



Screening, Assessment and Management of Fatigue in Adult Survivors of Cancer: An American Society of Clinical Oncology Clinical Practice Guideline Adaptation

OVERVIEW OF THE ASCO GUIDELINE ADAPTATION PROCESS

ASCO's adapted guidelines are informed by the ADAPTE methodology (1). The objective of the ADAPTE process (<http://www.adapte.org/>) is to take advantage of existing guidelines in order to enhance the efficient production, reduce duplication, and promote the local uptake of quality guideline recommendations. ASCO's adaptation process begins with a literature search to identify candidate guidelines for adaptation.

Adapted guideline manuscripts are reviewed and approved by the ASCO Clinical Practice Guidelines Committee (CPGC). The review includes two parts: methodological review and content review. The methodological review is completed by a member of the CPGC's Methodology Subcommittee and/or by ASCO senior guideline staff using the "Rigour of Development" subscale of the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument (2) (Appendix I). The Rigour subscale consists of seven items that assess the quality of the processes used to gather and synthesize the relevant data, and the methods used to formulate the guideline recommendations. In addition to this methodological review, ASCO staff conducts literature searches to identify relevant studies and additional systematic reviews, meta-analyses, and guidelines that have been published since the guideline being adapted was completed.

The content review is completed by an ad hoc Panel convened by ASCO that includes multidisciplinary representation in medical oncology, palliative oncology, psychiatry, general internal medicine, nursing, guideline methodology, implementation research and patient representation. The Panel is led by two Co-Chairs who have the primary responsibility for the development and timely completion of the guideline adaptation. Recommendations from the source guidelines are extracted into a summary matrix (Appendix II). Final review and approval is completed by the ASCO CPGC after approval by the ASCO Panel.

GUIDELINE SEARCH AND ASCO PANEL CONTENT REVIEW

As mentioned, the adaptation process starts with a literature search to identify candidate guidelines for adaptation on a given topic. 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, meta-analyses and other guidance documents addressing the screening, assessment, and care of cancer-related fatigue. The search of the health literature included MEDLINE, EMBASE, and the Cochrane Library. To identify guidelines not indexed in medical databases, an environmental scan was undertaken of guideline databases such as the National Guideline Clearinghouse and the Standards and Guidelines Evidence (SAGE) Directory of Cancer Guidelines. Finally, websites of organizations developing guidelines and medical specialties were searched and a Google™ search was undertaken to ensure that no guidelines were missed.

The guideline searches used combinations of the following search terms: fatigue, cancer, guideline, review, and survivor. Guidelines and reviews were excluded if they were published before 2009 and if they were written in a language other than English. Guidelines and reviews based on a clearly described systematic literature search were preferred; however, expert consensus guidance was also included for consideration. Narrative reviews and abstracts were excluded.

GUIDELINE DEVELOPMENT PROCESS

The Expert Panel held several teleconferences and corresponded frequently through email; progress on guideline development was driven primarily by the co-chairs along with ASCO staff. The purpose of the Expert Panel calls was for members to contribute content, provide critical review, interpret evidence, and finalize the guideline recommendations based upon the consideration of the evidence. All members of the Expert Panel participated in the preparation of the draft guideline document, which was then disseminated for external review and submitted to the *Journal of Clinical Oncology (JCO)* for peer review and publication. All ASCO guidelines are reviewed and approved by the ASCO Clinical Practice Guideline Committee prior to publication.

Appendix I: Rigour of Development Subscale of the Appraisal of Guidelines for Research and Evaluation II (AGREE II) Instrument (12)

Rigour of Development Subscale Item

Systematic methods were used to search for evidence.

The criteria for selecting the evidence are clearly described.

The strengths and limitations of the body of evidence are clearly described.

The methods used for formulating the recommendations are clearly described.

The health benefits, side effects and risks have been considered in formulating the recommendations.

There is an explicit link between the recommendations and the supporting evidence.

The guideline has been externally reviewed by experts prior to its publication.

A procedure for updating the guideline is provided.

