OBJECTIVE

Alberta clinicians will have the information and tools necessary to detect key symptoms of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and manage these symptoms over the long term.

TARGET POPULATION

Adults and children

EXCLUSIONS

None

PRACTICE POINT

Illness severity in ME/CFS ranges from mild (still able to work with effort) to extreme (bedbound needing 24 hour care). Pathological fatigue and post exertional malaise – out of proportion to exertion and taking more than 24 hours to recover – is the key to considering a diagnosis of ME/CFS.

RECOMMENDATIONS

PRACTICE POINT

Although there is currently no definitive test or validated tool to diagnose ME/CFS or single proven treatment, symptoms consistent with ME/CFS can be identified and managed successfully within the primary care setting.

SUGGESTED ASSESSMENT AND DIAGNOSIS (SEE ALGORITHM)

- ✓ Consider the Fukuda and Canadian consensus criteria which are most commonly reported in the literature and are available:
  - A validated, sensitive and specific tool (Canadian consensus) is suggested for use. See Table 1: ME/CFS symptom checklist. This tool is most specific in differentiating ME/CFS from psychiatric conditions and making a diagnosis.
  - "The Fukuda Criteria" require the presence of four of eight symptoms over six months. With no mandatory criteria the permutations are many (8X7X6X50). Limitations include heterogeneity, not having post exertional malaise (PEM) – the core symptom of ME/CFS as required for diagnosis, and psychiatric patients may be misdiagnosed as having ME/CFS from overlapping criteria, especially with major depressive disorder. See: http://www.cdc.gov/cfs/case-definition/1994.html
  - In addition, the Institute of Medicine recently suggested a simple three-question diagnostic tool. It is easy to use but lacks specificity for ME/CFS so will generate higher numbers of false positives than the Canadian criteria. See: https://iom.nationalacademies.org/~/media/Files/Report%20Files/2015/MECFS/MECFScliniciansguide.pdf

ME/CFS Symptom Checklist	
Symptoms	**Description of Symptom**
Pathological fatigue **Yes ☐ No ☐**	A significant degree of new onset, unexplained, persistent or recurrent physical and/or mental fatigue that substantially reduces activity levels and which is not the result of ongoing exertion and is not relieved by rest.
Post-exertional malaise & worsening of symptoms **Yes ☐ No ☐**	Mild exertion or even normal activity is followed by malaise: the loss of physical and mental stamina and/or worsening of other symptoms. Recovery is delayed, taking more than 24 hours.
Sleep problems **Yes ☐ No ☐**	Sleep is un-refreshing: disturbed quantity – daytime hypersomnia or nighttime insomnia and/or disturbed rhythm – day/night reversal Rarely there is no sleep problem
Pain **Yes ☐ No ☐**	Pain is widespread, migratory or localized: myalgia; arthralgia (without signs of inflammation); and/or headache – a new type, pattern or severity Rarely there is no pain
Two neurocognitive symptoms **Yes ☐ No ☐**	Impaired concentration, short term memory or word retrieval; hypersensitivity to light, noise or emotional overload; confusion; disorientation; slowness of thought; muscle weakness; ataxia
At least one symptom from two of these categories: **a) Autonomic** **Yes ☐ No ☐**	a) Autonomic: Orthostatic intolerance – neutrally-mediated hypotension (NMH);postural orthostatic tachycardia (POTS); light headedness; extreme pallor; palpitations; exertional dyspnea; urinary frequency; irritable bowel syndrome (IBS); nausea
b) Neuroendocrine **Yes ☐ No ☐**	b) Neuroendocrine: Low body temperature; cold extremities; sweating; intolerance to heat or cold; reduced tolerance for stress; other symptoms worsen with stress; weight change; abnormal appetite
c) Immune **Yes ☐ No ☐**	c) Immune: Recurrent flu-like symptoms; sore throats; tender lymph nodes; fevers; new sensitivities to food, medicines, odors or chemicals

Table 1: Validated ME/CFS Symptom Checklist

SYMPTOM MANAGEMENT

GENERAL PRINCIPLES AND CONSIDERATIONS

PRACTICE POINT

Many symptoms associated with ME/CFS are common in other chronic conditions and can be treated and/or managed as per usual care with a few symptoms requiring special considerations.

- ✓ Acknowledge the legitimacy of the condition and respect the patient's lived experience. Often patients are more ill than they look.
- ✓ Manage ME/CFS symptoms:
    - Develop a mutually agreed upon action plan (between patient and physician).
    - Prioritize symptoms and manage the most severe, disabling and problematic symptom(s) first.
    - Address symptoms using a stepwise approach over time.
    - DO NOT try to address all or too many symptoms in one visit.
    - Encourage patients to learn as much as they can about the condition allowing them to self-manage their symptoms using available resources, many of which are provided in this guideline.
    - Refer for group therapy if available.
        - Group sessions can be particularly beneficial for this patient population as they can learn from each other and feel supported. The Alberta Health Services (AHS) "Better Choices Better Health" program, although not disease specific, may be helpful. See http://www.albertahealthservices.ca/bcbh.asp.
- ✓ Consider a combination of non-pharmacological and pharmacological interventions (see Table 2 below).
- ✓ Monitor progress and assess for any other emerging conditions with regular patient follow-up.

Symptom	Suggested Management: Pharmacotherapy/Non-pharmacotherapy Approaches
Pathological fatigue	There are two evidence-based interventions for fatigue. There is active debate among experts as to the better approach. • Pacing: identifying one's energy at a given time and adapting activity level to energy level. If using this approach see Appendix B – Activity Log. There is less chance of symptom setback associated with pacing. • Graded exercise: gradually increasing activity level over time. If using this approach, careful monitoring is required as the patient can have a debilitating symptom setback if they inadvertently exceed their energy envelope too often or too severely. Using both interventions is possible by incorporating pacing within a graded exercise regimen.
Post-exertional malaise (PEM) & worsening of symptoms	• Same as above.

Symptom	Suggested Management: Pharmacotherapy/Non-pharmacotherapy Approaches
Sleep problems	✓ Use typical sleep hygiene principles (see Myhealth Alberta). ✓ Consider and if necessary prescribe sleep medication (see Appendix C) ✓ Refer to sleep specialist if a primary sleep disorder is suspected (one or more sleep disorders are present in 20% of cases).
Pain	✓ Identify the types of pain. ✓ Suggest using pacing activity log (see Appendix B). ✓ Assess the patient's need for and use typical pain medications. ✓ For fibromyalgia pain consider treatment options suggested in 2012 Canadian Guidelines for the Diagnosis and Management of Fibromyalgia Syndrome (http://fmguidelines.ca/?page_id=21). ✓ For migraine/headache see TOP's Guideline for Primary Care Management of Headache in Adults.
Neurocognitive symptoms	✓ Pace cognitive tasks similar to pacing physical activity. ✓ Plan important tasks for the "best time of day." ✓ Suggest strategies to keep information, appointments and personal items organized such as a "memory book." Keep common items (keys, glasses, wallet) in a central, consistent location. X Avoid high intensity or multisensory situations or events.
Autonomic	✓ Manage as per usual care.
Neuroendocrine	✓ Manage as per usual care.
Immune	✓ Consider anti-parasitics or antiviral therapy where pathogen(s) can be confirmed by testing.
Sensitivity to chemicals and drugs	✓ Patients with ME/CFS often have increased sensitivity to food, chemicals and medications and should avoid these irritants. There is no special diet for ME/CFS. ✓ Workplace accommodation is often required.
Other Symptoms/Co-Morbid Conditions Associated with ME/CFS	
Depression, mood and anxiety disorders	✓ Treat and manage co-morbid psychiatric conditions as per usual care. (**Note** that patients with ME/CFS tend to be more sensitive to medication side effects than primary psychiatric patients.) ✓ Suggest evidence-based psychotherapy, e.g., cognitive behavioural therapy, which would be the best fit for those patients who are depressed, anxious or hopeless as a result of their illness and to assist in optimizing self-management. (Note many PCNs in Alberta now offer doctoral level psychologist counselling and/or CBT programs. Physicians should inquire about availability in their PCN.)

