

SUMMARY

CHRONIC FATIGUE SYNDROME: STATE OF THE EVIDENCE AND ASSESSMENT OF INTERVENTION MODALITIES IN QUÉBEC

Introduction

Chronic fatigue syndrome (CFS) is characterized by debilitating fatigue not resulting from exertion, lasting longer than six months and associated with physical and neuropsychological symptoms common to other diseases such as cognitive deficits, impaired sleep, anthralgia, myalgia, headache, gastrointestinal symptoms, and tender lymph nodes. The course of this illness is variable and exhibits a pattern of alternating remission and relapse of unpredictable frequency and duration. In the absence of specific biochemical markers and specific diagnostic or imaging tests or techniques, the diagnosis of CFS relies on the presence of a cluster of clinical symptoms and on the exclusion of other diseases possibly underlying the fatigue.

Although CFS has been recognized by scientific researchers for several years, the non-specific character of its signs and symptoms and the fact that its pathophysiological mechanisms have not been completely elucidated mean that the syndrome is still poorly understood and continues to be viewed with skepticism both by the general public and by health and social service professionals.

That is why the Association Québécoise de l'Encéphalomyélite Myalgique (AQEM) approached the Minister and the Ministry of Health and Social Services to raise awareness about this syndrome and the care and services needed by people with CFS.

This is the context in which the Minister of Health and Social Services asked AETMIS to review the state of the evidence on CFS. The assessment was expected to specifically address different medical aspects of CFS: epidemiology, etiology and pathophysiology, along with its clinical and therapeutic management options. The Minister also wanted to know about best practices for CFS management and the education/training needs of the health professionals responsible for applying them. Organizational issues surrounding optimal CFS management for patients in Québec and its associated costs were also of interest.

Methodology

This report contains an evidence synthesis on CFS epidemiology, etiology and pathogenesis, a systematic review of the studies on the efficacy and safety of CFS treatments, and a review of the clinical practice guidelines on the diagnostic and therapeutic management or rehabilitation of patients with this illness. It addresses the intervention modalities providing optimal CFS management to help decision makers improve the care and services for people with CFS, and covers the professional and organizational aspects related to such management. An economic analysis of CFS treatment options was performed. The needs of Québec patients were specifically examined in a primary study based on CFS patient interviews.

The literature search strategy included literature reviews and health technology assessment reports published between January 1994 and February 2009. Primary studies undertaken between January 2005 and February 2009 were retrieved. The earlier date corresponds to the search closure date of the first of two major systematic reviews on CFS: the 2005 review by the National Institute for Health and Clinical Excellence (NICE) and the 2008 review by the Belgian Health Care Knowledge Centre (KCE). Only publications written in French, English, Spanish and Italian were selected for this report. An exhaustive grey literature search was performed in May 2008. A literature watch was initiated in February 2009.

Several of the tools used to appraise the quality of the studies come from the CASP (Critical Appraisal Skills Programme). The quality of the health technology assessment reports was determined with the checklist published by the International Network of Agencies for Health Technology Assessment (INAHTA), and the quality of the clinical practice guidelines was evaluated with the AGREE (Appraisal of Guidelines for Research and Evaluation) instrument.

The contextual analysis was performed by examining complementary documents from the grey literature and from Québec's medico-administrative databases and by consulting with care providers, especially from rehabilitation centres in Montréal and the city of Québec, and key stakeholders (professional associations, patient support groups, the Collège des médecins du Québec and the Ordre des ergothérapeutes du Québec). In addition, an online survey allowed us to gather information and opinions from specialist physicians and GPs. The systematic literature review on patients' needs and the primary qualitative study of CFS patients in Québec¹ are summarized in this report.

Epidemiology, etiology and pathophysiology

Population studies available in the international literature, which used the 1994 diagnostic criteria from the Centers for Disease Control and Prevention (CDC), indicate CFS prevalence rates ranging from 0.1% to 1.29% among youth aged 5 to 17 years and from 0.2% to 2.5% among adults. Extrapolating the rates obtained in these studies to the Québec population remains risky because of the differences in the study populations. Furthermore, no reliable statistical data exist to determine the prevalence of this syndrome in Québec. It may affect anywhere from thousands to tens of thousands of people and may lead to disability for many of them.

Various observational studies have attempted to establish a causal relationship between CFS and one or more biological, psychological, social or environmental risk factors. These studies, which had very heterogeneous methods and populations, did not allow to establish the cause of CFS.

