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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Survivorship
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Survivorship

Disclosure of Relevant Financial Relationships

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To view all of the conflicts of interest for the NCCN Guidelines panel, go to NCCN.org/guidelines/guidelines-panels-and-disclosure/disclosure-panels

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Survivorship, Version 1.2023

Featured Updates to the NCCN Guidelines

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ABSTRACT

The NCCN Guidelines for Survivorship are intended to help healthcare professionals address the complex and varied needs of cancer survivors. The NCCN Guidelines provide screening, evaluation, and treatment recommendations for psychosocial and physical problems resulting from adult-onset cancer and its treatment; recommendations to help promote healthy behaviors and immunizations in survivors; and a framework for care coordination. These NCCN Guidelines Insights summarize recent guideline updates and panel discussions pertaining to sleep disorders, fatigue, and cognitive function in cancer survivors.

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NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines Insights highlight important changes in the NCCN Guidelines recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.**

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The complete and most recent version of these NCCN Guidelines is available free of charge at NCCN.org.

GENERAL SLEEP HYGIENE[a,1,2,3]

- **Maintain a regular bedtime and waketime every day.**
- **Engage in regular physical activity in the morning and/or afternoon (SPA-1). Avoid moderate to strenuous physical activity within 3 hours of bed time.**
- **~~Increase exposure to bright light during the day~~ Exposure to daytime bright light, particularly in the morning.**
- **Reduce exposure to bright light (ie, computer, phone screens, light sources close to the eye) within a few hours before bedtime and during the night.**
- **Avoid heavy meals and limit fluid intake within 3 hours of bedtime.**
- **Avoid alcohol and nicotine too close to bedtime.**
- **Limit caffeine consumption and avoid caffeine consumption at least 4 hours before bedtime.**
- **Enhance sleep environment (dark, quiet room; comfortable temperature).**
- **Avoid looking at the clock when awake during the night.**
- **If necessary, limit daytime sleep to 1 short nap per day in the afternoon (no longer than 30 min).**
- **Turn off electronics and light-emitting sources at bedtime.**

Other Sleep Interventions
- If survivor is not able to fall asleep within 45 minutes or if they wake up in middle of night and can't fall back to sleep, consider using the following sleep strategy:
  - Get up, go to a different location, but stay in a darkened room and do non-stimulating activity like watching a relaxing TV show or reading a relaxing non-stimulating book. Once survivor feels sleepy again they should try to go to bed. The goal is to help the body associate the bed with sleeping.
- Other sleep interventions include the use of:
  - Sleep apps, meditation apps, breathing exercises, and strategies to reduce worrying (ie, write a "to do" list or set aside "worry time")

Footnote
[a] Sleep hygiene alone has not been shown to be effective, but should be part of the initial treatment of all survivors with sleep disorders and as a prevention strategy for insomnia disorder. Sleep hygiene alone is not the recommended treatment for insomnia, but should be used in conjunction with other treatments such as CBT-I and/or pharmacotherapy. Use of general sleep hygiene measures should not delay other interventions or referral to a specialist, especially if quality of life is impacted or if sleep problems (eg, insomnia) are severe (Edinger JD, et al. J Clin Sleep Med 2021;17:255-262).

References
[1] National Heart, Lung, and Blood Institute Working Group on Insomnia. Insomnia: Assessment and Management in Primary Care. 1998. NIH Publication. 98-4088.
[2] Kupfer DJ and Reynolds CF. Management of insomnia. N Engl J Med 1997;336:341-346.
[3] Lippmann S, Mazour I, Shahab H. Insomnia: therapeutic approach. South Med J. 2001;94:866-873.

