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Management of Fatigue in Adult Survivors of Cancer: ASCO–Society for Integrative Oncology Guideline Update

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ABSTRACT

ASCO–Society for Integrative Oncology (SIO) Guidelines provide recommendations with comprehensive review and analyses of the relevant literature for each recommendation, following the guideline development process as outlined in the ASCO Guidelines Methodology Manual. ASCO-SIO Guidelines follow the ASCO Conflict of Interest Policy for Clinical Practice Guidelines.

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PURPOSE To update the ASCO guideline on the management of cancer-related fatigue (CRF) in adult survivors of cancer.

METHODS A multidisciplinary panel of medical oncology, geriatric oncology, internal medicine, psychology, psychiatry, exercise oncology, integrative medicine, behavioral oncology, nursing, and advocacy experts was convened. Guideline development involved a systematic literature review of randomized controlled trials (RCTs) published in 2013-2023.

RESULTS The evidence base consisted of 113 RCTs. Exercise, cognitive behavioral therapy (CBT), and mindfulness-based programs led to improvements in CRF both during and after the completion of cancer treatment. Tai chi, qigong, and American ginseng showed benefits during treatment, whereas yoga, acupressure, and moxibustion helped to manage CRF after completion of treatment. Use of other dietary supplements did not improve CRF during or after cancer treatment. In patients at the end of life, CBT and corticosteroids showed benefits. Certainty and quality of evidence were low to moderate for CRF management interventions.

RECOMMENDATIONS Clinicians should recommend exercise, CBT, mindfulness-based programs, and tai chi or qigong to reduce the severity of fatigue during cancer treatment. Psychoeducation and American ginseng may be recommended in adults undergoing cancer treatment. For survivors after completion of treatment, clinicians should recommend exercise, CBT, and mindfulness-based programs; in particular, CBT and mindfulness-based programs have shown efficacy for managing moderate to severe fatigue after treatment. Yoga, acupressure, and moxibustion may also be recommended. Patients at the end of life may be offered CBT and corticosteroids. Clinicians should not recommend L-carnitine, antidepressants, wakefulness agents, or routinely recommend psychostimulants to manage symptoms of CRF. There is insufficient evidence to make recommendations for or against other psychosocial, integrative, or pharmacological interventions for the management of fatigue.

Additional information is available at www.asco.org/survivorship-guidelines.

ACCOMPANYING CONTENT

Appendix

Data Supplement

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INTRODUCTION

Cancer-related fatigue (CRF) is one of the most common and distressing side effects of cancer diagnosis and treatment. It is a persistent, often overwhelming feeling of physical, mental, and/or emotional exhaustion and differs from fatigue caused by exertion as it is not necessarily relieved by rest or sleep. CRF can affect people with cancer at any stage of the disease and at any time in the cancer trajectory, from diagnosis through long-term survivorship. Prevalence estimates indicate that 30%-60% of patients experience moderate to severe fatigue during treatment and 20%-30% continue to experience fatigue for months or years after treatment completion.[1-3] CRF has debilitating effects on all aspects of quality of life, including physical, emotional, social, and occupational functioning.[4] The etiology of CRF is complex and multifaceted, and it can be challenging to identify contributing factors since multiple causes frequently exist simultaneously, often with additive effects.[5] As another layer of complexity, the factors that precipitate fatigue may not be the same ones that lead to its persistence.[2,6] Multiple factors contribute to CRF, including the cancer itself, effects of cancer treatments, physical and psychological comorbidities (eg, depression), other physical symptoms (eg, pain, sleep disturbance), physical inactivity and deconditioning, and cognitive, emotional, and behavioral responses to diagnosis and treatment. Despite the high prevalence of CRF, patient management is often complicated by the misconception held by patients, their caregivers, and even clinical staff that fatigue is an inevitable and unavoidable consequence of cancer and its treatment.[5]

The purpose of this guideline update is to gather and examine the evidence published since the 2014 guideline by Bower et al[7] and offer a series of updated recommendations for management of CRF. Although the original guideline considered fatigue in patients with cancer after completion of primary treatment, the Expert Panel recognizes that the treatment landscape has changed and an increasing number of patients are on extended treatments, with the advent of targeted therapy and immunotherapy. As such, this update will encompass all adult cancer survivors, defined as beginning from the time of diagnosis onward. It addresses fatigue symptoms occurring at any stage, spanning from diagnosis through to end of life, and applies to individuals undergoing active cancer treatment and those who have completed their treatment. As screening and assessment for fatigue is improving, the research question was revised by the reconvened panel to focus on management and treatment of CRF only. Readers are encouraged to review the original guideline recommendations on screening and assessment, which the panel deemed as still relevant.[7]

GUIDELINE QUESTIONS

This clinical practice guideline addresses one overarching clinical question: What are the recommended treatment approaches in the management of adult cancer survivors with symptoms of CRF?

TARGET POPULATION AND AUDIENCE

Target Population

Survivors of adult cancer, defined as starting from the time of diagnosis to any time thereafter, with cancer-related fatigue.

Target Audience

Health care providers including oncologists, primary care providers, psychologists, psychiatrists, psychosocial professionals, exercise oncology professionals, rehabilitation professionals, integrative medicine practitioners, nurses, and others involved in the delivery of care for survivors as well as patients, family members, and caregivers of patients and survivors of cancer.

METHODS

Guideline Development Process

This systematic review-based guideline product was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise (Appendix Table A1).

The recommendations were developed by using an updated systematic review for evidence published after the previous guideline. PubMed was searched from January 2013 through to October 2023 for phase II and phase III randomized controlled trials (RCTs). The reference lists of all identified articles were also hand searched for additional studies.

As the guideline was being developed, concerns were raised that the updated body of evidence alone was inadequate to inform some recommendations. While the focus of the systematic review was deliberately placed on identifying and incorporating new evidence from the updated literature search, older trials that met search criteria were identified through existing systematic reviews or meta-analyses and considered when necessary to provide a more comprehensive evidentiary base from which to develop recommendations. When older studies aligned and supported the updated recommendations, they were not discussed further in this update. An aim of the update is to emphasize the contemporaneity of the research landscape and not provide an exhaustive discussion of older studies.

Articles were selected for inclusion in the systematic review on the basis of the following criteria.

- Population: adult patients with CRF under active cancer treatment and survivors after completion of treatment

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- Interventions: any pharmacologic or nonpharmacologic intervention used for the management of CRF in adult patients and survivors
- Comparisons: placebo (pharmaceutical, behavioral), sham treatment, or treatment versus no treatment (eg, waitlist control, treatment as usual)
- Outcomes: patient-reported fatigue, assessed using a valid and acceptable fatigue measure
- Sample size: at least 50 participants
- Time: from cancer diagnosis onward

Because of the overlapping scope and subtle differences in inclusion criteria, systematic reviews and meta-analyses were not included. Instead, the evidence base relied only on original RCTs rather than attempting to reconcile outcomes from numerous comparable, but slightly different, systematic reviews. Phase III RCTs that report the treatment effect on fatigue as a primary or secondary outcome were qualified for inclusion. Phase II RCTs, defined here as trials that included <100 participants, were considered for inclusion only if fatigue was a primary outcome.

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, and narrative reviews; and (3) published in a non-English language.

Ten full panel meetings were held, and members were asked to provide ongoing input on the updated guideline development protocol, quality and assessment of the evidence, generation of recommendations, draft content, and review and approve drafts during the entire development of the guideline. ASCO staff met routinely with the Expert Panel cochairs and corresponded with the panel via e-mail to coordinate the process to completion.

The language used to develop the recommendations reflects, in part, whether the evidence base comprised mostly studies limiting eligibility to individuals screened and diagnosed with CRF. When the supporting evidence included studies that restricted trial entry to patients with fatigue only, the phrase "manage symptoms" was used. If instead cancer survivors with a range of baseline levels of CRF were included, "reduce severity" phrasing was used. Ratings for type and strength of the recommendation and evidence quality are provided with each recommendation, defined in Appendix Table A2. The quality of the evidence for each outcome was assessed using some criteria from the Cochrane Risk of Bias tool, the Physiotherapy Evidence Database Scale, and elements of the GRADE quality assessment and recommendations development process.[8-10] Using components from these tools to assess study quality and the risk of bias in the behavioral intervention trials enabled a more precise evaluation of how particular biases might have affected the outcome measures. GRADE quality assessment labels, also known as certainty of the evidence (ie, high, moderate, low, very low), were assigned for each intervention by the project methodologist in collaboration with the Expert Panel cochairs and reviewed by the full Expert Panel. In general, the effectiveness of a specific intervention was considered substantiated when two or more independently conducted, robustly designed, RCTs with adequate sample sizes consistently report statistically significant effects. Expert opinion agreed that a well-designed RCT with over 100 participants could suffice for a recommendation if it investigated an established, reproducible intervention, the desirable effects outweigh the undesirable effects, and acceptance and feasibility were expected to be high.

All funding for the administration of the project was provided by ASCO.

Guideline Review and Approval

The draft recommendations were released to the public for open comment from November 29 through December 13, 2023. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree. See comments" were captured for every proposed recommendation with 149 written comments received for all 24 recommendations. A total of 90.9% of the 31 respondents either agreed or agreed with slight modifications to the recommendations, and 9.1% of the respondents disagreed. Expert Panel members reviewed comments from all sources and determined whether to maintain the original draft recommendations, revise with minor language changes, or consider major recommendation revisions.

All changes were incorporated into the final manuscript before ASCO Evidence-Based Medicine Committee (EBMC) and Society for Integrative Oncology (SIO) Clinical Practice Guidelines Committee (CPGC) review and approval. All ASCO and SIO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO EBMC and SIO CPGC before submission to the *Journal of Clinical Oncology* for editorial review and consideration for publication.

Guideline Updating

The ASCO and SIO Expert Panel and guidelines staff will work with cochairs to keep abreast of any substantive updates to the guideline. On the basis of formal review of the emerging literature, ASCO and SIO will determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

RESULTS

Characteristics of Studies Identified in the Updated Literature Search

A total of 2,169 studies were identified in the literature search. After applying the eligibility criteria, 96 RCTs remained and, along with 17 older trials (published before 2013) identified through existing systematic reviews or

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meta-analyses and included because of a paucity of new evidence, formed the evidentiary basis for the guideline recommendations.[11-40,41–60,61-85,86–115,116-124] Table 1 includes a breakdown of the 113 included studies by intervention category. Studies were also classified on the basis of whether participants were in active treatment, post-treatment, or the end-of-life or palliative care setting. Characteristics and results of the included studies are given in the Data Supplement (Tables S1-S4, online only).

The studies exhibit heterogeneity in the following aspects: (1) participant characteristics, including disease location, stage, ongoing oncologic treatment, and intent (curative versus palliative); (2) assessment tools and timing; (3) intervention features, including delivery method, content, duration, and fidelity; (4) control groups; (5) participant adherence to interventions, along with follow-up practices; and (6) adequacy of sample size, rigor of analytic methods, and risk of bias. The sample size of all included trials ranged from 50 to 877. Overall, the diversity in the included studies precluded a quantitative analysis and, as such, a qualitative review was performed.

Participant Characteristics

Many of the trials included patients with diverse cancer types and stages although approximately 36% of the studies focused exclusively on individuals with breast cancer. A total of 13% of studies focused on individuals with advanced cancer and/or those at the end of life.[37-39,65,69,105,106,109-113,118,119] Across included studies, the mean age of participants spanned from 45 to approximately 70 years, and the proportion of female participants varied, ranging from 11.5% to 100%, except for three trials exclusively involving men with prostate cancer.[15,41,46] No trials reported on gender versus biologic sex. In the context of US-based studies, reporting on ethnic and/or racial characteristics was variable in specificity and numbers. In studies that reported race, the participation of individuals other than White varied from 0% to 62%, with 43 studies reporting <30% ethnic and/or racial minoritized participation. Notably, most non–US-based studies did not provide information on the ethnic and/or racial characteristics of the participants.

Fatigue Eligibility Criterion and Outcome Assessment

Of the 113 RCTs, fatigue screening criteria of some type were used for study eligibility in 49 studies, whereas four additional studies were screened for a related symptom such as depression. Fatigue was the primary outcome in 93 trials and a secondary outcome in 20. Different fatigue measures were used and most often included the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) scale, Brief Fatigue Inventory (BFI), Multidimensional Fatigue Inventory (MFI-20), and Multidimensional Fatigue Symptom Inventory—Short Form (MFSI-SF) scales.

Intervention Characteristics

Interventions in the included studies were classified as exercise, psychosocial- and mindfulness-based, other integrative medicine modalities (eg, acupuncture, acupressure, dietary supplements, etc), and pharmacologic. The majority of nonpharmacologic interventions were delivered face-to-face although six studies involved remote options including telephone[67] or virtual, online sessions.[54,61,62,65,72]

Comparison Conditions

For the non-pharmacologic studies, the intervention arm was most often compared with a treatment-as-usual (26 studies) or waitlist control (16 studies); however, 23 studies included two or more active treatment arms. Attention controls were included in four trials and placebo was used in seven trials investigating supplements. All pharmacologic trials were placebo controlled.

Evidence Quality Assessment

The quality of evidence was assessed for all 113 included studies. This rating includes factors such as study design, fatigue as an eligibility criterion (in the post-treatment setting), consistency of results, directness of evidence, and magnitude of effect, assessed by one reviewer. Evidence quality ratings are provided in Table 2. Refer to Appendix Table A2 for definitions for the quality of the evidence, and the Methodology Manual for more information.

TABLE 1. Included Studies

Topic	Number of Studies	Summary of Results[a]
Nonpharmacologic interventions		
Exercise	40[b] RCTs[11-50]	Data Supplement (Table S1)
Psychosocial and mindfulness interventions	32[b] RCTs[39,51-75,120-125]	Data Supplement (Table S2)
Integrative medicine interventions	24 RCTs[76-99]	Data Supplement (Table S3)
Pharmacologic interventions	18 RCTs[100-115,118,119]	Data Supplement (Table S4)

Abbreviation: RCT, randomized controlled trial.
[a]Available in the Data Supplement.
[b]One trial included in both sections (Poort et al[39]).

