ME), are based on the 2015 Institute of Medicine (IOM) report, now the National Academy of Medicine (NAM). Here are the key criteria for diagnosis:

Required Symptoms:

1. Substantial Reduction or Impairment in Pre-Illness Activity Levels: This includes occupational, educational, social, or personal life activities that last for more than six months and are accompanied by fatigue that is often profound, of new onset, not the result of ongoing excessive exertion, and not substantially alleviated by rest.
2. Post-Exertional Malaise (PEM): Worsening of symptoms after physical, mental, or emotional exertion that would not have caused a problem before the illness. PEM often puts the patient in relapse that may last days, weeks, or even longer.
3. Unrefreshing Sleep: Patients with ME/CFS may not feel better or less tired after a whole night's sleep.

Additional Symptoms (at least one required):

1. Cognitive Impairment: Problems with thinking, memory, executive function, and information processing. These can be exacerbated by exertion, effort, prolonged upright posture, stress, or time pressure.
2. Orthostatic Intolerance: Worsening of symptoms upon assuming and maintaining an upright posture, measured by heart rate and blood pressure abnormalities during standing, bedside orthostatic vital signs, or head-up tilt testing.

Management

1. Pharmacological Treatments
2. Non-Pharmacological Treatments

Pharmacological Treatments

<u>Modern Medicine</u>

Antidepressants

*Examples:*Nortriptyline (10–30 mg at bedtime), Fluoxetine.

Purpose: Improves sleep and reduces pain. Useful for addressing associated depressive

symptoms but with limited efficacy due to serotonergic hypersensitivity.[13,14]

Steroids

Example: Hydrocortisone.

Purpose: May reduce fatigue; however, results are inconsistent across studies.[15,16]

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Examples: Acetaminophen, Ibuprofen.

Purpose: Relieves musculoskeletal pain commonly associated with CFS.[17]

Immunological Agents

Examples: Immunoglobulin G (IgG), Ribonucleic Acid.

Findings: Limited benefit shown in trials[18,19]

Monoamine Oxidase Inhibitors (MAOIs)

Example: Phenelzine.

Purpose: Shows modest benefits in patients with significant vegetative symptoms.[20,21]

Ilaj-Bil-Dawa

Chronic Fatigue Syndrome (CFS) can be a challenging condition to manage, but Unani medicine offers several natural remedies that may help ease its symptoms. Unani medicine, rooted in ancient Greek and Islamic traditions, focuses on restoring balance and harmony to the body through natural means. Here are some Unani remedies that may be beneficial for CFS:

Tukhm-e Khashkhash (Poppy Seeds): Poppy seeds are often used in Unani medicine for their calming and soothing properties. They are believed to help improve fatigue and promote relaxation, making them potentially beneficial for individuals with CFS. Poppy seeds can be consumed by grinding them into a powder and mixing them with honey or milk.

Zanjabeel (Ginger): Ginger is renowned for its anti-inflammatory and immune-boosting properties in Unani medicine. It is believed to improve circulation and enhance energy levels, which can be beneficial for combating fatigue associated with CFS. Ginger can be consumed fresh, as a tea, or incorporated into meals for its therapeutic effects.

Sibr (Aloe Vera): Aloe vera is valued in Unani medicine for its rejuvenating and energizing properties. It is believed to support immune function, improve digestion, and enhance overall vitality, which may help ease some of the symptoms of CFS. Aloe vera gel can be consumed internally or applied topically to reap its benefits.

Habb-e Mumsik Tilai (Black Seeds): Black seeds, also known as Nigella sativa, have been used in Unani medicine for centuries for their medicinal properties. They are believed to possess immune-modulating and anti-fatigue effects, which could be beneficial for individuals with CFS. Black seeds can be consumed whole, ground into a powder, or used to make oil for internal or external use.

Arq-e Gulab (Rose Water): Rose water is a common ingredient in Unani medicine known for its cooling and refreshing properties. It is believed to help improve stress, improve mood, and promote relaxation, which may be beneficial for individuals experiencing fatigue due to CFS. Rose water can be consumed orally, added to bathwater, or used as a facial toner.

Murakkabat

- Khameera Khashkhash
- Hab-e-Shifa
- Safoof-e-Musakkin
- Majoon Flasfa
- Hab-e-Asgandh

Differential Diagnosis [22,23,24,25]