SSD-A

Overview

The NCCN Survivorship Panel comprises a multidisciplinary group of experts that includes at least one of each of the following: medical and hematologic oncologists, radiation oncologist, surgical oncologist, pediatric oncologist, physician specializing in bone marrow transplantation, gynecologist, urologist, cardiologist, neurologist, primary care physician (PCP), supportive care specialist, psychologist, psychiatrist, nutrition scientist, nurse, epidemiologist, social worker, and cancer survivor/patient advocate. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Survivorship provide screening, evaluation, and treatment recommendations for late and long-term physical and psychosocial consequences of cancer and cancer treatment to aid healthcare professionals who work with survivors of adult-onset cancer. Preventive health guidance is also provided to help promote physical activity, a healthful diet and weight management, and proper immunizations. The guidelines also provide recommendations for coordination of survivorship care to help ensure that all needs are addressed.

There are currently >18 million cancer survivors in the United States, and this number is projected to surpass 22 million by 2030.[1,2] Unfortunately, a considerable number of survivors experience late and/or long-term physical and/or psychosocial effects of cancer and its treatment.[3–5] Sleep disturbances, fatigue, and cognitive decline are among the most common problems reported by survivors, and they often co-occur.[6–9] Poor sleep, fatigue, and cognitive difficulties can each have a profound impact on function and quality of life (QoL), and individuals experiencing these symptoms often do not fully participate in the roles and activities that make life meaningful.[10–12]

These NCCN Guidelines Insights provide an overview of these common concerns in the survivorship population, summarize relevant discussions of the latest data that occurred during the panel's most recent annual meeting, and illustrate the latest changes in the guidelines for these topics.

Sleep

Sleep disturbances include insomnia (trouble falling or staying asleep resulting in daytime dysfunction), excessive sleepiness (which can result from insufficient sleep opportunity, insomnia, or other sleep disorders), and sleep-related movement or breathing disorders (obstructive sleep apnea [OSA] or restless leg syndrome [RLS]).[13] Long-term sleep disturbances affect approximately one-third of cancer survivors.[14] Sleep disorders are a result of multiple factors, including disease- or treatment-related biologic

COGNITIVE BEHAVIORAL THERAPY FOR INSOMNIA (CBT-I)[1,a]

Strategy	Goal
Cognitive therapy[2] or internet-based cognitive behavioral therapy for insomnia	Challenge survivor's maladaptive beliefs and misconceptions about sleep disturbances
Stimulus control	Associate the bed/bedroom as a place for sleep or sexual activity only
Sleep restriction	Improve sleep continuity by: • Limiting time spent in bed[b] • Maintaining a regular sleep schedule by keeping a standard bedtime and wake time every day
Relaxation training	• Reduce physiologic and cognitive arousal at bedtime • Techniques include progressive muscular relaxation, deep breathing, meditation, yoga, and biofeedback • Visualization

Footnotes
[a] The American Academy of Sleep Medicine (AASM) includes a strong recommendation for multicomponent CBT-I and conditional recommendations for stimulus control, sleep restriction, and relaxation therapy as single-component therapy options for the treatment of insomnia. Edinger JD, Arnedt JT, Bertisch SM, et al. J Clin Sleep Med 2021;17:255-262.
[b] Match total amount of time spent in bed to the actual amount of time spent sleeping (no less than 5 hours).

References
[1] Data from Bootzin RR and Perlis ML. Nonpharmacologic treatments of insomnia. J Clin Psychiatry 1992;53(suppl):37-41.
[2] Johnson JA, Rash JA, Campbell TS, et al. A systematic review and meta-analysis of randomized controlled trials of cognitive behavior therapy for insomnia (CBT-I) in cancer survivors. Sleep Med Rev 2016;27:20-28.

