BEYOND TIRED

Helping patients cope with chronic fatigue syndrome

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Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic, potentially disabling condition characterized by extreme fatigue, persistent flu-like symptoms and other typical symptoms. It affects an estimated 0.4–1% of people and is six times more prevalent in women than men.[1-4] Public awareness of ME/CFS and healthcare professionals' knowledge about the condition frequently lag behind research, often leading to inadequate management.

Although no drug can cure or significantly decrease the core symptoms of ME/CFS, drugs are very useful for symptom management. Pharmacists are in an ideal position to educate patients about why certain drugs are being used and assist them in managing common side effects. This article provides an overview of ME/CFS, with a focus on pharmacotherapy based on the 2003 Canadian clinical practice guidelines developed by an international expert consensus panel.[5] Unlike previous diagnostic criteria and treatment recommendations, these guidelines are evidence-based and developed from the best available research.[6]

Etiology

ME/CFS is a heterogeneous group of disorders unlikely to have a single etiology.[7] Any etiological explanation would need to account for the differences in onset, symptoms and disease course among those affected. In at least half of patients, ME/CFS is triggered by an infection; several intracellular pathogens have been prospectively found to lead to ME/CFS, including Epstein-Barr virus, parvovirus B19, Coxiella burnetii (Q-fever) and Ross River virus.[5,8,9] However, the role of infection in chronic disease is less clear.[5]

Diagnosis

Diagnosis is made through recognition of a pattern of core symptoms (Table 1) and by ruling out other causes. No routine physical signs or laboratory abnormalities are diagnostic of the condition.[10] However, new tests are on the horizon, including genetic and proteonomic markers.[11]

Symptoms

Core symptoms in patients with ME/CFS are best described as flu-like symptoms (e.g., exhaustion, aches/pains, sore throat, swollen glands, upper respiratory symptoms, decreased appetite) that patients experience *all of the time*. Symptoms worsen with exertion.[5] Core symptoms also include sleep dysfunction and pain, as well as neurological symptoms (e.g., impaired memory and concentration, muscle weakness). Recovery from minor mental or physical activity can take days to weeks. Illness severity ranges from the 50% decrement in energy required for diagnosis to those who are bedridden and tube-fed; severity often fluctuates even within an individual.[5,12] Health status (e.g., impact on daily life) may be more severely affected in ME/CFS than in multiple sclerosis, congestive heart failure or diabetes.[13] Table 1 provides further details about core and noncore symptoms.

An estimated 60% of ME/CFS patients have co-morbid conditions, such as fibromyalgia syndrome (characterized by generalized muscle pain and joint stiffness, and the presence of "tender points" on physical examination) and/or multiple chemical sensitivity (multisystem reactions to low concentrations of a wide range of common chemicals).[12,14] Gastrointestinal symptoms (e.g., nausea, gas, bloating, diarrhea, constipation, abdominal pain) are common.[15] ME/CFS can be differentiated from common psychiatric conditions, such as depression and anxiety.[5] However, symptoms of depression and anxiety are common (approximately 40%) and are most often secondary to social and activity restrictions.[12]

table 1

Diagnostic criteria for ME/CFS in adults[5]

A diagnosis requires the concurrent presence of 5 major criteria plus 2 of 3 minor criteria, present for at least 6 months (onset usually distinct, but can be gradual).[a,b]

Major Criteria	Characteristics: selected examples
disabling fatigue	• physical and mental fatigue • reduced activity level by approximately 50% • new onset, unexplained, persistent
post-exertional malaise and/or fatigue	• worsening of symptoms (physical, cognitive or emotional) after minimal exertion • delayed recovery period of 24 hours or more
sleep dysfunction	• unrefreshing sleep • altered sleep pattern (e.g., quality, quantity)
pain	• in muscles or joints (but not inflammatory) • often widespread and migratory • headaches of new type, pattern or severity
at least 2 neurological/cognitive manifestations	• impaired concentration, short-term and working memory • difficulty processing information and with word retrieval • perceptual and sensory disturbances (e.g., ataxia, disorientation, inability to focus vision) • overload phenomena (e.g., cognitive, sensory, emotional) may lead to "crashes" and anxiety

A diagnosis requires at least 1 symptom in 2 of 3 minor criteria.