Table 2: Specific ME/CFS Symptom Management

✓ Use one treatment for multiple symptoms where possible (see Table 5).

PRACTICE POINT

The evidence on effectiveness of complementary alternative medicine (CAM) in ME/CFS is weak. However some patients may benefit. The physician's role is to support the patient in his/her choice of CAM and assist in minimizing any harm.

Children

- ✓ Manage children and adolescents with ME/CFS similarly to adults. For additional information see page 29 of: http://iacfsme.org/portals/0/pdf/Primer_Post_2014_conference.pdf.

Fibromyalgia (FM)

Fibromyalgia is present in about half of all individuals with ME/CFS.

- ✓ Manage symptoms for individuals with FM similar to management of ME/CFS.
- ✓ See http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3856149 for more information and a comparison of existing FM guidelines.

Additional Resources for Physicians and Patients

- ✓ See Appendix D for a listing of ME/CFS provider resources and programs available in Alberta.
  - Although the ME/CFS Primer for Clinical Practitioners (2014 revision) is not an evidence-based guideline, it is evidence-informed and provides practical information that may be helpful for guiding care of patients with ME/CFS: http://www.iacfsme.org/Portals/0/PDF/Primerfinal3.pdf.

Background

Introduction

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is the current terminology used to describe a physical condition most commonly associated with post-exertional malaise, debilitating fatigue, pain, cognitive problems, sleep dysfunction as well as many other neurologic, immune and autonomic symptoms.[1] The most significant feature of ME/CFS is the post-exertional malaise – a worsening of symptoms after minimal physical or mental activity that can continue for hours, days or weeks. Rest and sleep can provide some relief from the fatigue and the other symptoms but often not enough to cope with activities of daily living. In addition, reduced physical and/or cognitive functioning is common. Although ME/CFS is a physical illness, psychological symptoms may also be present.

The evidence reviewed (existing guidelines and systematic reviews) on ME/CFS (diagnosis, treatment and management) was found to be either conflicting, not yet available for inclusion or absent to make recommendations at this time. However recommendations have been made based on the best available evidence at this time and/or expert opinion.

EPIDEMIOLOGY

Onset usually occurs between the ages of 30 and 50 years, but may occur at almost any age. The prevalence in adolescents and children is uncertain, but appears to be lower than in adults, with equal numbers of boys and girls affected. There is no high quality epidemiological data for Canada. The Statistics Canada Community Health Survey (2014) estimates Canadian prevalence at 407,789, or 1.4% of Canadians 12 years and older.[2]

ETIOLOGY

Over the past three decades, there has been substantial progress advancing the understanding of ME/CFS. Most agree that ME/CFS is a heterogeneous condition with multiple triggers and clinical courses. Both predisposing and precipitating factors are thought to contribute to the developing condition.

Predisposing Factors	Precipitating and Causal Factors
Mostly occurs among female gender adults Can be familial or inherited[3]	ME/CFS is thought to occur following:[4] • Environmental toxin exposure • A recent vaccination • A significant physical or emotional trauma • Occasionally no identifiable trigger

Table 3: Predisposing, Precipitating and Casual Factors Contributing to ME/CFS

Patients have associated the onset of their ME/CFS after a flu-like illness. In some cases, ME/CFS follows infection with a known viral infection, human herpes viruses or enteroviruses.[5,6]

A number of viruses and/or the antibodies against them have been found more frequently in patients with ME/CFS than in control populations[7-10] suggesting that a virus or viruses may play a causative and/or ongoing role. However a recent study by Hornig et al., the largest to date, fails to find evidence of any active infection.[11] This suggest that infection may play a "hit and run" role leaving the immune system impaired. Impaired NK and T Cell function are most replicated findings in ME/CFS.[12-14]

Figure 1 depicts ME/CFS as a multi-systemic disorder[15] Studies which assess the effects of exertional challenges with physical (exercise or orthostatic) or cognitive (mental) tasks are more consistent than studies where no trigger is used. These studies may eventually help to confirm the primary symptom being post-exertional.[16-22]

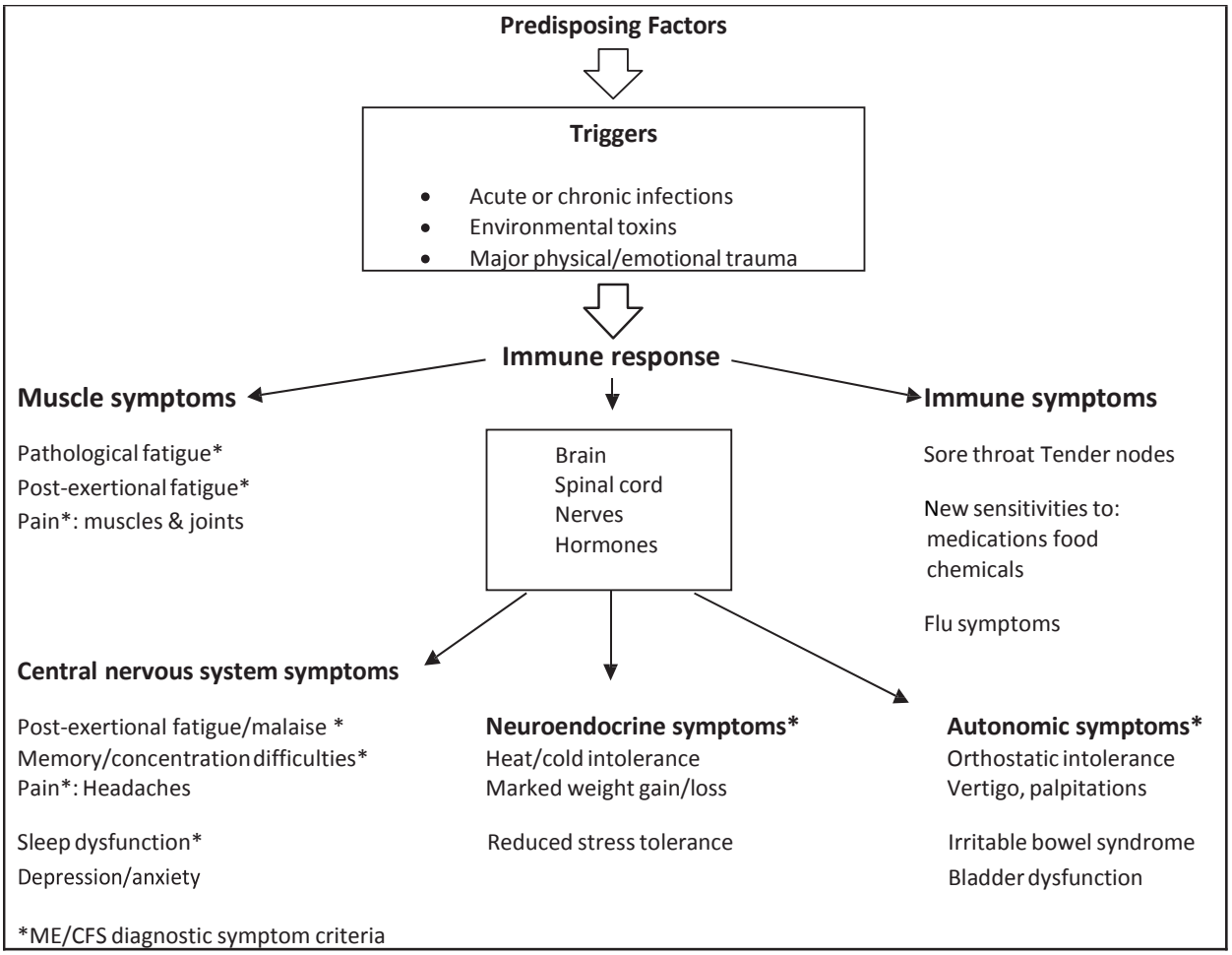

Figure 1: Reproduced with permission from Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis ME/CFS Primer for Clinical Practitioners International[15]