SSD-B

changes in sleep and wake regulation, the stress of diagnosis and treatment, and side effects of therapy (eg, pain, fatigue).[15] These sleep disturbances can persist after treatment due to lasting symptoms, such as anxiety and depression; side effects from medications; and maladaptive behaviors, such as shifting sleep times, excessive time in bed because of fatigue, and unplanned daytime naps.[15–17] Importantly, sleep disorders have been shown to be a risk factor for suicide.[18]

Improvements in sleep quality lead to improvements in fatigue, mood, and overall QoL.[19] In addition, there is some evidence that better sleep quality may correlate with improved survival in people living with and after cancer.[20,21] Unfortunately, many cancer survivors receive suboptimal care because they are not screened for sleep disorders and thus are not referred for treatment.[22]

Screening, Evaluation, and Management of Sleep Disorders

Survivors should be screened for possible sleep disorders, including insomnia, OSA, RLS, and circadian rhythm sleep–wake disorders, at regular intervals, especially when they experience a change in clinical status or treatment. If there are significant concerns regarding sleep quality, treatable or modifiable contributing factors should be assessed and managed. Comorbidities that can contribute to sleep problems include alcohol and substance abuse disorder, obesity, cardiac dysfunction, endocrine dysfunction, respiratory disorders, anemia, neurologic disorders (including chemotherapy-induced peripheral neuropathy), pain, fatigue, and emotional distress. In addition, some medications, both prescription and over-the-counter, can contribute to sleep issues. For instance, pain medication, antiemetics, antihistamines, antidepressants, and antipsychotics can all contribute to sleep disturbance.

The panel recommends cognitive behavioral therapy for insomnia (CBT-I) as the preferred treatment for insomnia. A meta-analysis of randomized controlled trials in cancer survivors found strong evidence that CBT-I can produce large and durable effects on insomnia severity.[23] Sleep hygiene education should also be included in the initial treatment of all survivors with sleep disorders and as a prevention strategy for insomnia disorder, but only as part of a multicomponent approach with CBT-I or pharmacologic treatment.[24] Sleep hygiene alone has not been shown to be effective for insomnia, and its use should not delay other interventions or referral to a specialist, especially if QoL is impacted or if sleep problems are severe.[24] Sleep hygiene education includes many practical recommendations, such as maintaining a regular bedtime and

PRINCIPLES FOR CHOOSING AN FDA-APPROVED HYPNOTIC AS SECOND-LINE THERAPY:[a-f]

- **Does the patient have difficulty initiating or maintaining sleep?**
- **Does the patient have both sleep onset and sleep maintenance difficulty?**

AGENT	HELPS WITH SLEEP INITIATION	INCREASES TOTAL SLEEP TIME	INDICATED FOR SLEEP INITIATION AND MAINTENANCE
Zolpidem	+	+	–
Zolpidem CR	+	+	+
Zaleplon	+	–	–
Eszopiclone	+	+	+
Ramelteon	+	±	–
Temazepam	+	+	+
Doxepin (3–6 mg)	–	+	+
Suvorexant	+	+	+
Lemborexant	+	+	+
Daridorexant	+	+	+

[a] These agents should only be used after all other methods have been deemed unsuccessful. CBT-I is the preferred first-line treatment option (SSD-2).
[b] Data from the Physicians' Desk Reference (ed 66). Montvale, NJ: PDR Network, LLC; 2012.
[c] Inform patients that taking hypnotic medications may cause complex sleep-related behaviors (eg, sleep driving, sleep eating).
[d] Other commonly used medications for insomnia include sedating medications such as antidepressants (eg, trazodone, mirtazapine), antihistamines, atypical antipsychotics, other benzodiazepine receptor agonists, and nutritional/herbal supplements (eg, melatonin). They do not have an FDA-approved indication for the treatment of insomnia, and do not have enough data to be recommended for routine use. Trazodone is one of the most commonly used medications for insomnia, but due to paucity of evidence of its long-term efficacy and safety, it is not recommended for routine use (Kansagara D., et al. Ann Intern Med 2016;165:892; Sateia MJ, et al. J Clin Sleep Med 2017;13:307-349; Wilt TJ, et al. Ann Intern Med 2016;165:103-112).
[e] Most of these agents, with the exception of ramelteon, doxepin, suvorexant, and lemborexant are benzodiazepine receptor agonists and can be associated with dependence, misuse, and withdrawal. Assessment for the continued need of hypnotics is recommended every 1–3 months.
[f] Refer to package insert for specifics regarding potential for drug-drug interactions, side effects, risk of dependency, black box warnings, or other problems with these drugs.

