

A Pan-Canadian Practice Guideline: Screening, Assessment and Care of Cancer-Related Fatigue in Adults with Cancer

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Conflict of Interest Disclosures

Each member of the National Advisory Group acting in the role of the guideline expert panel completed a Conflict of Interest Document. No conflicts of interest were identified by members of the practice guideline writing team that could have compromised the recommendations contained within this document.



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Executive Summary

Question

What are the optimum assessment parameters following screening and effective interventions for management of fatigue in adults with cancer who are identified as experiencing symptoms of fatigue or tiredness on the Edmonton Symptom Assessment System (ESAS)?

Outcomes of interest include improvement in cancer-related fatigue and/or loss of energy (vigour) in adult cancer patients, appropriate assessment and management of fatigue in adults with cancer.

Objective

The objective of this practice guideline is to inform Canadian health authorities, program leaders, administrators and professional health care practitioners about the optimum assessment following screening, and effective interventions for managing fatigue in adult patients with cancer whose fatigue has been identified using the ESAS.

Assessment Processes and Scope

To clarify the guideline scope and assessment processes, operational definitions are as follows:

Screening

Screening is a process that provides a snapshot of a patient's problems or concerns. Brief psychometrically valid measures are used to quickly flag a problem or concern to identify patients who are at risk for a poor health outcome. Tiredness is often identified as the initial state patients experience along the continuum of fatigue, which extends from initial tiredness to severe fatigue and exhaustion and is important as an initial screen for fatigue. The ESAS tool has a "tiredness" domain and the tiredness item score is used as the screening tool for the algorithm presented as well as the fatigue care map included herein. Screening is a relatively crude indicator of a problem, and it is essential to further elaborate the problem using a more comprehensive assessment approach (with valid cut-offs) to target appropriate intervention strategies.

Comprehensive Assessment

In contrast to screening, a comprehensive assessment is a detailed appraisal of many factors that may contribute to a particular problem such as fatigue. A comprehensive assessment may involve a combination of procedures, checklists and measurement tools to identify specific contributing factors to symptoms. Domains may include health status, coping skills, risk factors, pertinent history, co-morbidities, current relief or management of symptoms, patient values, preferences and social circumstances. Direct-care providers such as family physicians, oncologists and nurses are responsible for assessing a patient's fatigue following its identification and/or severity from an initial screen. A comprehensive assessment is typically followed by a more focused assessment to guide appropriate interventions.



Focused Assessment

A focused assessment is more targeted to clarify the extent of and most appropriate interventions for fatigue identified through screening and a comprehensive assessment. The focused assessment is used to identify new or overlooked problems and to facilitate subsequent management. Obtaining a definitive clinical diagnosis may be a component of a focused assessment and is typically conducted by direct-care providers. In the case of fatigue, direct-care providers may use tools to identify the extent of functional impairment caused by the fatigue as well as co-morbid depression or other contributing factors. Tools with established cut-offs facilitate identification of patients who require referral to specialists for co-morbid depression. In the case of depression associated with fatigue, a clinical diagnosis of depression can only be made by practitioners specifically trained and skilled in the use of the *Diagnostic and Statistical Manual of Mental Disorders* and whose role includes diagnostic assessments.

Target Population

This practice guideline pertains to adults with cancer at any phase of the cancer continuum, regardless of cancer type, disease stage or treatment modality. It does not focus specifically on management of fatigue in adults prior to a cancer diagnosis but recognizes this as a risk factor in the assessment process. If differences apply (e.g., care interventions depending on clinical status), these differences are noted in the text.

Target Users

This practice guideline is intended to inform Canadian health authorities, program leaders and administrators, as well as health care professionals who provide care to adults with cancer. The guideline is interprofessional in focus and the recommendations are applicable to direct-care providers (e.g., nurses, social workers and family practitioners) in diverse care settings. The scope of practice for different professions may vary according to governmental or professional regulatory standards, and users of this guideline are expected to exercise skill and judgment in determining whether the application of the recommendations is within their scope of practice. It is not the intent of this guideline to make recommendations for specialist practitioners (e.g., hematologists, immunologists and psychiatrists). Depending on the factors contributing to fatigue, additional guideline documents should be accessed for management recommendations on specific conditions (e.g., sleep, pain or depression guidelines). Users may wish to adapt this guideline to fit their local health care context and resources.



Introduction

Fatigue associated with cancer or cancer treatment is different from fatigue experienced in the daily life of the general adult population. Although definitions of cancer-related fatigue vary, elements include a subjective feeling of tiredness or exhaustion prompted by cancer or cancer treatment that is disproportionate to the level of recent exertion, is not relieved by rest and interferes with usual daily activities. Given the high rate of fatigue reported among cancer patients and survivors, frequent screening and assessment is essential so that appropriate management can be initiated before the fatigue disrupts quality of life.

Methodology

Practice Guideline Development

The Cancer Journey Advisory Group of the Canadian Partnership Against Cancer established a National Advisory Group to develop pan-Canadian guidance on the screening, assessment and care of cancer-related fatigue in adults with cancer. Specifically, the intent was to produce algorithms and recommendations for uptake into practice by Canadian health care professionals who provide care to adult patients with cancer. A further aim was to express the recommendations as action statements in order to develop a knowledge product that could be used as part of an implementation plan to guide the practice of direct-care providers.

Literature Search

A systematic search of clinical practice guideline databases, guideline developer websites and the published health literature was conducted to identify clinical practice guidelines, systematic reviews and other guidance documents addressing the screening, assessment and care of cancer-related fatigue in adults with cancer. The search of the health literature included MEDLINE, EMBASE, CINAHL and the Cochrane Library recent to December 2009.

Literature Search Strategy

The search used separate or combined terms: cancer, neoplasm, fatigue, asthenia, cancer fatigue, screening, assessment, interventions, guidelines, recommendations, practice guidelines, management of cancer-related fatigue, pharmacological and non-pharmacological treatments.

Study Selection Criteria

Clinical practice guidelines and other guidance documents published after 2003 and in the English language were eligible for inclusion. The key areas of interest were guidelines or evidence-based practices or best practices focused on screening and/or assessment and/or treatment (pharmacological and non-pharmacological) and/or overall management of fatigue symptoms in adults with cancer.

Literature Search Results

Two clinical practice guidelines were identified in the search of the literature and comprise the primary evidence base for this practice guideline. One guideline was produced by the National Comprehensive Cancer Network (NCCN) and the other was produced by the Oncology Nursing Society (ONS). In addition, seven guidance

documents and four systematic reviews were used to provide supplementary, but mainly indirect, evidence to help inform the development of the screening and care algorithms and recommendations.

Critical Appraisal

The two practice guidelines were assessed for reporting quality with the AGREE II Instrument, with scores derived by at least two independent reviewers. The supplementary evidence was not appraised for quality.

Results

The evidence informing the identified practice guidelines and the supplementary information ranges from randomized controlled trial (RCT) data to expert consensus opinion. Overall, the evidence supports that screening for fatigue should include a detailed history to determine an individual's treatment status, fatigue pattern, the effects of fatigue on various areas of functioning and contributing risk factors, especially those that are reversible. Patients should receive education about fatigue, symptom management and relevant services in the treatment centre and community. Once reversible causes of fatigue are treated (e.g., depression, anemia, anxiety, pain, nutrition deficiencies, and hypothyroidism), non-pharmacologic interventions include:

- Enhancing activities and exercise,
- Conserving energy,
- Managing stress management and psychosocial interventions,
- Reducing sleep disturbance.

Of the non-pharmacologic approaches to reduce fatigue, the benefits of exercise and psychosocial interventions have the strongest evidence, supported by randomized trial data. Psychosocial interventions include education (psycho-educational or cognitive behavioural), support groups, individual counselling and stress management. Although a variety of pharmacologic agents are available to treat cancer-related fatigue, the evidence on their use is inconclusive and the potential benefits versus harms are not clear enough to recommend their use until further high-quality studies are conducted.

External Review

A draft version of this report was circulated for comment and review to 25 health care professionals from across Canada who provide care to adult cancer patients. The majority of respondents supported the guideline recommendations, and revisions to the care plans were made based on their feedback.

Conclusions

The National Advisory Group concluded that it is reasonable to routinely screen adult cancer patients for fatigue using standardized screening tools. Comprehensive and focused assessments are needed to establish the extent and nature of the fatigue symptoms and their impact on physical functioning. Members of the interprofessional clinical team share responsibility for assessments and treatment. When symptoms are identified, the clinical team must decide when referral to an appropriately trained

professional is needed based on the factors contributing to the fatigue or using established cut offs identified through valid and reliable tools.

In terms of treatment, fatigue and weakness may be related to other identifiable and potentially treatable conditions, such as depression and anemia. Reversible contributing factors that are treatable should be addressed first, and non-pharmacological or psychosocial interventions, such as physical activity and cognitive behavioural therapy, should be considered to reduce stress and optimize sleep quality. The National Advisory Group reviewed the use of pharmacological agents to treat fatigue, which are considered experimental and, at this time, do not recommend their use.

The management of cancer-related fatigue must be tailored to the individual patient, who should be fully informed of the options and have the opportunity to take part in decision-making regarding self-management. Each practice setting should have agreed protocols for managing fatigue that include expectations or standards of the clinical team, including processes for referral to appropriate specialists.

Cancer-Related Fatigue Recommendations

The following recommendations and tools for application are based on the expert consensus of the Cancer Journey Advisory Group of the Canadian Partnership Against Cancer, which is composed of clinical experts and fatigue researchers, and informed primarily by two clinical practice guidelines from credible guideline development groups.^{1,2}

1. Screening for Cancer-Related Fatigue

(Based on the expert consensus of the National Advisory Group and informed by NCCN category 2A, ONS expert opinion)*

- All health care providers should routinely screen for the presence of fatigue from the point of diagnosis onward.
- All patients should be screened for fatigue at their initial visit, at appropriate intervals (e.g., daily for inpatients, routine and follow-up visits for outpatients, and self-monitoring for those post-treatment) and as clinically indicated, especially with changes in disease status.
- Screen with a valid and reliable tool that includes reportable scores (dimensions) that are clinically meaningful and have established cut-offs (e.g., Screening for Distress Tool, which includes Edmonton Symptom Assessment System [ESAS] and Canadian Problem Checklist [CPC]).
- For inpatients who are unable to assign a numeric value to rate their fatigue, a rating of mild, moderate or severe may be used.

* Please see the NCCN and ONS guidelines for descriptions of evidence categories.

2. Comprehensive and Focused Assessment of Cancer-Related Fatigue

(Based on the expert consensus of the National Advisory Group and informed by NCCN category 2A, ONS category “likely to be effective”, ONS expert opinion)*

- Screen for fatigue and if moderate or severe fatigue is detected through screening (ESAS tiredness greater than 4), individuals should have a comprehensive and a focused assessment to identify the nature and extent of the fatigue symptoms.
- Medical and substance-induced causes of fatigue should be ruled out (e.g., anemia, infection, nutrition deficiencies, medication or treatment side effects).
- Assessments should be a shared responsibility of the clinical team, with designation of those who are expected to conduct assessments based on scope of practice.
- Assessment should include a history of fatigue (e.g., disease status, pre-treatment activity levels, fatigue onset, pattern, duration, changes over time, interference with function and daily living), contributing risk factors (e.g., depression, anemia, pain, nausea, sleep disturbance, co-morbidities), a physical exam, a review of symptoms and a self-assessment of causes contributing to fatigue.
- Promote open communication among the patient, family and the clinical team to facilitate discussions about the experience of fatigue and its effects on daily functioning.
- As a shared responsibility, the clinical team must decide when referral to an appropriately trained professional is needed (i.e., all patients with an ESAS score in the severe range, or with certain accompanying factors or symptoms, or a cut-off score identified using valid and reliable tools for assessment of symptoms of fatigue).

3. Treatment and Care Options for Cancer-Related Fatigue

(Based on the expert consensus of the National Advisory Group and informed by NCCN categories 1 and 2A, ONS categories “recommended for practice” and “likely to be effective”, ONS expert opinion)*

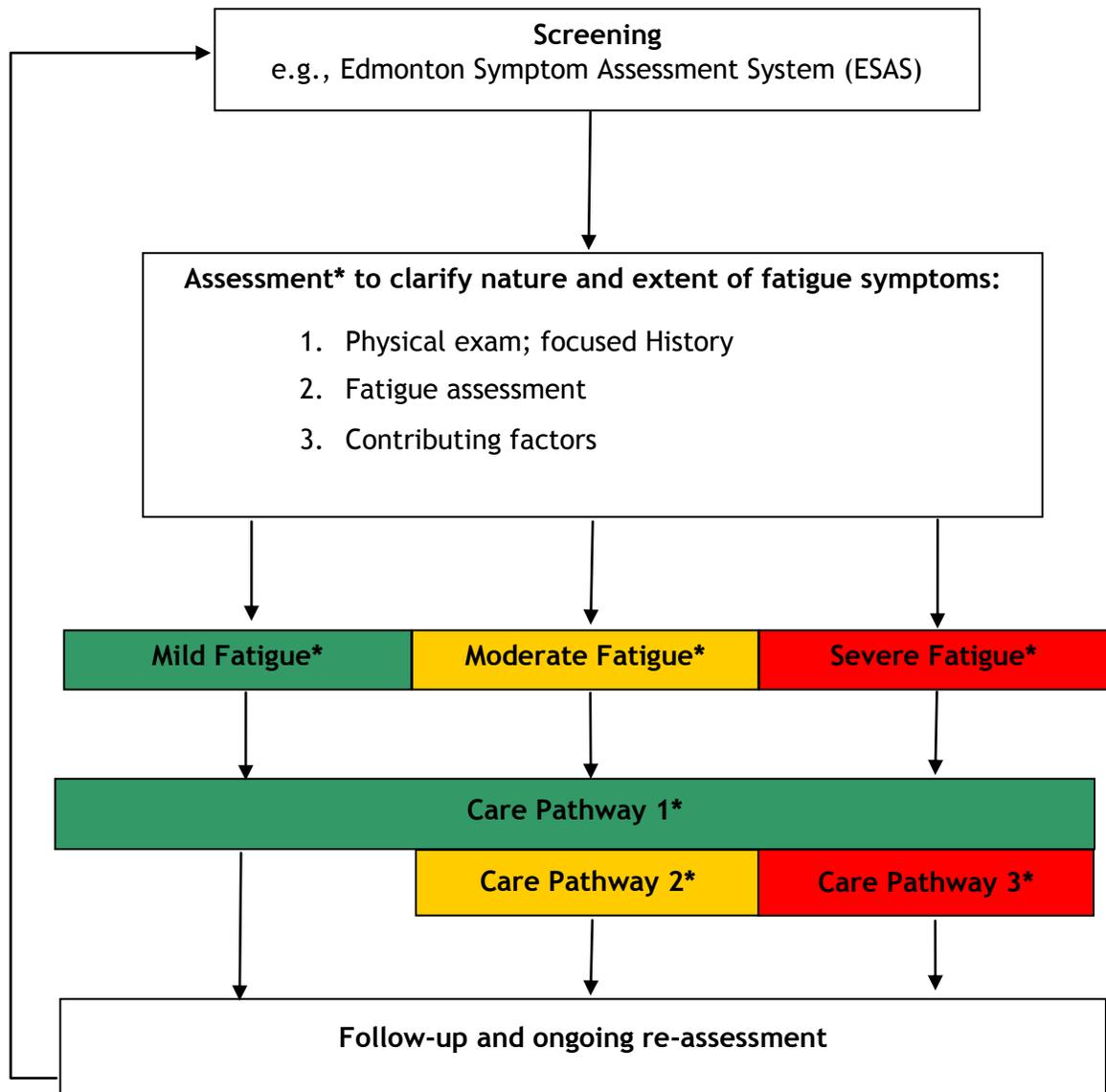
- Address all medical and substance-induced treatable contributing factors first (e.g., pain, depression, anxiety, anemia, sleep disturbance, nutrition, activity level, medication side-effects, and co-morbidities).
- Actively encourage all patients to engage in a moderate level of physical activity during and after cancer treatment (e.g., 30 minutes of moderate intensity activity most days) unless contraindicated. Moderate activity includes aerobic (e.g., fast walking, cycling or swimming) and resistance (e.g., weights) training.
- Additional non-pharmacologic interventions include nutrition consultation, optimizing sleep quality, psychosocial interventions to improve coping with fatigue (e.g., cognitive behavioural therapy, stress management or support groups), relaxation, massage and attention restoring therapy (e.g., exposure to natural environments).