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TABLE 2. GRADE Summary Table

	Summary of Findings		Certainty Assessment	
Therapy or Modality	No. Studies No. of Participants Screened for Fatigue Follow-up Positive/Negative Results	Intervention	Risk of Bias	Quality of Evidence Notes
Patients during cancer treatment				
Exercise	17 RCTs, N = 2,606 2/17 trials screened for fatigue Follow-up: range, 6 weeks to 1 year 13 Exercise *v* (WL or attention) Control 9/13 studies showed benefit Four trials compared different exercise interventions 2/4 studies showed positive results 1 study reported some short-term benefit of higher *v* lower intensity 1 study showed that addition of resistance led to improvement over control	Aerobic (cardio) with or without resistance training with or without diet High- and low-to-moderate-intensity Walking program Resistance training	Intermediate	Inconsistency not serious 12/17 studies in patients with breast cancer 60% of studies adequately powered for fatigue Moderate certainty of evidence Strength of the recommendation is strong on the basis of a large body of evidence showing consistent benefits for CRF Benefits have consistently been seen with interventions that combine aerobic and resistance training, as well as resistance only interventions. Some studies have shown benefits for home-based walking, but results are less consistent
Tai Chi or Qigong	Five RCTs (two tai chi, two qigong, one both), N = 498 1/5 trials screened for fatigue Follow-up: range, 21 days to 12 weeks 4/5 positive trials Negative trial for intervention that included both; study was underpowered	Qigong and/or tai chi Baduanjin qigong Chan-Chuang qigong	Intermediate	Inconsistency not serious Indirectness not serious Moderate certainty of evidence Strength of recommendation is strong on the basis of positive trials showing consistent benefits for CRF
Yoga	Three RCTs, N = 360 0/3 trials screened for fatigue Follow-up: range, 1 week to 12 months 1/3 positive trials	Tibetan yoga Eischens yoga Dru yoga All have hatha yoga component	High	Inconsistency; Additional large-scale trials needed to resolve ambiguity stemming from the presence of both positive and negative trials Indirectness not serious Insufficient certainty of evidence
CBT	Three RCTs, N = 480 1/3 trials screened for fatigue Follow-up: range, 12 weeks to 6 months All positive trials	CBT alone CBT + hypnosis	Intermediate	Inconsistency not serious Indirectness not serious Moderate certainty of evidence Strength of recommendation is strong on the basis of positive trials showing consistent benefits for CRF
Mindfulness-based programs	Three RCTs[a] N = 404 0/3 trials screened for fatigue Follow-up: 8 to 14 weeks All positive trials	MBSR Mindfulness meditation	Intermediate	Inconsistency not serious Indirectness not serious Moderate certainty of evidence Strength of recommendation is strong on the basis of positive trials showing consistent benefits for CRF
Psychoeducation	Three RCTs, N = 504 0/3 trials screened for fatigue Follow-up: up to 21 weeks 2/3 positive trials	Educational interventions	Intermediate	Inconsistency not serious Indirectness not serious Moderate certainty of evidence Strength of recommendation is conditional based on heterogeneity in studies in terms of type of education, length of intervention, and comparator used
Solution-focused therapy	One RCT, N = 124 Not screened for fatigue Positive trial	Identifying and implementing effective ways of coping with fatigue	Low	Single study, patients with CRC, not screened for fatigue Indirectness not serious Insufficient certainty of evidence on the basis of single trial of experimenter-developed intervention
PMR	One RCT, N = 92 Not screened for fatigue Follow-up: 12 weeks Positive trial compared with single time attention-matched breast cancer education control group	PMR, 20 min/day	Low	Single study, <100 patients, all with breast cancer, not screened for fatigue Indirectness not serious Insufficient certainty of evidence
Acupressure	Two RCTs, N = 157 1/2 trials screened for fatigue Follow-up: 9 weeks to 5 months One positive, one negative trial	Acupressure at ST36 SP6 LI4 KI3	Intermediate	Inconsistency. Additional large-scale trials needed to resolve ambiguity stemming from the presence of both positive and negative trials Indirectness not serious Insufficient certainty of evidence

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TABLE 2. GRADE Summary Table (continued)

	Summary of Findings		Certainty Assessment	
Therapy or Modality	No. Studies No. of Participants Screened for Fatigue Follow-up Positive/Negative Results	Intervention	Risk of Bias	Quality of Evidence Notes
Coenzyme Q10	One RCT, N = 236 Not screened for fatigue Follow-up: 24 weeks Negative trial	CoQ10 (100 mg three times per day)	Intermediate	Single study, patients with breast cancer, not screened for fatigue Indirectness not serious Insufficient certainty of evidence
Ginseng	Four RCTs,[a] N = 974 2/4 trials screened for fatigue Follow-up: range, 29 days to 16 weeks Three positive, one negative trial Negative trial in patients with advanced cancer	Panax ginseng extract (400 mg twice daily) Korean red ginseng (1,000 mg twice daily) Fermented red ginseng extract (3,000 mg total daily dose) American ginseng (Panax quinquefolius) (1,000 mg twice daily)	Intermediate	Inconsistency not serious Indirectness not serious Heterogeneity in the method of fatigue assessment and intervention type, formulation, and dosing thereby lowering the certainty of evidence Strength of recommendation is conditional on the basis of heterogeneity in studies in terms of screening for fatigue, preparations, and dosing of ginseng
Guarana	Two RCTs, N = 147 2/2 trials screened for fatigue Follow-up: 21 days One positive, one negative trial	Guarana (50 mg twice daily, 12.5 mg twice daily, 7.5 mg twice daily)	Intermediate	Inconsistency. Additional large-scale trials needed to resolve ambiguity stemming from the presence of both positive and negative trials Indirectness not serious Small total sample size Heterogeneity in intervention dosing Insufficient certainty of evidence
L-carnitine	One RCT, N = 376 Screened for fatigue Follow-up: 4 weeks Negative trial	L-carnitine (1 g of oral liquid L-carnitine or placebo twice daily)	High	Single study, screened for fatigue High-grade, treatment-related toxicities reported Low certainty of evidence Strength of recommendation against use is conditional on the basis of evidence from a single trial, lack of efficacy, and potential for adverse effects
Brain wave vibration meditation	One RCT, N = 102 Not screened for fatigue Follow-up: 24 weeks Negative trial	Brain wave vibration meditation	Intermediate	Single study, small sample size, not screened for fatigue Indirectness not serious Insufficient certainty of evidence
Music and music therapy	Two RCTs, N = 216 0/2 trials screened for fatigue Follow-up: up to 3 weeks Both positive trials	Music therapy right before RT sessions Single music intervention while undergoing chemotherapy	Intermediate	Inconsistency not serious Indirectness not serious Insufficient certainty of evidence on the basis of heterogeneity in intervention type, administration, frequency, and lack of screening for fatigue
Reflexology	One RCTs, N = 72 Not screened for fatigue Follow-up: 5 days Positive trial	Foot reflexology	Low	Single study, small sample size, not screened for fatigue Indirectness not serious Insufficient certainty of evidence
Wakefulness agents	Four RCTs, N = 1,062 2/4 trials screened for fatigue Follow-up: range, 28 to 56 days All negative trials	Armodafinil 150 mg or 250 mg once daily Modafinil 100 mg daily, increased to 200 mg once daily	High	Inconsistency not serious Indirectness not serious Moderate certainty of evidence Strength of recommendation against use is strong on the basis of consistent results of limited efficacy and potential for adverse effects
Psychostimulants	One RCT, N = 148 Screened for fatigue Follow-up: 4 weeks Negative trial	Methylphenidate 18 mg tablet; one tablet on days 1-7, two tablets on days 8-14, and three tablets on days 15-28	Intermediate	Single trial, patients with different cancer types, screened for fatigue Indirectness not serious Moderate certainty of evidence Strength of recommendation against routine use is conditional on the basis of evidence from a single trial, lack of efficacy, and potential for adverse effects
Antidepressants	One RCT, N = 549 Screened for fatigue Follow-up: 8 weeks Negative trial	20 mg of oral paroxetine hydrochloride once daily	Intermediate	Single trial Indirectness not serious Strength of recommendation against use is conditional on the basis of evidence from a single trial, lack of efficacy, and potential for adverse effects
Minocycline	One RCT, N = 66 Not screened for fatigue Follow-up: 4 months Negative trial	Minocycline 100 mg twice daily	High	Single trial, small sample size, patients with advanced or metastatic CRC, not screened for fatigue Indirectness not serious Insufficient certainty of evidence

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TABLE 2. GRADE Summary Table (continued)

	Summary of Findings		Certainty Assessment	
Therapy or Modality	No. Studies No. of Participants Screened for Fatigue Follow-up Positive/Negative Results	Intervention	Risk of Bias	Quality of Evidence Notes
Patients after cancer treatment and/or end of life				
Exercise	Nine RCTs, N = 1,377 1/9 trials screened for fatigue Follow-up: range, 6 weeks to 1 year 5/9 trials found positive results 6 studies have fatigue as primary outcomes (4/6 powered for fatigue) Three studies have fatigue as secondary outcomes (none powered, 2/3 positive)	Aerobic (cardio) with or without resistance training with or without diet High- and low-to-moderate-intensity Walking program Deep water aquatic exercise	Intermediate	Inconsistency not serious Indirectness not serious Moderate certainty of evidence Strength of the recommendation is strong on the basis of consistent results in studies powered for fatigue
Exercise in advanced cancer and/or end of life	Three RCTs, N = 347 1/3 trials screened for fatigue Follow-up: range 8-16 weeks None of the trials found positive results	Individualized PA program Unsupervised, moderate intensity aerobic exercise program Graded exercise therapy	Intermediate	Inconsistency not serious Indirectness not serious Poor adherence, no significant increase in activity in the intervention group Insufficient certainty of evidence on the basis of heterogeneity in intervention type, administration, frequency, and lack of screening for fatigue
Tai chi or qigong	One RCT, N = 87 Screened for fatigue Follow-up: 12 weeks Positive trial	Qigong and tai chi Easy	Intermediate	Single study, small sample size, patients with breast cancer Indirectness not serious Insufficient certainty of evidence
Yoga	Two RCTs, N = 558 0/2 trials screened for fatigue, 1/2 trials screened for sleep disturbance Follow-up: range, 4 weeks to 3 months Questionable power for fatigue, fatigue not primary focus 2/2 positive trials	Hatha yoga Yoga for Cancer Survivors: YOCAS	Intermediate	Inconsistency not serious Indirectness not serious Low certainty of evidence Strength of recommendation is conditional on the basis of few trials and no screening for fatigue
ACT-based health behavior	One RCT, N = 410 Not screened for fatigue Negative trial	ACT approach to address health behavior	Intermediate	Single study, CRC survivors, not screened for fatigue Indirectness not serious Insufficient certainty of evidence on the basis of single trial, not screened for fatigue
Attention and interpretation therapy	One RCT, N = 200 Not screened for fatigue Positive trial	Stress management and psychological resilience training	Intermediate	Single study, patients with CRC, not screened for fatigue Indirectness not serious Insufficient certainty of evidence on the basis of single trial of experimenter-developed intervention
CBT	Three RCTs, N = 325 3/3 trials screened for fatigue Follow-up: range, 12 weeks to 6 months All positive trials	CBT aimed to reduce severe fatigue and fatigue-related disability (one study in person, one web-based) CBT-based self-care plus hypnosis	Low	Inconsistency not serious Indirectness not serious Moderate certainty of evidence Strength of the recommendation is strong on the basis of a large body of evidence showing consistent benefits for CRF in screened patients
CBT advanced cancer or end of life	One RCTs, N = 134 Screened for fatigue Follow-up: 14 weeks Positive trial	CBT	Low	Single study, screened for fatigue Indirectness not serious Low certainty of evidence Strength of recommendation is conditional on the basis of evidence from a single trial
Protocolized patient-tailored treatment	One RCT, N = 152 Screened for fatigue Positive trial	Supportive care intervention, focused on symptom management in advanced cancer	Intermediate	Single study, patients with advanced cancer Indirectness not serious Insufficient certainty of evidence on the basis of single trial of experimenter-developed intervention
Psychoeducation (+)	Eight RCTs, N = 2,035 4/8 trials screened for fatigue Follow-up: range, 6 weeks to 6 months 4/8 positive trials	Psychological education Supportive and Survivorship education Health-related self-efficacy and behavior change	Intermediate	Inconsistency; Additional large-scale trials needed to resolve ambiguity stemming from the presence of both positive and negative trials Indirectness not serious Heterogeneity in type of psychoeducation, length of intervention, and comparator used. Half the studies did not screen for fatigue as part of inclusion criteria Insufficient certainty of evidence

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TABLE 2. GRADE Summary Table (continued)

	Summary of Findings		Certainty Assessment	
Therapy or Modality	No. Studies No. of Participants Screened for Fatigue Follow-up Positive/Negative Results	Intervention	Risk of Bias	Quality of Evidence Notes
Mindfulness-based programs	Four RCTs, N = 837 Follow-up: 6 weeks to 6 months 2/4 trials screened for fatigue, 1/4 trials screened for depression All positive trials	MBCT eMBCT MAPS MBSR	Intermediate	Inconsistency not serious Indirectness not serious Moderate certainty of evidence Strength of recommendation is strong on the basis of consistent results of benefit for CRF
Self-management health app	One RCT, N = 799 Screened for fatigue Follow-up: 12 weeks Positive trial	Untire app, which includes components of CBT, psychoeducation, mindfulness meditation, exercise instruction, and positive psychology	Intermediate	Single study, screened for fatigue Indirectness not serious Insufficient certainty of evidence on the basis of single trial of experimenter-developed intervention
Collaborative care intervention	One RCT, N = 261 Not screened for fatigue Follow-up: 6 months Negative trial	Web-based stepped collaborative care intervention (included access to a psychoeducational website and to a collaborative care coordinator with training and experience with CBT and psycho-oncology)	Intermediate	Single study, did not screen for fatigue Indirectness not serious Insufficient certainty of evidence on the basis of single trial of experimenter-developed intervention
Acupressure	One RCT, N = 288 Screened for fatigue Follow-up: 6 and 10 weeks Positive trial	Self-administered (3 min/point) relaxing acupressure and stimulating acupressure	Low	Single study, screened for fatigue Indirectness not serious Low certainty of evidence Strength of recommendation is conditional on the basis of evidence from a single trial
Acupuncture	Two RCTs, N = 399 2/2 trials screened for fatigue Follow-up: 6-7 weeks Fatigue primary outcome in both trials and adequately powered One positive, one negative trial	Acupuncture (bilaterally or unilaterally needling 7 points)	Intermediate	Inconsistency; additional large-scale trials needed to resolve ambiguity stemming from the presence of both positive and negative trials Indirectness not serious Insufficient certainty of evidence
Bright light therapy	Two RCTs, N = 247 2/2 trials screened for fatigue Follow-up: 25-28 days One positive, one negative trial	Bright light therapy, used via a light therapy device	Intermediate	Inconsistency; additional large-scale trials needed to resolve ambiguity stemming from the presence of both positive and negative trials Indirectness not serious Insufficient certainty of evidence
Ginseng	One RCT,[b] N = 364 Screened for fatigue Follow-up: 8 weeks Negative trial	American ginseng (Panax quinquefolius) (1,000 mg twice daily)	Low	Single study, included patients both during and after cancer treatment Indirectness not serious Insufficient certainty of evidence
Massage	One RCT, N = 66 Screened for fatigue Follow-up: 6 weeks Positive trial	Swedish massage therapy	Low	Single study, small sample size, survivors of breast cancer Indirectness not serious Insufficient certainty of evidence
Mistletoe	One RCT, N = 220 Not screened for fatigue Follow-up: 12 months Positive trial	Mistletoe extract (extract of Viscum album [L.] quercus) 0.01-10 mg 3 times/week	Intermediate	Single study, patients with inoperable locally advanced or metastatic pancreatic carcinoma, not screened for fatigue Indirectness not serious Insufficient certainty of evidence
Melatonin	One RCT, N = 72 Screened for fatigue Follow-up: 2 weeks Negative trial	Melatonin 20 mg once daily for 1 week, washout 2 days, placebo for 1 week	Intermediate	Single trial, patients with stage IV cancer, different types Indirectness not serious Insufficient certainty of evidence
Mx	Two RCTs[a], N = 174 2/2 trials screened for fatigue Follow-up: 4-13 weeks Both positive trials	Infrared laser Mx; 10.6 μm on the ST36 (bilateral), CV4, and CV6 (acupoints) Mx at acupoints CV8 and CV12 using ignition-type Mx, and L14 and ST36 using electrical Mx	Intermediate	Inconsistency not serious Included patients both during and after cancer treatment Indirectness not serious Strength of recommendation is conditional on the basis of 2 small trials with heterogeneity in terms of administration and scheduling of moxibustion
Omega polyunsaturated fatty acids	One RCT, N = 97 Screened for fatigue Follow-up: 6 weeks Positive for Omega-6 (on Symptom Inventory, but not on BFI)	High-dose Omega-3 (taken twice daily for total dose of 3.3 g/d of DHA plus EPA) Low-dose Omega-3 and 6 (taken twice daily for total dose of 1.65 g/d of DHA and EPA) High-dose Omega-6 (taken twice daily for total dose of 6 g/d)	Low	Single study, small sample size, survivors of breast cancer Indirectness not serious Insufficient certainty of evidence