SSD-C

waketime; increasing daytime exposure to bright light and reducing it near bedtime; and limiting screen time, heavy meals, fluid intake, alcohol, nicotine, and caffeine near bedtime.

In addition, regular physical activity in the morning and/or afternoon should be encouraged for survivors with sleep problems. Physical activity can improve sleep in individuals without cancer,[25–27] and data show that it may also improve sleep in patients with cancer and survivors.[28–35]

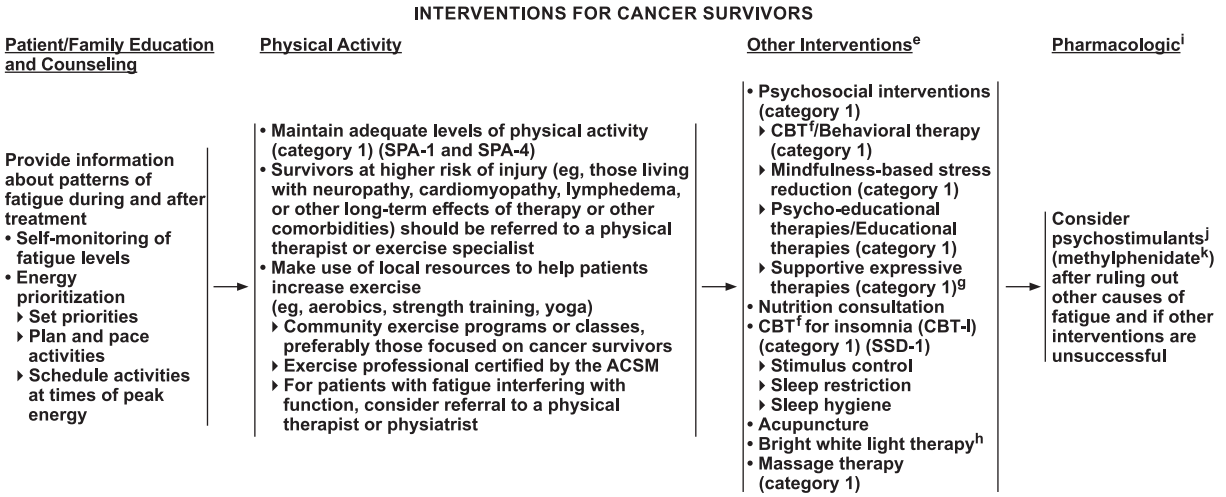
Many pharmacologic treatments for sleep disturbances are available, including FDA-approved hypnotics for insomnia. Many of these hypnotics are benzodiazepine receptor agonists and can be associated with dependence, abuse, and withdrawal. The panel therefore recommends that survivors taking these medications be assessed every 1 to 3 months to determine whether the medication is still needed. In addition, survivors should be informed that hypnotic medications may cause complex sleep-related behaviors (eg, sleep driving, sleep eating). Antidepressants, antihistamines, atypical antipsychotics, other benzodiazepine receptor agonists, and nutritional/herbal supplements (eg, melatonin) are often used off-label for the treatment of insomnia, even though limited to no efficacy or effectiveness data are available for this use.[36,37] The panel noted that these medications can be associated with significant risks and should be used with caution.

Referral to a sleep specialist if one is available can be considered, especially for OSA, RLS, parasomnias, circadian rhythm disorders, narcolepsy, and chronic or refractory insomnia.

Panel Discussion and Recent Updates

This year, the panel discussed the recommendation for exposure to bright light. Data in noncancer populations show that bright light therapy can be an effective treatment to help synchronize circadian rhythms and improve sleep.[38,39] It is noninvasive with little to no side effects and can also improve mood. The recommendation in the 2022 version of the NCCN Guidelines was to "increase exposure to bright light during the day" as part of general sleep hygiene. The panel consensus was that the light in the morning has the strongest effect. They therefore adjusted the wording to: "Exposure to daytime bright light, particularly in the morning" (see SSD-A, page 794).