- For patients on active treatment or on long-term follow-up post-treatment who have moderate to severe fatigue, consider referral to rehabilitation (e.g., physical or occupational therapy, and physical medicine).
- All patients should be offered specific education about fatigue prior to the start of treatment and when fatigue is identified, plus advice on strategies (e.g., physical activity, energy conservation, stress reduction and distraction) to manage fatigue.
- At this time, the use of pharmacologic agents to treat cancer-related fatigue is considered experimental and therefore is not recommended (e.g., psycho-stimulants, sleep medications, trials of low-dose corticosteroids such as prednisone or dexamethasone) except for selected patients at the end of life with severe fatigue.
- Promote ongoing self-monitoring of fatigue levels as a late or long-term cancer or treatment problem in post-treatment survivors.
- For those on active treatment and for those with advanced, progressive disease, repeat ESAS screening and assessment as needed to determine any change in both subjective and objective aspects of fatigue.

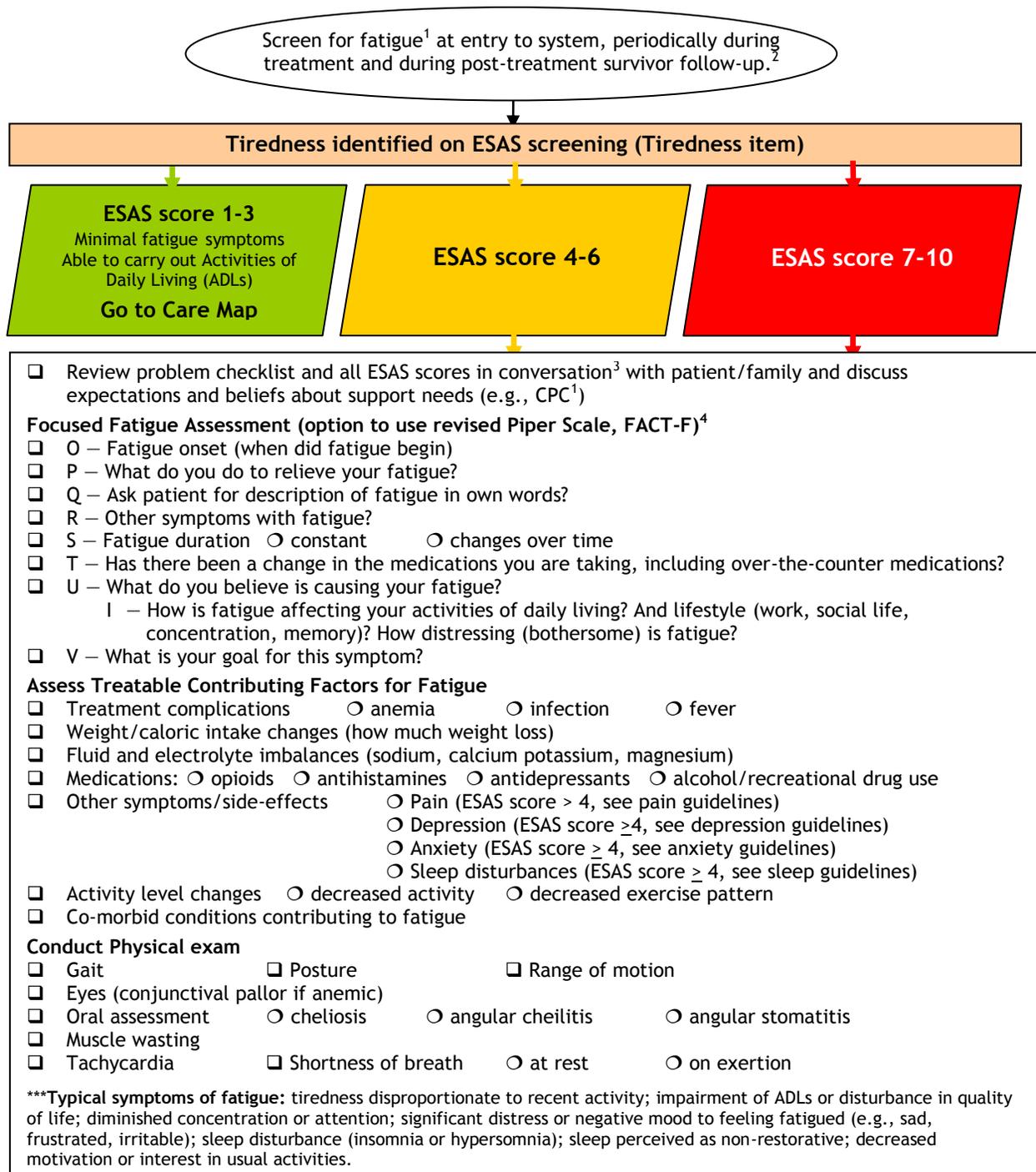


**Algorithm: Screening, Assessment and Care –
Cancer-Related Fatigue in Adults with Cancer**



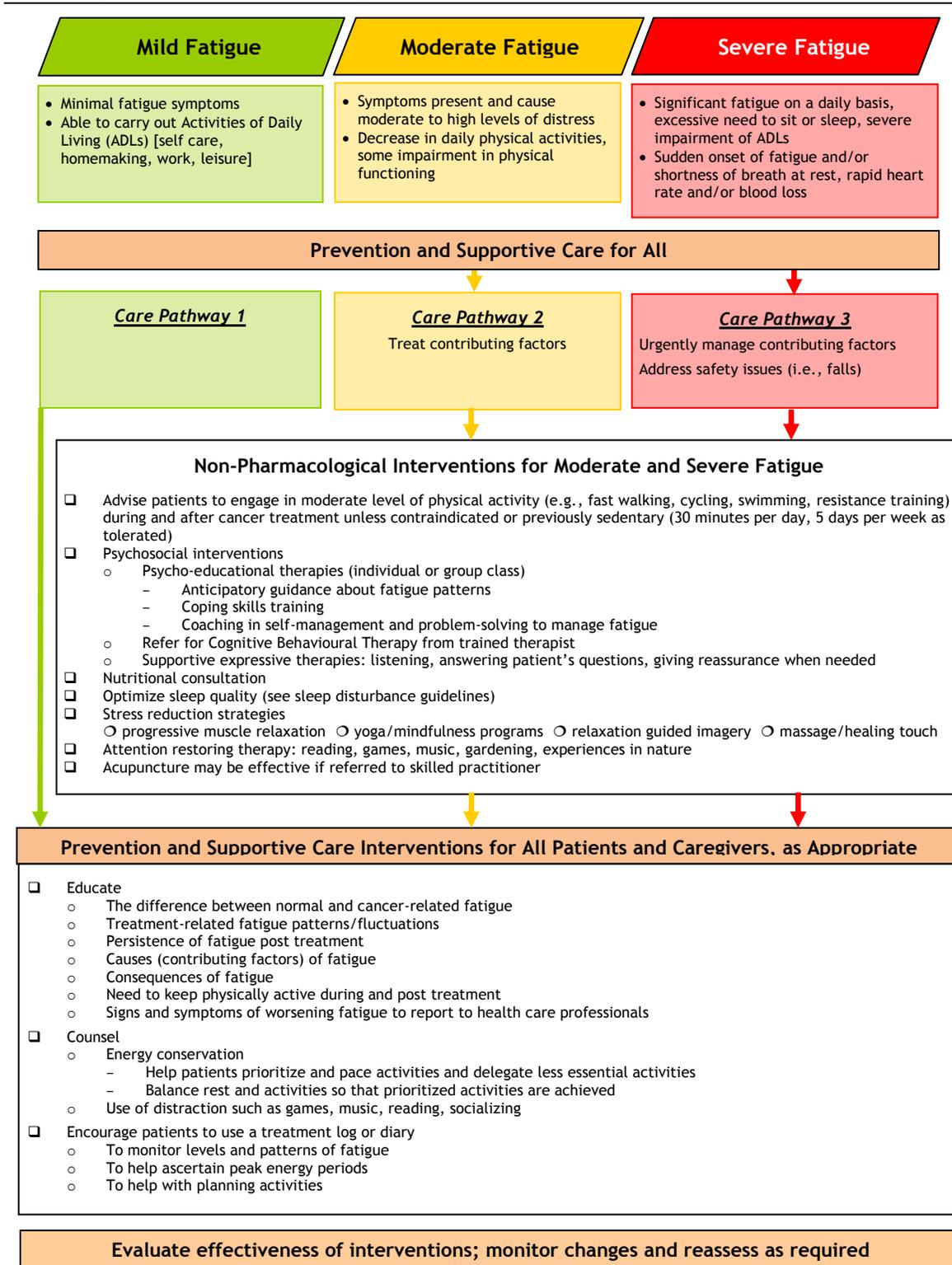
* See following page for detailed algorithm components.

Screening and Assessment - Cancer-Related Fatigue in Adults with Cancer*



* Please see the full guideline for a description of the acronyms used, as well as the copyright and disclaimer prior to use.
 1 Use Screening for Distress Tool (SDT), which includes Edmonton Symptom Assessment System (ESAS) and Canadian Problem Checklist (CPC).
 2 At initial diagnosis, start of treatment, regular intervals during treatment, end of treatment, post-treatment or at transition to survivorship, at recurrence or progression, advanced disease, when dying, and during times of personal transition or re-appraisal such as family crisis, during survivorship, when approaching death.
 3 The health care team for cancer patients may include surgeons, oncologists, family physicians, nurses, social workers, psychologists, patient navigators and other health care professionals
 4 OPQRSTU(I)V Acronym: O = Onset; P = Provoking/Palliating; Q = Quality; R = Region or Radiating; S = Severity & Duration; T = Treatment; U = Understanding/I=Impact; V = Values

Care Map - Cancer-Related Fatigue in Adults with Cancer*



* Please see the full guideline for a description of suggested interventions, as well as the copyright and disclaimer prior to use.

ESAS Screening Tool and Canadian Problem Checklist

Edmonton Symptom Assessment System (ESAS)

Date of Completion: _____ Time: _____

Please circle the number that best describes:

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst possible pain
Not tired	0	1	2	3	4	5	6	7	8	9	10	Worst possible tiredness
Not nauseated	0	1	2	3	4	5	6	7	8	9	10	Worst possible nausea
Not depressed	0	1	2	3	4	5	6	7	8	9	10	Worst possible depression
Not anxious	0	1	2	3	4	5	6	7	8	9	10	Worst possible anxiety
Not drowsy	0	1	2	3	4	5	6	7	8	9	10	Worst possible drowsiness
Best appetite	0	1	2	3	4	5	6	7	8	9	10	Worst possible appetite
Best feeling of wellbeing	0	1	2	3	4	5	6	7	8	9	10	Worst possible feeling of wellbeing
No shortness of breath	0	1	2	3	4	5	6	7	8	9	10	Worst possible shortness of breath
Other problem	0	1	2	3	4	5	6	7	8	9	10	

Completed by: Patient Family
 Health Professional Assisted by family or health professional

Canadian Problem Checklist

Please check all of the following items that have been a concern or problem for you in the past week including today:

Practical:

- Work/School
- Finances
- Getting to and from appointments
- Accommodation

Emotional:

- Fears/Worries
- Sadness
- Frustration/Anger
- Changes in appearance
- Intimacy/Sexuality

Spiritual:

- Meaning/Purpose of Life
- Faith

Social/Family:

- Feeling a burden to others
- Worry about family/friends
- Feeling alone

Informational:

- Understanding my illness and/or treatment
- Talking with the health care team
- Making treatment decisions
- Knowing about available resources

Physical:

- Concentration/Memory
- Sleep
- Weight



Full Practice Guideline Evidence Report

Question

What are the optimum assessment parameters following screening and effective interventions for management of fatigue in adults with cancer who are identified as experiencing symptoms of fatigue or tiredness on the Edmonton Symptom Assessment System (ESAS)?

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Objective

The objective of this practice guideline is to inform Canadian health authorities, program leaders, administrators and professional health care practitioners about the optimum assessment following screening, and effective interventions for managing fatigue in adult patients with cancer whose fatigue has been identified using the ESAS.