SYMPTOM IDENTIFICATION

A systematic review noted that eight case definitions have been used to define ME/CFS; those for ME, require the presence of post-exertional malaise, and represent a more symptomatic subset of the broader ME/CFS population. From the review it appears that researchers are unable to determine differences in accuracy between case definitions because there is no universally accepted reference standard for diagnosing ME/CFS. Some tools are more simplistic and user friendly than others but as a result compromise sensitivity and specificity, and some include criteria for ME/CFS not found in other case definitions. Furthermore, self-reported symptom scales may differentiate ME/CFS patients from healthy controls but have not been thoroughly tested to determine their validity and generalizability in larger populations.

In the absence of a gold standard test, healthcare providers should diagnose ME/CFS using validated diagnostic criteria and clinical experience.[1,23]

PATIENT HISTORY

Clinicians must take a thorough medical and social history to accurately identify the core symptoms of ME/CFS. Several visits with the patient are often necessary given the complex history, number of symptoms and cognitive difficulties experienced by some patients.

DIAGNOSIS

The information collected should include pre-illness functioning including job/school performance, social and family relationships, and their current living situation including daily routine activities, stressors, major life changes, and support. Assessing the patient's ability to function in their day to day life will make visible the significant challenges they're experiencing due to the illness. The symptoms in ME/CFS can be of greater severity than in other chronic conditions.[24] A review of their past medical records, diagnostic reports, and lab tests may also provide useful information to assist in the assessment.

OPTIONS FOR IDENTIFYING ME/CFS

The Institute of Medicine (IOM) diagnostic criteria was established in 2015 to allow for more practical and simple diagnosis.[25]

The diagnosis requires that the patient have the following three symptoms: 1. A substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities, that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest 2. Post exertional malaise 3. Un-refreshing sleep
At least one of the two following manifestations is also required: 1. Cognitive impairment* 2. Orthostatic intolerance **Frequency and severity of symptoms should be assessed. The diagnosis of ME/CFS should be questioned if patients do not have these symptoms at least half of the time with moderate, substantial, or severe intensity.[25]*

Table 4: IOM Diagnostic Criteria

These IOM criteria were developed to improve ease and practicality for diagnosing ME/CFS in primary care. However ease of use comes at the cost of specificity. A recent paper suggests that using this tool alone results in a 2.8 times increase in estimated prevalence.[26] This means patients with many other medical and psychiatric disorders will be misdiagnosed as having ME/CFS. In order to increase confidence of diagnosis in patients screening positive for ME/CFS using IOM criteria, one could follow with the more detailed and validated Canadian Consensus Criteria. However, there are no studies to date supporting this "triaging" or combination approach.

THE CANADIAN CONSENSUS CRITERIA (CCC) – A VALIDATED SYMPTOM CHECKLIST

These criteria have been operationalized and shown to best differentiate between patients with ME/CFS and those with psychiatric conditions. In a study comparing the CCC with the other commonly used Fukuda[23] criteria, patients diagnosed using the CCC had significantly lower rates of current psychiatric diagnoses (47.8%) than patients diagnosed using the Fukuda criteria (75.0%).[27]

To identify probable ME/CFS using the Canadian Consensus Criteria (CCC), the patient must have the following:

- Pathological fatigue, post-exertional malaise, sleep problems, pain, two neurocognitive symptoms, and at least one symptom from two of the following categories: autonomic, neuroendocrine and immune.
- The fatigue and the other symptoms must persist, or be relapsing for at least six months in adults, or three months in children and adolescents. A provisional diagnosis may be possible earlier.
- The symptoms cannot be explained by another illness.
- Improved identification of ME/CFS can be achieved by measuring the severity and frequency of the listed symptoms (see Table 1)

SYMPTOM CHARACTERISTICS:

- A sudden onset is most common, but the onset may be gradual.
- Symptoms usually vary from day to day or during the day.
- Relapses and remissions are frequent.
- Post-exertional symptom flare-ups may occur immediately or they can be delayed 24 hours or more.
- If pain and/or sleep disorder are absent, ME/CFS can be diagnosed if the illness has an abrupt onset.

EXCLUSIONARY ILLNESSES:

All conditions that lack a diagnostic test require a list of exclusionary conditions to assist with diagnosis. Many other illnesses have symptoms which overlap with ME/CFS. Other active disease processes that could explain the major symptoms of fatigue, sleep disturbance, pain, and neurocognitive dysfunction must be ruled out by history, physical examination and medical testing. The list below was first suggested in 1988,[28] repeated with some changes in 1994[23] and then in the CCC 2003.[1] This list has not been validated.

- Anemias
- Autoimmune diseases such as rheumatoid arthritis, lupus
- Cardiac disease
- Endocrine disorders such as diabetes, Addison's disease, thyroid disease, menopause
- Infectious diseases such as tuberculosis, HIV/AIDS, chronic hepatitis, Lyme disease
- Intestinal diseases such as celiac or Crohn's disease
- Malignancies
- Neurological disorders such as multiple sclerosis, Parkinson's disease, myasthenia gravis
- Primary psychiatric disorders and substance abuse (but not clinical depression)

- Significant pulmonary disease
- Primary sleep disorders such as sleep apnea

NON-EXCLUSIONARY CONDITIONS:

These non-exclusionary conditions come from the CCC and list the conditions which commonly co-occur with and are not thought to exclude a diagnosis of ME/CFS. There are several studies to show these conditions co-occur[29-31] but there is no rigorous validation of this list.

- Some co-morbid entities commonly occur in association with ME/CFS. They include: allergies, fibromyalgia (FM), irritable bowel syndrome (IBS) and multiple chemical sensitivities (MCS).
- Any medical condition that has been adequately treated and is stable
- Any isolated physical abnormality or laboratory test that is insufficient to diagnose an exclusionary condition
- ME/CFS and FM are often closely associated and are considered to be overlapping syndromes.
- If the patient has unexplained, prolonged fatigue but has an insufficient number of symptoms to meet the criteria for ME/CFS, the illness should be classified as idiopathic chronic fatigue.

If the patient does not meet all criteria the patient should be treated for existing symptoms and monitored.