CBT-I has been shown to be effective for improving both sleep and fatigue in cancer survivors.[23,40,41] CBT-I is a multicomponent intervention that combines cognitive therapy strategies with education about sleep regulation, stimulus control, sleep restriction, sleep hygiene, relaxation



[e] Interventions should be culturally specific and tailored to the needs of patients and families along the illness trajectory, because not all patients may be able to integrate these options due to variances in individual circumstances and resources.
[f] A type of psychotherapy that focuses on recognizing and changing maladaptive thoughts and behaviors to reduce negative emotions and facilitate psychological adjustment.
[g] Supportive expressive therapies (such as support groups, counseling, and journal writing) facilitate expression of emotion and foster support from one or more people.
[h] Bright white light therapy of 1250–10,000 lux is most frequently self-administered in the early morning for ~~30–90~~ 30–40 minutes. Timing needs to be adjusted for those who sleep during the day. ~~Johnson J, et al. J CA Survivorship 2018;12:206-215.~~ Xiao P, et al. J Pain and Symptom Manage 2022;63:e188-e202.
[i] Pharmacologic interventions remain investigational, but have been reported to improve symptoms of fatigue in some patients.
[j] Psychostimulants are at times used to treat cancer-related fatigue. A number of studies have evaluated their efficacy in the setting of active treatment and results have been mixed. There are extremely limited data regarding the use of these agents in the post-treatment setting.
[k] Methylphenidate should be used cautiously and should not be used until treatment- and disease-specific morbidities have been characterized or excluded. Optimal dosing and schedule have not been established for use of psychostimulants in patients with cancer.

SFAT-5

training, and/or other counter-arousals methods.[24] CBT has been the preferred first-line treatment for insomnia in the NCCN Guidelines for several years. In 2021, this recommendation was clarified to specify that it referred to CBT-I, based on clinical guidelines from the American Academy of Sleep Medicine (AASM). At the 2023 panel meeting, it was noted that the supplemental chart of cognitive behavioral treatments did not specify CBT for insomnia. In addition, panel members noted that CBT was shown third in a list of 4 items. As the preferred option, panel members suggested that it be moved to the top of the list. The panel also added a footnote noting the AASM's strong recommendation for CBT-I and the weaker recommendation for the other options (see SSD-B, page 795).

Daridorexant is a selective dual orexin receptor antagonist (DORA) that was FDA approved in December 2022. The guidelines already included 2 other DORAs in a table of FDA-approved hypnotic therapies that can be considered for second-line therapy: suvorexant and lemborexant. The panel noted that, among the 3 DORAs, daridorexant has the shortest half-life at approximately 8 hours. The panel unanimously agreed to add daridorexant to the table (see SSD-C, opposite page). The panel also decided to add a caution against the routine use of trazodone for treatment of insomnia in cancer survivors, because it is commonly prescribed despite a lack of data on its efficacy and safety.[42,43]

Fatigue

NCCN defines cancer-related fatigue as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning." Fatigue is nearly universal during cancer treatment, and as many as 52% of cancer survivors experience persistent fatigue for years after the completion of active therapy.[44] Receipt of chemotherapy, radiation therapy, endocrine therapy, targeted therapy, and/or cellular therapy are predisposing factors for cancer-related fatigue, but it can also be seen in patients who are treated with surgery alone.