Assessment Processes and Scope

To clarify the guideline scope and assessment processes, operational definitions are as follows:

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Screening is a process that provides a snapshot of a patient's problems or concerns. Brief psychometrically valid measures are used to quickly flag a problem or concern to identify patients who are at risk for a poor health outcome. Tiredness is often identified as the initial state patients experience along the continuum of fatigue, which extends from initial tiredness to severe fatigue and exhaustion and is important as an initial screen for fatigue. The ESAS tool has a "tiredness" domain and the tiredness item score is used as the screening tool for the algorithm presented as well as the fatigue care map included herein. Screening is a relatively crude indicator of a problem, and it is essential to further elaborate the problem using a more comprehensive assessment approach (with valid cut-offs) to target appropriate intervention strategies.

Comprehensive Assessment

In contrast to screening, a comprehensive assessment is a detailed appraisal of many factors that may contribute to a particular problem such as fatigue. A comprehensive assessment may involve a combination of procedures, checklists and measurement tools to identify specific contributing factors to symptoms. Domains may include health status, coping skills, risk factors, pertinent history, co-morbidities, current relief or management of symptoms, patient values, preferences and social circumstances. Direct-care providers such as family physicians, oncologists and nurses are responsible for assessing a patient's fatigue following its identification and/or severity from an initial screen. A comprehensive assessment is typically followed by a more focused assessment to guide appropriate interventions.



Focused Assessment

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Target Population

This practice guideline pertains to adults with cancer at any phase of the cancer continuum, regardless of cancer type, disease stage or treatment modality. It does not focus specifically on management of fatigue in adults prior to a cancer diagnosis but recognizes this as a risk factor in the assessment process. If differences apply (e.g., care interventions depending on clinical status), these differences are noted in the text.

Target Users

This practice guideline is intended to inform Canadian health authorities, program leaders and administrators, as well as health care professionals who provide care to adults with cancer. The guideline is interprofessional in focus and the recommendations are applicable to direct-care providers (e.g., nurses, social workers and family practitioners) in diverse care settings. The scope of practice for different professions may vary according to governmental or professional regulatory standards, and users of this guideline are expected to exercise skill and judgment in determining whether the application of the recommendations is within their scope of practice. It is not the intent of this guideline to make recommendations for specialist practitioners (e.g., hematologists, immunologists and psychiatrists). Depending on the factors contributing to fatigue, additional guideline documents should be accessed for management recommendations on specific conditions (e.g., sleep, pain or depression guidelines). Users may wish to adapt this guideline to fit their local health care context and resources.

Background

Fatigue associated with cancer or cancer treatment is different from fatigue experienced in the daily life of the general adult population. Although definitions of cancer-related fatigue vary, elements include a subjective feeling of tiredness or exhaustion prompted by cancer or cancer treatment that is disproportionate to the level of recent exertion, is not relieved by rest and interferes with usual daily activities.¹

While most patients will likely experience a decrease in fatigue severity after their cancer treatment ends, cancer-related fatigue can be experienced at all stages of the

disease trajectory, including post-treatment survivorship.^{1,3,4,5} Cancer-related fatigue is very common, with prevalence estimates ranging from 17% to 66% in breast cancer survivors³ and 70% to 100% across all cancer patients.¹ For many, cancer-related fatigue is the most distressing side effect of cancer – more distressing than pain or nausea – and causes the most disruption of normal functioning.^{6,7} Since cancer-related fatigue limits an individual's ability to perform activities that are associated with daily living and has an impact on both personal and social roles within the family and the community, it can have a profound negative impact on overall quality of life.^{1,8}

Although the exact mechanisms underlying the onset and persistence of cancer-related fatigue are not well understood, most now agree that the etiology of cancer-related fatigue is multi-factorial and arises from a complex interplay of physical, mental, emotional, environmental, physiological and pathological factors.⁹ Symptom perceptions are also emerging as a contributing factor.¹⁰ Underlying medical factors include anemia, disease and treatment-related factors (e.g., infections and biological mechanisms such as inflammatory cytokines) and co-morbid conditions.^{1,11} Other factors include nutrition, decreased activity and symptoms that cluster with fatigue such as sleep disturbance, pain, anxiety and depression.^{1,4,12} Despite cancer-related fatigue being a devastating symptom, it remains a largely unrecognized and poorly managed problem for both cancer patients and survivors.^{8,13} Given the high rate of fatigue reported among cancer patients and survivors, frequent screening and assessment is essential so that appropriate management can be initiated before fatigue disrupts quality of life.^{1,14}

In spite of unclear etiology of cancer-related fatigue, there is a body of research to guide health care professionals working with people with cancer to help prevent and manage fatigue. The purpose of this practice guideline is to give practical information and guidance to health care professionals to identify and manage fatigue in adult patients with cancer.

Methodology

Practice Guideline Development

The Cancer Journey Advisory Group of the Canadian Partnership Against Cancer established a National Advisory Group to develop pan-Canadian guidance on the screening, assessment and care of cancer-related fatigue in adults with cancer. Specifically, the intent was to produce algorithms and recommendations for uptake into practice by Canadian health care professionals who provide care to adult patients with cancer. A further aim was to express the recommendations as action statements in order to develop a knowledge product that could be used as part of an implementation plan to guide the practice of direct-care providers.

This practice guideline was developed according to the ADAPTE methodology,^{15,16} with assessment of the quality of guidelines in accordance with the AGREE II reporting convention.^{17,18}

Prior to completion, the National Advisory Group distributed the draft report on several occasions to the Cancer Journey Advisory Group for feedback concerning the collection, interpretation and synthesis of the evidence, as well as the development and content of the recommendations and related evidence-based algorithm. Members

of the Cancer Journey Advisory Group reviewed and discussed the final version of the guidelines to reach consensus on the recommendations.

The National Advisory Group is composed of nurses, psychologists, an administrator, a patient education specialist, a dietitian, researchers, a coordinator of provincial oncology guidelines with content expertise in each of the topic areas, a pharmacist, a research coordinator and a guidelines methodologist. Two members of the group are cancer survivors to ensure that consumers' views also informed the development of this practice guideline. In addition, clinical experts in fatigue were asked to review the guideline in depth to ensure that recommendations were consistent with current empirical knowledge and the evidence reviewed.

As part of external review, content experts and key stakeholders across the country were invited to review and provide input on the document. Final consensus was reached through a formal vote of the 16 member Cancer Journey Advisory Group, with 13 members voting to approve the document as written, one member requesting a minor edit and two members not voting.

Updating Plan

As part of an updating strategy, the literature will be periodically reviewed (bi-annually) and the guideline will be updated as new or compelling evidence is identified. This guideline was developed through a partnership between the Canadian Partnership Against Cancer: Cancer Journey Advisory Group and the Canadian Association of Psychosocial Oncology.

Literature Search

The following electronic databases were searched to December 2009 for practice guidelines or systematic reviews of the literature: MEDLINE, EMBASE, CINAHL, the Cochrane Library, the Guidelines International Network (www.g-i-n.net), the National Guidelines Clearinghouse (www.guideline.gov) and the Canadian Partnership Against Cancer "SAGE" Inventory of Cancer Guidelines (www.cancerview.ca). In addition, the websites of the National Institute for Health and Clinical Excellence (NICE), the Scottish Intercollegiate Guideline Network (SIGN), the National Comprehensive Cancer Network (NCCN) and provincial guideline organizations (Cancer Care Ontario, Vancouver Island Health Authority and Fraser Health in British Columbia, and Cancer Care Nova Scotia) were searched for additional guidelines.

As a quality control measure, results of the literature search were compared with a March 2007 environmental scan of psychosocial, supportive or palliative standards, guidelines or guides to practice conducted by the Canadian Partnership Against Cancer, and also with a fatigue literature search conducted by the Pan-Canadian Oncology Symptom Triage and Remote Support (CO-STaRS) group, which was completed in January 2010 and comprised an abstract and title search of the EMBASE, MEDLINE, PsychINFO and CINAHL databases (2004-2010).

Literature Search Strategy

The search used separate or combined terms: cancer, neoplasm, fatigue, asthenia, cancer fatigue, screening, assessment, interventions, guidelines, recommendations,

practice guidelines, management of cancer-related fatigue, pharmacological and non-pharmacological treatments.

Study Selection Criteria

To be eligible for inclusion, clinical practice guidelines, systematic reviews and other guidance documents, such as those outlining evidence-based or best practices, had to focus on the screening and/or assessment and/or treatment (pharmacological or non-pharmacological) and/or overall management of fatigue symptoms. The target populations had to include adults aged 18 years and older, diagnosed with any type of cancer, at any disease stage, in any phase of the cancer journey, and who were treatment naïve or had experienced a variety of treatment modalities. Evidence had to be published after 2003 and be written in English.

Outcomes of interest included improvement in cancer-related fatigue or loss of energy (vigour) in adult cancer patients, appropriate screening and/or assessment, and the appropriate management of fatigue in adults with cancer. Fatigue could be assessed by validated fatigue scales or by any method of self-evaluation. Fatigue could be measured in terms of characteristics such as intensity, duration or frequency.

Results

Two clinical practice guidelines were identified in the search of the literature and make up the primary evidence base for this practice guideline. One guideline was produced by the National Comprehensive Cancer Network (NCCN)¹ and the other was produced by the Oncology Nursing Society (ONS).² In addition, seven guidance documents¹⁹⁻²⁵ and four systematic reviews²⁶⁻²⁹ were used to provide supplementary, but mainly indirect, evidence to help inform the development of the screening and care algorithms and recommendations.

The two practice guidelines were selected for their evidence-base, currency and quality. Since the time of the original search of the literature, an updated NCCN fatigue guideline has been released³⁰; however, with no substantive differences between the two versions, the data contained in this report were not updated to reflect the newer version.

Of the supporting data, a total of 19 guidelines, guidance documents or systematic reviews were retrieved and examined. Twelve were excluded for the following reasons: five were either based on data produced prior to 2003 or were not guidelines for practice (e.g., lay information, clinical knowledge summary, articles about guidelines), four were not specific to cancer patients (e.g., chronic fatigue syndrome) and three did not address cancer-related fatigue management in a comprehensive manner (e.g., curriculum information and guidelines focused on a different topic). The supporting documents were included to clarify background information, provide additional detail in the guidelines and to cover any gaps in the knowledge.

Of the four systematic reviews identified, a formal assessment of systematic review quality was not conducted; however, checks were made to ensure the systematic reviews were explicit in how studies were selected (clear inclusion and exclusion criteria) and assessed, clear about attempts to minimize biases and specific about how studies were integrated to form the recommendations.

Table 1. Literature Search Results

Author Year (Reference)	Title
Clinical Practice Guidelines	
NCCN 2009 ¹	NCCN Clinical Practice Guidelines in Oncology – Cancer-Related Fatigue, V.2.2009
ONS 2007 ²	Putting Evidence into Practice (PEP): Evidence-Based Interventions for Fatigue During and Following Cancer and Its Treatment
Supporting Guidance Documents	
ONS 2009 ¹⁹	Putting Evidence into Practice: Improving Oncology Patient Outcomes
CPAC/CAPO 2009 ²⁰	A Pan-Canadian Clinical Practice Guideline: Assessment of Psychosocial Health Care Needs of the Adult Cancer Patient
CCO 2004 ²¹	Telephone Nursing Practice and Symptom Management.
CCO 2005 ²²	Palliative Care Collaborative Care Plan – Fatigue (cancer patients): Collaborative Care Plan for Fatigue
CPAC 2009 ²³	Guide to Implementing Screening for Distress, The 6th Vital Sign – Moving Towards Person-Centered Care. Part A: Background, Recommendations and Implementation
Fraser 2006 ²⁴	Hospice Palliative Care Program Symptom Guidelines
NCI 2010 ²⁵	Fatigue (PDQ®): Supportive care - Health Professional Information
Systematic Reviews	
Brown 2009 ²⁶	Cancer-Related Fatigue and Its Association with Depression and Anxiety: A Systematic Review
Cramp 2008 ²⁷	Exercise for the Management of Cancer-Related Fatigue in Adults
Goedendorp 2009 ²⁸	Psychosocial Interventions for Reducing Fatigue during Cancer Treatment in Adults
Kirkova 2006 ²⁹	Cancer Symptom Assessment Instruments: A Systematic Review

Notes: NCCN = National Comprehensive Cancer Network
 ONS = Oncology Nursing Society
 CPAC = Canadian Partnership Against Cancer
 CAPO = Canadian Association of Psychosocial Oncology
 Fraser = Fraser Health
 CCO = Cancer Care Ontario
 NCI = National Cancer Institute

Critical Appraisal

Table 2 shows that the two practice guidelines were assessed for reporting quality using the AGREE II Instrument. The AGREE II Instrument is a critical appraisal tool and an important aid in the selection of the best-quality guidelines for use in practice.¹⁷ The decision was made to include both of the appraised guidelines since the NCCN guideline¹ is used to inform practice in large organizations such as comprehensive cancer centres in the United States, and the ONS guideline² scored 50% on rigour, an important domain indicating methodological quality. The level of evidence is clear in both of the guidelines, they are based on prominent expert consensus and they are currently in widespread use.

Table 2. Critical Appraisal of Clinical Practice Guidelines

Domains (AGREE II)	NCCN (v.2.2009)	ONS (2007)
1. Scope and Purpose	58%	53%
2. Stakeholder Involvement	42%	31%
3. Rigour of Development	24%	50%
4. Clarity of Presentation	86%	72%
5. Applicability	44%	29%
6. Editorial Independence	79%	29%
No of reviewers	2	2

Characteristics of the Included Guidelines

NCCN Clinical Practice Guidelines in Oncology - Cancer-Related Fatigue, V.2.20091

Scope and Content: NCCN practice guidelines are developed by expert committees and are reviewed and updated annually. They consist primarily of recommendations for evaluation, treatment and follow-up care of identified conditions. The recommendations are organized in terms of clinical pathways. The NCCN guideline (v.2.2009, Fatigue) includes children (5-6 years, 7-12 years) and all those older than 12 years, with separate algorithm paths for those younger than 12 years of age and for those older than 12 years of age. Recommendations for screening precede interventions. The interventions are divided according to clinical status (on active cancer treatment, post-treatment and at the end of life).

Patient Groups: Patients with cancer (5-6 years, 7-12 years, older than 12 years of age) who are in the post-diagnosis trajectory.

Intended Users: Physicians and other health care professionals who provide care to adult cancer patients.