OTHER EXISTING CRITERIA

The Fukuda criteria developed in 1994 by consensus under the auspices of the Centers for Disease Control and Prevention in the USA. These criteria, requiring four or more of eight common symptoms, have been operationalized and validated. However, the presence of post exertional malaise (the core symptom of ME/CFS) is not required and there are no mandatory symptoms. As a result, the Fukuda criteria define a heterogeneous group. Some primary psychiatric patients are misdiagnosed as having ME/CFS due to overlapping criteria.[27]

The International Consensus Criteria[32] has not been operationalized or validated. It is complicated for physicians to use and validity is unclear. The rates of psychiatric disorder diagnosed using this criteria, is higher than when using the CCC or Fukuda criteria. This is likely owing to the large number of symptoms required for diagnosis.[33] In population studies, greater numbers of physical symptoms are associated with higher rates of psychiatric diagnosis.[34]

A recent systematic review states that no definition can be considered a Gold Standard in ME/CFS until there is an objective test to compare it with.[35] However, as discussed, the CCC appears to best differentiate ME/CFS from psychiatric cases. The AHRQ report also states that treatment trials should refrain from using the Oxford criteria.[36] The criteria are less rigorous and may include patients with fatigue as their only symptom. Therefore this tool is too sensitive and includes too many non-ME/CFS patients diagnosed as such should not be used for either clinical or research purposes.

MANAGEMENT OF ME/CFS SYMPTOMS

GENERAL CONSIDERATIONS

With a few exceptions, the symptoms associated with ME/CFS such as pain and unrefreshing sleep are similar to symptoms associated with other chronic conditions seen in primary care. In many cases these symptoms can be managed similarly. As with any chronic condition, it is important to acknowledge that the patient has a valid clinical condition and that it is not hypochondriasis, a mental disorder such as depression, anxiety or something they have created for attention. This is especially critical in ME/CFS as there is no laboratory proof of diagnosis. The patient should be educated about the illness (see contact information in Appendix D for additional resources) and be an active participant in determining a care plan. Patients who need more guidance on activity management and diet can be referred to other health care providers such as physiotherapists and dietitians that are knowledgeable about ME/CFS and appropriate management, if available.

Symptoms can often be effectively treated with a combination of non-pharmacological and pharmacological interventions. Ongoing regular follow-up is important to monitor progress and assess for newly emerging conditions. People with ME/CFS also get common but unrelated conditions such as heart disease, cancer, arthritis etc.

Given the large number of symptoms often experienced, it is optimal to choose interventions that address more than one symptom. The following table illustrates treatments that may be used to manage multiple ME/CFS symptoms.

Symptoms	Medication – Tricyclics	Pacing Activities	Other sedating antidepressants	Sedating prophylactic pain medications, e.g., pregabalin
Fatigue/post-exertional malaise		✓		
Sleep problems	✓	✓	✓	✓
Pain	✓ General, FM and Migraine	✓		✓
Depression/anxiety/mood disorder	✓		✓	
Neurocognitive problems		✓		

Table 5: Patient Symptoms and Treatment Options

FATIGUE AND POST-EXERTIONAL MALAISE

PACING VERSUS GRADED EXERCISE THERAPY (GET)

Managing fatigue and post exertional malaise is at the core of stabilizing patients with ME/CFS. There are two evidence-based, widely used approaches to fatigue management: pacing and graded exercise. Pacing involves identifying one's energy at a given time and adapting activity level to energy level. Graded exercise involves gradually increasing activity level irrespective of the impact on symptoms. There is an active debate in the field about which approach is better for which types of patients. There are treatment studies and review papers supporting both approaches. The variability in results may be due to the heterogeneity of study participants given the lack of a gold standard diagnostic test. While there are several studies concluding positive results from graded exercise,

many experts in the field continue to use a pacing approach.[15] Because there are benefits and support for both interventions, it may be best to incorporate pacing within a graded exercise regimen.

Pacing (applicable for most symptom clusters)

Pacing is a strategy of staying within the range of activity required to avoid exacerbating fatigue and post-exertional malaise.[37-39] Individuals need to learn how much they can do at a given time without exacerbating their symptoms. One must remember that the effects of activity are often cumulative over days to weeks and onset of post exertional malaise can be delayed for several days. This requires self-awareness and self-evaluation. Activities of daily living use energy and therefore are considered exercise. These activities may be enough exercise for some patients or excessive exercise for others. The ideal range is very individual and is often referred to as the "energy envelope." Staying within one's energy envelope is associated with a better outcome than frequently pushing beyond.[38] To stay within the energy envelope, some patients need to decrease their activity while others need to increase activity. An individual's energy envelope is discerned by noting the response to changes in activity level.

To pace effectively, an individual may divide tasks into smaller parts with rest periods between each task. For patients with orthostatic symptoms, horizontal rests are especially helpful. Patients should remain as active as possible while avoiding fatigue-worsening over-exertion. Keeping an activity log helps to determine the best combination of activity and rest. An example of an activity log is available in Appendix B.

Cognitive Behaviour Therapy and Graded Exercise Therapies

In ME/CFS, both cognitive behavioural therapy (CBT) and graded exercise therapy (GET) have been rigorously studied using randomized control trial (RCT) analysis). These two treatments are often offered together. Many of the studies of CBT and GET in ME/CFS and the meta-analyses of these studies conclude that both therapies are beneficial.[40-44] However on closer analysis of the literature, there are several areas of concern.

First, these therapies were developed based on the assumption that ME/CFS is a psychological condition in which "inaccurate and unhelpful beliefs, ineffective coping behaviour, negative mood states, social problems and pathophysiological processes all interact to perpetuate the illness."[45] There is now an extensive literature showing that many of the assumptions underlying the use of CBT and GET in ME/CFS are incorrect for some or even most patients with ME/CFS. Specifically, the mental health of patients with ME/CFS is not reflective of their coping style;[46] high rather than low activity level is a risk factor for ME/CFS;[47] physical illness severity and not psychological distress is the strongest predictors of outcome[5] and measurable pathophysiologic processes are reported in thousands of peer reviewed papers. Both the recent reports by the National Institutes of Health and the Institute of Medicine state that "ME/CFS is not a psychological condition."[25,48]

Second, the patient selection for the CBT/GET trials that form the bulk of the "evidence" for their effectiveness used the Oxford criteria despite the obvious shortcomings as discussed. These criteria lack specificity and allow many psychiatric patients to be misdiagnosed with ME/CFS. It is now recommended that these criteria not be used for research or clinical diagnosis.[35]

Third, although the authors of a recent meta-analysis conclude that there is "no evidence suggesting that exercise therapy may worsen" outcomes,[49] data not included in this systematic review suggest otherwise. Patients in several large national surveys report that when exercise is increased causing over-exertion relapse of symptoms can result.[50-52] Although harms are not well reported in the RCTs, one trial reports patients receiving GET reported more adverse events compared with those receiving cognitive behavior therapy (CBT), adaptive pacing, or usual care; one trial reported more withdrawals of patients receiving GET, one trial had a high percentage of patients refusing repeat exercise testing, and several other trials reported more withdrawals of patients receiving GET, all compared with controls.[44]

A growing literature shows that some patients with ME/CFS are unique from individuals with other conditions in that they are not able to replicate a maximal exercise test two days in a row despite objectively measurable maximal effort.[16,53,54] Patients with other, serious medical conditions, even end stage heart disease and COPD are able to replicate their effort even if it is subnormal. The two-day cardio pulmonary exercise test (CPET) protocol may be a way to measure post exertional malaise though the side effects of the test are considerable and less rigorous tests are being sought.

A recent systematic review of 23 papers suggests that the post exertional malaise reported by patients with ME/CFS correlates with pronounced response in the complement system (i.e. C4a split product levels), oxidative stress system (i.e., enhanced oxidative stress combined with a delayed and reduced anti-oxidant response), and an alteration in the immune cells' gene expression profile (increases in post-exercise interleukin-10 and toll-like receptor 4 gene expression).[55] These data suggest that increased activity has measurable physiological consequences and should be undertaken with caution in ME/CFS.