The proposed pathophysiologic mechanism of cancer-related fatigue is multifactorial and likely includes proinflammatory cytokines, neuroinflammation, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, circadian rhythm desynchronization, disrupted energy metabolism, skeletal muscle wasting, neurotransmitter dysregulation, and vagal afferent activation.[44,45]

Persistent cancer-related fatigue can affect QoL and function in profound ways, including the ability to work

COGNITIVE FUNCTION FOLLOWING CANCER TREATMENT

General Principles

- **Growing evidence supports the validity of the patient-reported experience of cognitive dysfunction associated with cancer diagnosis and treatments.**
- **Neuropsychological testing and brain imaging have demonstrated abnormalities in patients diagnosed with and treated for cancer.**
- **Currently no effective brief screening tool for cancer-associated cognitive dysfunction has been identified. Existing diagnostic tools do not strongly correlate with patient reports of cognitive dysfunction. The Mini-Mental State Examination (MMSE®)[a] and similar screening tools lack adequate sensitivity for the more subtle decline in cognitive performance most commonly seen in cancer survivors.**
- **There is limited evidence to guide management of this condition.**
- **Patients benefit from validation of their symptom experience, a thorough evaluation of this concern and related issues, and education.**
- **Cognitive ~~function~~ concerns should be systematically assessed using self report.**
- **Providers need to be aware that self-report of cognitive concerns, or the lack thereof, is not a surrogate for measurement of the presence or absence of impairment in cognitive function.**
- **Imaging studies may not be helpful, except to rule out structural abnormalities as indicated by high-risk illness, or focal neurologic deficits or comorbidities.**
- **Patients who report cognitive impairment should be screened for potentially reversible factors that may contribute to cognitive impairment (ie, depression, sleep disturbance, fatigue, delirium).**
- **These guidelines address cognitive function of survivors with non-CNS malignancies who did not have CNS-directed therapies.**

[a] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-198.

SCF-1

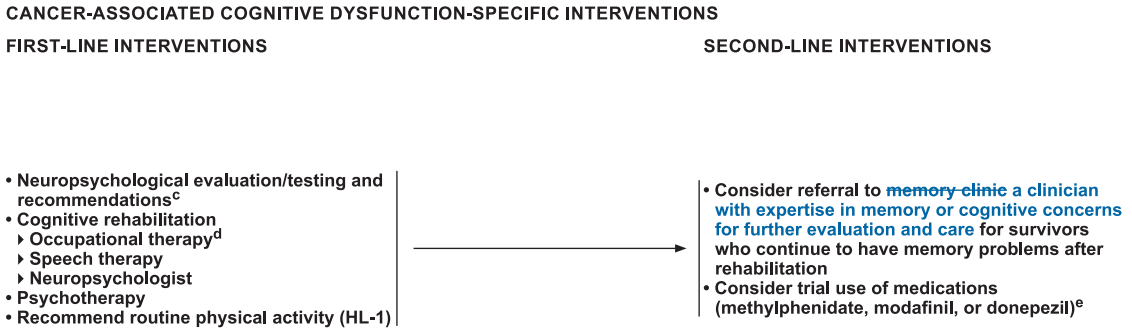
and support oneself and one's family, with wide-ranging consequences not only for the cancer survivor but also for the entire family unit.[46] As one example, severe fatigue in survivors of Hodgkin lymphoma is associated with a decreased likelihood of employment.[10] In fact, fatigue can cause disability-related issues for cancer survivors, because obtaining or retaining disability benefits from insurers is often difficult for patients with cancer-related fatigue. Nevertheless, fatigue remains underreported, underdiagnosed, and undertreated in cancer survivors.[44,47]

Screening, Evaluation, and Management of Fatigue

All survivors should be screened for fatigue to ensure that those with moderate to severe fatigue receive proper workup and are treated promptly and effectively. Because fatigue is a subjective experience, clinicians must rely on patients' descriptions of their fatigue level. The panel recommends the use of a severity scale (eg, 0–10; none, mild, moderate, or severe). Studies in patients with cancer have revealed a marked decrease in physical functioning at a reported fatigue level of ≥7 on a scale of 0 to 10.[48,49]

Survivors with scores indicating no or mild fatigue require no further assessment or interventions; these patients should be rescreened at regular intervals. They should also receive education and counseling on general strategies for fatigue management. Patients with scores indicating moderate or severe fatigue should be evaluated further with a more focused history and physical examination. Screening for common contributing factors such as emotional distress, sleep disturbance, pain, and the use of prescriptions or over-the-counter medications or supplements is also recommended, and possible medical causes of fatigue should be assessed (eg, cardiac disease, gastrointestinal or hepatic dysfunction, hypothyroidism). It is important to note that a more extensive workup to screen for the presence of metastatic disease or other comorbidities is warranted if moderate to severe fatigue begins after or worsens >6 months after the completion of therapy, or when other symptoms are present, such as pain, pulmonary complaints, or unintentional weight loss.