Several hypotheses have tried to explain the pathophysiology of CFS, the most common one being post-infectious encephalomyelopathy. These hypotheses were driven by the discovery of numerous neurological, neuro-endocrine, immunological, psychological and genetic

abnormalities through advanced imaging and laboratory techniques. Nevertheless, these abnormalities remain isolated and sometimes contradictory findings that are non-reproducible from one study to another, which does not allow definitive conclusions to be drawn on the pathophysiology of CFS.

Diagnostic management

Diagnosis of CFS is still primarily clinical and relies largely on a number of criteria obtained from experts and researchers consensus. The clinical accuracy and reliability of these lists of criteria intended for epidemiological research have not been validated. In the absence of a comparison of the classifications, the CDC criteria published in 1994 are recognized internationally and the most widely used in clinical and epidemiological studies.

History taking of CFS has not been investigated in diagnostic studies. This helps establish the presence and duration of symptoms, and particularly those of fatigue. A physical and mental examination helps document the signs and symptoms of CFS and rule out other conditions possibly underlying the fatigue. There are no standard biochemical, histological or medical imaging tests specific enough to diagnose CFS in children and adults. No study has assessed the diagnostic performance of combining clinical criteria with imaging or laboratory tests. Some tools to assess fatigue basically produced for research purposes have been validated and used in CFS studies.

According to the clinical practice guidelines consulted, the detection of severe, prolonged fatigue and functional deterioration requires a good clinical evaluation and diagnostic tests to exclude an organic or a psychiatric condition that could explain the fatigue and to detect the presence of comorbidities.

Therapeutic management

Numerous therapies – psychological, physical, pharmacological, nutritional or alternative – have been used to achieve symptomatic relief in patients with CFS. Except for cognitive behaviour therapies and graded exercise therapies or programs, few of these therapies have been studied in randomized controlled trials.

1. Hjelholt Pedersen V. Care and support needs of people with chronic fatigue syndrome/myalgic encephalomyelitis in Québec. 2010. Montréal: Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS). Available online : <http://aetmis.gouv.qc.ca>.

Cognitive behaviour therapies

Cognitive behaviour therapies (CBTs) are psychotherapy approaches that involve modifying problem thoughts and behaviours with methods that emerged from psychology research.

Two meta-analyses, several secondary studies synthesizing numerous randomized controlled trials (RCTs), updated with two primary studies on the efficacy of CBTs, were analyzed for this report. Cognitive behaviour therapies, used either alone or in combination with other interventions and compared with standard care or another intervention, were analyzed. Despite the widely heterogeneous study populations and interventions, the efficacy of these therapies in adults was found to be superior to that of standard care but possibly comparable to other psychotherapies for reducing fatigue, depression and anxiety and for improving patients' quality of life. These beneficial outcomes were observed immediately after therapy and lasted for several months, sometimes up to 12 months post-treatment in a variable proportion of subjects. In children, these treatments helped reduce fatigue symptoms and improve school attendance, sometimes up to 18 months post-treatment. Moreover, these treatments did not cause adverse effects. Clinical practice guidelines recommend these therapies for adults with CFS.

Graded exercise programs or therapies

Graded exercise programs or therapies (GEPs/GETs) involve a rehabilitation approach designed to counter the adverse effects of prolonged inactivity on the muscular and cardiorespiratory systems, which is caused by the syndrome and contributes to perpetuating the symptoms. Gradually increasing activities or doing structured exercises under the supervision of a therapist would seem to improve patients' physical and mental condition.

According to the two systematic reviews consulted, GEPs are more effective and safer than standard care and relaxation techniques for relieving fatigue and for improving functional capacity, quality of sleep and quality of life in some adults with CFS in the short term, from three to six months post-treatment. No adverse effects have been reported.

The long-term benefits of these programs have not been established.

Clinical practice guidelines recommend that GEPs be individually tailored by qualified therapists to suit patients' preferences and desired outcomes, especially for children younger than 12 years and for the severely ill.