Minor criteria	Characteristics: selected examples
autonomic	• orthostatic intolerance (disturbances in regulation of blood pressure and pulse, e.g., hypotension, postural orthostatic tachycardia and neurally-mediated hypotension) • vertigo/lightheadedness • nausea/irritable bowel syndrome • urinary frequency, bladder problems • palpitations with or without arrhythmia
neuroendocrine	• loss of thermostatic stability (body temperature subnormal, sweating, recurrent feelings of fever/cold extremities) • heat/cold intolerance • abnormal appetite/anorexia (weight change) • hypoglycemia • symptoms worsen with stress
immune	• tender lymph nodes • recurrent sore throat • recurrent flu-like symptoms and/or general malaise • new sensitivities to foods, medications and/or chemicals

a *Note:* idiopathic chronic fatigue is diagnosed when a patient has unexplained fatigue of 6 months or more, but does not have symptoms that meet the above diagnostic criteria

b Symptoms in children are similar to those in adults. For further details, see: Jason LA, Bell DS, Rowe K, et al. A pediatric case definition for myalgic encephalomyelitis and chronic fatigue syndrome. J Chronic Fatigue Syndrome 2006;13:1-53.

table 3

Overview of pharmacotherapy for ME/CFS[5, 19, 20, 23-30]

DRUG CLASS	COMMENTS
Sleep improvement[a] For drugs that may also be used for pain control, doses to promote sleep are generally lower.	
Sleep initiators	**Zopiclone:** 5–15 mg hs. Higher doses usually needed where sleep disruption and illness are more severe. As effects last 3–4 hours, may repeat ½ dose upon awakening in middle of night. Risk of tolerance or withdrawal with long-term use is minimal. **L-tryptophan:** 500–5000 mg at bedtime; due to its 2–4 hour duration of action, may repeat ½ dose upon awakening in middle of night. Increases depth of sleep. Better absorbed if taken with carbohydrates, not protein. In approximately 10% of patients, may cause patients to be more awake/alert. **Benzodiazepines:** In general, not recommended. Clonazepam may assist patients with physical restlessness or anxiety that prevents sleep. May be used in combination with doxepin for rapid and prolonged sleep.
Sleep sustainers	***Antidepressants*** **Amitriptyline:** 10–50 mg 1–2 hr before bedtime. Onset of action may be slow (e.g., in those with poor digestive function) **Doxepin:** 2–20 mg hs. Start with low dose and increase gradually, as tolerated **Trazodone:** 25–100 mg 30 min before bedtime ***Other*** **Cyclobenzaprine:** 10 mg hs. Gabapentin, mirtazapine (helpful when there is concurrent depression; can cause nightmares). Quetiapine may be useful for initiating and sustaining sleep, especially in anxious people. **Melatonin:** 3–6 mg hs can help maintain circadian rhythm; helpful in some people, although no evidence that melatonin production is abnormal in ME/CFS.
Pain[a] Start with mildest analgesic; use more potent agents only as necessary. For mild to moderate pain, prn therapy may be used; for severe pain, round-the-clock use is needed to prevent breakthrough pain.	
Analgesics	Acetaminophen and NSAIDs (e.g., celecoxib, ibuprofen, ketorolac, naproxen). In patients with high pain levels that severely limit functioning, opioids may be warranted.
Antidepressants	Amitriptyline: 5–100 mg hs. Initiate at lowest dose, increase gradually as tolerated. Benefits seen in 2–4 weeks. Doxepin: (5–100 mg hs), nortriptyline (10–100 mg hs) or SNRI (e.g., duloxetine, venlafaxine) may be used.
Anticonvulsants	Valproate: Can decrease central pain and assist in preventing migraines. (Note: carbamazepine is rarely used) Gabapentin: 100–300 mg tid. Start at low dose (e.g., 100 mg qam) and titrate dose up or down as tolerated. May help individuals with neuropathic pain, anxiety or depression.