Management of fatigue in cancer survivors includes nonpharmacologic interventions as first-line treatment. In fact, high-level evidence supports the recommendations for routine physical activity and for several types of psychosocial interventions (eg, CBT).[50–53] Patient education regarding typical patterns of fatigue during and after treatment can help patients cope and set reasonable expectations regarding improvements in energy after the completion of cancer therapy, and can also help address concerns that persistent fatigue after the completion of



[c] Neuropsychological evaluation and intervention may be therapeutic and validating. Evaluation may also be necessary if an individual is pursuing disability benefits and cognitive impairment is a contributing factor to work limitation.
[d] Occupational therapy strategies focus on improvement of cognitive functioning and may be most effective for an individual who notes the impact of specific functional limitations (ie, word finding, comprehension or task completion, quality-of-life or role expectations).
[e] Overall the evidence for these medications is lacking, but there may be some benefit in select survivors or certain clinical scenarios.

SCF-4

therapy is evidence of disease recurrence. Counseling can help patients develop strategies for self-monitoring of fatigue and techniques such as energy prioritization that may be helpful in the immediate posttreatment period.[54]

Contributing factors such as pain, distress, anemia, and sleep disturbances should also be addressed. In a randomized controlled trial of 152 patients with advanced cancer who endorsed fatigue, treatment of accompanying physical symptoms, including pain, nausea, vomiting, and shortness of breath, resulted in a significantly higher impact on general fatigue, activity, and motivation than usual care.[55]

Pharmacologic interventions are reserved for situations when other interventions have been unsuccessful and after ruling out other causes of fatigue. The psychostimulant methylphenidate is used to treat fatigue, although data regarding its use to treat fatigue in cancer survivors are very limited. A 54% response rate to methylphenidate was reported in a phase II trial of 37 breast cancer survivors.[56] Meta-analyses have yielded conflicting conclusions regarding its effectiveness in cancer-related fatigue.[51,57–59] Further study is warranted.

Panel Discussion and Recent Updates

Bright light therapy has been shown to reduce cancer-related fatigue.[60] As noted earlier, it can be part of the management of sleep disorders as well. The panel noted that a recent systematic review identified 13 randomized clinical trials and showed a significant improvement in cancer-related fatigue across a variety of cancer types.[60] However, the studies had different intensities of illumination (measured in lux) and durations, with a wide variation. Therefore, the panel adjusted their recommendation to allow for a large range of lux. They believe that 30 to 40 minutes is a sufficient duration for survivors to see improvements in fatigue (see SFAT-5, page 797).

The panel also discussed whether to add American ginseng as a management option for survivors experiencing fatigue. One trial showed that it could be safe and effective for patients during therapy.[61] However, the trial showed no effect in patients who had completed treatment. Also, 2 systematic reviews since that time have concluded the data are insufficient to consider it as a standard treatment.[62,63] The panel thus decided not to add American ginseng as an option for the treatment of fatigue in cancer survivors.

Cognitive Function

Cognitive dysfunction may be a consequence of tumors themselves, but is most commonly connected with chemotherapy (referred to as “chemobrain” in the lay literature)

or other cancer treatments, including hormonal/endocrine therapy, radiation, and surgery.[64–66] Cognitive concerns (eg, problems with learning, memory, concentration, processing speed, executive function) are reported by approximately 46% of cancer survivors.[67] The prevalence varies by cancer type, ranging from >80% of survivors of central nervous system (CNS) tumors; around half of survivors who had breast cancer, lymphoma, colorectal cancer, or head and neck cancer; 30% of those who had testicular cancer; and <20% of those who had prostate cancer.[67] Younger age; female gender; being separated, divorced, or widowed; working part-time or being unemployed; and having a lower household income are all associated with an increased likelihood that a survivor perceives cognitive dysfunction.[67] It also varies depending on the type of treatment received; those with a history of chemotherapy are approximately 5-fold more likely to report cognitive difficulties than those treated with surgery or radiation. For some survivors, cognitive decline may continue over time after treatment, and symptoms may persist long-term.[68,69]