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TABLE 2. GRADE Summary Table (continued)

	Summary of Findings		Certainty Assessment	
Therapy or Modality	No. Studies No. of Participants Screened for Fatigue Follow-up Positive/Negative Results	Intervention	Risk of Bias	Quality of Evidence Notes
Wakefulness agents	After treatment One RCT, N = 328 Screened for fatigue Follow-up: 8 weeks Negative trial	Armodafinil 150 mg or 250 mg once daily for 8 weeks	Intermediate	Single trial, patients with high-grade glioma, screened for fatigue Indirectness not serious Moderate certainty of evidence Strength of recommendation against use is conditional on the basis of evidence from a single trial, lack of efficacy, and potential for adverse effects
	Advanced cancer or EOL Two RCTs, N = 291 2/2 trials screened for fatigue Follow-up: range, 7 to 28 days Both negative trials	Modafinil 100 mg once daily, increased to 200 mg once daily Modafinil 200 mg once daily		Inconsistency not serious Indirectness not serious Moderate certainty of evidence Strength of recommendation against use is conditional on the basis of few trials, lack of efficacy, and potential for adverse effects
Psychostimulants	After treatment One RCT, N = 154 Screened for fatigue Follow-up: 8 weeks Positive trial	d-Methylphenidate 5 mg twice daily increasing to a maximum of 50 mg per day (dosing frequency: twice or three times daily)	Intermediate	Single trial, patients with mixed cancer types, screened for fatigue Indirectness not serious Moderate certainty of evidence Strength of recommendation against routine use is conditional on the basis of evidence from a single trial and potential for adverse effects
	Advanced cancer or EOL Five RCTs, N = 520 4/5 trials screened for fatigue Follow-up: 6 -15 days 4/5 negative trials	Methylphenidate 5-25 mg/day (5 mg every 2 hours, as needed, up to 20 mg or 10 mg at breakfast and 5 mg at the other meals with daily doses adjusted between 10 and 25 mg/day) D-Methylphenidate 5 mg twice daily, escalated by 5 mg twice daily to a maximum of 15 mg twice daily Dexamphetamine 20 mg/day (10 mg twice daily)		Inconsistency not serious Indirectness not serious Moderate certainty of evidence Strength of recommendation against routine use is conditional on the basis of lack of efficacy and potential for adverse effects, but the acknowledgment that CRF at the end of life can be debilitating, and some clinicians may choose to try psychostimulants for symptom management
Steroids	Advanced cancer or EOL One RCT, N = 132 Screened for fatigue Follow-up: 15 days Positive trial	Dexamethasone 4 mg twice daily	Intermediate	Single trial, patients with advanced cancer, mixed types, screened for fatigue Indirectness not serious Low certainty of evidence Strength of recommendation is conditional against evidence from a single trial and potential for adverse effects

Abbreviations: ACT, acceptance and commitment; BFI, Brief Fatigue Inventory; CBT, cognitive behavioral therapy; CRC, colorectal cancer; CRF, cancer-related fatigue; DHA, docosahexaenoic acid; eMBCT, web-based mindfulness-based cognitive therapy; EOL, end of life; EPA, eicosapentaenoic acid; MAPS, mindful awareness practices; MBCT, mindfulness-based cognitive therapy; MBSR, mindfulness-based stress reduction; Mx, moxibustion; PMR, progressive muscle relaxation; RCT, randomized controlled trial; RT, radiation therapy; WL, wait list.
[a]One RCT included patients both during and after cancer treatment.
[b]RCT included patients both during and after treatment.

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Overall risk of bias ranged from low to high (Data Supplement 2, Table S5). Many trials had small sample sizes (although all enrolled ≥50 participants) and/or high attrition rates affecting statistical power and lowering confidence in the findings. Indeed, the most common domain of high risk bias, found in 47% of RCTs, was missing data from attrition because of dropout, loss to follow-up, or patients continuing in the trial but missing assessments for other causes. Many studies (42%) failed to use intention-to-treat (ITT) analyses, thereby increasing the risk of bias because of missing outcome data.

With the exception of 13 studies[33,49,57,58,65,68,74,86,91,95,120,126,127] all other studies provided a statistical power calculation; however, certain trials were inadequately powered to detect changes, a condition exacerbated in the absence of screening for fatigue.

Unchanged Recommendations

Recommendations on Screening for CRF, Comprehensive and Focused Assessment, Laboratory Evaluation, Care Options, and Treatment of Contributing Factors from the original guideline remain unchanged.[7] Readers are encouraged to refer to the original publication for guidance in these areas.

RECOMMENDATIONS

During Treatment

All recommendations for patients with CRF during active treatment are available in Table 3.

1.1. Exercise Literature Review Update and Clinical Interpretation

A total of 17 trials (N = 2,606), with 20 publications,[11-27,128-130] assessing exercise interventions in patients undergoing cancer treatment were identified in the updated literature search. Of the 17 trials, two screened patients for fatigue as part of study eligibility[13,27]; the others did not screen but were instead designed to manage increases in fatigue that often occur during treatment, 12 focused solely or largely on breast cancer,[11-14,16,18-20,22-25] and 11 were noted to be adequately powered for fatigue. Four trials compared different exercise interventions (high *v* low intensity, aerobic *v* resistance *v* combination),[12,15,19,25] and 13 trials compared exercise to a waitlist or attention control.[11,13-18,20-24,27] In examining the trials that investigated the effects of exercise versus control conditions, nine out of the 13 trials demonstrated significant benefits of the exercise interventions. Trials had sample sizes ranging from 50 to 577 patients and tested exercise modalities, including home-based walking, combined aerobic and resistance exercises, and resistance-only interventions. Intervention modalities also differed, including home-based unsupervised, in-person supervised, and remotely supervised exercise programs. Risk of bias ranged from low to high in the 17 trials, with an overall risk of bias assessed as intermediate.

Of the four trials comparing different exercise modalities or intensities, with sample sizes that ranged from 54 to 577, there were largely no significant differences in the impact of the different exercise interventions on fatigue, making it difficult to determine if one form of exercise provides superior benefit in

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TABLE 3. Summary of Recommendations During Active Cancer Treatment

Recommendation	Evidence Quality	Strength of Recommendation
General note. The following recommendations (strong or conditional) represent reasonable options for patients depending on clinical circumstances and in the context of individual patient preferences. Recommended care should be accessible to patients whenever possible		
1.1. Clinicians should recommend exercise (aerobic, resistance, or a combination) to reduce the severity of fatigue during cancer treatment. Exercise should be tailored according to the individual patient's abilities and may be either supervised or unsupervised	Moderate	Strong
Note. Benefits for fatigue have consistently been seen with interventions that combine aerobic and resistance training and resistance-only interventions. The choice of exercise modality, intensity, and duration should be based on several important considerations, including patient preference, availability, accessibility, likelihood of adherence, safety, and cost		
1.2. Clinicians should recommend cognitive behavioral therapy (CBT) with or without hypnosis to reduce the severity of cancer-related fatigue in adults undergoing cancer treatment	Moderate	Strong
1.3. Clinicians should recommend mindfulness-based programs to reduce the severity of cancer-related fatigue in adults undergoing cancer treatment. Mindfulness-based programs may include mindfulness-based stress reduction (MBSR)	Moderate	Strong
1.4. Clinicians should recommend tai chi or qigong, practiced at a low to moderate intensity, to reduce the severity of cancer-related fatigue in adults undergoing cancer treatment	Moderate	Strong
1.5. Clinicians may recommend psychoeducation to reduce the severity of cancer-related fatigue in adults undergoing cancer treatment	Moderate	Conditional
1.6. Clinicians may recommend American ginseng (Panax quinquefolius) at a dose of 2,000 mg daily[a] to manage symptoms of cancer-related fatigue in adults undergoing cancer treatment	Low	Conditional
1.7. Clinicians should not recommend wakefulness agents, such as modafinil or armodafinil, to manage symptoms of cancer-related fatigue in adults undergoing cancer treatment	Moderate	Strong
1.8. Clinicians should not recommend L-carnitine to manage symptoms of cancer-related fatigue in adults undergoing cancer treatment	Low	Conditional
1.9. Clinicians should not routinely recommend psychostimulants, such as methylphenidate, to manage symptoms of cancer-related fatigue in adults undergoing cancer treatment	Moderate	Conditional
1.10. Clinicians should not recommend antidepressants, such as paroxetine, to manage symptoms of cancer-related fatigue in adults undergoing cancer treatment	Moderate	Conditional
No recommendation. There is insufficient evidence to make recommendations for or against acupressure, coenzyme Q10, guarana, brain wave vibration meditation, minocycline, music or music therapy, progressive muscle relaxation, reflexology, solution-focused therapy, or yoga to reduce the severity of cancer-related fatigue in adults undergoing cancer treatment	Insufficient	No Recommendation for or against

NOTE. The strength of the recommendation is defined as follows: strong: in recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects. In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects. All or almost all informed people would make the recommended choice for or against an intervention. Conditional/weak: in recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists. In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists. Most informed people would choose the recommended course of action, but a substantial number would not.

[a]While there is no conclusive evidence regarding the optimal administration schedule, twice-daily dosing, preferably in the morning and before noon to avoid disrupting sleep patterns, may be considered.

preventing or lessening fatigue during treatment than other forms.[12,14,15,19] One study found high-intensity resistance and endurance exercise yielded significantly lower physical fatigue compared to low-to-moderate-intensity exercise in patients undergoing (neo-) adjuvant treatment, but the magnitude of effect did not reach the minimal clinically important difference of two points.[12] Further, there were no differences between groups in other CRF dimensions. A year-long RCT in patients with prostate cancer undergoing androgen deprivation therapy that compared three exercise regimens—resistance plus impact loading, aerobic plus resistance, and aerobic only—found that all modalities had a beneficial effect on fatigue relative to waitlist control.[15] These trials thus provide strong evidence that exercise during treatment can help to reduce fatigue incidence and severity, but they do not provide information regarding the optimal type or dose of exercise.

Evidence identified in the updated systematic review included trials of diverse exercise types, administration methods, and schedules, posing challenges in determining optimal durations, frequencies, and intensities for exercise programs during cancer treatment. In totality, the current evidence supports the efficacy of exercise for CRF across diverse modalities and settings. These findings are consistent with several systematic reviews and meta-analyses, as well as recent guidelines.[131,132] The American College of Sports Medicine 2019 RoundTable report reviewed evidence from RCTs during and after cancer treatment, with the objective of developing frequency, intensity, time, and type (FITT) prescriptions for the management of symptoms and side effects in patients with cancer.[23] The Round Table panel concluded that moderate-intensity aerobic exercise for a minimum of three sessions per week, a combination of aerobic exercise and resistance training sessions 2-3 times per week, and resistance training twice weekly are all effective approaches for reducing CRF.[132]

Incorporating exercise into the treatment of patients with cancer requires attention to a number of considerations, including comorbidities, treatment-related toxicities, and the individual's baseline physical activity and conditioning.[131] The 2022 ASCO Exercise, Diet, and Weight Management During Cancer Treatment guideline[131] reviewed safety considerations for exercise during cancer treatment and concluded that exercise could safely be performed during active treatment administered for curative intent, but recommended that patients confer with their oncology provider before beginning an exercise program. The guideline also notes that although some patients can safely engage in unsupervised exercise, others might benefit from a structured exercise program or consultation with an exercise oncology professional before independently undertaking exercise.[131] Efforts are underway to develop methods for triaging patients to the most appropriate exercise oncology resources to safely and effectively help them to increase exercise during and after cancer treatment.[133]

It is important to note that only two of the trials reviewed used fatigue as a screening criteria and enrolled patients with elevated fatigue. Although both trials found benefit, it remains unclear at this time whether exercise is effective for reducing fatigue in patients undergoing treatment who are already experiencing CRF (*v* those at risk for CRF as a result of initiating cancer treatment). As with other factors, patients' current fatigue status should be considered when making exercise recommendations.

1.2. Cognitive Behavioral Therapy Literature Review Update and Clinical Interpretation

Two phase III RCTs that assessed cognitive behavioral therapy (CBT) were identified in the updated literature search[52,53] and two additional older phase II studies[51,121] investigating CBT met inclusion criteria. However, one of the updated trials[53] was deemed to have important deficiencies in design, including lack of a control group, and, as such, was not incorporated as part of the evidence base to inform the recommendation, leaving three trials investigating CBT in patients undergoing cancer treatment. Fatigue was the primary outcome in all trials, and one screened for fatigue.[51] In 200 patients with breast cancer who were receiving 6 weeks of radiotherapy and were not screened for fatigue, CBT plus hypnosis was compared to an attention control group.[52] The hypnosis component included suggestions for reducing fatigue and distress during treatment. Patients randomly assigned to CBT plus hypnosis had significantly lower levels of fatigue at the end of radiotherapy and at 4-week and 6-month follow-up compared to the control group (all $P < .001$).[52] The trial was assessed to be at a low risk of bias. Statistically significant differences in visual analog scale (VAS) Global Fatigue scores were also observed for CBT alone compared to usual care in another trial that enrolled 60 fatigued patients with cancer undergoing cytotoxic therapy.[51] This trial had a small sample size, baseline imbalances between groups, inadequate allocation concealment at the start of the study, and high patient attrition, thereby increasing the risk of bias to high. Finally, a trial in 220 patients with various malignancies found that CBT given during curative cancer treatment led to significantly lower fatigue 2 months after cancer treatment compared to usual care.[121] This trial was at a low risk of bias. Of note, a follow-up study found that the beneficial effects of CBT were most pronounced among patients with concentration and memory problems.[134]

Given the positive results of the three trials included in this review, the panel concluded that CBT is efficacious in reducing fatigue in patients undergoing cancer treatment. Findings from these trials are consistent with a broader literature on the efficacy of CBT for reducing fatigue in patients with other illnesses.[135-137] CBT-based interventions recognize the intricate interplay between psychological and physical factors and address the maladaptive cognitions and behaviors that are known to influence fatigue (eg, catastrophizing).[138] The assumption of CBT-based interventions is *not* that fatigue and other symptoms are "all in a patient's head". Instead,

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these approaches recognize that although fatigue may be precipitated by cancer and its treatment, patients' cognitive and behavioral coping strategies play an important role in its severity and persistence. There remains a paucity of trials testing CBT in patients undergoing treatment, with notable variations observed in intervention components across existing studies. Future studies are warranted using CBT during cancer treatment, to confirm or refute these findings. Another clinical consideration for this intervention is the challenge of finding trained therapists to deliver CBT focused on fatigue reduction. Web-based CBT interventions have demonstrated efficacy for fatigue in the post-treatment setting[54] and should also be evaluated during treatment.