Levels of Evidence: NCCN does not publish standard search strategies that apply across all guideline areas (NCCN personal communication, May 2010). Because the NCCN guidelines are process-oriented and describe the continuum of care of cancer patients, NCCN cannot perform systematic reviews for each of the decision points in their guidelines. Instead NCCN relies on the expert knowledge of the 20 to 30 members on each of their guideline panels. The NCCN panels are multidisciplinary and are composed of disease-specific clinician researchers. The NCCN process involves annual multidisciplinary review of each guideline at each of the 21 NCCN member institutions. As part of the institutional review process, any requested change must be supported by a current citation of evidence and each panel member also provides citations for any relevant publications or abstracts that have become available in the previous year. NCCN staff collate the results of these reviews and provide significant new papers to the panel members in advance of the panel review meeting. NCCN finds this to be an efficient way to keep abreast of new data and to ensure it is considering the range of published new data (NCCN personal communication, May 2010).

Recommendation decisions are therefore consensus-driven, with explicit review of the scientific evidence. When possible, recommendations are based on high-level (randomized trials or meta-analysis) evidence. NCCN recommendations therefore



represent a uniform consensus among panel members informed by evidence or clinical experience. All cancer-related fatigue recommendations are category 2A unless otherwise indicated. See NCCN guideline for a full description of evidence categories.

Putting Evidence into Practice (PEP): Evidence-Based Interventions for Fatigue During and Following Cancer and Its Treatment, ONS (2007)²

Scope and Content: The ONS PEP Fatigue guidelines are evidence-based and address the question of which interventions are effective in preventing and treating fatigue for patients with cancer. The ONS guidelines are based on systematic review and critique of empirical evidence by expert panel members. The guidelines do not address screening or assessment directly.

Patient Groups: Pediatric or adult patients with cancer who are anywhere in the post-diagnosis trajectory, including active treatment (surgical oncology, medical oncology, biotherapy, radiotherapy), follow-up or the end of life.

Intended Users: Primarily nurses, but relevant to all oncology health professionals who provide care to adult cancer patients.

Levels of Evidence: The literature was searched for meta-analyses, systematic reviews and RCTs. ONS critically appraised the identified evidence sources from strongest (multiple, well-designed, randomized, controlled trials with samples of more than 100 subjects) to weakest (e.g., qualitative designs, case studies and opinions). From there, interventions are classified using a weight-of-evidence schema. Five categories of evidence are described. See ONS guideline for a full description of evidence categories.

Synthesizing the Evidence

A recommendation matrix was first created to summarize and compare the two guidelines (Appendix I). The comparisons presented are based on the recommendation matrix template used by the National Guidelines Clearinghouse. Definitions of fatigue (see Appendix I) were added, and AGREE scores and contributing risk factors were compared in this document.

Descriptions of the evidence were written to summarize and highlight key evidence-based statements from the two guidelines, covering the areas of screening, assessment and contributing factors, as well as treatment and care options. The key evidence-based statements were used as a foundation to identify relevant information in the supporting documents and to lead to building and populating the algorithm framework. At this time, a series of action statements (screening, assessment, and treatment and care options) for fatigue were also developed from the key evidentiary base and recommendations.

The supporting documents were included to clarify background information, provide details in the guidelines and to cover any gaps in the knowledge. Thus, the algorithm and recommendations/action statements are based on the best available current evidence or expert consensus. Any evidence underlying the original practice guidelines was left unchanged, and the evidence base for the synthesized recommendations was described in totality.

Screening Evidence

The NCCN guideline¹ recommends screening all patients for fatigue as a vital sign at their initial clinic visit, at appropriate intervals during and/or following cancer treatment and as clinically indicated (recommendation grade 2A). Suggested intervals are daily screening for inpatients and at subsequent and routine follow-up visits for outpatients. Screening includes asking patients “How would you rate your fatigue on a scale of 0-10 over the past 7 days?” For Age > 12 years, 0 = no fatigue, 10 = worst fatigue you can imagine, with cut-off scores of none to mild being 0-3, moderate 4-6 and severe 7-10. The authors note that if a patient is unable to assign a numeric value to their fatigue, they can rate their fatigue as mild, moderate or severe, and also that family members may provide useful information about the effect of fatigue on the patient’s functioning over time.

The authors of the ONS guideline² do not provide a specific fatigue screening protocol; however, they state elsewhere that patient self-report is the best assessment given the subjectivity of fatigue experiences.¹⁹ In terms of tools to measure fatigue intensity, ONS provides examples and asks patients to rate their fatigue from 0 to 10 based on what best describes how they feel that day. Cartoon graphics are used to assess fatigue along the following scale: 0 = No Fatigue, 1 to 3 = Mild Fatigue, 4 to 6 = Moderate Fatigue, 7 to 9 = Extreme Fatigue, 10 = The Worst Fatigue. Examples of contributing factors include depression, pain, nausea, anemia and sleep disturbance.

The CCO palliative collaborative care plan²² is consistent with the ONS guideline² and reports that the patient’s own description of fatigue is the most reliable indicator of fatigue severity. The authors of the CCO guidance also suggest that the ESAS screening tool be used daily for inpatients and for each visit with patients in the community to evaluate tiredness. The 0 to 10 scale of ESAS plus administering at every clinic visit is consistent with the NCCN guideline.¹ The CCO telephone nursing practice guideline²¹ asks patients to score their feeling of fatigue on a scale of 0 to 10: 0 = no problems to 10 = total exhaustion, with cut-off scores similar to NCCN.¹ The Fraser Health report²⁴ includes a 1 to 10 scale in their assessment of fatigue intensity (0 = none, 10 = worst possible) and asks “Right now?”, “At best?”, “At worst?”, “On average?”

In Canada, the ESAS is a commonly administered screening tool followed by the Canadian Problem Checklist. The ESAS, initially developed as a brief symptom assessment tool for palliative patients,³¹ is a valid and reliable assessment tool that screens for nine common symptoms experienced by cancer patients (pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, wellbeing and shortness of breath).³² The severity of each symptom at the time of ESAS screening is rated on a numerical scale from 0 to 10, with 0 meaning that the symptom is absent and 10 that it is the most severe; results are trended over time. A systematic review of cancer symptom assessment instruments found that the ESAS is a psychometrically sound instrument.²⁹ The ESAS has been validated in a variety of populations, including both advanced cancer populations and patients earlier in the cancer trajectory.^{33,34}

The ESAS range (0-10) and cut-off scores for tiredness (none to mild 0-3, moderate 4-6 and severe 7-10) are similar to the NCCN fatigue screening cut-offs.¹ For further information about the ESAS, please see the Canadian Partnership Against Cancer’s guide to implementing screening for distress.²³

In terms of who screens for fatigue, the NCCN guideline¹ indicates that a health care professional screens for presence or absence of fatigue and severity. The ONS guideline² report primarily targets nurses but is not explicit about who should screen for fatigue. The CCO telephone symptom management guideline²¹ focuses on nursing practice, implying that nurses should conduct screening. The other supporting documents are not explicit in who should screen for fatigue.^{19,20,22-25} The Fraser Health symptom guidelines²⁴ were developed for use by interprofessional providers in primary care or other applicable settings, which implies any health professional could screen for fatigue.

While there is no agreed-on approach for the screening of fatigue, there is consistent agreement among the guidelines and supporting documents that regular screening for fatigue is a useful approach for all patients. Daily screening of inpatients is recommended as well as at every clinic visit and follow-up for patients who have been taken off or completed treatment.^{1,22} A range of single-item or multiple-item screening tools and self-report assessments are available for oncology care providers to incorporate into their practice.¹² In terms of cut-off scores on a 1-10 scale, there is agreement that below 4 denotes no to mild fatigue, 4 to 6 moderate fatigue, and greater than 7 severe fatigue. Patients' reports of fatigue intensity (mild, moderate, severe) may be used if the patient is not able to assign a numeric value to the fatigue experienced.¹ Regardless of tool or approach, the key point is that comparable data and information is obtained at each screening to detect changes over time.

Assessment Evidence

If a patient is flagged during screening (ESAS score ≥ 4), further comprehensive and focused assessment is required to clarify the nature and extent of the fatigue.²⁰ The NCCN guideline¹ also recommends expanding the initial screening to further assessments if there is clinical evidence of moderate to severe fatigue (score ≥ 4). Further assessments include an in-depth fatigue history and a physical exam. Focused history includes clinical status and medications. In-depth history (comparable to a comprehensive and a focused assessment as defined earlier in this document) of fatigue includes onset, duration, pattern, change over time, associated or alleviating factors, and interference with function.¹ Fatigue seldom occurs by itself and commonly clusters with symptoms such as sleep disturbance, emotional distress (depression and/or anxiety) and pain.^{1,26} The health care professional or team must therefore also assess the patient for key factors known to contribute to fatigue, such as pain, emotional distress (depression and/or anxiety), sleep disturbance, nutrition, medication side effects, anemia and hypothyroidism.¹ According to the NCCN guideline, the comprehensive assessment should be conducted by a health care professional who has received training in fatigue evaluation.¹ A physical exam can include gait, posture, range of motion, eyes (conjunctival pallor if anemic) and mouth (cheliosis/angular cheilitis and/or angular stomatitis [reddened shiny tongue] if vitamin deficiencies).^{24,25}

The ONS fatigue guideline reports that a detailed assessment of risk, contributing factors and information obtained from a clinical measurement tool are essential for monitoring fatigue.² In addition, the authors recommend that screening for etiologic factors is likely to be effective as a fatigue management strategy. Examples of etiologic factors for fatigue include pain, nausea, depression, cardiomyopathy, hypothyroidism,

pulmonary dysfunction, anemia, sleep disturbance and sedation secondary to specific medications such as opiates, antidepressants and antihistamines.²

From the supporting documents, CCO²¹ provides a two-tiered assessment (general assessment followed by symptom assessment) equivalent to the NCCN1 focused history and includes diagnosis and treatment details, current medications and allergies. The CCO symptom assessment is also equivalent to the NCCN guideline¹ in terms of in-depth fatigue history and assessment of treatable contributing factors. Elements include onset, duration, activities of daily living, nutrition, activity levels and sleep pattern. According to the Fraser Health report,²⁴ ongoing comprehensive assessment includes interview, physical assessment (as appropriate for symptoms), medication review, medical and surgical reviews, sleep patterns, psychosocial review, review of physical environment and appropriate diagnostics. Fraser Health uses an acronym for health professionals to determine the cause, effectiveness and impact on quality of life for the patient and their family. The acronym, OPQRSTU(I)V, refers to

- O = onset
- P = provoking/palliating
- Q = quality
- R = region/radiation
- S = severity
- T = treatment
- U = understanding; I = impact
- V = values

Assessment components of the NCI report²⁵ are consistent with the CCO and Fraser Health reports,^{21,24} with the exception that NCI also recommends asking patients specifically about job performance (in addition to effects of fatigue on activities of daily living) and including a psychiatric evaluation (including evaluation for depression) as part of the initial fatigue assessment. This allows the NCI to use the International Classification of Diseases, 10th edition criteria for diagnosing cancer-related fatigue because a strict application of the criteria requires the use of a semi-structured psychiatric interview to ensure that cancer-related fatigue symptoms are not related to underlying psychiatric co-morbidity.¹²

Taken together, the two guidelines^{1,2} and three of the supporting documents^{21,24,25} are consistent in terms of the assessment areas if fatigue concerns are flagged during screening. Further assessment should be comprehensive and include:

- The fatigue pattern: onset, duration, change over time
- The patient's description of fatigue and/or a subjective (self-reported) measure (i.e., valid tools) of intensity
- Alleviating and aggravating factors, including risk factors and times of vulnerability:
 - Disease status, treatment history, treatment-related symptoms
 - Sleep and/or rest patterns, relaxation habits
 - Current medications, including alcohol or other risk substances



- Possible stressors (e.g., life events such as recent bereavement or loss, change in home setting, financial resources or support system)
- Nutrition intake and any appetite or weight changes
- Level of activity
- Effects of fatigue on activities of daily living and lifestyle (work, social life, concentration, short-term memory)
- Any underlying reversible contributing factors (e.g., anemia, depression, anxiety, pain, dehydration, nutritional deficiencies [e.g., protein, calories, vitamins], sedating medications [e.g., opioids, benzodiazepines], neurotoxic therapies, infection, fever, sleep disturbances or inactivity)
- Physical examination and clinical observation, including gait, posture and range of motion
- Other contributing factors (e.g., dyspnea, muscle wasting)

Fatigue Symptoms

A general description of cancer-related fatigue is a sensation of tiredness that is persistent, not linked to activity or exertion and not relieved by sleep or rest.^{1,22,25} The NCCN¹ guideline and four supporting documents^{19,21,22,25} are consistent regarding the common symptoms and typical pattern of cancer-related fatigue. Cancer-related fatigue in adults can include:

- Tiredness or exhaustion disproportionate to recent activity
- Impairment in important areas of functioning (e.g., daily tasks, work, social life, other)
- Diminished concentration or attention
- Significant distress or negative mood related to feeling fatigued (e.g., sad, frustrated, irritable)
- Sleep disturbance (insomnia or hypersomnia)
- Decreased motivation or interest in engaging in usual activities or disturbance in quality of life
- Sleep perceived as non-restorative or non-refreshing

In terms of mild, moderate or severe fatigue as an assessment outcome (i.e., beyond screening), this distinction was not explicitly reported in either of the two guidelines.^{1,2} The NCCN guideline¹ did report that the MOS-SF-36 Physical Functioning subscale can be used as a guide in practice for decision-making. The CCO report²¹ distinguishes between non-urgent, urgent or emergent fatigue in palliative patients, where non-urgent patients can carry out their activities of daily life and severe (emergent) fatigue is characterized by shortness of breath at rest, chest pain, tachycardia, sudden onset of severe fatigue or rapid blood loss.²¹ As an alternative, the NCI²⁵ proposes using the International Classification of Diseases, 10th edition to diagnose cancer-related fatigue. Along with other criteria (disruption of function, selected underlying factors, mood), specific symptoms must have been present every day or nearly every day during the same two-week period in the past month.²⁵ Using specific criteria to diagnose cancer-related fatigue is useful from a research and



treatment decision-making perspective (i.e., medical model) but complicated by the different signs and symptoms of cancer-related fatigue that may or may not be present in an individual. In addition, responses to a symptom can be highly variable between individuals and there is also concern that individuals below threshold may not always receive the care they need.^{12,25}

In summary, fatigue is a very commonly reported symptom among cancer patients and survivors. If the intensity is identified as moderate or severe from screening, further assessment by a health care professional is triggered. To characterize the individual's fatigue pattern and identify all contributing factors, there is consistency among the synthesized guidelines and supporting documents regarding the necessary components of a comprehensive assessment. The patients' descriptions of their fatigue are also an important element due to the subjective experience of fatigue.^{1,2} Oncology care providers must educate themselves about fatigue and promote open communication with patients and their families about the experience of fatigue and how it affects daily life. Assessment tools or checklists can help to assess for the presence of fatigue and its intensity, and to help identify treatment options.