NOTE: Each subscale item is rated on a 7-point scale from 1 (strongly disagree) to 7 (strongly agree). The score for the Rigour of Development domain is calculated by summing the scores across individual items in the domain and across all raters, subtracting the lowest possible score for that domain ($1 \times \# \text{ items} \times \# \text{ of raters}$), then standardizing the total score as a proportion of the maximum possible score ($7 \times \# \text{ items} \times \# \text{ raters}$) minus the lowest possible score.

Appendix II: Recommendation Matrix

Domain	Pan-Canadian Guideline	NCCN Guidelines
Developer(s)	Collaborative partnership between the Canadian Partnership Against Cancer (CPAC) and the Canadian Association of Psychosocial Oncology (CAPO). CAPO is the steward of this guideline.	National Comprehensive Cancer Network
Year Published	February 2011	November 21, 2012 (Fatigue) March 8, 2013 (Survivorship)
Literature Search Currency	December 2009	N/A
Methodology	<ul style="list-style-type: none"> • ADAPTE Methodology <ul style="list-style-type: none"> ○ Included systematic review ○ Guidelines adapted: NCCN 2009 and ONS supplementary systematic reviews • AGREE II • Expert Consensus 	Expert Consensus
Literature Search	MEDLINE, EMBASE, CINAHL, the Cochrane Library, the Guidelines International Network (www.g-i-n.net), the National Guidelines Clearinghouse (www.guideline.gov), "SAGE" Inventory of Cancer Guidelines (www.cancerview.ca), environment scan (e.g. Website search of NICE, SIGN, NCCN, CCO)	N/A

Domain	Pan-Canadian Guideline	NCCN Fatigue	NCCN Survivorship
Clinical 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)?	N/A	N/A
Definition	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 that is not relieved by rest and interferes with usual daily activities.	Cancer-related fatigue is 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.	Same as NCCN Fatigue, plus: These guidelines are focused on fatigue after the completion of cancer treatment and/or in patients who are in clinical remission.

Domain	Pan-Canadian Guideline	NCCN Fatigue	NCCN Survivorship
Screening	<ul style="list-style-type: none"> - 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. <p><i>(Based on the expert consensus of the National Advisory Group and informed by NCCN category 2A, ONS expert opinion*)</i></p>	<p>Screen every patient for the presence or absence of fatigue (see algorithm, pg. 7)</p> <ol style="list-style-type: none"> 1. If fatigue is present, a quantitative or semiquantitative assessment should be performed and documented. For example, on a 0 to 10 numeric rating scale (zero = no fatigue and 10 = worst fatigue imaginable), mild fatigue is indicated as a score of 1 to 3, moderate fatigue as 4 to 6, and severe fatigue as 7 to 10. 2. If the screening process determines that fatigue is absent or at a mild level, the patient and family should receive education and common management strategies for fatigue. 3. Periodic re-screening and re-evaluation are recommended. Inpatients should be screened daily and outpatients screened at subsequent routine and follow-up visits. 4. It should be emphasized that survivors or patients who have completed treatment must still be monitored for fatigue because fatigue may exist beyond the period of active treatment. 	<p>Sample survivorship care survey (pg. 8):</p> <ol style="list-style-type: none"> 1. Do you feel persistent fatigue despite a good night's rest? Yes/No 2. Does fatigue interfere with your usual activities? Yes/No 3. How would you rate your fatigue on a scale of 0 (none) to 10 (extreme) over the past month? 0-10 <p>SCREENING (algorithm pg. 28): Screen every patient for fatigue as vital sign at regular intervals.</p> <p>Severity: 0-10 scale (0 = no fatigue, 10 = worst fatigue you can imagine) or none, mild, moderate, severe.</p>