1.3. Mindfulness-Based Programs Literature Review Update and Clinical Interpretation

The updated literature search identified three RCTs that met the inclusion criteria.[70,75,125] Fatigue was the primary outcome in two of these trials,[75,125] and none screened for fatigue. One phase II, assessor-blinded, three-arm RCT in 92 patients with early breast cancer investigated a 12-week mindfulness meditation program and a progressive muscle relaxation (PMR) intervention compared to a control group, which consisted of a brief education session before the start of cancer treatment.[70] Compared to the control group, mindfulness meditation resulted in a significant reduction in BFI scores at weeks 12 and 14 ($P = .002$). Another phase III trial in 192 patients with newly diagnosed breast cancer[75] found patients randomly assigned to 8-week mindfulness-based stress reduction (MBSR) program exhibited improvement in fatigue compared to an active control group that included a series of cancer recovery and health education classes ($P < .001$). Improvements reached a peak at 1 month post-MBSR and leveled at that time. An additional trial in 120 patients with differentiated thyroid cancer receiving radioactive iodine therapy investigated the effectiveness of an 8-week MBSR program, starting 8 weeks before cancer therapy.[125] Patients randomly assigned to the MBSR group showed significantly greater improvements in fatigue 1 week after concluding the last MBSR session and 3 months after hospitalization for cancer therapy ($P = .037$ for both). All trials had low risk of bias in quality elements assessed, except for loss to follow-up in one trial, where there was a high dropout rate.[75]

The evidence base for mindfulness-based programs has grown considerably since publication of the previous guideline, and current evidence supports the efficacy of mindfulness-based approaches for reducing symptoms of fatigue during active cancer treatment. Two of the three trials included in this review evaluated MBSR, a structured 8-week intervention that involves weekly group sessions and daily meditation practice. MBSR and similar interventions have demonstrated beneficial effects on physical and emotional symptoms in other clinical populations[137] and these programs have become more widely available, including online. Even daily practice of mindfulness meditation may help reduce CRF,[139] although the evidence here is less robust. Clinicians should have a menu of possible interventions to offer to patients for fatigue, and mindfulness-based programs are an evidence-based option.

1.4. Tai Chi or Qigong Literature Review Update and Clinical Interpretation

A total of five RCTs (N = 498) evaluating Chen-style qigong and/or tai chi exercises were included from the updated literature search,[46-49] four of which showed significant improvement in fatigue scores as compared to conventional care, waitlist controls, or light exercise groups in patients with a variety of cancer types.[45,47-49] Fatigue was measured by the BFI[46-48] or the MFSI-SF[45,49] with follow-up ranging from 21 days to 12 weeks. Fatigue was the primary outcome in all trials; however, only one trial[48] screened for fatigue and two of the five trials reported adequate power for fatigue.[47,48] Nonetheless, the fact that interventions were found to be beneficial in these studies is noteworthy and, given varying baseline fatigue levels and inadequate power, may represent a conservative test of efficacy. Risk of bias ranged from low to high.

Many integrative medicine practices, such as tai chi or qigong, are widely available in the community and are practiced to maintain health and well-being in the general population. The evidence reviewed examined Chen-style tai chi and qigong and participants in these trials practiced these mind-body exercises for 20-60 minutes, 3-5 times per week throughout their cancer therapy. Their evaluation as intervention strategies to help manage fatigue during cancer treatment shows a meaningful benefit in clinical trials and should be offered to patients. These practices may capitalize on the effectiveness of both mindfulness and exercise, which each individually are beneficial in the mitigation of CRF.

1.5. Psychoeducation Literature Review Update and Clinical Interpretation

No new trials on psychoeducation during cancer treatment were identified in the updated literature review. Instead, three trials (N = 504) identified from existing systematic reviews qualified and form the evidence base.[120,122,124] One trial assessing psychoeducation plus nursing support for CRF in 103 chemotherapy-naïve patients found the intervention group, compared to a standard care group, reported significantly lower levels of fatigue ($P < .05$).[122] Similarly, another trial assessed the effectiveness of a psychoeducational intervention in mitigating CRF among 109 women undergoing adjuvant chemotherapy for early-stage breast cancer.[124] Results indicated that, in the short term, the control group, which received general cancer education sessions, exhibited significantly greater increases in worst and average fatigue, FACT-F, and Piper fatigue severity and interference measures immediately after the intervention ($P < .05$). However, these

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differences were not sustained at later assessments. A third study, assessing the efficacy of an information and behavioral skills intervention in alleviating fatigue and sleep disturbance in 292 individuals undergoing chemotherapy found no significant effects for fatigue.[120]

Psychoeducation is widely available in oncology practice settings and often is a component of chemotherapy teaching sessions provided to patients before embarking on therapy. To the extent that this educational opportunity can prepare patients for the likelihood of fatigue that almost universally occurs with cancer treatment, it is a teachable moment. Research suggests that psychoeducational interventions tailored to address the multifaceted nature of CRF can improve patients' understanding of fatigue mechanisms, coping strategies, and overall quality of life. Furthermore, such interventions may foster a sense of empowerment and control over fatigue, enhancing patients' self-management skills and reduce distress associated with fatigue symptoms. However, combining psychoeducational interventions with another evidence-based treatment may be optimal, as its effectiveness as a standalone therapy is not consistently robust.

1.6. Ginseng Literature Review Update and Clinical Interpretation

The updated literature search identified four RCTs conducted to assess ginseng versus placebo or usual care in managing CRF. Three trials included 610 patients undergoing cancer treatment[84-86] and one phase III trial randomly assigned 364 patients with cancer currently undergoing or having completed curative-intent treatment.[87] Dose and type of ginseng investigated varied in the trials and only two trials screened for fatigue.[84,87] Two trials were assessed to be at low risk of bias,[85,87] one intermediate, [84] and one at high risk of bias.[86] High risk of bias elements included lack of ITT analysis, unclear allocation concealment methods, and possible imbalance in baseline characteristics between groups.

In a trial of American ginseng at a dose of 1,000 mg twice daily, fatigue was improved in the ginseng group compared with the placebo group as measured by the MFSI-SF (change scores at 8 weeks 20; standard deviation [SD] = 27 *v* 10.3 [SD = 26.1], respectively, $P = .003$).[87] However, the BFI total score was not significantly different between the arms. A subgroup analysis that divided subjects based on whether they were receiving or completed cancer treatment showed that the subjects undergoing cancer therapy allocated to the ginseng arm had significant improvement in CRF at 4 and 8 weeks compared with those in the placebo arm. No significant change was observed in patients who had completed treatment.[87] In contrast, oral Panax ginseng extract in 127 fatigued patients with advanced cancer found Panax ginseng caused a significant reduction in the severity of CRF as measured by Edmonton Symptom Assessment System (ESAS); however, it was not more effective than placebo in improving CRF when measured by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) subscale at 29 days, its primary endpoint.[84] In patients with colorectal cancer, 1,000 mg twice daily of Korean red ginseng (Panax ginseng C.A. Meyer) significantly reduced CRF as evaluated by the BFI at 8 ($P = .013$) and 16 weeks ($P = .019$) compared to placebo in the per-protocol set of patients (n = 330) but not the full-analysis set (N = 409).[85] After 60-day treatment with 3,000 mg (total daily dose) of fermented red ginseng extract (Panax ginseng steamed at 98°C to 100°C for 2 to 3 hours),[140] total Fatigue Symptom Inventory scores were significantly lower in the ginseng group compared to those allocated to usual care ($P < .01$), in patients with advanced non–small cell lung cancer.[86] Both longer administration of ginseng and higher dosing led to significant improvements in fatigue compared to shorter interventions and lower doses. The two trials with short intervention periods (ie, 29 days and 4 weeks) did not find significant improvement in fatigue.[84,87] In contrast, interventions that ranged from 8 weeks to 16 weeks,[85-87] even when investigating the same dose and ginseng product,[87] found significant improvements in fatigue severity. Higher doses ranging from 2,000 to 3,000 mg per day had a significantly improved fatigue severity,[85-87] while 400 mg twice daily ginseng intervention was ineffective at improving fatigue.[84] A prior pilot study found that doses >1,000 mg daily (divided into twice daily dosing) showed nonsignificant trends in fatigue improvement.[141]

These four RCTs investigate different preparations of the two main species of ginseng, American ginseng (*Panax quinquefolius*) and Asian ginseng (Panax ginseng) all of which contain ginsenosides the active components of ginseng, although in different quantities.[142] Both species showed promise for improving fatigue. However, how ginsenosides are extracted from the ginseng root changes the amount and thus the actions of the ginsenosides. Ginseng extracted using methanol has shown estrogen-like effects, leading to increased breast cancer cell growth.[143-145] In contrast, ginseng products obtained through water extraction or from unextracted ground root do not exhibit estrogenic effects. Notably, studies have indicated that water-extracted American ginseng can inhibit the growth of breast cancer cells, regardless of their sensitivity to estrogen.[143,145] While these results have not been confirmed in either animal or human studies, in an abundance of caution avoiding methanolic ginseng extracts is advised in hormone receptor–positive cancers. A variety of ginseng products are available for sale. Methanolic extracts are almost always further dried and placed in capsules making it necessary to read labels to know which extraction process was used. There have also been reports of potential drug interactions, and a case report indicated the possibility of increased risk of hepatoxicity.[146,147] Some ginsenosides could also induce CYP34A substrates and increase clearance of substrate drugs, but impacts in humans may not be clinically significant.[148]

1.7. Wakefulness Agents Literature Review Update and Clinical Interpretation

Three RCTs (N = 185) identified in the updated literature search and one older qualifying trial (N = 877) investigated

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the wakefulness agents, armodafinil[100-102] and modafinil,[103] for CRF in patients with mixed cancer types. While fatigue was the primary outcome in all trials, only two screened patients for fatigue as part of eligibility criteria.[100,103] Regardless of whether patients were screened for fatigue or not, 150 mg of armodafinil once daily did not have a statistically significant effect on fatigue compared to placebo over 4-6 weeks.[100-102] Similarly, a large trial of 877 randomly assigned patients with mixed cancer types and fatigue at the beginning of their cancer treatment, found 200 mg modafinil once daily was not significantly more effective than placebo for fatigue (P = .08) in the 631 patients with evaluable data.[103] However, when patients were divided into three categories of fatigue severity, a statistically significant group difference (P = .033) for those in the severe fatigue category emerged, favoring the drug.[103] High risk of bias elements included high attrition and failure to use ITT analyses.

Clinical studies have shown limited efficacy of wakefulness agents, namely modafinil and armodafinil, in alleviating CRF. The inability of these wakefulness agents as compared to placebo to improve CRF at the various doses and durations used in clinical trials limits the use of these agents for treatment of CRF in patients with cancer receiving cancer treatment. Additionally, the long-term effects and safety profile of these agents in the context of patients with cancer remain unclear. The limited effect on CRF may be due to the lack of these wakefulness agents addressing the many factors that contribute to CRF in patients with cancer undergoing treatment. Nonetheless, for individuals with severe baseline CRF, modafinil may be useful.[103] However, additional research is necessary to validate this finding.

1.8. L-Carnitine Literature Review Update and Clinical Interpretation

One RCT investigated L-carnitine in patients with invasive malignancies (N = 376) during cancer therapy who were screened for presence of fatigue.[90] After 4 weeks, differences in fatigue were not statistically significant between those receiving 1 g oral liquid L-carnitine twice daily or placebo. The trial was assessed to be at high risk of bias due to unclear ITT analysis methods and high loss to follow-up.

L-carnitine has frequently been suggested as a possible treatment for many different types of fatigue due to its role in energy production in the body. L-carnitine plays a significant role in energy metabolism and can prevent muscle wasting.[149] Despite a mechanistic rationale for improving fatigue, evidence from one adequately powered trial in patients screened for fatigue undergoing treatment for mixed invasive malignancies failed to show benefit. This is consistent with findings from existing meta-analyses on L-carnitine for CRF.[150]

1.9. Psychostimulants Literature Review Update and Clinical Interpretation

The updated literature search did not identify any new trials that met the inclusion criteria in patients undergoing cancer treatment. As such, evidence identified through existing systematic reviews was included. One qualifying trial, a phase III, double-blind, placebo-controlled RCT, investigated methylphenidate for CRF in 148 patients with different types of cancer.[107] Participants were screened for fatigue and had a score of 4 or more on a subjective fatigue level screening scale that ranged from 0 to 10. An 18 mg tablet of methylphenidate was administered once daily on days 1 through 7, two tablets on days 8 through 14, and three tablets on days 15 through 28. At 4 weeks, there were no statistically significant differences between methylphenidate and placebo (P = .68).[107]

Despite having some benefit in certain patients with CRF in clinical practice, evidence from one adequately powered trial reports that methylphenidate is not more effective in reducing CRF than placebo. Therefore, clinicians should not routinely prescribe methylphenidate at this time in patients undergoing cancer treatment due to the lack of clarity of long-term side effects and safety, potential interactions with other medications, and potential risk of addiction. The observed ineffectiveness could be attributed, at least in part, to the placebo effect noted in the control arm. Furthermore, future trials should consider targeting a select group of patients where methylphenidate may exhibit greater benefits, such as individuals with CRF experiencing opioid-related drowsiness or depression.[110,151,152]

1.10. Antidepressants Literature Review Update and Clinical Interpretation

The updated literature search did not identify any new trials that met the inclusion criteria in patients undergoing cancer treatment. As such, evidence identified through existing systematic reviews was included. One qualifying trial, a phase III, double-blind, placebo-controlled RCT, investigated paroxetine for CRF in 549 patients with solid cancer scheduled to begin the first of at least four cycles of chemotherapy without concurrent radiation therapy or interferon treatment.[114] The study did not reveal any statistically significant alleviation of fatigue for paroxetine when compared to placebo.

While antidepressants may be effective in treating depression and related symptoms, their use for CRF has not shown consistent benefits in clinical trials. Placebo-controlled studies and evidence from a Cochrane review[153] have failed to demonstrate significant improvements in CRF alone with antidepressant medications. As recommended in the original guideline,[7] all medical and treatable contributing factors to fatigue, including depression, should be addressed first. When addressing both fatigue and depression in a patient with cancer, the potential side effects and interactions with

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other medications must be considered and the risk-benefit ratio of antidepressant use should be assessed over time. ASCO recommendations for first-line treatment of depression in patients with cancer is not antidepressants, rather behavioral treatments like CBT and MBIs are recommended.[154] Of note, the few trials conducted in this area have focused on selective serotonin reuptake inhibitors (eg, paroxetine), and there is interest in evaluating other antidepressants that work through different pathways to address CRF (eg, bupropion, a norepinephrine-dopamine reuptake inhibitor).[155]

Inconclusive Interventions Literature Review Update and Clinical Interpretation

Based on the current body of evidence, no recommendations can be made for or against these listed interventions. Although some interventions may hold potential benefit for CRF, additional robust studies are required to substantiate effectiveness due to the significant methodologic concerns, small sample sizes, and/or compliance with the interventions in the identified studies.

Acupressure. Effectiveness of acupressure for fatigue in patients undergoing cancer treatment is not yet established due to too few trials with small sample sizes. An RCT in 57 patients with lung cancer not screened for fatigue failed to find a significant difference in the Tang fatigue rating scale scores between acupressure with or without essential oils and sham acupressure administered for 5 months.[77] Another trial in 100 patients with lung cancer screened for fatigue found acupressure did reduce CRF scores compared to routine care ($P < .01$).[76] High risk of bias elements included high attrition, lack of ITT analysis, and unclear allocation concealment and therapist training.