Contributing (Risk) Factors

While both the NCCN¹ and ONS² guidelines list contributing risk factors (Table 3), the authors of the ONS guideline indicated that their list is largely based on the NCCN guideline, and both separate specific fatigue symptoms from contributing factors and co-morbidities. Four of the supporting documents^{21,22,24,25} align with the majority of the contributing factors reported by NCCN¹ and ONS.² The CCO report²¹ also includes disease process, stress and changes in activity or exercise patterns as part of contributing risk factors. Fatigue patterns vary depending on clinical status and specific treatment regimens. For example, fatigue often peaks near the end of radiation and tapers off over several months, whereas those receiving cytotoxic chemotherapy may experience daily variation in fatigue.¹ Of note, medications other than chemotherapy may contribute to feelings of fatigue. For example, opioids used to relieve pain are often associated with sedation. In addition, sedation may also be a side effect from medications such as antihistamines, benzodiazepines and tricyclic antidepressants. Fatigue symptoms may therefore be compounded if multiple medications are being administered.^{1,22,25}

The NCCN guideline¹ reports other individual risk factors associated with fatigue in post-treatment disease-free patients. Other risk factors include pre-treatment fatigue, anxiety and depression levels, physical activity levels, coping methods and cancer-related stressors, co-morbidities, type of malignancy, prior treatment patterns (e.g., higher fatigue with combination-modality therapy) and the late effects of treatment.¹ The CCO report²² also lists underlying psychiatric conditions and co-morbidities as part of contributing risk factors.

Table 3. Risk Factors for Cancer-Related Fatigue

Physical Symptoms	NCCN	ONS	Supporting
Shortness of breath	—	√	√
Heart palpitations	—	√	—
General lack of energy	√	√	—
Contributing (Risk) Factors	NCCN	ONS	Supporting
Anemia	√	√	√
Endocrine dysfunction (e.g., hypothyroidism, hypogonadism, adrenal insufficiency)	√	√	√
Cardiac dysfunction (e.g., cardiomyopathy)	√	√	√
Pulmonary dysfunction	√	√	√
Fluid and electrolyte imbalances	√	√	√
Weight/caloric intake/nutritional deficiencies	√	—	√
Pain	√	√	√
Depressed mood/depression	√	√	√
Emotional distress	√	√	√
Sleep disturbances	√	√	√
Medication side effects profile (i.e., sedation)	√	√	√
Infection	√	—	√
Nausea	—	√	—
Hepatic, renal, neurologic dysfunction	√	—	√
Decreased activity or fitness	√	—	√
Pain	—	—	√
Fever	—	—	√
Treatment side effects	—	—	√
Individual Risk Factors	NCCN	ONS	Supporting
Disease status (e.g., on active treatment, at end of life)	√	—	—
History of psychiatric problems (e.g., depression, anxiety)	√	—	√
Coping methods and cancer-related stressors	√	—	—
Pre-treatment activity levels	√	—	—

Note: NCCN = National Comprehensive Cancer Network; ONS = Oncology Nursing Society

Treatment and Care Options Evidence

If any treatable contributing factors are present, the NCCN guideline¹ recommends treating these conditions (e.g., pain, anemia and depression) first using appropriate practice guidelines. Table 4 shows that subsequent recommendations include non-pharmacological and pharmacological interventions and consideration of referral to specialist services depending on types of problems (e.g., social worker or nutrition expert) before follow-up and re-evaluation. In terms of non-pharmacological approaches, the NCCN guideline¹ reports that randomized controlled trial data indicate that enhanced physical activity, cognitive-behavioural therapy and psychosocial interventions focused specifically on fatigue will improve fatigue symptoms. It recommends 30 minutes of moderate intensity activity on most days of

the week.¹ This recommendation is based on the U.S. Surgeon General recommendations for all populations. However, disease status (on active cancer treatment, long-term follow-up, advanced disease or end-of-life) determines the optimal fatigue management strategies.¹ Exercise should be used cautiously in the presence of bone metastases, neutropenia, low platelet counts, anemia or fever, weighing risks and benefits.¹ In some cases, a modified exercise regimen can be recommended. For example, a neutropenic patient should avoid environments with high risk for infection (such as gyms and swimming pools). The NCCN guideline¹ also recommends periodic re-screening and re-evaluation for all patients and survivors, specifically daily for inpatients, on subsequent clinic visits for outpatients and self-monitoring for survivors.

Underlying the ONS intervention recommendations² is the assumption that patients have been rated as having moderate to severe fatigue. Table 5 shows that exercise is the only intervention that ONS recommends for practice; a recommendation based on randomized controlled trial data. ONS also recommends moderate exercise several times per week (e.g., walking, cycling, swimming or resistance exercises). Other interventions described as likely to be effective include energy conservation, education and cognitive behavioural approaches (e.g., sleep hygiene strategies and strategies to influence sleep disrupting thoughts) and relaxation training using breathing. The goal of energy conservation and activity management is to balance rest and activities so that prioritized activities are more likely achieved. Cognitive behavioural approaches generally include assessment and focus on the ways in which thinking patterns influence perceptions of problems and behaviour and focus on cognitive re-framing. ONS recommends that education benefits all patients and includes coping strategies, counselling and support, coaching in fatigue management and information.² ONS also reports that progressive muscle relaxation is likely to be effective, although the percentage of fatigued individuals who learn and practice this intervention may be very small.

Table 4. NCCN Treatment and Psychosocial/Supportive Care Strategies¹

	Level*
General strategies for all patients	
Self-monitoring of fatigue, energy conservation, distraction (e.g., games, music, reading, socializing)	All 2A
On active treatment OR on long-term follow-up	
Non-pharmacologic	
Exercise (activity enhancement) as appropriate: In line with U.S. Surgeon General for all populations, 30 minutes of moderate intensity activity (e.g., walking, cycling) most days of the week, with intensity of exercise depending on individual patient circumstances. Begin with low intensity and duration of exercise and progress slowly, modifying the exercise plan as conditions change (e.g., accumulating the 20 to 30 minutes of activity in short intervals as needed).	1
Cognitive behavioural therapy: A type of psychotherapy also labelled a psychosocial intervention, to reduce negative emotions and facilitate psychological adjustment.	1
Psychosocial interventions to reduce stress and increase psychosocial support (evidence that fatigue is reduced, but often a secondary endpoint) (e.g., support groups, education, counselling, coping strategies).	1
Attention-restoring therapy (e.g., experiences in natural environments).	2A
Sleep therapy: cognitive behavioural therapy for sleep (stimulus control, sleep restriction, sleep hygiene) plus breathing control, muscle relaxation, guided imagery to promote relaxation.	2A
Nutrition consultation; nutrition counselling.	2A
Pharmacologic	
After ruling out other causes, consider psycho-stimulants (however, pharmacological interventions remain under investigation), treat for anemia (see NCCN cancer-and-chemotherapy induced anemia guidelines), consider sleep medication.	All 2A
At end of life	
Non-pharmacologic	
Exercise (activity enhancement) as appropriate: In line with U.S. Surgeon General for all populations, 30 minutes of moderate intensity activity (e.g., walking, cycling) most days of the week, with intensity of exercise depending on individual patient circumstances. Begin with low intensity and duration of exercise and progress slowly, modifying the exercise plan as conditions change (e.g., accumulating the 20 to 30 minutes of activity in short intervals as needed).	1
Psychosocial interventions to reduce stress and increase psychosocial support (evidence that fatigue is reduced, but often a secondary endpoint) (e.g., support groups, education, counselling, coping strategies).	1
Attention-restoring therapy (e.g., experiences in natural environments).	2A
Sleep therapy: cognitive behavioural therapy for sleep (stimulus control, sleep restriction, sleep hygiene) plus breathing control, muscle relaxation, guided imagery to promote relaxation.	2A
Nutrition consultation; nutrition counselling.	2A
Pharmacologic	
After ruling out other causes, consider psycho-stimulants (however, pharmacological interventions remain under investigation), treat for anemia (see NCCN cancer-and-chemotherapy induced anemia guidelines), consider sleep medication, consider corticosteroids (prednisone or dexamethasone).	All 2A

*See NCCN guideline for further information on evidence categories.

Table 5. Treatment and Care Options Supported by ONS²

	Level*
Exercise (walking, cycling, swimming, resistive exercise, or combined exercise) several times per week	RFP
Screening for potential etiologic factors and managing as appropriate	LTBE
Energy conservation and activity management	LTBE
Education and information provision	LTBE
Measures to optimize sleep quality (sleep hygiene)	LTBE
Relaxation training	LTBE
Massage and healing touch	LTBE

Note: RFP = recommended for practice (based on at least two RCTs);
LTBE = likely to be effective (based on single RCT and consensus).

*See ONS guideline for further information on evidence categories.

The ONS guideline reports that the correction of anemia with erythropoiesis-stimulating agents may be a beneficial intervention for some patients to reduce fatigue; however, the potential benefits must be balanced with potential harms and clinicians and patients must consider individual circumstances and priorities.²

At the time ONS conducted its evidence summary,² it reported that there was insufficient or poor quality data to establish the effectiveness of various pharmacological, psycho-educational or cognitive behavioural therapies, as well as complementary or alternative interventions (Table 6). Please note that the more recent NCCN guideline³⁰ reports level I evidence for cognitive behavioural therapies.

Table 6. Interventions Not Supported by ONS

Pharmacological strategies: paroxetine, methylphenidate, donepezil, bupropion sustained-release, modafinil, venlafaxine, sertraline	
Combination therapy: dietary supplements and lipid replacement/antioxidant supplementation	
Combination therapy: aromatherapy, foot soak, reflexology	
Individual and group psychotherapy	Expressive writing
Hypnosis	Structured rehabilitation (more than exercise alone)
Targeted anti-cytokine therapy	Reiki
Yoga	Mindfulness-based stress reduction
Acupuncture	Art, music, animal-assisted therapy
Distraction-virtual reality immersion	Levocarnitine supplementation
Vitamin supplementation	Adenosine 5' triphosphate infusion
Lectin-standardized mistletoe extract	Essiac
Chinese medicinal herbs	Omega-3 fatty acid supplementation

Note: Please see the full ONS guideline for definitions of the interventions and citations.²

A recent Cochrane review by Zhang et al.³⁵ concurs with the ONS findings, and although promising, the evidence supporting recommending Chinese medicinal herbs to treat the side-effects (e.g., nausea, vomiting, fatigue) of chemotherapy in populations of breast cancer patients is limited. Another Cochrane review²⁸ examined psychosocial interventions in a randomized setting designed to reduce fatigue during

cancer treatment in adults (e.g., facilitated support groups, cognitive behavioural therapy, psychotherapy with a trained professional and fatigue intervention during home visit). Overall, fatigue reduction was more pronounced and effective with interventions specific to fatigue (e.g., education about fatigue and activity management) rather than interventions focused on distress or pain reduction, for example. With limited studies, however, the authors were not able to identify any essential components that reduce fatigue during treatment.

In agreement with the NCCN¹ and ONS² guidelines, evidence for the use of drug therapy for the management of cancer-related fatigue is considered inconclusive. A Cochrane intervention review of 27 trials detected mixed results,³⁶ with methylphenidate (Ritalin) appearing to be effective for cancer-related fatigue; however, due to small sample sizes, more research was needed to confirm its role.

The NCI document²⁵ reported that, based on limited experience, psycho-stimulants may be considered only in the treatment of severe fatigue. According to the NCCN guideline,¹ there were no reports of whether psycho-stimulants were useful for treating fatigue in cancer survivors. In addition, optimal dosing and schedules have not been established for use of psycho-stimulants in cancer patients. The consideration of psycho-stimulants for the treatment of severe fatigue and corticosteroids for the treatment of severe fatigue in patients at the end of life is therefore based on limited research. Erythropoietin and darbepoetin (for anemia) were reported as effective for cancer-related fatigue in patients who were anemic as a result of chemotherapy.³⁶ There is therefore some evidence for the use of erythropoiesis-stimulating agents for treating cancer-related anemia. Concurring with the ONS guideline,² Minton et al.³⁶ caution about the use of erythropoietin and darbepoetin, reporting that optimal dose, treatment duration and maintenance level associated with better quality of life and relief of cancer-related fatigue have not been clearly established. Progestational steroids and paroxetine, an antidepressant, were found to be no better than placebo.³⁶ The NCCN guideline¹ does not recommend the use of antidepressants to reduce fatigue.

Treatment and care recommendations from the NCI²⁵ plus three other supporting documents^{21,22,24} that focused on palliative patients are overall consistent with the NCCN¹ and ONS² treatment and care recommendations.

In summary, the guidelines and supporting documents agree that all patients should receive specific targeted education about fatigue plus information about symptom management and relevant services in the treatment centre and the community. Once any reversible causes of fatigue are treated (e.g., depression, anemia, anxiety or pain), non-pharmacologic approaches include exercise combined with other strategies to conserve energy (modifying rest and activity), sleep hygiene, improved nutrition and reduced stress (modifying, enhancing coping). Of all the non-pharmacologic approaches to improve fatigue symptoms, the strongest evidence from randomized controlled trial data is for exercise and psychosocial interventions. The physical activity recommendations are general because of a lack of high-quality research to inform specific physical activity approaches and prescriptions for cancer populations.^{1,27,37} However, exercise regimens must be tailored to the individual, taking into account factors such as age, disease status, pre-treatment activity levels and co-morbidities.

Although a variety of pharmacologic agents are available to treat cancer-related fatigue, the evidence is inconclusive. Most promising were drugs that stimulate red blood cell production (in anemic patients) and drugs that improve concentration levels. Further drug studies are necessary to inform this topic. The guidelines and supporting documents agree that any pharmacologic treatment should be used under expert supervision and their effect(s) monitored closely.