table 3–cont'd

Other	Baclofen: 5–20 mg tid as tolerated; cyclobenzaprine (up to 10 mg tid – dose generally higher than used for sleep). Pregabalin: Similar effects to gabapentin. Recent studies show benefit in neuropathic pain and fibromyalgia pain. Side effects include sedation and weight gain.
Fatigue or cognitive dysfunction	
Stimulants	Used very sparingly due to tolerance and tendency to cause overactivity (and subsequent "crash"); best used periodically for important outings. Dextroamphetamine (5 mg qam and at noon); methylphenidate 5–10 mg bid; modafinil 100 mg qam (& 100 mg at noon, if needed)
Orthostatic intolerance[b]	
Various classes	Fludrocortisone: 0.05–0.2 mg daily; increases salt/water retention, may inhibit vasodilation. Monitor for potassium loss, BP increase. Ensure adequate salt/water intake.
	Midodrine: 2.5 mg tid to start; increase to 5 mg tid, as tolerated; acts as vasopressor to increase BP in patients with orthostatic hypotension, increases vascular tone and may be helpful in patients with low BP and edema of the lower extremities.
	Sodium chloride: NMH and POTS may respond to oral sodium chloride (up to 10–15 g/day) with adequate water intake. Sea salt is preferred, because it contains no additives (table salt may contain aluminum and other additives). IV normal saline is used clinically, but there are no large studies to support it.
Other	Beta-blockers: (e.g., atenolol) may be used for tachycardia secondary to low or unstable BP Meclizine for vertigo
Anxiety	
Various agents	Benzodiazepines, SSRIs or buspirone may be used.
Depression	
Antidepressants - SSRIs	Various SSRIs may be used. Note: typically not effective for fatigue; may interfere with sleep. May have more gastrointestinal, sexual dysfunction and sleep impairment side effects than other antidepressants.
Antidepressants - other	SNRIs (duloxetine, venlafaxine): watch for increase in diastolic BP Bupropion (fewer sexual side effects and more energizing than other antidepressants) Tricyclic antidepressants (e.g., amitriptyline, doxepin, nortriptyline): not used first line due to side effects at antidepressant doses
Other	Improvement has been reported with St. John's wort, acetyl-l-carnitine, NADH, alpha-interferon, IV magnesium, coenzyme Q10
HPA axis abnormalities	
Fludrocortisone	0.1–0.2 mg daily (used in combination with other agents)
DHEA	15–90 mg daily (usual dose range 25–50 mg daily). Use only for documented DHEA deficiency. A controlled prescription drug prepared in compounding pharmacies.
Immune dysfunction	
Ampligen (investigational)	A double-stranded RNA given IV over a six-month period. Has been investigated as an immune stimulator, viral modulator. Phase III trial results not yet published. Not yet marketed in Canada.
Essential fatty acids (e.g., from fish oil, primrose oil, flaxseed oil).	Anti-inflammatory and immune modulators. Note: Many fish oil brands contain contaminants (e.g., heavy metals, PCBs). Nutrasource Diagnostics, an independent testing site at the University of Guelph (www.nutrasource.ca/ifos_new), tests for such contaminants and publishes a list of exceptionally pure products. Note: High-dose EPA (3–5g/day) may be helpful for depression in patients who cannot tolerate antidepressants
Antivirals	Valacyclovir: 1 g q6h x 6–18 months. Used when confirmed chronic infection with viruses such as EBV, CMV or HHV6A. Confirmation should be made by repeated elevated antibody titres or quantitative PCR (looks for viral DNA in blood or tissues)
Antibiotics	Antibiotics (e.g., azithromycin, ciprofloxacin, clarithromycin, doxycycline) are being investigated for confirmed mycoplasma, chlamydia infections. Trials have used for several months or until improvement is noted, followed by multiple courses of pulse therapy. Confirmed, active chronic Lyme disease may require IV antibiotics if oral treatment is ineffective.

how I wish I could sleep again…"

Dr. Charles Lapp, director, Hunter-Hopkins Center, describing the characteristics signs of ME/CFS. Dr. Lapp's practice has focused on CFS/ME for more than 20 years.

table 3–cont'd

Nausea	
Various drugs	Granisetron, ondansetron (limited trials; early results positive, but very expensive agents). Older drugs (e.g., chlorpromazine, metoclopramide) may cause side effects with prolonged use.