Coenzyme Q10. One phase III RCT was identified that assessed the benefits of coenzyme Q10 (CoQ10) in 236 patients with newly diagnosed breast cancer and planned adjuvant chemotherapy.[83] CoQ10 at a total dose of 300 mg/day (taken as 100 mg three times per day) plus 300 IU vitamin E was compared to placebo plus the same dose of vitamin E. Participants were not screened for fatigue. Although the study was adequately powered, no significant differences were detected between the CoQ10 and placebo arms at 24 weeks for scores on the Profile of Mood States Fatigue Subscale ($P = .257$) or the FACIT-F tool ($P = .965$). Fatigue examined at 24 weeks is adequate to see a clinical response from CoQ10 and the 300 mg total dose is on the upper end used to treat other health conditions,[156] although some studies have used as high as 600 mg/day. All would imply that CoQ10 is not an effective treatment for cancer fatigue. However, since the one clinical trial was in a mostly White (87%) group of newly diagnosed patients with breast cancer who were receiving chemotherapy, future studies are needed to establish whether CoQ10 has a role in CRF in a broader cancer population.

Guarana. The effect of guarana for CRF compared to placebo was assessed in two RCTs (N = 147) conducted in patients with breast cancer undergoing chemotherapy who were screened for fatigue.[88,89] No statistically significant improvement in fatigue, as measured by the BFI, was found at 21 days in one trial.[89] However, guarana significantly improved the FACIT-F scores compared to placebo on days 21 ($P < .01$) and at day 49 ($P = .02$) in the other trial.[88] There was uncertainty in whether important baseline differences between treatment groups existed[89] and uncertainty in attrition.[88,89] and use of ITT analyses.[89] Due to the inconsistencies between these two studies future robust RCTs are needed to clarify if guarana has a role in treating CRF.

Brain wave vibration meditation. One phase III trial in 102 patients with breast cancer receiving radiation therapy after breast cancer surgery, not screened for fatigue, investigated brain wave vibration meditation, a technique that combines simple movements, such as lightly shaking one's head side-to-side, movements of a part of the body in a rhythmic fashion, as well as music, action, and positive messages.[92] Brain wave vibration "moving" meditation therapy was found to reduce fatigue compared with the nonintervention control group ($P = .030$).[92] Fatigue was a secondary outcome in this trial and a high number of patients were lost to follow-up or didn't complete the required minimum number of sessions.

Minocycline. The effect of minocycline for CRF was assessed in one RCT of 66 patients with advanced colorectal cancer who were scheduled for oxaliplatin-based chemotherapy.[115] No statistically significant alleviation effect was found for minocycline, at a dose of 100 mg twice daily, compared to placebo. The study was assessed to have a high risk of bias.

Music and music therapy. Two phase III RCTs investigated music for CRF in patients with breast or gynecological cancer not screened for fatigue. In one trial (N = 116), a trained and experienced music therapist conducted individual 30- to 40-minute music therapy sessions twice a week right before radiotherapy.[95] Results showed music therapy significantly improvement FACT-F scores (mean value 67.95) compared with the control group (mean value, 51.59) at the final assessment ($P = .009$), which was during the last week of radiotherapy. Another trial (N = 100) investigated a single session music intervention for 45 minutes by CD player with headphones, delivered by a trained music therapist to patients undergoing chemotherapy.[96] MFSI scores, a secondary outcome, were statistically significantly improved in the music group compared to those undergoing routine nursing care with no music at the 1 week time point ($P < .001$), but this effect was not sustained at 3 weeks. Additional research is necessary to validate the results obtained in the current trials.

Progressive muscle relaxation. One phase II trial (N = 92) investigated a PMR intervention, 20-minute every day, for a total of 12 weeks in patients with breast cancer receiving adjuvant paclitaxel.[70] PMR was compared to a mindfulness meditation group and a control group that included a single time attention-matched education on breast cancer before the start of chemotherapy. Both the

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PMR and mindfulness meditation groups resulted in a significant reduction in BFI scores compared to the control group at weeks 12 and 14 (P = .002). While the trial was assessed to be at low risk of bias, additional investigation is necessary to validate these results.

Reflexology. One randomized trial (N = 72) investigated reflexology in patients with cancer during treatment.[98] Foot reflexology for 15 minutes per foot per day for 5 consecutive days found a statistically significant benefit in fatigue in 72 patients with lymphoma compared to the usual care group (P < .05).[98] The trial had low risk of bias in all domains. Additional evidence is required to confirm the results.

Solution-focused therapy. The effectiveness of a solution-focused therapy (SFT), an active form of psychotherapy that focuses on the patient's experience rather than the problem, for CRF in patients undergoing cancer treatment was investigated in one trial (N = 124).[66] SFT, offered for 30 minutes on the first day of every chemotherapy course once a month for a total of 6 months, resulted in significantly lower fatigue than usual health education about CRF (P < .005).[66] Further research is required to confirm these findings.

Yoga. Three RCTs investigating the effects of yoga on fatigue in patients with breast or prostate cancer undergoing treatment, and not screened for fatigue, were identified in the updated literature search.[40-42] In 50 patients with prostate cancer undergoing radiation therapy, patients in the yoga arm reported significantly less fatigue than those in the control arm, with global fatigue, effect of fatigue, and severity of fatigue subscales showing statistically significant differences (P < .0001).[41] In contrast, the other two yoga trials (N = 435) found no differences between yoga and usual care in fatigue levels over time.[40,42] Due to inconsistent findings, methodological concerns, and important differences in the nature and duration of yoga in the three trials, it is not possible to draw robust conclusions on the benefits of yoga in patients undergoing cancer therapy.

After Treatment

All recommendations for patients with CRF after treatment are available in Table 4.

2.1. Exercise Literature Review Update and Clinical Interpretation

There is an existing large evidence base supporting exercise in cancer survivors.[126,157-159] Updating the literature search identified nine new exercise trials (N = 1,377), published in 11 manuscripts [28-36,160,161] that met the inclusion criteria, two of which included patients (N = 160)[35,36] both during and after cancer treatment. Only one of the nine trials screened patients for fatigue as part of study eligibility,[28] and fatigue was a primary outcome in six trials,[28,30,33-36] although only four[28,30,35,36] were noted to be adequately powered for fatigue. Three trials compared different exercise intensities, timing, or supervision level,[30,31,35] and six trials compared exercise to a waitlist or attention control.[28,29,32-34,36] Of the trials comparing different exercise intensities, timing, or supervision, no significant difference in fatigue was detected for high-intensity compared to low-to-moderate intensity resistance and endurance exercise in 277 patients with mixed cancer types.[30] However, compared to a waitlist control, both high and low-to-moderate intensity showed significant improvements in general fatigue and physical fatigue at 12 weeks.[30] In 211 patients with lung cancer, a significant difference in fatigue between early-initiated postoperative rehabilitation (14 days after surgery) and late-initiated postoperative rehabilitation (14 weeks after surgery) was detected from baseline to 14 weeks (P = .017) in favor of the early group and from 14 to 26 weeks (P = .020) in favor of the late group.[31] No significant difference between groups was found from baseline to 26 weeks (P = .551) or 52 weeks (P = .431). A trial comparing a self-directed exercise program versus a partially supervised exercise program versus treatment as usual found no significant difference between groups at 12 weeks in general fatigue (P = .234).[35]

Of the trials comparing exercise to waitlist or treatment as usual, one trial investigating an exercise intervention that also included behavioral or cognitive components in survivors of breast cancer found the exercise interventions significantly improved fatigue intensity (P = .004) and interference (P < .001) compared to usual care, with clinically meaningful effects sustained for fatigue intensity (P = .038) and fatigue interference (P = .002) 3 months after intervention completion.[32] Another trial in 68 patients with breast cancer found that deep water aquatic exercise (60 minutes, 3 times per week for 8 weeks) resulted in a greater decrease in fatigue compared to usual care in all dimensions (affective [P < .001], sensory [P < .001], cognitive [P < .001], severity [P = .040] and the total score [P < .001]).[28] In 90 patients with breast cancer, those randomly assigned to receive an oncologist verbal recommendation to exercise plus a cancer-specific yoga DVD reported a 50% greater reduction in fatigue at 8 weeks than those receiving the verbal recommendation only (P = .02).[36] However, three trials assessing 12 week,[29] 18 week,[33] or 6 month exercise[34] interventions failed to detect a significant impact of exercise on fatigue. It was unclear if any of these three trials were adequately powered for fatigue. Risk of bias ranged from low to high in the nine trials, with an overall risk of bias assessed as intermediate.

Similar to studies of exercise interventions during cancer treatment, and given the heterogeneity of the interventions tested, it is challenging to determine the type and dose of exercise that is most effective for managing CRF. Nonetheless, exercise in the form of aerobic and resistance training, and low to moderate intensity, should be recommended. Individual needs should be considered and support (eg, need for supervision or more structured programs, availability of resources, behavioral motivation) should be provided to optimize exercise adherence. Support may also be provided through local and institutional resources such as physical and occupational therapies and rehabilitation.

TABLE 4. Summary of Recommendations After Active Cancer Treatment

Recommendation	Evidence Quality	Strength of Recommendation
General note. The following recommendations (strong or conditional) represent reasonable options for patients depending on clinical circumstances and in the context of individual patient preferences. Recommended care should be accessible to patients whenever possible		
2.1. Clinicians should recommend exercise (aerobic, resistance, or a combination) to reduce the severity of cancer-related fatigue symptoms in adults who have completed cancer treatment. Whenever possible, exercise should be tailored according to the abilities of the individual patient and may be either supervised or unsupervised	Moderate	Strong
2.2. Clinicians should recommend cognitive behavioral therapy (CBT) to manage symptoms of cancer-related fatigue in adults who have completed cancer treatment. CBT may be delivered in person or via a web-based program	Moderate	Strong
2.3. Clinicians should recommend mindfulness-based programs to reduce the severity of fatigue in adults who have completed cancer treatment. Mindfulness-based programs may include mindfulness-based stress reduction (MBSR), mindfulness-based cognitive therapy (MBCT), and mindful awareness practices (MAPs) and may be delivered in person or via a web-based program	Moderate	Strong
2.4. Clinicians may recommend yoga to reduce the severity of cancer-related fatigue in adults who have completed cancer treatment, especially in women with breast cancer	Low	Conditional
2.5. Clinicians may recommend acupressure to manage symptoms of cancer-related fatigue in adults who have completed cancer treatment	Low	Conditional
2.6. Clinicians may recommend moxibustion to manage symptoms of cancer-related fatigue in adults who have completed cancer treatment	Low	Conditional
2.7. Clinicians should not recommend wakefulness agents, such as modafinil or armodafinil, to manage symptoms of cancer-related fatigue in adults who have completed cancer treatment	Moderate	Conditional
2.8. Clinicians should not routinely recommend psychostimulants, such as methylphenidate, to manage symptoms of cancer-related fatigue in adults who have completed cancer treatment	Moderate	Conditional
No recommendation. There is insufficient or inconclusive evidence to make recommendations for or against acceptance and commitment (ACT)–based or attention-based interventions, acupuncture, bright light therapy, ginseng, massage, mistletoe, or omega fatty acids, psychoeducational interventions, self-management health app, tai chi or qigong to reduce the severity of cancer-related fatigue in adults who have completed cancer treatment	Insufficient	No Recommendation for or against

NOTE. The strength of the recommendation is defined as follows: strong: in recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects. In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects. All or almost all informed people would make the recommended choice for or against an intervention; conditional/weak: in recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists. In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists. Most informed people would choose the recommended course of action, but a substantial number would not.

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2.2. CBT Literature Review Update and Clinical Interpretation

The updated literature search identified two trials[54-56] (N = 227) in patients who had completed cancer treatment that met the inclusion criteria. One older qualifying trial in 98 disease-free survivors of cancer,[55] identified from existing systematic reviews, was also considered as part of the evidence base informing the recommendation. Each of the three included trials had a low risk of bias, were specifically designed to measure fatigue, and study participants met a severity cutoff score for study inclusion. Despite the variation in number and duration of therapy sessions, trials consistently reported that patients allocated to CBT showed a statistically and clinically significantly greater decrease in CRF than patients in usual care or waitlist control groups, whether the intervention was delivered in person[55,56] or via a web-based program.[54]

CBT has demonstrated beneficial effects on fatigue among individuals screened for fatigue and those with related symptoms (eg, depression, anxiety, fear of recurrence) after treatment completion. Given the high level of evidence from RCTs designed specifically to address fatigue, clinicians should work to identify clinical providers of CBT for fatigue in their community settings. Web-based programs have also shown efficacy[54] and have greater potential for dissemination. This should be considered an important offering on the menu of interventions to manage post-treatment fatigue.

2.3. Mindfulness-Based Programs Literature Review Update and Clinical Interpretation

Three eligible trials (N = 736) that examined the effects of mindfulness-based programs on CRF in cancer survivors were identified in the updated literature search.[71-73] One additional qualifying trial identified as part of the original guideline development was also included to inform the recommendation.[74] In two of the trials[72,74] fatigue was a study eligibility criterion, one study screened for depression,[71] and the other trial did not screen patients for study entry.[73] One phase III, multisite trial conducted with younger breast cancer

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survivors with elevated depressive symptoms (N = 247) found that 6 weeks of Mindful Awareness Practices (MAPs) led to a statistically significant reduction in fatigue relative to waitlist control at postintervention ($P < .001$), 3-months follow-up ($P = .039$), and 6-months follow-up ($P = .002$).[71] MAPs also led to decreases in depressive symptoms (primary outcome) and other symptoms. Similarly, MBSR demonstrated greater symptom improvement in fatigue (severity and interference; $P = .01$) in 322 breast cancer survivors compared to usual care at 6 weeks and 12 weeks.[73] A third trial investigating the efficacy of mindfulness-based cognitive group therapy in reducing severe chronic fatigue in cancer survivors with mixed diagnoses found the proportion of clinically improved participants after completion of the mindfulness-based intervention was 30%, compared to 4% in the waiting list condition ($P = .007$).[74] Moreover, the mean fatigue score at postmeasurement was significantly lower in the intervention group than in the waiting list group corrected for pretreatment level of fatigue.[74] In a web-based version of this intervention (web-based mindfulness-based cognitive therapy [eMBCT]), tested in 167 cancer survivors, fatigue severity decreased significantly more in the eMBCT group compared to an unguided active control condition receiving psychoeducational e-mails ($P = .004$).[72] The overall risk of bias was intermediate, although two trials had high risk of bias due to attrition and lack of ITT analysis methods.[72,74]

Mindfulness training is widely available in the community and is practiced by many individuals to improve their functioning and well-being. Thus, it is not surprising that this mind-body intervention has been extensively evaluated to manage fatigue as well as other symptoms common in patients with cancer post-treatment (eg, depression and anxiety). This review identified four RCTs of moderate quality with strong evidence of benefit in the setting of post-treatment fatigue. Although the specific type of mindfulness varied across studies, the consistency of the findings in this setting indicates that clinicians should identify and provide relevant resources for referral of patients. Mindfulness-based programs appear to have beneficial effects on a range of patient-reported outcomes, including anxiety and depressive symptoms,[154,162] sleep disturbance, vasomotor symptoms, intrusive thoughts, positive psychological processes (eg, positive affect, meaning, and peace), and inflammatory biology.[71,163] Not all patients will decide to avail themselves of this practice, but making patients aware of its potential benefits is the most important first step.