Domain	Pan-Canadian Guideline	NCCN Fatigue	NCCN Survivorship
Comprehensive and Focused Assessment	<ol style="list-style-type: none"> 1. Screen for fatigue and if moderate or severe fatigue is detected through screening (ESAS tiredness greater than 4), individuals should have a comprehensive and focused assessment to identify the nature and extent of the fatigue symptoms. 2. Medical and substance-induced causes of fatigue should be ruled out (e.g., anemia, infection, nutrition deficiencies, medication or treatment side effects). 3. 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. 4. 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, comorbidities), a physical exam, a review of symptoms and a self-assessment of causes contributing to fatigue. 5. Promote open communication among 	<p>Focused history and physical examination:</p> <ul style="list-style-type: none"> - When fatigue is rated as moderate to severe, with a score 4-10, a more focused history and physical examination should be conducted as part of the primary evaluation phase as outlined in the algorithm. <p>Focused history:</p> <ol style="list-style-type: none"> 1. Assessment of patient’s current disease status, the type and length of treatment and the patient’s response to treatment - Rule out recurrence or progression of malignancy - Prescription medications/OTCs and supplements 2. Review of systems 3. In-depth fatigue assessment - Onset, pattern, duration - Change over time - Associated or alleviating factors - Interference with function 4. Social support status/availability of caregivers <p>Assessment of treatable contributing factors:</p>	<p>History and physical (H&P):</p> <ol style="list-style-type: none"> 1. Focused fatigue history <ul style="list-style-type: none"> - Onset, pattern, duration - Change over time - Associated or alleviating factors - Interference with function 2. Evaluate disease status <ul style="list-style-type: none"> - Evaluate risk of recurrence based on stage, pathologic factors, and treatment history - Perform review of systems to determine if other symptoms substantiate suspicion for recurrence 3. Assessment of treatable contributing factors: <ul style="list-style-type: none"> - Comorbidities <ul style="list-style-type: none"> • Alcohol/substance abuse • Cardiac dysfunction • Endocrine dysfunction (e.g., hypothyroidism, hypogonadism, adrenal insufficiency) • Pulmonary dysfunction • Renal dysfunction • Anemia • Arthritis

the patient, family and the clinical team to facilitate discussions about the experience of fatigue and its effects on daily functioning.

6. 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).

(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)*

- Medication/side effects (e.g., sedation)
- Pain
- Emotional distress (depression, anxiety)
- Anemia
- Sleep disturbance (e.g., insomnia, narcolepsy, obstructive sleep apnea, restless leg syndrome)
- Nutritional deficits/imbalance
- Weight/caloric intake changes
- Fluid electrolyte imbalance: sodium, potassium, calcium, magnesium
- Decreased functional status (decreased level of activity, deconditioning)
- Comorbidities
- Alcohol/substance abuse
- Cardiac dysfunction
- Endocrine dysfunction (e.g., hot flashes, hypothyroidism, hypogonadism, adrenal insufficiency)
- Gastrointestinal dysfunction
- Hepatic dysfunction
- Infection
- Neurologic dysfunction
- Pulmonary dysfunction
- Renal dysfunction

All recommendations are category 2A unless otherwise indicated.

- Medications (consider persistent use of sleep aids, pain medications, or antiemetics)
- Emotional distress (screen for anxiety and depression)
- sleep disturbances (e.g., insomnia, sleep apnea, vasomotor symptoms, restless leg syndrome)
- Pain
- Nutritional issues
 - Weight/caloric intake changes
 - Deconditioning

As a shared responsibility, the clinical team must decide when referral to an appropriately trained professional is needed.

Laboratory Evaluation:
Consider performing laboratory evaluation based on presence of other symptoms, onset, and severity of fatigue.

CBC with differential:

- Compare end-of-treatment hemoglobin/hematocrit with current values
- Assess other cell lines (WBC

and platelets)

Comprehensive metabolic panel:

- Assess electrolytes
- Assess hepatic and renal function

Endocrinologic evaluation:

- TSH
- Consider more comprehensive evaluation or referral to specialist if other symptoms present

Imaging:

1. Consider radiologic assessment if high risk of disease recurrence OR if accompanying signs and symptoms suggest presence of metastatic disease
2. Consider ECHO or MUGA for patients treated with an anthracycline, trastuzmab, bevacizumab, or other VEGF or HER2 targeted therapy
3. Consider chest x-ray and oxygen saturation testing for pulmonary complaints

All recommendations are category 2A unless otherwise indicated.