Abbreviations: BP = blood pressure; CMV = cytomegalovirus; DHEA = dehydroepiandrosterone; DNA = deoxyribonucleic acid; EBV = Epstein-Barr virus; EPA = eicosapentaenoic acid; HHV6A = human herpes virus 6A; HPA = hypothalamic-pituitary-adrenal; IV = intravenous; ME/CFS = myalgic encephalomyelitis/chronic fatigue syndrome; NADH = nicotinamide adenine dinucleotide; NMH = neurally-mediated hypotension; NSAIDs = nonsteroidal anti-inflammatory drugs; PCBs = polychlorinated biphenyls; PCR = polymerase chain reaction; POTS = postural orthostatic tachycardia syndrome; RNA = ribonucleic acid; SNRIs = serotonergic norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors

[a] Clinical trials are lacking in ME/CFS patients; potential benefits based on efficacy in clinical trials relating to other medical conditions
[b] For orthostatic intolerance, NMH and POTS, use a combination of therapies: volume expansion (increase salt intake, add fludrocortisone if salt becomes ineffective); add a beta-blocker (e.g., atenolol – increases fill-time of heart); add alpha-1-agonist (e.g., midodrine – increases venous tone).

table 4

Additional resources for pharmacists and patients

WEBSITES

National ME-FM Action Network
• **www.mefmaction.net**

This advocacy group spearheaded development of the 2003 Canadian ME/CFS guidelines (full text available for free download)

FM-CFS Canada
• **www.fm-cfs.ca/resources-p.html**

Includes *A CFS Guide for Pharmacists* (2008) and *A Fibromyalgia Guide for Pharmacists* (2008)

US Centers for Disease Control and Prevention – Chronic Fatigue Syndrome
• **www.cdc.gov/cfs/**

Provides detailed information and links

Co-Cure ME/CFS & Fibromyalgia
• **www.co-cure.org/**

Updates on new research and advocacy from around the world

BOOK

Bested AC, Logan AC. (primary author is a Canadian physician) ***Hope and help for chronic fatigue syndrome and fibromyalgia.*** Nashville: Cumberland House; 2006.

A very readable overview of CFS/ME and FMS, current treatments and future directions. Includes input from a lawyer concerning long-term disability matters (e.g., occupational, insurance issues).

Prognosis

Prognosis depends on illness severity and duration; those with severe symptoms or a longer duration of illness do more poorly.[16] Unlike many other serious conditions, the prognosis for children and adolescents is better than in adults.[17]

Only three to six per cent of those who have ME/CFS symptoms for three years or more fully recover.[18] This suggests that early diagnosis and treatment may be important. An estimated 25% of ME/CFS patients are unemployed or receiving disability payments due to the condition, and fewer than 20% have been accurately diagnosed.[10]

Treatment

Evidence-based treatments target symptoms with the goal of maximizing the patient's ability to maintain function in everyday activities and, where applicable, slowly extending the boundaries of these activities.[5,10] Table 2 (available online) provides an overview of therapies for ME/CFS, while Table 3 provides more detailed information about drug therapy. Ideally, the beneficial effects of medications will be balanced against their adverse effects (e.g., sedation, cognitive dysfunction); this judgment is made primarily by the patient.

Individuals with ME/CFS may respond to very low doses of medication (e.g., amitriptyline 5 mg/day, cyclobenzaprine 2 mg/day) and tend to be more sensitive to drug side effects. They also usually need a longer duration of treatment (e.g., treating sleep disorders with a hypnotic for only two weeks is not sufficient).[5]

The pharmacist's role

Therapy for ME/CFS patients often includes off-label use of a variety of medications, which may be initiated at very low doses. In many cases, specially compounded medications are required, and dosage schedules may be complex, with doses titrated according to response.