2.4. Yoga Literature Review Update and Clinical Interpretation

The updated literature search identified many studies investigating yoga for CRF in cancer survivors; however, only two trials (N = 558) met the inclusion criteria.[43,44] One phase III trial assessed 90-minute Hatha yoga, twice per week for 12 weeks versus a waitlist control group. After adjusting for baseline levels, mean fatigue was not significantly different in the yoga and control groups at the immediate post-treatment assessment ($P = .058$) but was significantly lower in the yoga group at the 3-month post-treatment assessment ($P = .002$).[43] Another trial conducted in 358 cancer survivors experiencing persistent sleep disturbances found participants randomly assigned to the yoga intervention (Yoga for Cancer Survivors: YOCAS) at 2 days per week, each lasting 75 minutes for 4 weeks had significantly greater improvements in CRF post-intervention compared to those receiving standard survivorship care ($P < .01$).[44] Both trials had low risk of bias in all quality elements assessed, except for not using ITT analyses in one trial.[43]

These trials support the efficacy of yoga for reducing fatigue in cancer survivors, although the strength of the recommendation is tempered by the fact that neither of the trials screened for fatigue or had fatigue as the primary outcome. Both interventions used Hatha-based yoga programs, which involve physical postures (including seated, standing, and supine poses) and breathing techniques performed at low to moderate intensity. There is preliminary evidence that the YOCAS approach may also be beneficial for older survivors,[164] although this group is more vulnerable given higher rates of frailty and other comorbidities. More research is required to verify the efficacy of these yoga programs in trials specifically targeting and powered for CRF.

2.5. Acupressure Literature Review Update and Clinical Interpretation

One phase III RCT investigating acupressure for CRF in patients with cancer who had completed cancer treatment at least 12 months prior to study enrollment was identified in the updated literature and met inclusion criteria.[78] In 288 survivors of breast cancer screened for fatigue, relaxing and stimulating acupressure both significantly improved BFI scores compared to usual care at 6 and 10 weeks ($P < .001$), with no significant difference between acupressure arms. The mean percentage fatigue reduction was 34% in relaxing acupressure, 27% in stimulating acupressure, and −1% in usual care after 6 weeks.[78] The trial was assessed to be at low risk of bias.

This recommendation is based on one study that was only conducted in early-stage breast cancer survivors of which 90% were White women.[78] The two acupressure groups (relaxing and stimulating acupressure) were not significantly different from one another, although in a separate pilot study in 43 early-stage breast cancer survivors the relaxing acupressure resulted in a significantly greater reduction of fatigue and was superior to the stimulating acupressure.[165] Self-acupressure is quick to learn, has few and minor adverse effects, and is relatively inexpensive. It can be learned from either a free self-guided mobile app or from a single session with a licensed acupuncturist.[166]

2.6. Moxibustion Literature Review Update and Clinical Interpretation

Two qualifying, phase II RCTs (N = 174) investigating moxibustion, delivered via a machine that applied heat, were identified in the updated literature review.[94,99] One trial investigated Infrared laser moxibustion on CRF in 78 fatigued patients with cancer both during or after treatment.[94] Moxibustion sessions were 20 minutes, held three times per week for 4 weeks. Patients treated with moxibustion had significantly less fatigue than those in the sham group (3.0 *v* 4.4; $P = .002$). The improvement in fatigue persisted to week 8 ($P = .006$). A second multicenter, assessor-blinded, three-arm RCT investigated 8 weeks of machine-delivered moxibustion compared to sham moxibustion, also for 8 weeks, and to usual care in 96 fatigued patients who had completed cancer treatment.[99] BFI scores significantly decreased in moxibustion group compared to the usual care group (mean difference of −1.92, $P < .001$ at week 9 and mean difference of −2.36, $P < .001$ at week 13). Although the sham group also showed significant improvement during the treatment period, with no difference between moxibustion and sham, only the moxibustion group showed improvement after 4 weeks of follow-up (mean difference of −1.06, $P < .001$).

Moxibustion, a Traditional Chinese Medicine technique, shares its theoretical background with acupuncture but has its own effects related to thermal stimulation, biophysical effects, and depending on the form, aromatic and herbal effects.[99] The forms of moxibustion tested in these studies were machine-delivered and did not involve plant material. Several mechanisms may explain its potential efficacy in CRF management, including localized heat application that can enhance blood circulation and potentially improve energy levels.[167] It may also modulate neurotransmitters and regulate the hypothalamic-pituitary-adrenal axis, reduce oxidative stress, and promote relaxation.[167] Acupuncturists select specific points based on the patient's particular symptoms and this tailored approach may enhance treatment outcomes. As moxibustion is noninvasive, it is generally well-tolerated and carries minimal risk of adverse effects.[94,99] However, despite promising findings, rigorous research is needed to elucidate moxibustion's precise mechanisms and guide its integration into clinical practice.

2.7. Wakefulness Agents Literature Review Update and Clinical Interpretation

One randomized multicenter, phase III, double-blinded, placebo-controlled clinical trial, in adults (N = 328) with high-grade glioma and moderate-to-severe fatigue who were clinically stable at least 4 weeks after completing radiation therapy was identified in the updated literature search.[104] Patients were randomly assigned to armodafinil (150 mg or 250 mg once daily) or placebo over 8 weeks. There was no statistically significant difference for clinically meaningful improvement in the BFI usual level of fatigue from baseline to end of week 8, between the 150 mg armodafinil, 250 mg armodafinil, and placebo arms: 28% (95% CI, 20 to 38); 28% (95% CI, 19 to 38); and 30% (95% CI, 21 to 40), respectively ($P = .94$). While the trial had a low risk of bias for all elements assessed, there were important and significant imbalances between groups at baseline in BFI usual level of fatigue in the past 24 hours and BFI global fatigue scores.

Similar to trials conducted in patients undergoing treatment, the one study that met our inclusion criteria in the post-treatment setting found no benefit for armodafinil in improving CRF compared to placebo. The limited effect on CRF may be due to the lack of these agents addressing the range of factors that contribute to CRF in patients with cancer who have completed treatment, which includes biological, psychological, and behavioral processes.[2] The lack of benefit observed in this well-powered trial and the potential risk for long-term adverse effects led to our recommendation against use of these agents in the post-treatment setting. Further research may better inform the role of wakefulness agents for CRF in survivors of cancer.

2.8. Psychostimulants Literature Review Update and Clinical Interpretation

The updated literature search did not identify any new trials in patients who have completed cancer treatment that met the inclusion criteria. As such, evidence identified through existing systematic reviews was included. One qualifying randomized, double-blind, placebo-controlled, parallel-group trial evaluated the potential therapeutic effect and safety of d-methylphenidate (D-MPH) in the treatment of 154 patients with different types of cancer and chemotherapy-related fatigue.[108] Participants were screened and met International Classification of Diseases, Tenth Revision criteria for CRF. At an initial total dose of 10 mg per day (5 mg twice daily) and increased to a maximum of 50 mg per day (dosing frequency could be twice or three times daily) over 8 weeks, D-MPH resulted in a greater improvement in mean change from baseline FACIT-F total score compared with placebo at week 8, which was the primary endpoint ($P = .02$). However, there was a higher rate of adverse events in the D-MPH treatment group and significantly more patients treated with D-MPH compared with patients treated with placebo had adverse events that led to study discontinuation ($P = .02$). The trial had a low risk of bias in all elements assessed.

Clinical trial data indicate limited effectiveness of methylphenidate compared to placebo to support its routine use. Patients with cancer often experience multifaceted symptoms and challenges, and addressing fatigue solely with methylphenidate may not address the underlying causes. Furthermore, higher rates of adverse events,[108] potential interactions with other medications, and the long-term safety of methylphenidate in patients with cancer remain uncertain. Additionally, individual patient

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characteristics, such as comorbidities and different cancer types and treatments, may influence the drug's effectiveness and tolerability. However, it is important to acknowledge that certain patients with cancer might still derive benefits from psychostimulants in addressing conditions beyond CRF, such as fatigue induced by opioids and cancer treatment–related cognitive changes.[168,169] Given the complex nature of CRF and the potential for side effects associated with methylphenidate, a more comprehensive and individualized approach, considering alternative interventions and patient-specific factors, should be prioritized over the use of methylphenidate in the routine management of CRF.

Inconclusive Interventions Literature Review Update and Clinical Interpretation

Based on the current body of evidence, no recommendations can be made for or against these listed interventions. Although some interventions may hold potential benefit for CRF, additional robust studies are required to substantiate effectiveness due to the significant heterogeneity of interventions, methodologic concerns, small sample sizes, and/or compliance with the interventions in the identified studies.

Acceptance and commitment–based or attention-based interventions. The effectiveness of acceptance and commitment (ACT)–based health behavior[67] and attention and interpretation–based interventions[68] on CRF were investigated in two trials in cancer survivors not screened for fatigue. Evidence of benefit was found for attention and interpretation therapy[68] compared to usual care, but no significant intervention effects were seen for CRF with ACT-based health behavior intervention.[67] Further research is required to confirm findings from existing trials.

Acupuncture. Effectiveness of acupuncture for chronic fatigue in patients who completed cancer therapy was assessed in one trial identified in the updated literature search[80] and one older trial.[79] A large RCT included 302 patients with breast cancer who had persistent fatigue (≥5 on 10-point scale).[79] The trial found that after 6 weeks, acupuncture reduced the mean General Fatigue Score significantly more than usual care (−3.11 [95% CI, −3.97 to −2.25]; $P < .001$). The trial was assessed to have a low risk of bias. In contrast, a smaller RCT in 97 fatigued patients with cancer failed to find a significant difference in the BFI scores at days 42 and 49 between acupuncture and sham acupuncture ($P = .9$).[80] Furthermore, no long-term reduction of fatigue scores was observed at the 6-month evaluation ($P = .7$). Bias may have been introduced due to missing data, as a nontrivial number of patients (13 in the acupuncture group, 11 in the sham group) did not complete questionnaires at post-treatment follow-up. Moreover, whether the studied acupuncture regimen (once weekly for 6 weeks) was intensive or long enough to improve postchemotherapy fatigue is not clear. Given the inconsistent results and resulting ambiguity of the role acupuncture can play, further large-scale trials are required to confirm the effectiveness of acupuncture for CRF in patients who have completed cancer treatment.

Bright light therapy. Two trials investigating bright light therapy for fatigued patients after cancer therapy were identified in the updated literature search.[81,82] In one phase II trial, 81 participants with mixed cancer types were randomly assigned to receive a light therapy device that produced either bright white light (intervention) or dim red light (active control), used daily for 30 minutes upon waking for 28 days.[82] Participants in a bright light therapy group reported a 1.49-point greater reduction in MFSI-SF total score after each week of light use than those in the dim red light group ($P = .034$). This amounted to a 17% greater reduction in fatigue among those in the bright light group after 4 weeks, relative to those in the dim red light group.[82] In the second trial, a phase III RCT in 166 fatigued survivors of lymphoma found no significant differences between bright light therapy and dim white light control in the improvement of fatigue over time, as measured by a VAS ($P = .23$), MFI ($P = .73$), and Works and Social Adjustment Scale ($P = .56$).[81] Baseline imbalances,[82] unclear loss to follow-up rates,[81] and uncertainty in whether appropriate ITT analyses were used[82] increased the risk of bias in the included studies, although overall risk of bias was assessed as intermediate.

Ginseng. As described previously, the one identified phase III RCT of American ginseng in 364 patients with cancer during and after treatment found ginseng at a dose of 1,000 mg twice daily improved fatigue in patients undergoing cancer therapy but not in those who had completed treatment.[87] Further research is required to clarify the role of ginseng for CRF in patients who have completed cancer treatment.

Massage. The updated literature search identified one small phase II trial in 66 survivors of breast cancer with persistent fatigue (>25 on BFI).[91] The trial investigated 6 weeks of once-weekly Swedish massage therapy (SMT), lasting 45 minutes and performed by licensed massage therapists, versus light touch (light laying on of hands, in the same sequence and for the same amount of time as the SMT treatment) versus a waitlist control group. There was a significant treatment-by-time interaction for fatigue, with large, standardized treatment effect sizes indicating superiority of SMT over light touch and waitlist control, as well as for superiority of light touch over waitlist control ($P < .0001$). The mean decrease in MFI fatigue for the SMT group exceeded the minimum clinically meaningful difference of 10 points. Although the trial had an overall low risk of bias, larger trials are required to confirm these findings.

Mistletoe. One phase III randomized trial investigating mistletoe extract was identified in the updated literature search.[93] In 220 patients with pancreatic cancer, mistletoe extract at a dose of 0.01-10 mg three times a week for 12 months was found to significantly improve European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire (EORTC QLQ-C30) scores for fatigue (compared to treatment as usual; $P < .001$). The trial

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had an overall intermediate risk of bias and additional investigation is necessary to validate these results.

Omega fatty acids. The updated literature search identified one phase II trial investigating high-dose Omega-3 (O3) versus low-dose O3 and Omega-6 (O3/O6) versus high-dose Omega-6 (O6) for 6 weeks in 97 fatigued survivors of breast cancer.[97] The study found that the O6 group had a statistically significant reduction in CRF level, as measured by the single-item fatigue question on the Symptom Inventory (primary outcome), compared with the O3 group ($P < .01$) and the O3/O6 group ($P = .048$). There were no statistically significant differences in the BFI total score, a secondary outcome, in the O6 group compared with the O3 group ($P = .13$) or the O3/O6 group ($P = .17$). While the study exhibited a low risk of bias, larger trials are necessary to validate these results.

Psychoeducational interventions. Eight RCTs (N = 2,035) investigating the effects of psychoeducational interventions on fatigue in patients with cancer, the vast majority of whom had completed cancer therapy, were identified in the updated literature search.[57-61,63,64,170] There was considerable variability in the type and duration of the interventions, and the majority did not focus explicitly on fatigue. Four trials screened for fatigue,[59-61,63] and fatigue was a primary outcome in five.[57,59,60,63,64] Four trials found patients in the psychoeducation intervention group showed a statistically significant reduction in CRF compared to the control group.[58,60,64,170] In contrast, the other four trials found no significant differences in fatigue levels between psychoeducation and usual care or waitlist controls.[57,59,61,63] While older trials of psychoeducation[122,124,171-173] provide some support for educational interventions, clinical use of patient education programs on their own to optimally reduce CRF after treatment completion is not well established. Due to methodological concerns and important differences in the type of psychoeducation interventions and their components, length of intervention, comparators, and instruments used for assessment, it is not possible to draw robust conclusions on the benefits of psychoeducation in cancer survivors based on the current body of evidence.

Self-management health app. One trial investigating the effectiveness of a self-management mHealth app in reducing fatigue among both patients with cancer and survivors was identified.[123] The study recruited individuals experiencing CRF and randomly assigned them into intervention (n = 519) and control (n = 280) groups. The intervention group gained immediate access to the Untire app, which includes components of CBT, psychoeducation, mindfulness meditation, exercise instruction, and positive psychology, while the control group received access after a 12-week delay. Results indicated that the intervention group exhibited significantly greater improvements in fatigue severity and fatigue interference. Future studies are needed to confirm the effectiveness of a multimodal fatigue intervention delivered via an app for individuals other than middle-aged female patients with breast cancer.

Tai chi and qigong. A phase II RCT in 87 fatigued survivors of breast cancer was identified in the updated literature search.[50] Patients were randomly assigned to qigong and tai chi or sham qigong for 12 weeks. Qigong and tai chi led to a significantly greater decrease in fatigue at both the postintervention ($P = .005$) and 3-month follow-up ($P = .024$).[50] The study had low risk of bias in all elements assessed, except it was not designed to include an ITT analysis, thereby increasing its overall risk of bias.

End of Life

All recommendations for patients with CRF at the end of life are available in Table 5.

3.1. CBT Literature Review Update and Clinical Interpretation

The updated evidence review identified one phase III RCT in patients with advanced cancer.[39] The trial in 134 severely fatigued patients (≥35 Checklist Individual Strength [CIS]-Fatigue score) receiving palliative care treatment found CBT, offered up to 10 individual 1-hour sessions over 12 weeks, significantly reduced fatigue at 14 weeks compared with usual care ($P = .003$). Moreover, positive effects of CBT were sustained for 3 months after the intervention.[39] The study was assessed to have a low risk of bias.