Immunological and pharmacological therapies

Some RCTs with small numbers of adult subjects investigated intravenous immunological treatments, such as Poly 1 Poly C₁₂U. This medication has led to a significant improvement in general health status and cognitive capacity. Some pharmacological therapies have shown promise, but the evidence quality was compromised by the small number of RCTs, the small sample sizes, and their often contradictory results. Some products, such as dexamphetamine, seem to diminish fatigue symptoms, while most pharmacological therapies brought only partial symptomatic relief or treated only associated conditions, such as depression, anxiety and sleep disturbances. Moreover, several of them caused adverse effects severe enough to justify halting the trials. These included antivirals (acyclovir), immunoglobulins and several anti-depressants, including selective serotonin reuptake inhibitors (SSRIs). Clinical practice guidelines recommend that pharmaceutical approaches be limited to treating conditions associated with CFS, such as depression.

Alternative therapies, nutritional supplements and diets

Acupuncture, massage therapy, homeopathy and osteopathy have yielded encouraging results for alleviating CFS symptoms, but these results need to be confirmed by higher quality studies with larger numbers of subjects. Limited clinical reductions of fatigue have been documented with L-carnitine supplements, essential fatty acids, acelydine combined with amino acids, and magnesium administered intramuscularly. No significant improvements have been reported with low-sugar or low-yeast diets. The studies on this topic included in the literature review consulted had several methodological limitations. Side effects were reported, especially with magnesium (rash)

and general supplements (nausea). Better studies are also required to determine the efficacy and safety of nutritional supplements and diets in the management of CFS.

Approaches using combined interventions

The combination of different interventions, patient education and physical activity or other CFS management programs seem to alleviate some of the fatigue and to improve short-term functional capacity, compared with no treatment, standard care or relaxation techniques. These approaches require further investigation before any conclusions can be drawn about their effectiveness.

Patient care and services: organization and costs

In several European countries, services for CFS patients are limited to a few hospital centres, most services being part of programs for other diseases (e.g., cancer). Italy, the United Kingdom, Norway and Belgium have set up referral centres offering patients diagnostic tests and different therapies. The United Kingdom stands out from the others by having organized clinical network co-ordinating centres (CNCCs), referral centres for adult and pediatric patients, and a network of 36 locally coordinated primary-care clinics. These local, multidisciplinary clinics include rehabilitation and occupational re-integration services. Conversely, Australia has no structured organization, but clinical practice guidelines are provided to primary-care physicians.

Uncertainty remains over the cost-effectiveness of therapies such as CBT and GET because only one good-quality economic study from Netherlands has examined this issue specifically for CFS. That study showed that a course of CBT cost €20,516 (CA\$26,893)² per additional patient showing clinically significant improvement and €51,642 (CA\$67,694) for each additional quality-adjusted life-year (QALY) gained, according to the perspective of health-care system. If the societal perspective were chosen, the cost per QALY gained would decrease to €21,375 (CA\$28,019), owing to a reduction in productivity losses. The practice guideline produced by NICE (2007) reports the

2. €1 = CA\$1.310832. Source: OCDE – http://stats.oecd.org/Index.aspx?datasetcode=SNA_TABLE4 (accessed: January 15, 2010).

results of the same study from the perspective of the U.K. National Health Service (NHS),³ which is closer to that of the MSSS, and estimates the incremental cost-effectiveness to be £16,036 (CA\$30,111)⁴ per QALY gained⁵. According to the sensitivity analyses performed in that guideline, this result varied according to utility gains.

As for Québec, the cost per patient treated in a rehabilitation centre was estimated on the basis of information obtained from our surveys. A program with a little over two full-time therapists could cost approximately \$215,467 per year. However, given that the exact prevalence of this illness in Québec is not known, it remains impossible to estimate the number of programs and rehabilitation centres that would be needed to meet demand.

Few studies have evaluated the impact of CFS on work productivity, employment and reliance on disability benefits, and the available ones have several methodological limitations. This applies in particular to the two secondary studies on employment and CFS that were identified. It is also difficult to describe or model the economic burden of CFS in Québec because of the lack of specific data on the prevalence and social costs of this illness.

Professional training

Forty or so health and social service professionals in Québec (occupational therapists, kinesiologists, GPs and specialists, physiotherapists, psychologists) shared their opinions and experiences with CFS by taking part in individual or group interviews or by completing an online survey. Most of the participants mentioned that there is no organization of structured care or services. Most of the therapists interviewed mentioned a lack of experience in applying CBTs and GEPs/GETs for these particular patients. All the professionals mentioned their lack of knowledge about the syndrome. The survey respondents were nevertheless favourable

3. The calculations include only CBT costs and visits to a health professional (family physician, specialist physician, physiotherapist and psychologist).