Many MS/CFS patients are advised to avoid chemical additives and agents that could trigger exacerbations. Pharmacists can assist in selecting additive-free products (e.g., soaps, personal hygiene products, toothpastes) and verify that over-the-counter and prescription medications do not contain triggers (e.g., caffeine, gluten). They can also source nondrug items (e.g., mercury-free fish oils), as well as devices to help patients sleep (e.g., eyeshades, earplugs) and monitor symptoms (e.g., pedometers, blood pressure monitors). Pharmacists can help monitor for drug and supplement interactions, as well as side effects that could further limit functional capacity. They can also provide useful information and resources to empower patients and their families to cope with ME/CFS (Table 4).

Conclusion

ME/CFS patients are understandably frustrated with the devastating effects of the condition on their lifestyle, as well as the prognosis. By acknowledging this, pharmacists can reinforce that there is no "one regimen fits all" approach to treating ME/CFS and help to tailor therapies to the individual's (sometimes changing) needs. pp

References and Table 2 are available at www.pharmacygateway.ca (Go to Publication Archives, *Pharmacy Practice*, December/January 2009, Chronic Fatigue Syndrome).

table 2

Overview of treatment program for ME/CFS [5, 15,19-23]

PROGRAM COMPONENT	SELECTED STRATEGIES
The treatment program should incorporate lifestyle/management techniques and self-help therapies to maximize coping skills, while minimizing impairment.	
Patient education	• Careful self observation to identify what makes one better or worse (e.g., charting and diaries; for good charts, see book listed in Table 4) • Avoid or manage aggravators (e.g., viral infections, overactivity, certain foods or drugs, stress or chemical exposures)
Self-development	• Set emotional/personal boundaries and find enjoyable activities within fatigue limits • Plan for regular "fun activities" (especially important for the severely affected)
Sleep hygiene	• Conserve energy; pace activities to avoid increasing adrenaline release near bedtime • Establish regular bedtime, calm/dark sleep environment • Eyeshades, blackout blinds help ensure darkness. This promotes melatonin production, which may aid sleep • Ear plugs (e.g., beeswax, silicon are the best low-cost plugs) or custom ear plugs (block over 80% of noise) • Introduce hypnotic agent, if necessary
Dietary considerations	• Balanced, nutritious diet recommended (organic if feasible) • Ensure adequate caloric intake, with sufficient protein and "good" fat in diet (e.g., fish, nuts, seeds) • Test for food sensitivities; eliminate those that trigger symptoms (e.g., food additives) • Ensure adequate salt intake (up to 10–15 g/day; along with adequate water intake, helps with hypotension and postural orthostatic tachycardia syndrome) • Caffeine triggers adrenaline release, which increases activity and can lead to "crashes"
Fitness	• Remain as active as possible in daily activities • Short spans of activity (e.g., 3 x 10 minutes) preferable to a single longer period • Lie down between activity periods • Increase activity by 10% per month, if tolerated • If symptoms worsen, cut back slightly; don't quit altogether
Cognitive behaviour therapy	• Patient identifies what he/she can do to make the situation better • Avoid comparing oneself to healthy people (this is too discouraging) • Avoid being pushed by self or others into activities that are beyond one's limits • Notice self-talk and identify self-defeating scripts (e.g., "there must be something wrong with me" versus "I'm doing the best I can") • Split goals into small, manageable parts and tackle them one at a time
Managing orthostatic intolerance	• Fidget/flex leg muscles when standing in one place • Take horizontal breaks (e.g., lie down - helps blood return from extremities) • Move slowly from sitting/lying to standing position • Use compression stockings or support hose • Medications, as needed (see Table 3)
Managing/coping with pain	• Pace activities to minimize pain exacerbations • Improve core strength to reduce painful overuse of peripheral muscles • Physical therapies (e.g., physio, massage, chiropractic) can offer short-term symptom relief; active therapy (e.g., core strength exercise, walking) required for longer-term benefit • Pharmacotherapy, as needed (see Table 3)

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