In summary, all patients with ME/CFS have post exertional malaise (PEM) which limits the ability to exercise. No study of CBT and/or GET has measured post exertional malaise (PEM). Many of the CBT and GET studies use the Oxford criteria which have been severely criticized by the Association for Health Research Quality.[35] Many others used the Fukuda criteria. Neither the Oxford nor Fukuda criteria require the presence of PEM, a core symptom of ME/CFS. Studies using the Oxford criteria had higher effect sizes for CBT and GET than studies using the Fukuda criteria but effect sizes are small. Harm may have been underreported.[50] Effect sizes for CBT in ME/CFS outside RCTs are lower than within RCTs for example. [56] The systemic review by Nijs et al. – the only one reporting on objective measures – shows adverse immune and inflammatory reactions in ME/CFS patients post exercise and this may be the mechanism of harm.[55]

Therefore, CBT can be helpful in ME/CFS but is rarely if ever curative or sufficient. Other treatment options should be considered based on specific symptoms as well as ongoing monitoring of symptoms and reassessment of treatments.

Sleep Problems

Sleep problems are well documented in ME/CFS using polysomnography studies including: alpha intrusion into deep sleep, cyclic alternating rhythm and increased inspiratory resistance however no single diagnostic abnormality has been identified. Abnormalities include: initial insomnia, frequent waking, non-restorative sleep (i.e., waking up feeling unrefreshed or as tired as before going to sleep) stiffness or soreness and mental fogginess lasting a few hours after waking. Hypersomnia tends to

occur early in the illness and insomnia develops as the illness progresses. Primary sleep disorders occur in 20% of individuals with ME/CFS even in individuals not appearing "at risk."

Non-pharmacologic treatment should be prescribed at the outset and patients should commit to trying improved sleep hygiene before or with sleep medication General sleep hygiene suggestions recommended for patients in general and often helpful for patients with ME/CFS include:[57]

- ✓ Perform relaxing wind-down activities for one hour prior to bed time.
- ✓ Ensure regular sleep and wake times.
- ✓ Pace activities so symptom exacerbation including adrenaline spikes doesn't interfere with sleep.
- ✓ Avoid taking naps after 3 p.m. but rest and relax as needed.
- ✓ Spend time in the morning under full spectrum light (sunshine) either outdoors, by a window, or use artificial light.[58]
- ✓ Reduce or eliminate caffeine-containing beverages and food.
- ✓ Use earplugs or soundproofing for noise, sleep in a different room if you have and hear (a snoring) bedroom partner.
- ✓ Ensure the bedroom is dark by using a sleep mask or black-out window coverings.
- ✓ Get up and move to another room if you can't sleep and do a quiet activity such as reading, listening to soft music, or relaxation tapes until sleepy but do not use a computer, iPad, or TV.
- ✓ Do not try to force sleep.
- ✓ Try a carbohydrate snack at bedtime.[59]

Pharmacologic Treatment

Cognitive behavioural therapy insomnia (CBT-I) has not been formally tested in ME/CFS. A recent meta-analysis shows CBT-I to be more effective than no treatment in insomnia co-morbid with varied medical and psychiatric conditions.[60] Thirty-six percent of subjects were fully remitted with treatment vs only 17% of controls. Therefore, even if CBT-I is similarly helpful in patients with insomnia due to ME/CFS, the majority of patients will require additional treatment to optimize daytime function.

Because ME/CFS is a chronic condition, long term medication use may be required. Therefore, the risk/benefit profile over the long term must be carefully assessed. Ongoing review is required with periodic attempts to decrease or change medications as symptoms vary over time. Medications which address co-morbidities are commonly used.

Since patients are often sensitive to medication side effects, sedating medications should be started at a low dose. The medication should be taken early enough so that sedation occurs close to the patient's usual bed time. Given this sensitivity follow-up is important, i.e., no longer than one month after starting medication and until the patient is on a stable dose. If tolerance to one medication develops, it may be more effective to change/rotate medications than to continue one type of drug ongoing. See Appendix C for commonly used sleep medications in ME/CFS.

PAIN

Ongoing pain is a common symptom in ME/CFS. Pain can be localized or widespread and ranges from mild to severe. Headaches are common, particularly migraine-type headaches. If chronic widespread pain is a complaint, a fibromyalgia evaluation is indicated as between 21 and 61% of ME/CFS patients also have fibromyalgia[30,31,61,62] (see Special Considerations: Fibromyalgia). Localized pain such as migraine and arthritis should be treated as pain begets more pain due to neuroplastic changes in the brain.[63]

Non-pharmacologic pain management is very individual. Treating fibromyalgia pain in ME/CFS is similar to treating pain in fibromyalgia. One may try: pacing activities (see Appendix B), exercise, (aerobic is best for those with fibromyalgia pain according to the Ottawa Consensus)[64,65] physical therapy, massage, stretching, acupuncture, hydrotherapy, chiropractic, yoga, Tai Chi and meditation (relaxation response).[66,67] See Appendix D for pain management programs/resources in Alberta.

PHARMACOLOGIC TREATMENT

See Appendix E for medications commonly used to treat pain that can be used for patients with ME/CFS. One treats pain symptoms in ME/CFS similarly to pain in other chronic medical conditions:

- Use the lowest effective dose, titrate carefully and monitor closely.
- Select an agent based on the type of pain, e.g., arthritis, abdominal, fibromyalgia, other neuropathic, headache.
- Opiates are discouraged and should be used as a last resort and cautiously. If opiates are considered, it is preferable to refer the patient to a pain specialist.

NEUROCOGNITIVE PROBLEMS

Neurocognitive issues are very common in ME/CFS and are a significant source of impairment especially with regard to work. Most commonly affected are: working memory, processing speed and attention.[68-73] Patients complain of slow and effortful thinking. They have poor short term memory, problems tuning out extraneous stimuli and difficulty finding the right word to use. Individuals with ME/CFS often work more slowly and need more breaks than healthy individuals due to post exertional malaise. Neurocognitive impairment can be validated (quantitatively) by neurocognitive testing which is widely available in Alberta through (fee for service) psychologists. To locate a registered psychologist in Alberta see http://www.cap.ab.ca/registry.aspx.

To sustain functional capacity patients must learn how to pace their cognitive activities and manage stress. Cognitive functioning is often slower to improve than other symptoms

Managing cognitive difficulties:[15]

- Use a "memory book or device " to document important activities, tasks, events, appointments etc. (and keep the book in an open location where it can't be misplaced).
- Develop habits such as leaving keys or glasses or always parking in the same spot.
- Try to avoid situations where multisensory bombardment and fast-paced activity is likely to occur.

- Limit time and intensity of cognitive effort (similar to pacing physical activity).
- Limit or discontinue (i.e., take a break from) cognitive effort with exacerbation of cognitive symptoms.

For students with ME/CFS who need accommodation due to the illness, a resource entitled: "Teach ME" is helpful and can be found on the ME-FM Action Network website: http://www.mefmaction.com/images/stories/Support/Teach_Me_Eng.pdf.

Pharmacologic Treatment

See Appendix F for medications used to treat the cognitive symptoms. Stimulants can be helpful when patients complain of excessive daytime "sleepiness" versus "fatigue." Excessive sleepiness can be measured by a score of greater than 10 on the Epworth sleepiness scale and may require a workup for primary sleep disorders and referral to sleep specialist

Although stimulants can be helpful, they can be poorly tolerated or lead to "crashes" due to over-activity. This can cause long term setbacks. Stimulants including caffeine should be used with caution.