Each practice setting must develop methods to provide or make referrals for psychosocial, nutritional, educational and pharmacological (as appropriate) interventions. For example, multidisciplinary teams should have agreed protocols for fatigue management (e.g., medicine, nursing, social work, physical therapy or nutrition). These should include recommendations for referral and care pathways.

Strengths and Weaknesses of the Body of Evidence

The NCCN recommendations¹ were primarily founded on consensus among respected authorities based on combined clinical experience with large numbers of patients or evidence ranging from phase II to large cohort studies to case series to reports from expert committees to individual practitioner experience. There was some consensus based on randomized controlled trials (category I) in the areas of activity enhancement and exercise, and psychosocial interventions (e.g., stress management, support groups, cognitive behavioural therapy) for the treatment of fatigue.

The evidentiary base for the ONS fatigue guideline² included systematic reviews, meta-analyses, RCTs, case studies, and expert opinion and consensus. The grade and quality of evidence was systematically evaluated and stated clearly by ONS using a weight of evidence classification schema. The only intervention in the management of fatigue that ONS recommends with high-level evidence is exercise.

The strengths of the body of evidence include the acknowledgement that fatigue is a significant problem that needs to be addressed and also the inclusion of findings from high-level randomized controlled trials. Weaknesses include the lack of a universally agreed-on definition of cancer-related fatigue and a lack of consensus over the best way to measure fatigue. There is a wide range of approaches, including single- and multiple-item tools, available to measure fatigue (tiredness, physical, emotional) and screening criteria vary (e.g., 7 days, now or today). Psychometric properties are therefore not consistent.¹² As a result, there is a range of estimates of the prevalence of cancer-related fatigue and many studies are not comparable. In addition, there is no systematic approach to the management of fatigue, and since the etiology and mechanisms regarding fatigue in cancer patients are variable, there is considerable variation in practice in the management of fatigue.²⁵

A further weakness of the body of evidence is the scientific literature informing this topic. There is a relative lack of studies on general cancer populations, with more research conducted on women affected by breast cancer, which influences the external validity of findings.² In terms of fatigue management, the focus tends to be on practice/interventions once fatigue occurs (e.g., largely as a side-effect of treatment) rather than on prevention. There is little known regarding the management of fatigue in survivors. More efforts are needed in the form of high-quality intervention studies of tailored exercise programs and/or cognitive behavioural therapy to identify the most beneficial elements, using only a few fatigue measures

that have been validated.³⁶ More randomized controlled trials are needed to assess drug therapy and improve outcome variables using valid measures. More research is also needed to understand the science of fatigue and to learn about underlying mechanisms.

External Review of the Evidence Summary Report

Reviewer Feedback

A draft version of this report was reviewed by 14 health care professionals from across Canada who provide care to adult cancer patients. Any changes made to the report as a result of feedback from external reviewers are summarized in the *Modifications* section below.

Methods

Health care professional feedback was obtained through an online survey of practitioners from across Canada. External reviewers were initially contacted by email followed by three reminder emails. The survey consisted of 20 items evaluating

- their current professional role and use of cancer fatigue guidelines;
- the relevance of the recommendations;
- the methods used to search and synthesize the literature;
- results and summary of the recommendations;
- how likely they would be to use the guidelines in their current practice.

The Cancer Journey Advisory Group reviewed the results of the external review, addressed each comment and made modifications accordingly.

Results

Of the 25 practitioners approached, a total of 14 responses were received from health care professionals from Alberta (2), British Columbia (1), Nova Scotia (1), Ontario (9) and Quebec (1). Key results are summarized in Table 8. The roles of the health care professionals were varied and included administrators (3), dieticians (2), a guidelines developer (1), a family physician (1), nurses (3), an occupational therapist (1), a physiotherapist (1), a rehabilitation clinician (1), social workers (2), a writer (1) and a researcher (1). The majority of the respondents (57.1%) indicated that they do not currently follow a guideline on fatigue for adult cancer survivors. Of those that did, one reported using a variety of sources, one reported using the ESAS and three reported that they used the NCCN guideline¹ as their source.



Table 8. Summary of External Review Survey Results

Survey Items	Number (%)			
	Strongly Agree	Agree	Somewhat Agree	Other ^a
The overall objective of the fatigue guideline is specifically described.	6 (42.9)	6 (42.9)	0 (0.0)	2 (14.2)
The target population for the fatigue guideline is clearly described.	5 (35.7)	6 (42.9)	2 (14.2)	1 (7.1)
The target users of the fatigue guideline are clearly described.	6 (42.9)	6 (42.9)	0 (0.0)	2 (14.2)
Systematic search methods for identifying relevant guidelines for adaptation were used.	6 (42.9)	6 (42.9)	1 (7.1)	1 (7.1)
The methods for formulating the fatigue recommendations are clearly described.	5 (35.7)	5 (35.7)	2 (14.2)	2 (14.2)
The recommendations for fatigue are easily identifiable.	7 (50.0)	4 (28.6)	1 (7.1)	2 (14.2)
The recommendations for fatigue are appropriate.	3 (21.4)	10 (71.4)	0 (0.0)	1 (7.1)
The recommendations for fatigue are feasible.	2 (14.2)	8 (57.1)	2 (14.2)	2 (14.2)
When applied, the fatigue guideline will produce more benefits than harms.	8 (57.1)	4 (28.6)	2 (5.6)	2 (5.6)
The fatigue guideline is supported with tools for application.	3 (21.4)	5 (35.7)	4 (28.6)	2 (14.2)
How likely would you be able to apply the recommendations in the fatigue guideline in clinical practice?	Very Likely	Likely	Somewhat Likely	Other^b
	2 (14.2)	8 (57.1)	1 (7.1)	3 (21.4)

^a Respondents replied Disagree, Undecided or Not Applicable

^b Respondents replied Undecided or Not Applicable

Summary of Written Comments

The majority of the health care professionals provided written comments. The following are the main points contained in the comments:

- One reviewer requested clarity regarding copyright of the document and the updating procedure.
- Reviewers requested guidance on fatigue for children with cancer and specific recommendations during treatment, post treatment and at the end of life.
- Several reviewers commented on the use of fatigue tools. One reviewer thought that while the use of the ESAS as the basic screening tool for fatigue was reasonable, the 4/10 cut-off point for further follow-up may be a little high and should be the subject of further research. One reviewer suggested the FACIT-F and PROMIS scales for more detailed assessments, and two questioned whether the Canadian Problem Checklist should be part of routine screening. Given that the CPC tool is seen as part of distress assessment, a request for contextualization was made. One reviewer suggested a quick nutrition screen such as using the first four boxes of the PG-SGA or the MST would aid the professional that is using the fatigue tool to better assess the nutrition component and help determine if a referral to a dietitian is needed.



- Several reviewers commented that, while the recommendations were clearly stated, the algorithms were in need of revision. A number of suggestions were incorporated into the algorithms.
- One reviewer commented that the guideline seems muddled and that targeted interventions with defined outcomes are not that clear. In addition, the exercise piece and how to conserve energy are identified but need some detail. Nutrition is also weak and needs to be integrated into this guideline.
- Several reviewers commented that it would be difficult to apply the recommendations because of the lack of clarity around the recommendations, challenges related to available resources in medical environments to assess and intervene, and the additional time needed to integrate the screening tool into practice. Several reviewers commented on the need for knowledge translation and uptake since there is currently variation in clinical practice.
- When asked how the fatigue recommendations compared to their current clinical practice, reviewers commented that their current practices aligned or mostly aligned with the recommendations; however, the guideline now provides the evidence to support current clinical practice and it will help reinforce good clinical practices and support clinicians who may just be starting to practice.

Modifications and Actions

In response to the comments provided by the 14 health care professionals acting as external reviewers, the following modifications were made:

- Further detail on copyright and the updating procedure were added to the guidelines methodology section.
- The needs of children differ from that of adults and it was decided that guidance for children would be outside of the scope of this guideline. In addition, from the onset, it was decided that the recommendations and algorithms would be developed to be applicable to patients at all points along the cancer continuum and not be broken down according to clinical status.
- The National Advisory Group recognizes that comprehensive assessment may involve a combination of procedures, checklists and measurement tools to identify specific contributing factors to a symptom problem, and that there are many options to choose from, each with unique strengths and weaknesses. While the National Advisory Group expects other tools and resources will be accessed, the tools recommended in this guideline were selected on the basis of their routine use in clinical practice and from the standpoint of offering comprehensive assessment of symptoms that are often overlapping with other domains besides fatigue.
- The algorithms were revised on the basis of the feedback received.
- In terms of comments related to challenges in applying the recommendations, the algorithms were revised to improve clarity, and it is hoped the availability of high-quality guidance in clinical practice can serve as the foundation and the impetus for establishing the best in patient care.
- It is clear that the guideline recommendations align with many aspects of current practice and it is hoped that, on implementation, further alignment will be reached and patients will receive standard and consistent care across jurisdictions.

Guideline Implementation

As part of next steps, practice protocols for professionals, patient versions and workshops with key health providers across a variety of jurisdictions are being planned to promote the uptake of the guideline across Canada. The guideline will also be translated into French and a formal communications plan will be developed to maximize dissemination.

When selecting the interprofessional panel, a key consideration is the ability of the panel members to disseminate and implement the guideline in their respective jurisdictions. The partnership with the Canadian Association of Psychosocial Oncology will also ensure greater exposure for the guideline and support its implementation. The guideline will be posted on the Internet on the websites of the Canadian Partnership Against Cancer (Cancer Journey Advisory Group) and the Canadian Association of Psychosocial Oncology, and will also be published in a peer-reviewed journal. Further, this guidance document will be disseminated through cancer advocacy survivorship groups, including the Canadian Cancer Action Network and the Canadian Cancer Society. In addition, a summary of the guideline will act as an implementation tool, which will be distributed widely.

There was no evidence identified that provided insight into the potential resource implications of applying the recommendations, and it is well known that there is much variability in resources across the various Canadian health jurisdictions. While the resources needed to implement the recommendations are unknown, there are also the resources consumed to offer current services to consider, and it is intuitive that increasing the health and wellbeing of cancer survivors is an investment well worth making. The guideline recommendations were developed for implementation in a variety of health settings, and criteria to monitor or audit the organization of care or clinical practice are clearly defined throughout the document. In many cases, either the services are offered or they are not and that will be the initial criteria to assess services. As the re-organization of services takes place, program evaluation will be a very valuable component of optimizing care for cancer survivors.



Conclusions

The National Advisory Group concluded that it is reasonable to routinely screen adult cancer patients for fatigue using standardized screening tools. Comprehensive and focused assessments are needed to establish the extent and nature of the fatigue symptoms and their impact on physical functioning. Members of the interprofessional clinical team share responsibility for assessments and treatment. When symptoms are identified, the clinical team must decide when referral to an appropriately trained professional is needed based on the factors contributing to the fatigue or using established cut offs identified through valid and reliable tools.

In terms of treatment, fatigue and weakness may be related to other identifiable and potentially treatable conditions, such as depression and anemia. Reversible contributing factors that are treatable should be addressed first, and non-pharmacological or psychosocial interventions, such as physical activity and cognitive behavioural therapy, should be considered to reduce stress and optimize sleep quality. The National Advisory Group reviewed the use of pharmacological agents to treat fatigue, which are considered experimental and, at this time, do not recommend their use.

The management of cancer-related fatigue must be tailored to the individual patient, who should be fully informed of the options and have the opportunity to take part in decision-making regarding self-management. Each practice setting should have agreed protocols for managing fatigue that include expectations or standards of the clinical team, including processes for referral to appropriate specialists.



Cancer-Related Fatigue Recommendations

The following recommendations and tools for application are based on the expert consensus of the Cancer Journey Advisory Group of the Canadian Partnership Against Cancer, which is composed of clinical experts and fatigue researchers, and informed primarily by two clinical practice guidelines from credible guideline development groups.^{38,39}

1. Screening for Cancer-Related Fatigue

(Based on the expert consensus of the National Advisory Group and informed by NCCN category 2A, ONS expert opinion[†])

- All health care providers should routinely screen for the presence of fatigue from the point of diagnosis onward.
- All patients should be screened for fatigue at their initial visit, at appropriate intervals (e.g., daily for inpatients, routine and follow-up visits for outpatients, and self-monitoring for those post-treatment) and as clinically indicated, especially with changes in disease status.
- Screen with a valid and reliable tool that includes reportable scores (dimensions) that are clinically meaningful and have established cut-offs (e.g., Screening for Distress Tool, which includes Edmonton Symptom Assessment System [ESAS] and Canadian Problem Checklist [CPC]).
- For inpatients who are unable to assign a numeric value to rate their fatigue, a rating of mild, moderate or severe may be used.

2. Comprehensive and Focused Assessment of Cancer-Related Fatigue

(Based on the expert consensus of the National Advisory Group and informed by NCCN category 2A, ONS category “likely to be effective”, ONS expert opinion)*

- Screen for fatigue and if moderate or severe fatigue is detected through screening (ESAS tiredness greater than 4), individuals should have a comprehensive and a focused assessment to identify the nature and extent of the fatigue symptoms.
- Medical and substance-induced causes of fatigue should be ruled out (e.g., anemia, infection, nutrition deficiencies, medication or treatment side effects).
- Assessments should be a shared responsibility of the clinical team, with designation of those who are expected to conduct assessments based on scope of practice.
- Assessment should include a history of fatigue (e.g., disease status, pre-treatment activity levels, fatigue onset, pattern, duration, changes over time, interference with function and daily living), contributing risk factors (e.g., depression, anemia, pain, nausea, sleep disturbance, co-morbidities), a physical exam, a review of symptoms and a self-assessment of causes contributing to fatigue.

[†] Please see the NCCN and ONS guidelines for descriptions of evidence categories.