4. £1 (2006) = CA\$1.877703, based on the purchasing power parity (PPP) index. Source: OCDE – http://stats.oecd.org/Index.aspx?datasetcode=SNA_TABLE4 (accessed: January 15, 2010).

5. This ratio is below the willingness-to-pay threshold accepted in the United Kingdom and used to determine if an intervention is cost effective, that is, between £20,000 and £30,000.

to multidisciplinary or interdisciplinary case management even though the literature on these approaches is scarce and inconclusive.

The opinions gathered from Québec professionals did not allow us to determine what their education/training needs would be. We can nonetheless conclude that professionals have received little specific training on CFS, both during their university studies and as part of conferences or other continuing education activities.

Patients' needs

The issue of patients' needs was addressed in semi-structured interviews with twenty or so Québec patients with CFS. The participants we met primarily mentioned the need to (1) improve professionals' knowledge so that they recognize CFS as an illness; (2) disseminate information through various public activities and research on the illness; (3) improve coordinated care, which could be organized as a multidisciplinary management program, for example; (4) offer assistance services for daily living activities, transportation, and adaptation of work to the illness; (5) offer financial support for alternative therapies or for caregivers and offer easier access to low-rent housing; (6) offer psychological support to help CFS patients accept their illness and its consequences; and (7) provide access to professional help through support groups.

The needs expressed by the patients are also supported by a systematic review on the topic. Analysis of the interviews and the literature allowed us to conclude on the need to (1) improve professional education/training; (2) heighten recognition of CFS in the health and social services system; (3) offer more practical assistance with household chores, transportation and occupational rehabilitation; (4) offer psychological support geared to teaching CFS patients coping strategies to handle their physical symptoms and the emotional burden of the syndrome with its associated grief, isolation and stigmatization.

Conclusions and recommendations

Chronic fatigue syndrome (CFS) is a complex and heterogeneous illness with often debilitating effects affecting an undetermined proportion of the Québec population. This syndrome has been

defined by diagnostic criteria recognized for research purposes and is also listed in the World Health Organization's *International Classification of Diseases* (ICD-10).

Current research has so far not been able to establish one single cause for this illness. Although post-infectious encephalomyelopathy is the most frequently cited cause, CFS seems attributable to multiple neurological, psychological, immunological and endocrine factors modulated by patients' specific heredity and environmental stress.

Diagnosing CFS is a process of exclusion. It depends on medical history and physical examination because no specific diagnostic laboratory or imaging tests exist. These tests serve mostly to exclude the presence of associated conditions, such as depression.

Cognitive behaviour therapies (CBTs) and graded exercise programs or therapies (GEPs/GETs) seem to be effective and safe and are probably cost effective for alleviating CFS symptoms and improving patients' quality of life in the short term. Some pharmacological therapies have shown promise; others are more controversial and sometimes harmful. Most of them provide only symptomatic relief or treat only comorbidities, such as depression.

Different countries in Europe have structured care and services organized in the form of programs or service pathways to meet the physical and occupational rehabilitation needs of people with CFS. Other countries, like Australia, propose clinical practice guidelines and protocols to support primary-care management of CFS.

Several health and social service professionals admitted their lack of knowledge about the syndrome and voiced some skepticism about its actual existence. They expressed concern over the lack of specific patient management resources and mentioned that they had little experience with using therapies recognized as effective, such as CBTs.

The Québec patients we met bemoaned the generalized lack of knowledge about the syndrome among health and social service professionals. They said that they needed the syndrome to be recognized as a genuine illness for them to be able to access rehabilitation services, psychotherapy,

home-assistance services and financial assistance from private insurers and the government.

In light of these findings, AETMIS recommends the following:

- Organizers of continuing education in professional associations and corporations should include chronic fatigue syndrome in their programs.
- The Ministère de la Santé et des Services sociaux and network administrators should designate one or two centres of expertise dedicated to chronic fatigue syndrome. Their mission could include the following in particular:
 - training interdisciplinary teams of medical consultants able to diagnose this illness;
 - entering into agreements with community and institutional rehabilitation facilities to organize interdisciplinary therapeutic management of CFS patients;
 - taking part in training professionals enrolled in both university and continuing-education programs, for example, by organizing events such as symposiums, workshops and conferences on CFS;
 - promoting and supporting research on the epidemiology, etiology, pathophysiology and medical management of this illness.