Autonomic Disorders

Autonomic disorders are measureable and can be treated. (Orthostatic intolerance (OI) is common in ME/CFS patients complaining of dizziness, light-headedness, feeling faint and/or having heart palpitations. In individuals with ME/CFS low BP is associated with decreased blood flow to the brain and fatigue symptoms.[74,76] This is particularly common in younger patients. For patients diagnosed with orthostatic intolerance, the usual treatment approach should be offered (e.g., salt, fluids, florinef, midodrine). Note: Autonomic Clinics are available in both Edmonton http://www.albertahealthservices.ca/info/facility.aspx?id=1050704 and Calgary http://www.ucalgary.ca/utoday/issue/2015-10-22/first-autonomic-nervous-system-disorder-clinic-opens-calgary for patients with complex cases.

Neuroendocrine Disorders

Neuroendocrine disorders are treated as they would be treated for any other patient with neuroendocrine disorders. Common problems include: hypoadrenal function, hypothyroid, low sex hormone levels, endometriosis and polycystic ovarian syndrome.

Infections and Immunological Factors

Although common and often severe, infections and immunological symptoms associated with ME/CFS are challenging to diagnose and treat. Several viral, bacterial or parasitic infections have been identified in some cases of ME/CFS (e.g., herpes viruses, enteroviruses, B. burgdorferi, mycoplasmas, G. lamblia)[77] but none is universally found. Patients who catch common viral infections (the flu or a cold) often experience setbacks of their ME/CFS. Long-term antibiotics, anti-parasitics or antiviral therapy may be beneficial in patients where the presence of these pathogens is confirmed by testing, but testing is not widely available in Alberta.

Multiple Chemical Sensitivity (MCS)

MCS is a common symptom of ME/CFS (present in about 40% of cases).[31] Rather than an allergic response, the patient's sensitivity is to low levels of specific odors or chemicals, which cause an exacerbation of symptoms. For example, perfumes worn by others may cause problems. These patients may need advice on how to avoid the environmental chemicals which trigger symptoms. Patients with multiple food sensitivities who avoid food groups may need dietary counselling to rotate their foods to avoid malnutrition. By avoiding interactions and locations with volatile chemicals which cause symptoms, patients with MCS often become very isolated and mental health problems can develop. As with any other condition, validation of the patient's experience is critical to develop and maintain the therapeutic relationship. There is no evidence-based literature on the treatment of MCS. In the absence of rigorous study, three recent Canadian publications summarize the state of the knowledge to date.[78-80] Avoiding the chemical irritants (if known) should not involve terminating employment. The Canadian Human Rights Commission has advised on the need of workplace accommodation for avoiding certain chemical or other irritants.[80]

Depression/Anxiety/Distress

Similar to individuals with other chronic conditions, patients with ME/CFS often have emotional reactions to the realities of living with their condition. Reactive emotions such as frustration, anger, grief, fear, apprehension and generalized discouragement are common. These emotional reactions do not typically become a diagnosable psychiatric disorder but for some patients, clinically diagnosable major depressive disorder (MDD) or anxiety may co-exist with ME/CFS or precede the illness.

It is important to distinguish the secondary psychological reactions to ME/CFS from a MDD or anxiety disorder.

To distinguish between ME/CFS and MDD identify the presence of symptoms such as post exertional malaise that is unique to ME/CFS and does not occur in primary MDD. Other symptoms, e.g., recurrent flu-like symptoms, sore throats, tender lymph nodes, orthostatic intolerance and hypersensitivity to light, noise and medications also distinguish ME/CFS from a primary MDD.

If depression in the context of ME/CFS should take on specific characteristics of a major depressive disorder (MDD) i.e., anhedonia and suicidal thoughts are present, treat as per usual for a major depressive disorder with some considerations such as increased sensitivity to medications.

Pharmacologic Treatment for Depression

Patients with ME/CFS tend to be more sensitive than primary psychiatric patients to medication side effects. Therefore it is advised to start at a lower than usual dose and work up slowly. Antidepressant side effects such as specifically sedation and orthostatic hypotension, may exacerbate the symptoms of ME/CFS. The choice of medication should be based on minimizing side effects, maximizing therapeutic effects (e.g., treating more than depression) and antidepressant effectiveness.

Cognitive Behavioral Therapy (CBT)

According to one meta-analysis, CBT was found to be effective for fatigue, functional impairment, depression and anxiety.[41] Other studies suggest there is good evidence that CBT is helpful when used in patients with depression.[81] CBT can also assist in optimizing self- management. However, it should be noted that for patients with ME/CFS, CBT may not be sufficient as a stand-alone treatment and other interventions may be required

Other

Diet, Nutritional Supplementation and Alcohol

Although some patients find from experience that they do better avoiding certain foods or food groups, there is no evidence to date that supports a special diet for ME/CFS. In the absence of evidence, a common sense approach of ensuring adequate nutrition from a balanced diet is recommended while avoiding high fat foods, sugars and caffeine. Eating small frequent meals/snacks may be helpful for some individuals. An appropriate daily multivitamin and/or additional specific vitamin or mineral supplements (e.g., vitamin D and calcium if restricting dairy products) may be required to ensure that recommended nutrient intake is obtained. Getting nutrition from food sources is preferred to taking supplements. Referral to a dietitian, preferably knowledgeable in ME/CFS, may be necessary if dietary guidance is needed.

For reasons that are not understood, a large percentage of patients with ME/CFS become intolerant of alcohol. As a result alcohol addiction is rare in ME/CFS. Because of the sleep disturbing and sedating effects of alcohol, its use should be avoided or minimized.

Complementary and Alternative Medicine (CAM)

Like patients with other medical conditions without an evidence based treatment, patients with ME/CFS are vulnerable to trying expensive, non-established and speculative treatments in hope of a cure. A review of the evidence of such therapies revealed generally poor methodologies and little if any evidence of benefit. Equivocal evidence was found for traditional Chinese medicine and biofeedback. [15]

For patients who wish to try CAM, they should be informed about the lack of strong evidence of benefit. If they choose explore CAM treatments regardless, the physician should assist patients to avoid harm. Expert opinion is that patients willing to try different treatments regardless of the evidence, are demonstrating initiative and activation – both important characteristics of self-management of ME/CFS.

Special Considerations

Children

ME/CFS can occur at any age including childhood and adolescence and it can be difficult to diagnose especially under the age of ten. The prevalence of ME/CFS in children and adolescents is lower than in adults.[82] Children and adolescents may not think to report symptoms because they don't have a period of normalcy with which to compare. They can be misdiagnosed as having

behavioral disorders, school phobia, ADHD, a factitious disorder by proxy or considered lazy.[83,84] Once accurately diagnosed, treatment and management of MECFS in children is similar to treatment and management in adults with the complexity of involving the family. Children tend to have more severe symptoms than adults with pain and autonomic dysfunction being prominent. Despite the increased severity, children tend to have better outcomes than adults as long as they are treated respectfully and not forced to do things they cannot do.[85-87]

FIBROMYALGIA (FM)

Although Fibromyalgia (FM) is outside of the scope of this guideline, it occurs in between 21 and 61% of ME/CFS patients.[30,31,61,62] FMS and ME/CFS share some key symptoms such as fatigue, cognitive impairment and unrefreshing sleep. In ME/CFS post exertional malaise is the key symptom while in FM it is chronic widespread pain. FMS can be suspected by the typical grouping of FM symptoms and by exclusion of other inflammatory and metabolic diseases that could account for the symptoms. As with ME/CFS, diagnosis is completely dependent on subjective symptom reporting and functional impairment. There is currently no definitive diagnostic test or tool to diagnose this condition. The American College of Rheumatology (ACR) 2010 Preliminary Diagnostic Criteria for Fibromyalgia[88] has been suggested in FM guidelines for use to initially assess for FM, however, there are multiple competing versions of amendments to the ACR 2010 criteria awaiting further research.[88]

In Alberta there are few specialists (rheumatologists) who will consult with FM patients past the initial diagnosis.