The Poort et al[39] trial provides further evidence of the beneficial effects of CBT for patients with elevated fatigue, including those with advanced cancer. Despite potential challenges of finding clinicians to deliver CBT for fatigue, this approach could be considered for patients with advanced disease.

3.2. Steroids Literature Review Update and Clinical Interpretation

The updated literature search identified one phase III RCT that met the inclusion criteria.[118] In 132 patients with advanced cancer and with ESAS scores ≥4, dexamethasone at a dose of 4 mg twice a day for 14 days was effective in improving CRF at day 15 as measured by the FACIT-F subscale compared to placebo ($P = .008$).[118] Mean change from baseline with dexamethasone was 9 (SD = 10.3) and 3.1 (SD = 9.59) with placebo. The trial had low risk of bias in all domains, except loss to follow-up. Patient dropout resulted in fewer evaluable patients than needed to achieve desired power.[118] High mortality can be expected in trials accruing patients with advanced disease and/or in the palliative care setting. Attrition due to dropout has the potential to cause underpowering of analyses and it elevates the risk of bias. In the included trial, data loss did not differ across the study arms.

Corticosteroids such as dexamethasone are one of the most common adjuvant medications prescribed for the treatment of cancer-related symptoms such as pain, fatigue, anorexia,

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TABLE 5. Summary of Recommendations for Advanced Cancer or End of Life

Recommendation	Evidence Quality	Strength of Recommendation
General note. The following recommendations (strong or conditional) represent reasonable options for patients depending on clinical circumstances and in the context of individual patient preferences. Recommended care should be accessible to patients whenever possible		
3.1. Clinicians may recommend cognitive behavioral therapy (CBT) to manage symptoms of cancer-related fatigue in adults with advanced cancer and/or receiving treatment with palliative intent	Low	Conditional
3.2. Clinicians may recommend corticosteroids to manage symptoms of cancer-related fatigue in patients at the end of life where no contraindications exist. The risk-benefit ratio of corticosteroid use should be assessed over time	Low	Conditional
3.3. Clinicians should not recommend wakefulness agents, such as modafinil or armodafinil, to manage symptoms of cancer-related fatigue in adults with advanced cancer or at the end of life	Moderate	Conditional
3.4. Clinicians should not routinely recommend psychostimulants, such as methylphenidate, to manage symptoms of cancer-related fatigue in adults with advanced cancer or at the end of life	Moderate	Conditional
No recommendation. There is insufficient evidence to make recommendations for or against collaborative care intervention, exercise, melatonin, or protocolized patient-tailored treatment to manage symptoms of cancer-related fatigue among adults with advanced cancer or at the end of life	Insufficient	No Recommendation for or against

NOTE. The strength of the recommendation is defined as follows: strong: in recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects. In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects. All or almost all informed people would make the recommended choice for or against an intervention; conditional/weak: in recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists. In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists. Most informed people would choose the recommended course of action, but a substantial number would not.

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nausea, and well-being in patients at the end of life. A study[118] demonstrating the beneficial effects of corticosteroids on CRF is consistent with the results of prior research on steroids[174-177] in this setting. Although these trials did not meet all the eligibility criteria of our systematic review, the consistency of evidence of benefit supports the use of this agent. Furthermore, in prior studies, short-term use of corticosteroids was considered safe and significantly improved CRF with no difference in adverse events such as insomnia[118,175,178] between the steroid treatment arm and the placebo arm.

3.3. Wakefulness Agents Literature Review Update and Clinical Interpretation

The updated literature search identified two RCTs investigating modafinil for CRF in patients with advanced cancer.[105,106] Both trials screened for fatigue and included 291 total patients with advanced lung[105] or prostate and breast cancer.[106] Modafinil at a once daily dose of 100-200 mg was not significantly effective at alleviating CRF compared to placebo in either trial. Both trials had low risk of bias in quality elements assessed, except for loss to follow-up in one trial, where the attrition rate was 23%.[105]

Similar to that of clinical studies in patients receiving cancer treatment and in those after treatment, studies in advanced cancer have shown limited effectiveness of wakefulness agents, namely, modafinil and armodafinil, in improving CRF compared to placebo. The inability of these wakefulness agents to improve CRF at the dose and duration used in these clinical trials and the lack of clarity of potential risk for long-term adverse events limit the use of these agents.

3.4. Psychostimulants Literature Review Update and Clinical Interpretation

Two phase II RCTs of methylphenidate for CRF in advanced cancer that met the study inclusion criteria were identified in the updated literature search.[109,110] In a total of 290 patients screened for fatigue, total daily doses adjusted between 10 and 25 mg of methylphenidate given for 6 or 15 days did not significantly improve fatigue compared to placebo.[109,110] However, neither trial had a large enough sample size to achieve the specified power to detect a treatment effect. To supplement the updated evidentiary base, evidence from three older trials identified through development of the original guideline was also included. Two older trials[111,112] conducted in a total of 180 patients with advanced cancer who were screened for fatigue also found that methylphenidate failed to significantly improve fatigue, as measured by the selected instruments, compared to placebo. Another trial in 50 fatigued patients with advanced cancer, who were receiving palliative care, found dexamphetamine (10 mg twice daily) did not significantly improve BFI-measured fatigue compared to placebo after 8 days ($P = .27$).[113]

Methylphenidate was the most investigated pharmacological agent for the treatment of CRF especially in advanced cancer. The lack of effectiveness of methylphenidate compared to placebo indicates, in part, that methylphenidate may not target all the causes of the multifactorial etiology of CRF but may be beneficial in a specific subset of CRF patients (patients with CRF with anxiety or depression or CRF with drowsiness).[110] A trial of methylphenidate for the management of debilitating

fatigue at the end-of-life, when symptom management is essential for quality of life, should be cautiously administered by experienced individuals or teams with appropriate credentials for the assessment and treatment with methylphenidate. Continuous monitoring of patients using formal assessment tools is essential to ensure a sustained positive benefit-to-harm ratio. Further studies are needed for use of methylphenidate in combination with other CRF treatments (eg, exercise) or target patients with CRF with depression or drowsiness.[110,151,152]

Inconclusive Interventions Literature Review Update and Clinical Interpretation

Collaborative care intervention. One trial assessed the effectiveness of a collaborative care intervention that included access to a collaborative care coordinator with training and experience with CBT and psycho-oncology.[65] There was a reduction of fatigue observed at 6 months for the intervention group compared to the enhanced usual care arm (effect size of 0.26 [t(15) = 1.80), although this did not reach statistical significance (P = .09). However, fatigue was a secondary outcome, and it did not exclusively recruit patients with elevated fatigue. The trial was assessed to be at an intermediate risk of bias.

Exercise. Three randomized trials investigating exercise interventions compared to usual care failed to find a significant benefit in patients with advanced cancer.[37-39] In 112 patients with advanced lung cancer not screened for fatigue, FACT-T scores did not differ between an 8-week individualized physical activity program and usual care at 2 months (P = .62).[37] Similarly, in 101 patients with advanced breast cancer, not screened for fatigue, a 16-week unsupervised, moderate-intensity aerobic exercise program failed to produce a significant difference in fatigue between patients in the exercise group and those receiving usual care (P = .63).[38] Fatigue, as measured by the FACIT-F at 16 weeks, was a secondary outcome of this trial. A third trial in 134 severely fatigued patients (CIS-fatigue score ≥35) with advanced cancer receiving treatment with palliative intent found no difference between a 12-week supervised, graded exercise program, and usual care (P = .057).[39] While patients reported lower fatigue following the exercise intervention, the difference between groups didn't reach the threshold for statistical significance, likely due to the small sample size and low adherence.[39] Based on the current body of evidence, no recommendations can be made regarding exercise interventions for patients with advanced cancer or at the end of life.

Findings from recent systematic reviews and meta-analyses have been inconsistent for exercise interventions in the advanced cancer setting.[179-182] Evidence from systematic reviews reports exercise improved fatigue in only approximately half of all evaluated studies.[181,182] When data from six exercise trials in patients with cancer receiving palliative care were pooled, fatigue was significantly different between the exercise group and control group, favoring exercise (P = .008).[179] Interventions in the six trials varied considerably in type, supervision, length, intensity, frequency, and duration. Newer research conducted in five European countries plus Australia and presented at the 2023 San Antonio Breast Cancer Symposium showed that patients with metastatic breast cancer participating in a 9-month structured moderate- and high-intensity exercise program reported significantly less fatigue at 3, 6, and 9 months compared to those who did not engage in the program.[183] This large trial stands out from previous ones that influenced the recommendation due to its extended program duration. The need for a longer, ongoing exercise regimen may be necessary for patients with metastatic disease, given the prolonged duration of their treatments. While this trial offers support for supervised exercise in patients with metastatic disease, proceeding with caution in terms of safety and feasibility is paramount for patients with advanced cancer in the palliative care phase. Additional trials with larger sample sizes, that ensure participants receive the minimum required therapeutic dose, yet do not have exercise that is too intense and demanding for those with advanced cancer, are required to firmly establish the effectiveness of exercise on fatigue in this setting.

Melatonin. In one small phase II crossover RCT (N = 72), no significant differences in fatigue, as measured by the MFI-20, were found in patients with advanced cancer receiving 20 mg of melatonin (once daily) for 1 week compared to placebo.[119] The study had a low risk of bias in all domains.

Protocolized patient-tailored treatment. One trial was identified that investigated whether monitoring and protocolized treatment of physical symptoms could alleviate CRF.[69] In 152 fatigued patients with advanced cancer, individuals were randomly assigned to either protocolized patient-tailored treatment (PPT) or usual care. The PPT group, receiving nurse-led interventions based on symptom assessments, showed significant improvements in general fatigue at month 1 (P = .007) and month 2 (P = .005). While these findings indicate that nurse-led monitoring and protocolized treatment of physical symptoms are effective in alleviating fatigue in patients with advanced cancer, an important limitation is the difficulty of reproducing this multimodal intervention. As such, the evidence was deemed insufficient to recommend this protocolized treatment. However, addressing symptoms that can trigger, coincide with, and contribute to the persistence of fatigue is crucial.

DISCUSSION

Since publication of the initial ASCO guideline in 2014,[7] there continues to be active investigation of interventions to prevent and improve CRF. Advances in this area of research include trials with larger sample sizes that have included fatigue as a primary outcome and/or have screened patients for the presence of fatigue as a criterion for trial entry, which have greatly enhanced the strength of this literature. The number and diversity of these studies attest to the prevalence and impact of this symptom and its multifactorial nature. The majority of trials reviewed for this guideline

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focused on exercise, adding to an already robust literature in this area. There is compelling evidence that a variety of exercise programs are effective in reducing the severity of fatigue experienced during and after cancer treatment. These trials have typically taken a prevention approach and have not specifically screened for or targeted patients with fatigue. As such, it is unclear whether exercise is acceptable and effective as a first-line treatment for patients with persistent post-treatment fatigue. Given the benefits of exercise on broad dimensions of physical and emotional well-being, initiating or maintaining an exercise program should be helpful for all cancer survivors. Our review did not identify an optimal type, dose, intensity, or duration of exercise that is maximally effective for reducing CRF; benefits have been seen with interventions that combine aerobic and resistance training, as well as resistance-only interventions, offering maximal flexibility for survivors to choose a program that works for them. Other potentially more gentle movement-based therapies have shown beneficial effects on fatigue and may also be good options, with evidence supporting tai chi and qigong during treatment and yoga after treatment completion.

Another major category of interventions for CRF is psychosocial in nature and addresses the cognitive, behavioral, and emotional factors that may influence fatigue, either directly or indirectly. CBT and mindfulness-based programs both yield benefit for CRF during and after treatment. In the post-treatment setting, positive effects were seen in trials that screened for fatigue, demonstrating that these interventions are helpful in managing the persistent fatigue that causes serious disruption in quality of life in survivors. These interventions are typically delivered by trained providers, but web-based versions of effective in-person programs have also shown benefit[54,72] and may be more accessible and affordable. Clinicians may consider prioritizing recommendations for CBT and mindfulness interventions as initial strategies for managing post-treatment fatigue in this population, pending further research to substantiate the comparative effectiveness of different interventions. Psychoeducational interventions were also found to be helpful for patients during treatment although the evidence here was more mixed, perhaps because of the variability of these programs. In general, providing patients with general information about fatigue and adaptive coping strategies in a supportive environment is recommended but may not be sufficient to bring upon change in those with significant levels of fatigue. There was also evidence of benefit for psychosocial programs that did not fit neatly into a particular category, including interventions focusing on symptom management.[69] Because these were typically single trials of specialized interventions, the Expert Panel felt that the evidence to support them was either insufficient or inconclusive at this time. However, addressing symptoms that may precipitate, co-occur with, and help sustain fatigue is critical for effective patient care. Indeed, as discussed in the original 2014 guideline,[7] patients experiencing fatigue should also be evaluated and treated for contributing comorbid conditions that commonly cluster with fatigue, including pain, depression, anxiety, and sleep disturbance, as well as nutritional deficit, activity level, anemia, medication adverse effects.

A growing number of integrative therapies have been evaluated as treatments for CRF. This is a broad category that encompasses a range of different approaches, including acupuncture, acupressure, dietary supplements, etc On the basis of the current evidence, the panel concluded that American ginseng may be recommended for patients undergoing active treatment and acupressure may be recommended for patients who have completed treatment and are experiencing persistent fatigue. These recommendations are each based on single, rigorous trials, and additional research is needed to bolster the strength of the recommendation. Regarding dietary supplements, the cancer clinical team should ask patients with cancer if they are taking any supplements and, if yes, their purpose for use. If patients are using dietary supplements, the clinical team can ascertain any potential interactions, contraindications, and efficacy of use, and/or identify alternative approaches that might be more effective.

With respect to pharmacotherapies, results indicated that wakefulness agents, psychostimulants, and antidepressants were not effective in reducing CRF and should not be routinely recommended during or after cancer treatment or in patients with advanced disease for this indication. Corticosteroids may be considered to help manage fatigue in patients with advanced cancer. Importantly, the agents that have been tested to date have likely not directly targeted the biologic mechanisms underlying fatigue, which may account for their lack of efficacy. The biology of fatigue is complex, and a variety of mechanisms have been implicated in its etiology and persistence, including dysregulation in key neurotransmitter and neuroendocrine systems, cellular metabolism, and immune and inflammatory activities, with emerging evidence in the gut microbiome.[184-187] Many of these processes are potential targets for intervention, and agents that influence these processes are currently under investigation (eg, bupropion[155]; probiotic supplementation[188]). With continuous advances in our understanding of the biology of CRF, there are exciting opportunities for developing and testing targeted pharmacotherapies to help manage this symptom.

In an effort to maintain the relevance and validity of the guideline, the updated recommendations were crafted on the basis of the most recent and methodologically rigorous evidence. The strict inclusion criteria and reliance on primary studies ensured that the recommendations were informed by the strongest and most robust evidence. In addition, there was a deliberate focus on formulating recommendations that are not only clinically actionable but also reproducible. Trials with fewer than 50 participants or those with fewer than 100 patients where fatigue was a secondary

outcome were not included, nor were systematic reviews or meta-analyses. Moreover, assessing the therapeutic value of multimodal or unique investigator-developed interventions is limited by the difficulty in reproducing these interventions. As such, by adhering to a rigorous set of criteria, our guideline selectively incorporated only the most pertinent and robust evidence. This emphasis on formulating recommendations that are clinically actionable and reproducible, coupled with the methodological rigor used, distinguishes these recommendations from those found in more inclusive CRF guidelines.