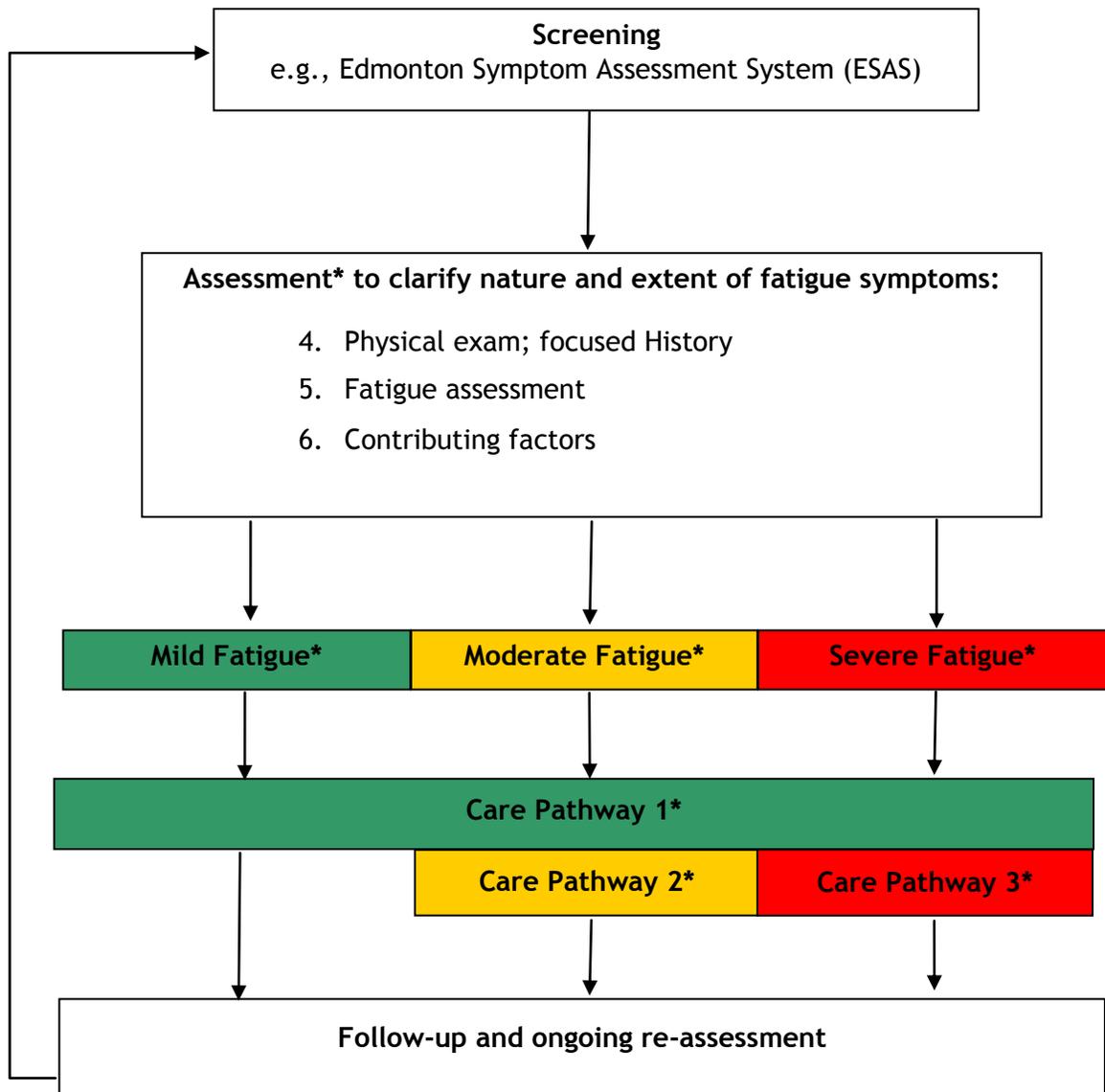
- Promote open communication among the patient, family and the clinical team to facilitate discussions about the experience of fatigue and its effects on daily functioning.
- As a shared responsibility, the clinical team must decide when referral to an appropriately trained professional is needed (i.e., all patients with an ESAS score in the severe range, or with certain accompanying factors or symptoms, or a cut-off score identified using valid and reliable tools for assessment of symptoms of fatigue).

3. Treatment and Care Options for Cancer-Related Fatigue

(Based on the expert consensus of the National Advisory Group and informed by NCCN categories 1 and 2A, ONS categories “recommended for practice” and “likely to be effective”, ONS expert opinion)*

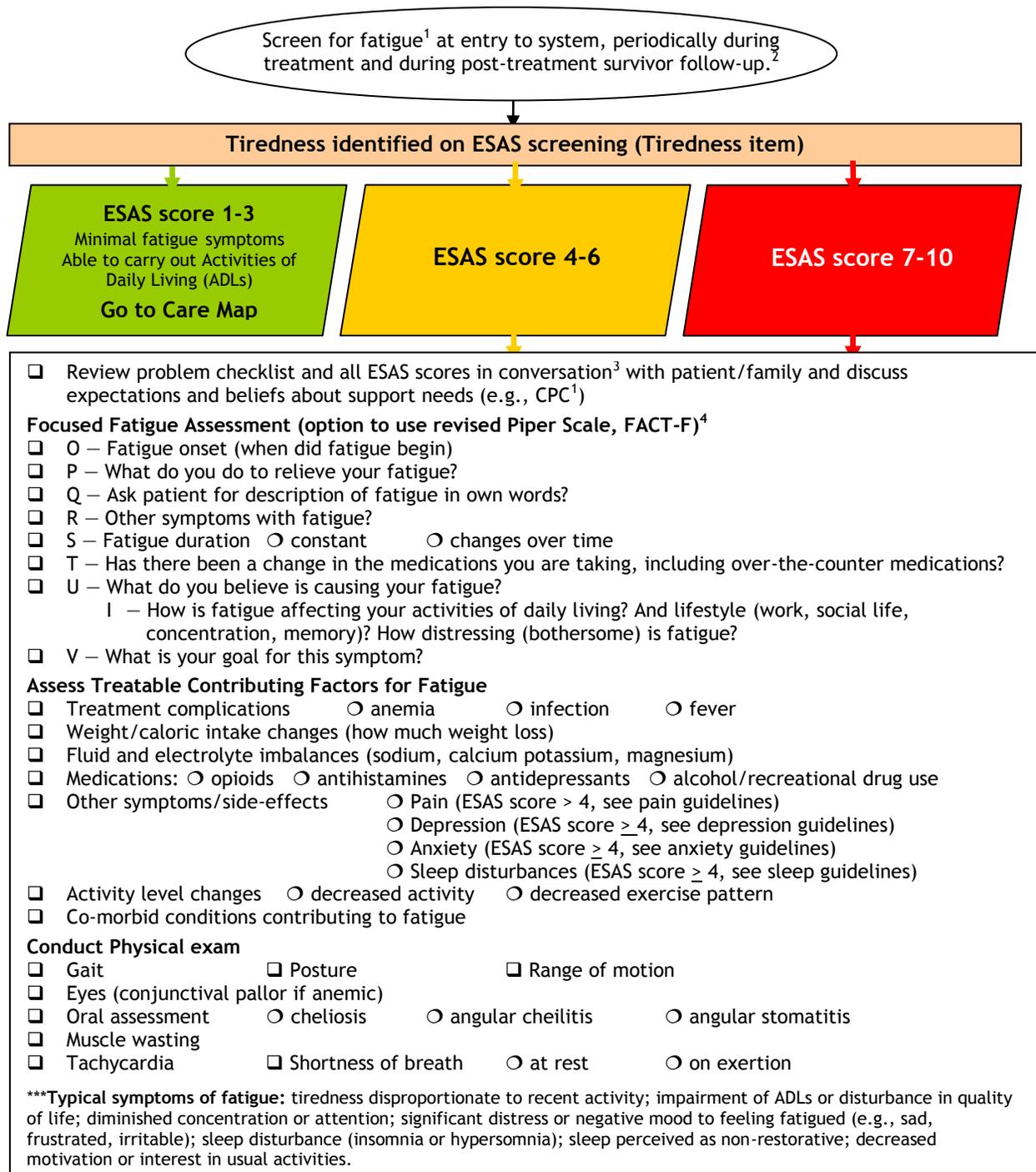
- Address all medical and substance-induced treatable contributing factors first (e.g., pain, depression, anxiety, anemia, sleep disturbance, nutrition, activity level, medication side-effects, and co-morbidities).
- Actively encourage all patients to engage in a moderate level of physical activity during and after cancer treatment (e.g., 30 minutes of moderate intensity activity most days) unless contraindicated. Moderate activity includes aerobic (e.g., fast walking, cycling or swimming) and resistance (e.g., weights) training.
- Additional non-pharmacologic interventions include nutrition consultation, optimizing sleep quality, psychosocial interventions to improve coping with fatigue (e.g., cognitive behavioural therapy, stress management or support groups), relaxation, massage and attention restoring therapy (e.g., exposure to natural environments).
- For patients on active treatment or on long-term follow-up post-treatment who have moderate to severe fatigue, consider referral to rehabilitation (e.g., physical or occupational therapy, and physical medicine).
- All patients should be offered specific education about fatigue prior to the start of treatment and when fatigue is identified, plus advice on strategies (e.g., physical activity, energy conservation, stress reduction and distraction) to manage fatigue.
- At this time, the use of pharmacologic agents to treat cancer-related fatigue is considered experimental and therefore is not recommended (e.g., psychostimulants, sleep medications, trials of low-dose corticosteroids such as prednisone or dexamethasone) except for selected patients at the end of life with severe fatigue.
- Promote ongoing self-monitoring of fatigue levels as a late or long-term cancer or treatment problem in post-treatment survivors.
- For those on active treatment and for those with advanced, progressive disease, repeat ESAS screening and assessment as needed to determine any change in both subjective and objective aspects of fatigue.

**Algorithm: Screening, Assessment and Care –
Cancer-Related Fatigue in Adults with Cancer**



* See following page for detailed algorithm components.

Screening and Assessment - Cancer-Related Fatigue in Adults with Cancer*



* Please see the full guideline for a description of the acronyms used, as well as the copyright and disclaimer prior to use.

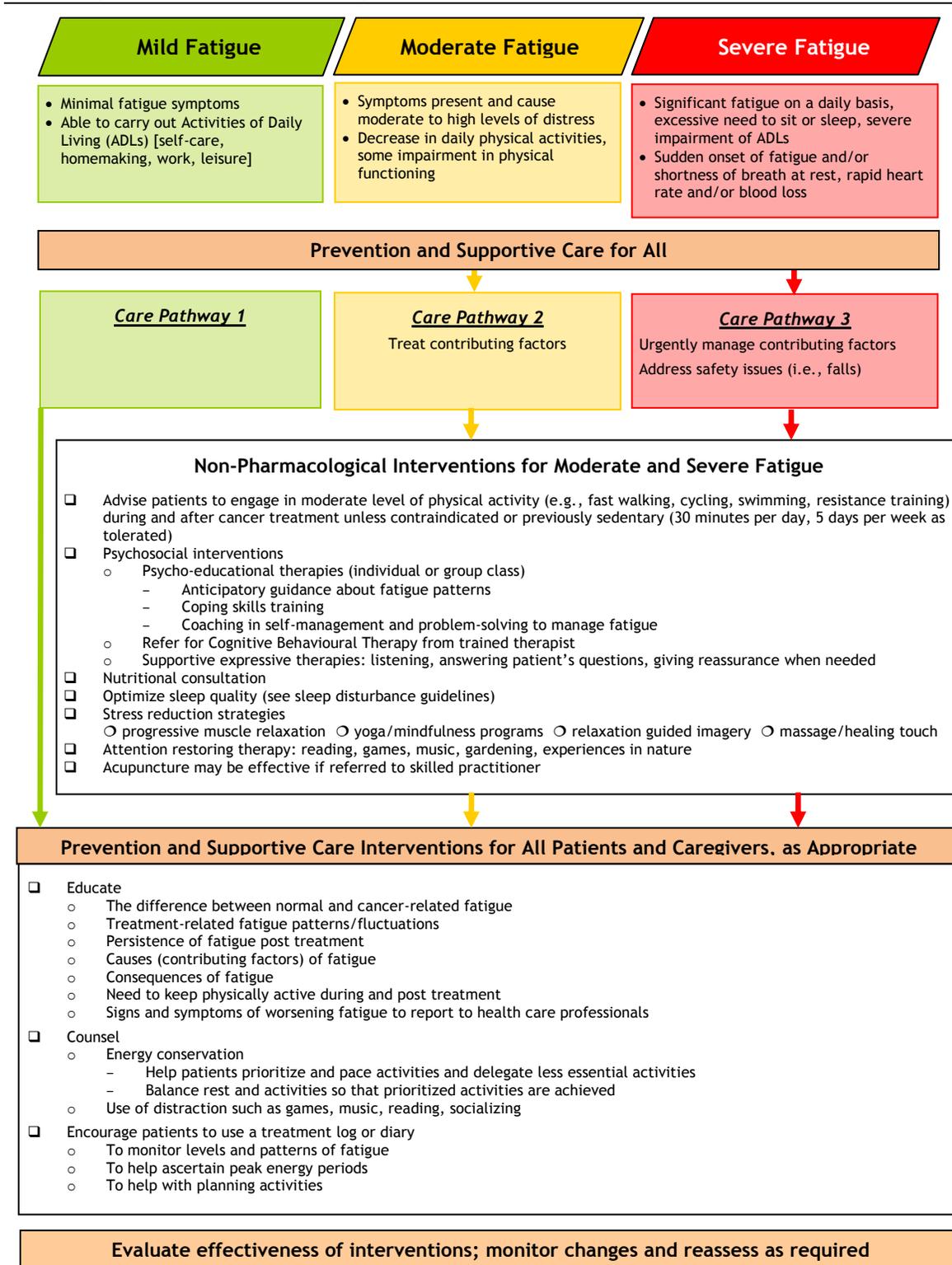
1 Use Screening for Distress Tool (SDT), which includes Edmonton Symptom Assessment System (ESAS) and Canadian Problem Checklist (CPC).

2 At initial diagnosis, start of treatment, regular intervals during treatment, end of treatment, post-treatment or at transition to survivorship, at recurrence or progression, advanced disease, when dying, and during times of personal transition or re-appraisal such as family crisis, during survivorship, when approaching death.

3 The health care team for cancer patients may include surgeons, oncologists, family physicians, nurses, social workers, psychologists, patient navigators and other health care professionals

4 OPQRSTU(I)V Acronym: O = Onset; P = Provoking/Palliating; Q = Quality; R = Region or Radiating; S = Severity & Duration; T = Treatment; U = Understanding/I=Impact; V = Values

Care Map - Cancer-Related Fatigue in Adults with Cancer*



* Please see the full guideline for a description of suggested interventions, as well as the copyright and disclaimer prior to use.