IMPLEMENTATION CONSIDERATIONS

- Specialists can provide the CPG as a resource for primary care physicians if and when patients are referred for ME/CFS.
- The CPG will be shared with Alberta Health Services Health Link as a resource and informing Health Link ME/CFS algorithms.
- The CPG will be circulated for use and information over time to related interest groups by the partners and champions participating in the development of the CPG.
- The CPG will be presented and promoted at events such as grand rounds or medical conferences by physicians participating in the development of the CPG.

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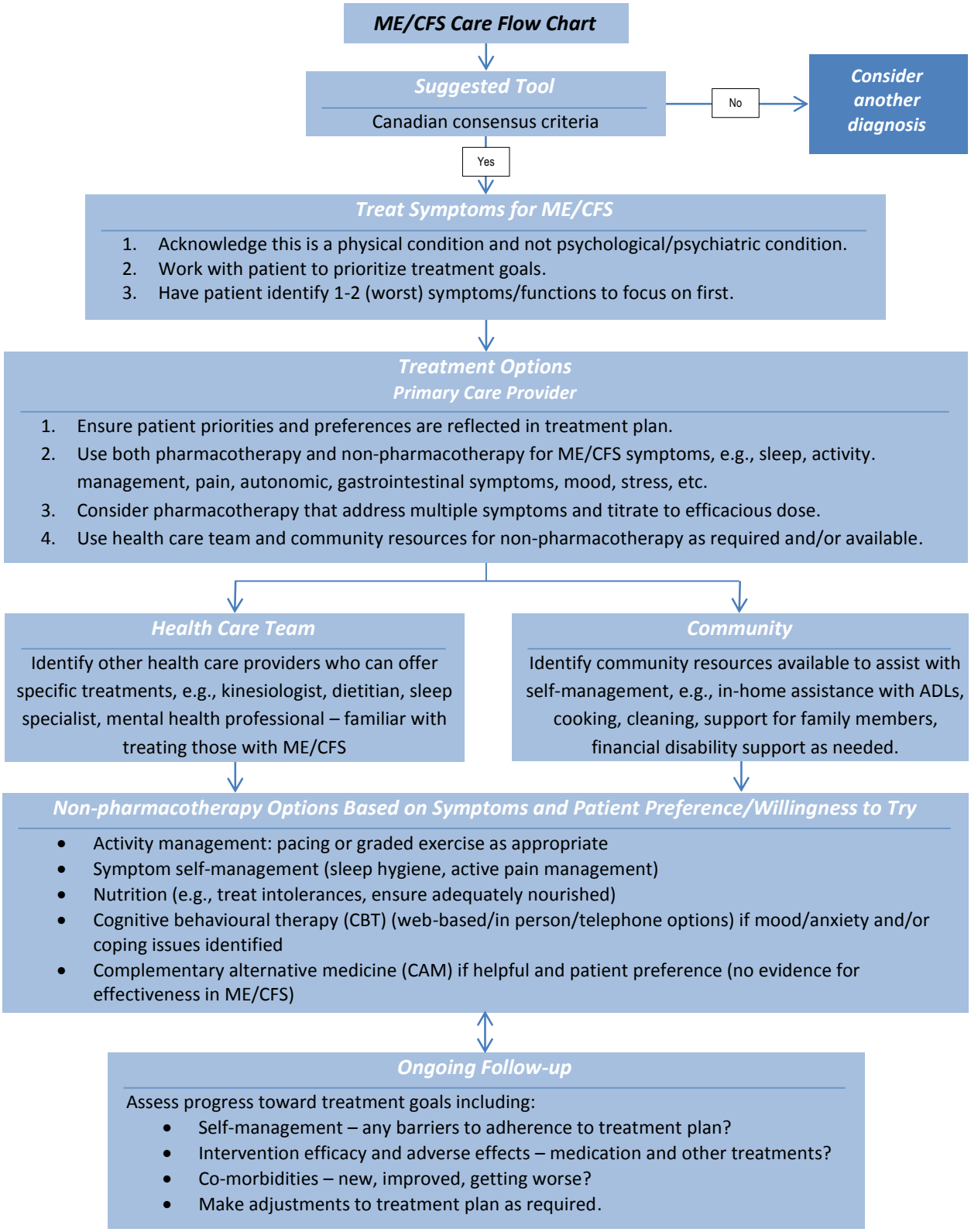
Suggested Citation

Guideline Committee

The committee consisted of representatives of family medicine, psychiatry, psychology and patients.

January 2016

APPENDIX A – ALGORITHM



APPENDIX B

ACTIVITY LOG:

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- Keep it in a handy place.
- Complete it every day for two weeks and when you make a change to your management.
- Take your completed logs to your doctor/other health care provider at follow-up visits.
- Your logs assist your doctor/other health care provider to adjust your treatment plan as needed.
- Completed logs may reassure your insurance company of your active ongoing participation in your treatment.

COMPLETING YOUR ACTIVITY LOG:

- You may change the times on the left hand side of the log to suit your usual schedule (e.g., if you usually get up at 10:00 a.m. and go to bed at 2:00 a.m., write 10:00 a.m. in as the first time, and adjust the other times accordingly).
- Please note your activities with one or two word(s) in the appropriate time slots (e.g., dressed, made bed, nap).
- Rest is defined as lying down, eyes shut, meditating or sleeping.

To better identify activity patterns coloring the log based on activity levels, e.g., red for exercise, yellow for sedentary activity, blue for sleep, will help patients identify which activity pattern works best for them.

ACTIVITY LOG

Activities (please specify)							
Sleep: Write number of hours slept and quality 1 = very poor 2 = poor 3 = fair 4 = good 5 = very good							
Functional Capacity Scale (see definitions of scale): Record your energy rating every 1-10 hour using the scale							
DAY	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**	**Sunday**
6 a.m.							
7 a.m.							
8 a.m.							
9 a.m.							
10 a.m.							
11 a.m.							
12 p.m.							
1 p.m.							
2 p.m.							
3 p.m.							
4 p.m.							
5 p.m.							
6 p.m.							
7 p.m.							
8 p.m.							
9 p.m.							
10 p.m.							
11 p.m.							
# Minutes Walked							
# Usable Hours/Day*							

*Number of usable hours/day = Number of hours NOT asleep or resting/meditating with eyes closed