SPECIAL COMMENTARY

Risk Factors and Prevention

There is significant variability in the experience of fatigue before, during, and after treatment, implying that certain patients may be more susceptible to this debilitating symptom.[189] Research in this domain has predominantly concentrated on demographic, medical, behavioral, and psychosocial risk factors and the neural, neuroendocrine, metabolic, and immune processes involved in the initiation and persistence of fatigue in patients with cancer and survivors.[2] Identifying key risk factors and understanding the mechanisms by which they affect fatigue can be valuable in the identification of individuals experiencing fatigue early in the disease trajectory. This knowledge can pave the way for developing focused interventions tailored to those most susceptible. In addition, understanding host factors that influence treatment response will facilitate decisions about which interventions will be most efficacious for which patients.

New Cancer Therapies

Since the publication of the original guideline, the oncology treatment landscape has changed and newer drugs such as immune checkpoint inhibitors (ICIs) and chimeric antigen receptor (CAR) T-cell therapies are more common. In patients treated with ICIs, fatigue occurs in 21%, 25%, and 36% of patients treated with anti–PD-[L]1, anti–cytotoxic T-lymphocyte–associated protein 4, and combination of ICIs, respectively.[190] Fatigue is most likely to occur after the first month after initiation of ICI therapy;[191] however, many patients report long-term fatigue.[192] Similarly, the most common symptom identified by patients related to treatment with CAR T-cell therapy was fatigue in 62% of patients.[193] Fatigue can also be a symptom of other forms of immunotherapy toxicity, including adrenal insufficiency, hypothyroidism, hypophysitis, hepatitis, renal insufficiency, pneumonitis, neurologic toxicities, and anemia.[190] The Society for Immunotherapy of Cancer recommends that an evaluation for patients with new or worsening ICI-related fatigue should include CBC count, comprehensive metabolic panel, thyroid-stimulating hormone, free thyroxine, morning cortisol, and adrenocorticotropic hormone.[190] If other organ-specific toxicities are ruled out, ICI-related fatigue should be managed similar to CRF. Although the trials reviewed for this guideline did not include patients undergoing treatment with immunotherapy, managing fatigue specifically in these patients is an important focus in future research.

Intervention Accessibility

The majority of published intervention trials for CRF involve in-person interventions delivered by trained providers. This restricts access and limits the reach of many interventions. However, the emergence of digital interventions presents a promising solution to this accessibility issue. By leveraging internet or mobile platforms, digital interventions can vastly increase accessibility to fatigue management programs. Nevertheless, the widespread implementation of these digital tools faces hurdles, particularly regarding funding.[194] The development of guided or fully automated digital interventions necessitates significant upfront investment costs, raising questions about sustainable funding models. While the scalability of digital interventions offers immense potential, the real-world uptake may be hindered by patient affordability concerns.[194] To ensure widespread adoption, it is crucial to devise funding mechanisms that cover maintenance expenses without imposing financial burdens on patients. One plausible approach within the US health care system involves integrating costs into insurance coverage, ensuring continual support for system maintenance and user assistance,[194] and thereby optimizing the impact of digital interventions in care for cancer survivors.

Older Adults With Cancer

Older adults with cancer often have unique needs and considerations when it comes to management of their CRF. Older patients with cancer might have multiple chronic conditions, increased medication burden, and decreased physical and cognitive function, which can exacerbate their experience of fatigue. In addition, they might have limited support systems and social isolation, intensifying their symptoms. As such, the treatment of CRF in older adults requires a comprehensive and individualized approach that accounts for such concerns. This may include the implementation of interventions that target modifiable risk factors, such as physical activity programs, as well as the provision of supportive care services, such as counseling and social support groups, to address the physical, emotional, and psychological impact of cancer and its treatment.

LIMITATION OF THE RESEARCH AND FUTURE RESEARCH

Studies investigating the management of fatigue in patients with cancer pose numerous challenges. Notably, the literature includes many studies on interventions for patients experiencing subthreshold levels of fatigue, making it challenging to observe treatment effects because of floor effects. Underpowered trials, unable to detect differences between treatment and control groups, are also a significant concern. Moreover, placebo effects cannot be discounted. Recent clinical trials and reviews have demonstrated the beneficial effect of placebo,

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with open-label placebo having a statistically significant and nontrivial impact on reducing CRF.[116,117,195,196] Future research should acknowledge the significant influence of the placebo effect and ensure adequate statistical power in study designs. Lack of intervention standardization is also an issue across studies of many treatment modalities. This lack of standardization hampers the comparability of studies and poses challenges for interpretation and reproducibility. Finally, because of the practical challenges of locating and assessing relevant non-English studies, this systematic review restricted studies to English language only. By excluding trials conducted in languages other than English, the review might have inadvertently missed valuable research, particularly for integrative therapies, which are often rooted in cultural and traditional practices and published in non-English journals. These additional studies could have contributed to a more comprehensive understanding of interventions effective for CRF. Nonetheless, this systematic review, with its strict inclusion criteria and reliance on primary studies, drew from the strongest and most robust evidence to inform the recommendations.

A recurring concern identified in our literature review pertains to the limited diversity in the samples used in studies. The predominant focus has been on White, well-educated, middle-age, upper and middle-class women diagnosed with breast cancer across various modalities. Consequently, making recommendations for individuals outside this demographic is challenging because of the evident research gap. To address these gaps, the Expert Panel urges researchers to actively target participants from more diverse racial and socioeconomic backgrounds, emphasizing cancers other than breast cancer. This cultural transformation aligns with a growing acknowledgment and emphasis on this priority from both researchers and funders, signifying a promising momentum toward inclusivity.

This guideline highlights scientific gaps in several interventions for CRF. To enhance the evidence base, it is essential to undertake meticulous intervention development, thorough testing, and well-designed and executed RCTs. In cases of mixed results, such as with acupuncture for post-treatment fatigue, it is crucial to conduct additional large-scale trials to address the ambiguity arising from a combination of positive and negative trial outcomes. Future trials should have fatigue as a primary outcome and include patients who meet a minimum threshold for fatigue. Surprisingly, there were relatively few studies identified in the systematic review that did so, including for interventions already assumed to be effective like exercise. Further research in fatigued patients would contribute to the evidence-base significantly.

PATIENT AND CLINICIAN COMMUNICATION

Effective implementation of guideline recommendations for CRF hinges upon robust communication between patients and clinicians. However, recent studies have highlighted critical gaps in patient-physician interactions regarding CRF.[197-199] Contrary to guideline recommendations, a significant proportion of physicians fail to address CRF adequately.[198] Barriers include insufficient knowledge, time constraints, and a lack of accessible screening tools or clear referral pathways. From the patient's perspective, additional hurdles emerge. During brief health consultations, the priority often centers on cancer control, leaving limited room for comprehensive fatigue discussions.[198] Patients may lack the stamina for extended visits solely dedicated to fatigue management. Furthermore, health care practitioners' attitudes toward fatigue—whether dismissive or empathetic—shape patient experiences and willingness to engage in dialogue.[197-199] When patients speak, all too often, clinicians interrupt them after only a few seconds.[200]

To bridge these gaps, fostering open communication becomes paramount. Patients should be encouraged to articulate their fatigue symptoms, describing severity, temporal patterns, and the impact on daily life. Active listening by clinicians allows tailoring of interventions to individual needs. Emphasizing shared decision making and realistic expectations—coupled with ongoing communication—forms the bedrock of effective CRF management. It is noteworthy to highlight the potential risk within certain cultures or among individuals who may refrain from disclosing alternative interventions used to manage CRF symptoms, such as herbal remedies, cannabis, or prayer, because of apprehension about potential criticism or judgment from health care providers, which could adversely affect treatment outcomes or healing processes. As we navigate the complexities of cancer care, addressing CRF requires collaborative efforts that honor both medical expertise and patient perspectives.

For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: ASCO Consensus Guideline.[201]

HEALTH EQUITY CONSIDERATIONS

Although ASCO and SIO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care or receive fragmented care. Factors such as race and ethnicity, age, socioeconomic status, sexual orientation and gender identity, geographic location, insurance access, and access to quality health care are known to affect cancer care outcomes.[202] People with cancer who are members of underserved groups suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving fragmented care or poor quality care.[203-206]

According to the American Association for Cancer Research 2022 progress report on cancer disparities, minoritized and underserved populations shoulder a disproportionate

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burden of the adverse effects of cancer and cancer treatment, including physical, emotional, psychosocial, and financial challenges. People with cancer who are Black consistently report poorer quality of life and physical and mental health compared with cancer survivors who are White, found in studies of breast, prostate, or colorectal cancer.[207-213] Underscoring this finding, significant factors like intergenerational poverty founded that mistrust of US medical systems and research, and cultural differences regarding behavioral health all contribute to this health disparity.[214]

Awareness of these disparities in access to care and barriers to uptake of treatments for CRF[215] should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these under-resourced populations. In addition, stakeholders should work toward achieving health equity by ensuring equitable access to both high-quality cancer care and research and addressing the structural barriers that preserve health inequities. At the institutional level, education in health equity and social determinants of health as well as documentation of patient descriptive characteristics in clinical care and in research, for example, race and ethnicity, gender identity, socioeconomic status, is essential. By systematically capturing and analyzing such data, perhaps by leveraging the electronic medical record, health care providers can identify and mitigate disparities in health care access and outcomes, thereby fostering greater equity in patient care delivery.

Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to all people with cancer. In addition, stakeholders should work toward achieving health equity by ensuring equitable access to both high-quality cancer care and research and addressing the structural barriers that preserve health inequities.[202]

GUIDELINE IMPLEMENTATION

ASCO-SIO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO's Practice Guideline Implementation Network (PGIN) on the panel. The additional role of this PGIN representative in the guideline panel is not only to assess the suitability of the recommendations to implementation in the community setting but also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among frontline practitioners and survivors of cancer and caregivers and also to provide adequate services in the face of limited resources. The guideline recommendations table and accompanying tools (available at www.asco.org/survivorship-guidelines) were designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN and through SIO. ASCO guidelines are posted on the ASCO website and most often published in the *Journal of Clinical Oncology*. SIO guidelines are posted on the SIO website and here are published in partnership with ASCO.

ASCO and SIO believe that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

For current information, including selected updates, supplements, slide sets, and clinical tools and resources, visit www.asco.org/survivorship-guidelines and https://integrativeonc.org/practice-guidelines/guidelines. The Data Supplement for this guideline includes additional evidence tables, information on quality assessment for RCTs, literature search details, and description of interventions. Guideline recommendations are also available in the free ASCO Guidelines app (available for download in the Apple App Store and Google Play Store). Listen to key recommendations and insights from panel members on the ASCO Guidelines podcast. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net and https://integrativeonc.org/knowledge-center/patients.

RELATED ASCO GUIDELINES

- Screening, Assessment, and Management of Fatigue in Adult Survivors of Cancer[7] (https://ascopubs.org/doi/10.1200/JCO.2013.53.4495)
- Exercise, Diet, and Weight Management During Cancer Treatment[131] (https://ascopubs.org/doi/10.1200/JCO.22.00687)
- Management of Anxiety and Depression in Adult Survivors of Cancer[154] (https://ascopubs.org/doi/10.1200/JCO.23.00293)
- Integrative Oncology Care of Symptoms of Anxiety and Depression in Adults With Cancer[162] (https://ascopubs.org/doi/10.1200/JCO.23.00857)
- Integrative Medicine for Pain Management in Oncology[216] (https://ascopubs.org/doi/10.1200/JCO.22.01357)
- Integration of Palliative Care Into Standard Oncology Care[217] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[201] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)

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GENDER-INCLUSIVE LANGUAGE

ASCO is committed to promoting the health and well-being of individuals regardless of sexual orientation or gender identity.[218] Transgender and nonbinary people, in particular, may face multiple barriers to oncology care including stigmatization, invisibility, and exclusiveness. One way exclusiveness or lack of accessibility may be communicated is through gendered language that makes presumptive links between gender and anatomy.[219-222] With the acknowledgment that ASCO guidelines may affect the language used in clinical and research settings, ASCO is committed to creating gender-inclusive guidelines. For this reason, guideline authors use gender-inclusive language whenever possible throughout the guidelines. In instances in which the guideline draws upon data on the basis of gendered research (eg, studies regarding women with ovarian cancer), the guideline authors describe the characteristics and results of the research as reported.

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EDITOR'S NOTE

This joint Society for Integrative Oncology and ASCO Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at https://integrativeonc.org/knowledge-center/patients and www.cancer.net, is available at https://integrativeonc.org/practice-guidelines/guidelines and www.asco.org/survivorship-guidelines.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Management of Fatigue in Adult Survivors of Cancer: ASCO–Society for Integrative Oncology Guideline Update

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APPENDIX 2. GUIDELINE AND CONFLICTS OF INTEREST

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/guideline-methodology). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

TABLE A1. Management of Fatigue in Adult Survivors of Cancer Expert Panel Membership

Name	Affiliation	Role or Area of Expertise
Julienne E. Bower, PhD, Co-chair	University of California, Los Angeles, Los Angeles, CA	Psychology
Karen Mustian, PhD, Co-chair	University of Rochester Medical Center, Rochester, NY	Exercise Physiologist
Yesne Alici, MD	Memorial Sloan Kettering Cancer Center, New York, NY	Psychiatry
Debra L. Barton, RN, PhD	University of Tennessee, College of Nursing, Knoxville, TN	Integrative Medicine and Nursing
Deborah Bruner, RN, PhD	Emory University, Atlanta, GA	Radiation Oncology
Beverly E. Canin	Breast Cancer Options, Kingston, NY	Patient Representative
Carmelita P. Escalante, MD	MD Anderson Cancer Center, Houston, TX	Internal Medicine
Patricia A. Ganz, MD	University of California, Los Angeles, Los Angeles, CA	Medical Oncology/Survivorship
Sheila Garland, PhD	Memorial University, St John's, Newfoundland, Canada	Integrative Oncology and Behavioral Sleep Medicine, Society for Integrative Oncology Representative
Shilpi Gupta, MD	Staten Island University Hospital, Staten Island, NY	PGIN Representative/Community Oncology
Heather Jim, PhD	Moffitt Cancer Center, Tampa, FL	Behavioral Oncology Research
Jennifer Ligibel, MD	Dana Farber Cancer Institute, Boston, MA	Medical Oncology
Kah Poh Loh, MBBCh BAO, MS	University of Rochester Medical Center, Rochester, NY	Hematology/Medical Oncology/Geriatric Oncology
Luke Peppone, PhD	Wilmot Cancer Institute, University of Rochester, Rochester, NY	Nutraceuticals
Debu Tripathy, MD	MD Anderson Cancer Center, Houston, TX	Medical Oncology, Society for Integrative Oncology Representative
Sriram Yennu, MD, MS	MD Anderson Cancer Center, Houston, TX	Medical Oncology/Pharmaceuticals/Palliative Care
Suzanna Zick, ND, MPH	University of Michigan, Ann Arbor, MI	Integrative Medicine in Cancer Survivorship, Society for Integrative Oncology Representative
Christina Lacchetti, MHSc	American Society of Clinical Oncology, Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)

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TABLE A2. Recommendation Rating Definitions

Term	Definitions
Quality of evidence	
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. Reliance on consensus opinion of experts may be reasonable to provide guidance on the topic until better evidence is available
Strength of recommendation	
Strong	In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects
	In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects
	All or almost all informed people would make the recommended choice for or against an intervention
Conditional/Weak	In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists
	In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists
	Most informed people would choose the recommended course of action, but a substantial number would not

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