ESAS Screening Tool and Canadian Problem Checklist

Edmonton Symptom Assessment System (ESAS)

Date of Completion: _____ Time: _____

Please circle the number that best describes:

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst possible pain
Not tired	0	1	2	3	4	5	6	7	8	9	10	Worst possible tiredness
Not nauseated	0	1	2	3	4	5	6	7	8	9	10	Worst possible nausea
Not depressed	0	1	2	3	4	5	6	7	8	9	10	Worst possible depression
Not anxious	0	1	2	3	4	5	6	7	8	9	10	Worst possible anxiety
Not drowsy	0	1	2	3	4	5	6	7	8	9	10	Worst possible drowsiness
Best appetite	0	1	2	3	4	5	6	7	8	9	10	Worst possible appetite
Best feeling of wellbeing	0	1	2	3	4	5	6	7	8	9	10	Worst possible feeling of wellbeing
No shortness of breath	0	1	2	3	4	5	6	7	8	9	10	Worst possible shortness of breath
Other problem	0	1	2	3	4	5	6	7	8	9	10	

Completed by: Patient Family
 Health Professional Assisted by family or health professional

Canadian Problem Checklist

Please check all of the following items that have been a concern or problem for you in the past week including today:

Practical:

- Work/School
- Finances
- Getting to and from appointments
- Accommodation

Emotional:

- Fears/Worries
- Sadness
- Frustration/Anger
- Changes in appearance
- Intimacy/Sexuality

Spiritual:

- Meaning/Purpose of Life
- Faith

Social/Family:

- Feeling a burden to others
- Worry about family/friends
- Feeling alone

Informational:

- Understanding my illness and/or treatment
- Talking with the health care team
- Making treatment decisions
- Knowing about available resources

Physical:

- Concentration/Memory
- Sleep
- Weight



Appendix I: Recommendations Matrix

Definitions of Cancer-Related Fatigue

NCCN: “A distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.”¹

ONS: “Cancer-related fatigue is the subjective feeling of tiredness or exhaustion prompted by cancer or cancer treatment that is disproportionate to level of recent exertion; and interferes with activities of daily living.”⁴⁰

1. Screening for Fatigue / Assessing Symptoms

<p>NCCN 2009¹</p>	<p>Screening all patients for fatigue as a vital sign at their initial clinic visit, at appropriate intervals during and/or following cancer treatment, and as clinically indicated (MS-2). Daily screening for inpatients and at subsequent and routine follow-up visits in outpatients (MS-3).</p> <p>Recommended screen: “How would you rate your fatigue on a scale of 0 to 10 over the past 7 days?” (For age > 12 yr: 0=no fatigue, 10=worst fatigue you can imagine).</p> <p>Comments: Recommendation grade 2A. Cut-off scores: None to Mild 0-3, Moderate 4-6, Severe fatigue is 7-10.</p> <p>NCCN provides a list of sources that link to frequently used measures of cancer-related fatigue. For example:</p> <ul style="list-style-type: none"> • Ahlberg, et al. Assessment and management of cancer-related fatigue in adults. <i>The Lancet</i>. 2003;362:640-50. Describes <i>Piper Fatigue Scale</i>, <i>Functional Assessment of Cancer Therapy-Fatigue (FACT-F)</i>, <i>Schwartz Cancer Fatigue Scale</i>, <i>Brief Fatigue Inventory</i>, <i>Cancer Linear Analogue Scale (CLAS)</i>. • Oncology Nursing Society • NCI lists : BFI, FACT-A, FACT-F, Piper Fatigue Self-Report Scale, the Schwartz Cancer Fatigue Scale, Fatigue Symptom Inventory, the Profile of Mood States Fatigue/Inertia Subscale, Lee’s Visual Analogue Scale for Fatigue, Cancer Fatigue Scale (www.cancer.gov/cancertopics/pdq/supportivecare/fatigue/HealthProfessional/, retrieved May 2010).
<p>ONS 2007²</p>	<p>Guideline does not detail screening for cancer-related fatigue symptoms but categorizes screening for treatable etiologic factors “likely to be effective” as a fatigue management strategy. For example, pain, nausea, depression, hypothyroidism, hypogonadism, cardiomyopathy, adrenal insufficiency, pulmonary dysfunction, anemia, sleep disturbance, fluid and electrolyte imbalances, emotional distress and sedation secondary to specific classes of medications (e.g., opiates, antidepressants, antiemetics, antihistamines). ONS¹⁹ discusses assessment and selected clinical measurement tools. ONS¹⁹ also notes that no matter what tool is used, the data should be comparable over different points in time. Examples of tools to assess fatigue symptoms: Brief Fatigue Inventory (BFI), Numeric Rating Scale (also known as ONS Fatigue Scale) and Revised Piper Fatigue Scale.¹⁹</p>

2. Assessment / Further Investigations / Tools (In-Depth Assessment)

<p>NCCN 2009¹</p>	<p>If moderate to severe fatigue identified through screening, health professional trained in fatigue evaluation must conduct a further assessment.</p> <p>Further assessment to include: physical exam, focused history, in-depth fatigue assessment and identification of contributing factors. This second phase should prompt referral to oncology social workers, nutrition experts or mental health professionals, depending on the problems identified.</p> <ul style="list-style-type: none"> • Physical exam • Focused history: disease status, treatment history, medications and treatment response; potential recurrence; review of organ systems. • In-depth fatigue assessment: onset, pattern, duration, change over time, associated or alleviating factors, interference with function (effects on normal functioning and daily living or enjoyable activities), patients assessment of the causes of fatigue. • Contributing factors: pain, emotional distress, sleep disturbance, anemia, nutrition, activity level, medication side effects profile (i.e., sedation) and other co-morbidities. <p>Comments:</p> <p>Nutrition assessment should evaluate weight gain or loss, caloric intake, impediment to nutrition intake, fluid and electrolyte imbalances. Consultation with a nutrition expert may be considered if there are substantial abnormalities.</p> <p>Activity level evaluation to include: current level of activity, changes in exercise and activity patterns, influence of de-conditioning.</p> <ul style="list-style-type: none"> • Can they accomplish normal daily activities? • Can they participate in formal or informal exercise programs? • What is the amount and frequency of exercise? • Has the patient modified exercise or other activity patterns since the development of fatigue? <p><i>Medications:</i> include over-the-counter, herbal, vitamins and other supplements; recent medication changes.</p>
<p>ONS 2007²</p>	<p>Guideline does not provide specific details about assessment. The ONS¹⁹ fatigue chapter suggests that assessment should include a self-report measure (due to subjectivity of cancer-related fatigue) and a detailed assessment of risk and contributing factors plus a clinical measurement tool. ONS¹⁹ also provides some examples of tools (BFI, Numeric Rating Scale [also known as ONS Fatigue Scale], and Revised Piper Fatigue Scale). Key symptoms noted by ONS¹⁹ “assessment guide (checklist format): shortness of breath, heart palpitations, general lack of energy.</p>

3. Treatment and Care Options

NCCN 20091

Treating any contributing factors is an initial step in managing fatigue (e.g., anemia, nutrition, pain). If a patient does not have a treatable contributing factor or continues to experience moderate to severe fatigue after treatment of the contributing factors, interventions should be considered depending on the clinical status of the patient (on active treatment, post-treatment, at the end of life).

Education and counselling are central to effective management. Additional interventions are pharmacological and non-pharmacological, although often a combination must be used.

Re-evaluation and monitoring of fatigue in all patients.

Non-pharmacological

Exercise (Category 1):

In line with the U.S. Surgeon General for all populations, it is reasonable to encourage all patients to engage in 30 minutes of moderate-level activity most days of the week. Individualize the exercise regimen, taking into account age, gender, disease status, cancer type and physical fitness level. Begin with discussions and with low intensity and duration of exercise, progress slowly and modify the exercise plan as conditions change. Timing, at least initially, might be 20- to 30-minute sessions, 3 to 5 times per week.

Comments: Exercise should be used cautiously in the presence of bone metastases, neutropenia, low platelet counts, anemia and fever, weighing risks and benefits (MS-9). In some cases, a modified exercise regimen can be recommended. For example, the neutropenic patient should avoid environments with high risk for infection (e.g., gyms, swimming pools).

Some patients may require referrals to exercise specialists such as physical therapy, physical medicine or rehabilitation for assessment and an exercise prescription. Referrals should be triggered by patients with co-morbidities (e.g., COPD, CVD), recent major surgery, substantial de-conditioning, limited range of movement or anatomical deficits.

Psychosocial Interventions (Category 1):

Patients should be counselled about stress management and strategies for dealing with depression and anxiety. Interventions may include education, support groups, individual counselling, a comprehensive coping strategy, cognitive behavioural therapy (CBT), stress management training or a tailored behavioural intervention.

Comments: Education and counselling should be used for all cancer patients but are particularly beneficial for those beginning fatigue-inducing treatments (e.g., educational interventions providing physical sensory information, anticipatory guidance, coping skills training and coaching) to reduce fatigue levels via self-management.

Attention-Restoring Therapy:

Experiences in natural environments may have a restorative influence.

Nutrition Consultation:

Consultation regarding nutrition abnormalities may be helpful in managing the nutritional deficiencies that result from anorexia, diarrhea, nausea and vomiting. Adequate hydration and electrolyte balance are also essential in preventing and treating fatigue.

Sleep Therapy:

Organized into 4 types: CBT, complementary, psycho-educational and informational, and exercise.

CBT: Stimulus control (maintaining a regular sleep and wake pattern, getting out of bed after 20 minutes if not sleepy), sleep restriction (limiting total time in bed, avoiding naps), sleep hygiene (avoid caffeine, ensure room setting conducive to sleep). Relaxation training may also have positive results.

Complementary: Guided imagery, progressive muscle relaxation and yoga are some examples reported to be promising.



Pharmacological

Pharmacological agents include antidepressants for depression and erythropoiesis stimulating agents for anemia.

NCCN suggest more research is needed on the use of psycho-stimulants (e.g., methylphenidate, modafinil, dexamphetamine) and low-dose corticosteroids (e.g., prednisone, dexamethasone) at end of life for those with severe fatigue. Of note, there are few studies and the optimal dosing and schedule have not been established for use of psycho-stimulants in cancer patients.

Carnitine is a micronutrient involved in energy production at the cellular level. Some chemotherapy agents cause a loss of Carnitine in urine. There is promise for L-carnitine in fatigue management but a large randomized clinical trial is needed.

ONS 2007²

Exercise: The only strategy that ONS classifies as “recommended for clinical practice.” The general pattern of results indicates that exercising several times per week (including walking, cycling, swimming, resistance exercise or a combination of aerobic and resistance exercise) can be effective in reducing fatigue during and following cancer treatment. However, additional research is still needed to systematically assess the safety of exercise (both aerobic exercise and strength training) and to tailor the type, intensity, frequency and duration of physical exercise to different tumour types (i.e., different cancer patient populations) and stages of the disease and treatments.

Energy conservation: Energy conservation is the deliberate and planned management of one’s activities and personal energy resources (balance rest and activity so valued activities can be maintained). Includes planning, delegating and prioritizing activities as well as pacing and resting. Energy conservation is rated “likely to be effective.”

Screening for potential etiologic factors and managing as appropriate: These treatable etiologic factors include pain, nausea and depression; hypothyroidism, hypogonadism, cardiomyopathy, adrenal insufficiency, pulmonary dysfunction, anemia, sleep disturbance, fluid and electrolyte imbalances, and emotional distress; and sedation secondary to specific classes of medications (e.g., opiates, antidepressants, antiemetics, antihistamines) or due to drug-drug interactions. According to the ONS guidelines, management of pain is “likely to be effective” in reducing a cancer patient’s fatigue.

Education and counselling: Education and counselling should be used for all cancer patients but are particularly beneficial for those beginning fatigue-inducing treatments (e.g., anticipatory guidance, coping skills training). Consultation regarding nutritional deficiencies that may result from anorexia, diarrhea, nausea and vomiting associated with cancer or its treatment may be useful.

Measures to optimize sleep quality

Relaxation: Techniques that focus on inducing a relaxed physical and mental state include progressive muscle relaxation.

Massage, healing touch, polarity therapy: Massage and healing touch (combined in some studies with centering, breathing and relaxing music) may be effective in reducing fatigue. Polarity therapy (an intervention hypothesized to promote healing, relaxation and wellbeing by un-blocking and balancing energy flow and re-establishing homeostasis within the human energy field) may be effective in reducing fatigue. Therapeutic modalities that incorporate massage and healing touch may be effective but more studies are needed.



4. Harms and Benefits

Benefits	
NCCN 20091	See the treatment and care interventions/options noted above.
ONS 2007 ²	See the treatment and care interventions/options noted above.
Harms	
NCCN 20091	<p>Pharmacological interventions should be used cautiously and should not be used until treatment and disease-specific morbidities have been characterized and ruled out.</p> <p>Optimal dosing and schedules have not been established for use of pharmacological interventions in cancer patients.</p>
ONS 2007 ²	<p>Exercise: safety and tailoring. Cautions for some populations.</p> <p>In general, there is little research on sleep drugs in cancer patients and a systematic assessment is needed regarding efficacy, safety and possible drug interactions.</p> <p>Correction of anemia with erythropoiesis-stimulating agent (ESA): Better-quality evidence is needed to unequivocally support the use of ESAs solely as an intervention to improve patient-reported outcomes such as fatigue. Although both epoetin and darbepoetin are generally well tolerated, the use of these agents specifically for the management of fatigue must be considered in light of safety issues, including an increased risk of thrombotic events, hypertension and concerns that ESAs may support or extend tumour growth in patients with head and neck cancer, breast cancer, non-small cell lung cancer or cervical cancer.</p> <p>Particular caution should be exercised in the use of ESAs at higher doses, with dosing to target a hemoglobin ≥ 12 g/dl, and with protracted ESA treatment. ESAs may not be indicated to treat anemia associated with malignancy or the anemia of cancer in patients with solid or non-myeloid hematologic malignancies (e.g., myeloma, chronic lymphocytic leukemia, non-Hodgkin lymphoma) or in patients at increased risk for thromboembolic complications. National clinical practice guidelines¹ and the guidance of the U.S. Food and Drug Administration should be used to direct the management of patients receiving ESAs, including decisions about patient monitoring, treatment thresholds, dose reductions, treatment discontinuation and the use of supplemental iron.^{1,19}</p>

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