FUNCTIONAL CAPACITY SCALE DEFINITION

The Functional Capacity Scale incorporates energy rating, symptoms severity, and activity level. The description after each scale number can be used to rate functional capacity.
0 = No energy, severe symptoms including very poor concentration; bed ridden all day; cannot do self-care (e.g., need bed bath to be given)
1 = Severe symptoms at rest, including very poor concentration; in bed most of the day; need assistance with self-care activities (bathing)
2 = Severe symptoms at rest, including poor concentration; frequent rests or naps; need some assistance with limited self-care activities (can wash face at the sink) and need rest afterwards for severe post exertional fatigue
3 = Moderate symptoms at rest, including poor concentration; need frequent rests or naps; can do independent self-care (can wash standing at the sink for a few minutes) but have severe post exertion fatigue and need rest
4 = Moderate symptoms at rest, including some difficulty concentrating; need frequent rests throughout the day; can do independent self-care (can take a shower) and limited activities of daily living (e.g., light housework, laundry); can walk for a few minutes per day
5 = Mild symptoms at rest with fairly good concentration for short periods (15 minutes); need a.m. and p.m. rest; can do independent self-care and moderate activities of daily living, but have slight post exertion fatigue; can walk 10-20 minutes per day
6 = Mild or no symptoms at rest with fairly good concentration for up to 45 minutes; cannot multitask, need afternoon rest; can do most activities of daily living except vacuuming; can walk 20-30 minutes per day; can do volunteer – maximum total time four hours per week, with flexible hours
7 = Mild or no symptoms at rest with good concentration for up to ½ day; can do more intense activities of daily living (e.g., grocery shopping, vacuuming), but may get post exertion fatigue if 'overdo'; can walk 30 minutes per day; can work limited hours, less than 25 hours per week; no or minimal social life
8 = Mild intermittent symptoms with good concentration; can do full self-care, work 40 hours per week, enjoy a social life, do moderate vigorous exercise three times per week
9 = No symptoms; very good concentration; full work and social life; can do vigorous exercise three to five times a week
10 = No symptoms; excellent concentration; over achiever (sometimes may require less sleep than average person).

APPENDIX C

MEDICATIONS TYPICALLY USED FOR PATIENTS WITH SLEEP PROBLEMS

Note: There are no studies specifically studying any sleep medications in ME/CFS. The suggestions below are based on expert consensus and clinical practice experience in ME/CFS and adapted from the literature on insomnia from other causes. Use compounding pharmacies if patients require lower than available doses.

Medication	Dose	Caution/Considerations for Use in ME/CFS
melatonin	1-3 mg 2 - 3 hours before bedtime	Use to stabilize circadian rhythm Benefit variable, but risks are low Could refer to the CFPA website as a reference.
zopiclone zolpidem	3.75 - 7.5 mg 2.5-10 mg	Use for sleep initiation Should allow at least eight hours in bed. • Behaviours like sleep eating and memory problems can occur. Risk of physical tolerance and dependence
cyclobenzaprine	2.5mg-10 mg	Use in low dose for co-morbid fibromyalgia and/or when muscle tension and pain interferes with sleep.
tricyclic antidepressants: amitriptyline, doxepin, nortriptyline	3-50 mg	Use for sleep initiation and maintenance and co-morbid pain • Take 1-3 hours before bedtime. May worsen dry mouth, constipation, orthostatic intolerance, or cause daytime sedation
trazodone	12.5-200 mg	Use for sleep initiation and maintenance
quetiapine	12.5-100 mg	Use in low dose with co-morbid anxiety May cause weight gain or extrapyramidal symptoms. Lengthens QTc interval.
gabapentin	100-1500 mg	Use in low dose with co-morbid pain May help restless legs syndrome.
pregabalin	25-450 mg	Use in low dose with co-morbid pain Helpful for nocturnal pain, but very sedating for some and weight gain is problematic.
antihistamines: diphenhydramine	50 mg	Anticholinergic side effects and tolerance are common Not suitable for long term, regular use
clonazepam	0.25-1 mg	Use for comorbid restless legs, muscle spasms or anxiety
ropinirole or pramipexole	0.125-0.25 mg	Use for comorbid restless legs syndrome
mirtazapine	7.5-15 mg	Use with comorbid anxiety and depression. May cause daytime sedation; tolerance develops quickly.

APPENDIX D

ADDITIONAL RESOURCES

- **Eleanor Stein, MD FRCP©** is available to consult (by phone) with physicians in Alberta requiring assistance with their patients. See http://www.eleanorsteinmd.ca/.
    - Phone: 403.287.9941

  Dr. Stein offers a 10 week disease-specific psychoeducational group session to individuals living in the Calgary area. The goal is to teach self-management. Dr. Stein's ability to take on new patients for assessment is limited. She is exploring the use of Telehealth to offer groups to patients in other areas of the province if there is a need.

ALBERTA HEALTH SERVICES RESOURCES

- Chronic Disease Management Program
  http://www.albertahealthservices.ca/info/Page11934.aspx
- Better Choices Better Health Program: a program to teach basic self-management (but is not disease specific)
  http://www.albertahealthservices.ca/services.asp?pid=service&rid=1054851
- Living Well With A Chronic Condition: a supervised exercise program that can be effective when patients are well enough to participate.
  http://www.albertahealthservices.ca/services.asp?pid=service&rid=1005671

ADDITIONAL INFORMATION RESOURCES:

- International Association of Chronic Fatigue Syndrome and Myalgic Encephalomyelitis (ME/CFS)
    - ME/CFS: A Primer for Clinical Practitioners (2014 Edition)
      http://iacfsme.org/portals/0/pdf/Primer_Post_2014_conference.pdf
- ME-FM Action Network http://www.mefmaction.com/

APPENDIX E

MEDICATIONS TYPICALLY USED FOR PAIN

Note: There are no studies specifically studying pain medications in ME/CFS. These suggested medications are based on expert opinion, expert consensus and clinical practice experience in ME/CFS and adapted from the Fibromyalgia and neuropathic pain literature.

Medication	Dose	Caution/Considerations for Use in ME/CFS
acetaminophen paracetamol	500-1000 mg prn (q8 hours)	Often ineffective
aspirin	300-600 mg prn q6-8 hours	Often ineffective
NSAIDS: diclofenac naproxen	 75-100 mg daily 500-1000 mg daily	Often ineffective. May exacerbate gastritis or reduce renal function.
tricyclics: amitriptyline, doxepin, nortriptyline	5-100 mg	Also helpful for most chronic pain – same dosage as for sleep: Take 1-3 hours before bedtime. May worsen dry mouth, constipation, orthostatic intolerance, or cause daytime sedation.
SNRIs: duloxetine	 20-90 mg daily	May increase sweating, bruxism, blood pressure or heart rate
opiates: codeine phosphate opiates such as oxycodone, hydrocodone; morphine	doses vary, consult guidelines	Constipation/habituation Opiates should be avoided if possible.
tramadol	50-100 mg, qd q 6-8 hours	Seizure risk and interaction with drugs that raise serotonin.
Additional Suggestions:		
pregabalin ME/CFS and fibromyalgia	25 – 400 mg	Effective for neuropathic pain but side effects of weight gain, sedation and cognitive symptoms problematic.
epival topiramate	250 - 500 mg bid 50- 400 mg/day	Helpful if migraine is part of symptom profile.

APPENDIX F

MEDICATIONS TYPICALLY USED FOR NEUROCOGNITIVE DISORDERS

Note: There are no studies specifically studying the use of stimulants in ME/CFS. In the absence of disease specific evidence this information is based on expert consensus, expert opinion, clinical practice experience and the literatures for fatigue in MS and depression. Stimulants need to be used with caution and can be counterproductive.

Medication	Dose	Caution/Considerations for Use in ME/CFS
Methylphenidate	5-20 mg tid	May be habituating
Dexamphetamine	5-10 mg tid	May affect BP and HR; may be habituating
Amphetamine salts	5-20 mg tid	May affect BP and HR; may be habituating
Modafinil	100-200 mg qd	Start with a small dose and increase slowly to the most effective dose.
Caffeine		Patients often self-medicate with caffeine containing products, may disturb sleep if taken late in the day