Domain	Pan-Canadian Guideline	NCCN Fatigue	NCCN Survivorship
Treatment and Care Options	<ol style="list-style-type: none"> 1. 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 comorbidities). 2. 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. 3. 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). 4. For patients on active treatment or on long-term follow-up post- 	<p>Patient/Family Education and Counseling</p> <ul style="list-style-type: none"> - Information about known pattern of fatigue during and following treatment - Self-monitoring of fatigue levels <p>General Strategies for Management of Fatigue</p> <ul style="list-style-type: none"> - Self monitoring of fatigue levels - Energy conservation <ul style="list-style-type: none"> - Set priorities - Pace - Delegate - Schedule activities at times of peak energy - Labor saving devices (see algorithm for details) - Postpone nonessential activities - Limit naps to <1 hour to not interfere with night-time sleep quality - Structured daily routine - Attend to one activity at a time - Use distraction (e.g., games, music, reading, socializing) 	<p>Treat contributing factors</p> <ol style="list-style-type: none"> 1) Medication/side effects 2) Pain (see SPAIN-1) 3) Emotional distress (See link to guidelines) 4) Anemia <ul style="list-style-type: none"> - Treat iron B12 folate deficiency, if present - Consider referral/further evaluation for persistent anemia or cytopenias 5) Sleep disturbance (See SSD-1) 6) Nutritional deficit/imbalance 7) Comorbidities <p>Patient/Family Education and Counseling</p> <ul style="list-style-type: none"> - Information about known pattern of fatigue during and following treatment - Self-monitoring of fatigue levels - Energy conservation <ul style="list-style-type: none"> o Set priorities o Pace o Schedule activities at times of peak energy

treatment who have moderate to severe fatigue, consider referral to rehabilitation (e.g., physical or occupational therapy, and physical medicine).

5. 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.
6. 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.
7. Promote ongoing self-monitoring of fatigue levels as a late or long-term cancer or treatment problem in post-treatment survivors.
8. 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

Specific Interventions – Non-pharmacologic

- Activity enhancement
- Physically-based therapies
- Psychosocial interventions
- Nutritional consultation
- Cognitive behavioral therapy

Specific Interventions - Pharmacologic

- Consider psychostimulants (methylphenidate or modafinil) after ruling out other causes of fatigue
- Treat for pain, emotional distress, and anemia as indicated per NCCN supporting care guideline
- Optimize treatment for sleep dysfunction, nutritional deficit/imbalance, and comorbidities
- Repeat screening and evaluation
- Supplements

End of life recommendations (*not listed, outside scope*)

All recommendations are category 2A unless otherwise indicated.

Physical Activity

- 1) Maintain adequate levels of physical activity (category 1) (See SE1, SE-4)
- 2) Survivors at higher risk of injury (e.g., those living with neuropathy, cardiomyopathy, lymphedema, or other long-term effects of therapy other than comorbidities) should be referred to a physical therapist or exercise specialist
- 3) Make use of local resources to help patients increase exercise
 - Exercise classes at cancer centers
 - Community programs focused on cancer survivors
 - For patients with severe fatigue interfering with function, consider referral to a physical therapist or physiatrist
- 2) Actively encourage all patients to engage in a moderate level of physical activity 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.

Other Behavioral Interventions^c

objective aspects of 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)*

- 1) Psychosocial interventions (category1)
 - Cognitive behavioral therapy/Behavioral therapy (category 1)
 - Psycho-educational therapies/Educational therapies (category1)
 - Supportive expressive therapies (category1)
- 2) Nutrition consultation
- 3) Cognitive behavioral therapy for sleep (category 1)
 - Stimulus control
 - Sleep restriction
 - Sleep hygiene

Pharmacologic

All recommendations are category 2A unless otherwise indicated.

References

- 1) ADAPTE Collaboration (2009). The ADAPTE process: resource toolkit for guideline adaptation. Version 2.0. [cited 2013 July 18]. Available from: <http://www.g-i-n.net>
- 2) Brouwers M, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, Fervers B, Graham ID, Grimshaw J, Hanna S, Littlejohns P, Makarski J, Zitzelsberger L for the AGREE Next Steps Consortium. AGREE II: Advancing guideline development, reporting and evaluation in healthcare. *Can Med Assoc J.* 2010. Dec 2010; 182:E839-842