1. **Major Depressive Disorder (MDD):**
   - **Symptoms:** Fatigue, sleep disturbances, cognitive impairment, and mood changes.
   - **Differentiation:** CFS patients often have post-exertional malaise (PEM) and unrefreshing sleep, which are less common in MDD.
2. **Fibromyalgia:**
   - **Symptoms:** Chronic widespread pain, fatigue, sleep disturbances, and cognitive difficulties.
   - **Differentiation:** Fibromyalgia is characterized by tender points and widespread pain, whereas CFS primarily involves severe fatigue and PEM.
3. **Hypothyroidism:**
   - **Symptoms:** Fatigue, weight gain, cold intolerance, and dry skin.
   - **Differentiation:** Thyroid function tests can help rule out hypothyroidism.
4. **Sleep Apnea:**
   - **Symptoms:** Fatigue, unrefreshing sleep, and daytime sleepiness.
   - **Differentiation:** Sleep studies can diagnose sleep apnea, which is characterized by repeated episodes of breathing cessation during sleep.
5. **Multiple Sclerosis (MS):**
   - **Symptoms:** Fatigue, cognitive impairment, muscle weakness, and neurological deficits.
   - **Differentiation:** MRI and other neurological tests can help distinguish MS from CFS.
6. **Anemia:**
   - **Symptoms:** Fatigue, pallor, shortness of breath, and dizziness.
   - **Differentiation:** Blood tests can diagnose anemia by measuring hemoglobin and hematocrit levels.
7. **Lyme Disease:**
   - **Symptoms:** Fatigue, joint pain, neurological symptoms, and a characteristic rash.
   - **Differentiation:** Serological tests can help diagnose Lyme disease.
8. **Adrenal Insufficiency:**
   - **Symptoms:** Fatigue, weight loss, hypotension, and hyperpigmentation.
   - **Differentiation:** ACTH stimulation tests can diagnose adrenal insufficiency.
9. **Diabetes Mellitus:**
   - **Symptoms:** Fatigue, polyuria, polydipsia, and weight loss.
   - **Differentiation:** Blood glucose tests can diagnose diabetes.

10. **Infections (e.g., HIV, Hepatitis):**

- **Symptoms:** Fatigue, fever, weight loss, and other systemic symptoms.
- **Differentiation:** Specific serological tests can diagnose infections

Management via Regimenal Therapies (Ilaj-bit-Tadbeer)

1. **Hammam (Bath Therapy):** Improves circulation, relaxes muscles, and alleviates fatigue. Recommended with warm water infused with herbs like *Barg-e-Sana*.
2. **Pashoya (Foot Bath):** Warm water foot baths with herbs like *Baboona, Nakhoona that* reduces stress and fatigue while promoting relaxation.
3. **Takmeed (Fomentation):** Application of warm compresses (dry or wet) to specific areas reduces localized pain and fatigue.
4. **Nutool (Irrigation):** Continuous pouring of warm herbal decoctions over the body or specific areas enhances relaxation and relieves fatigue symptoms.
5. **Hijama (Cupping Therapy):** It is believed to relieve musculoskeletal pain, reduce inflammation, and improve circulation, making it effective for conditions like back pain and muscle tension. Additionally, it is thought to promote detoxification by stimulating the flow of lymphatic fluids.
6. **Massage Therapy (Dalk):** Reduces muscle fatigue and enhances circulation.
7. **Exercise Regimens:** Graded aerobic exercises improve fatigue, fitness, and overall functionality.[26]

Dietary Modifications: Incorporation of energy-boosting foods, including honey (Asl) and almond oil (Roghan Badam).

Behavioral and Complementary Interventions

1. **Cognitive Behavioral Therapy (CBT):** Helps manage symptoms by teaching coping strategies and improving Mental resilience shows improvement in up to 70% of patients when provided in structured sessions.[27,28]
2. **Relaxation Techniques:** Practices like mindfulness, yoga, and deep breathing enhance mental clarity and reduce stress.

Discussion

For those living with CFS, every day can be a battle against exhaustion and its debilitating effects. Simple tasks that many take for granted become monumental challenges. Imagine feeling utterly drained after a short walk or being unable to concentrate on a conversation due to cognitive fog. These are the realities faced by individuals with CFS, and they often struggle to explain the depth of their exhaustion to others who cannot see the illness.

One of the greatest difficulties in dealing with CFS is the lack of understanding from society and sometimes even from healthcare professionals. Because its symptoms can vary widely and there are no definitive diagnostic tests, CFS is often misdiagnosed or dismissed altogether. This can lead to feelings of frustration, isolation, and disbelief for those affected, exacerbating the already significant emotional toll of the condition.

However, Chronic Fatigue Syndrome Day is more than just a reminder of the challenges faced by those with CFS; it is also an opportunity to celebrate resilience and promote advocacy and support. Across the globe, individuals, organizations, and communities come together to raise awareness, share resources, and offer solidarity to those affected by this often-overlooked illness.

Advocacy efforts on CFS Day aim to educate the public and healthcare professionals about the realities of living with the condition, emphasizing the need for increased research funding, improved diagnostic criteria, and better access to treatment options. Through grassroots initiatives, social media campaigns, and public events, advocates work tirelessly to ensure that CFS receives the attention and recognition it deserves.

Moreover, CFS Day serves as an inspiration of hope for those living with the condition. It is a day when they can connect with others who understand their struggles, find validation for their experiences, and feel empowered to speak out and demand better care and support. It is a reminder that they are not alone in their journey and that their voices matter.

Chronic Fatigue Syndrome (CFS) can be a challenging condition to manage, but Unani medicine offers several natural remedies that may help ease its symptoms. Unani medicine, rooted in ancient Greek and Islamic traditions, focuses on restoring balance and harmony to the body through natural means.

Conclusion

It is essential to note that while Unani remedies may provide relief for some individuals with CFS, their effectiveness can vary from person to person. It is always best to consult with a qualified healthcare practitioner before trying any new remedies, especially if someone has underlying health conditions or are taking medication. Additionally, incorporating lifestyle changes such as maintaining a balanced diet, practicing stress-reduction techniques, and getting adequate rest and exercise can also play a crucial role in managing CFS symptoms.

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