The underlying mechanisms of cancer-related cognitive changes are not known. A recent study in breast cancer survivors aged >60 years found that increased levels of C-reactive protein were associated with lower self-reported cognition.[70] This and other evidence suggests a possible role for chronic inflammation in cognitive problems after cancer treatment.[71] Furthermore, structural neuroimaging studies have supported the hypothesis that damage to white and/or gray matter of the brain may play an important role in cognitive deficits after chemotherapy treatment, and functional MRI studies show that changes in brain activity accompany cognitive complaints or cognitive deficits in survivors.[71,72] In addition, insomnia and fatigue, which are both common in cancer survivors, may negatively influence cognitive function.[7,9,73] Psychosomatic effects can also contribute, as evidenced by a study of patients to be treated with chemotherapy that found that those who were informed of the possible cognitive side effects were more likely to report cognitive dysfunction and perform worse on neuropsychological testing than uninformed patients.[74]

Cognitive dysfunction can profoundly impact QoL and function; tasks may be left incomplete and there may be difficulty finding words or remembering things. Such examples can affect a person's job performance.[75]

Screening, Evaluation, and Management of Cognitive Dysfunction

Survivors should be screened for cognitive concerns by asking questions such as, "Do you have difficulties with remembering things" and "Does your thinking seem slow?" Assessment is through self- and caregiver-report. Survivors who report cognitive impairment should be evaluated for potentially reversible factors that may contribute to cognitive impairment, including emotional distress, pain, fatigue, and sleep disturbance. They should also be assessed for other possible contributing factors, such as medication side effects (including over-the-counter medications and supplements), alcohol use, and new-onset vitamin deficiencies and endocrinopathies. For those with focal neurologic deficits, neuroimaging is indicated to rule out structural abnormalities (ie, brain or CNS disease). In addition, imaging in the absence of focal findings may be appropriate for patients deemed to be at high risk for recurrence or metastatic disease involving the CNS.

For the management of cognitive decline, the NCCN Survivorship Panel recommends the use of nonpharmacologic interventions whenever possible, with pharmacologic interventions as a last line of therapy in survivors for whom other interventions have been insufficient. Prospective data to inform the use or potential benefits of nonpharmacologic interventions for cancer survivors who report cognitive dysfunction are limited. However, survivors are likely to benefit from validation of their symptom experience and should be reassured that, in most survivors, cognitive dysfunction does not worsen over time. Instruction in self-management and coping strategies (eg, using planners, reminder notes, and/or smart phone technology; keeping items in the same place) can be very helpful. Discontinuation or limitation of medications known to cause or contribute to cognitive impairment should be attempted, and assistance with the management of emotional distress, pain, sleep disturbances, and fatigue should be provided.

Formal neuropsychological evaluation by a trained specialist when available can be therapeutic and validating. Evaluation may also be necessary if an individual is pursuing disability benefits and cognitive impairment is a contributing factor to work limitation. Cognitive rehabilitation, including occupational therapy, speech therapy, and treatment by a neuropsychologist, may also be useful.[76,77] Psychotherapy is another option. Importantly, routine physical activity should be encouraged. Substantial evidence shows that physical activity enhances cognitive function in individuals with mild cognitive impairment, although few studies specific to cancer survivors have been reported.[78–80]

If nonpharmacologic interventions have been insufficient, referral to a clinician with expertise in memory or cognitive concerns for further evaluation and care can be considered. A trial of medications such as methylphenidate, modafinil, or donepezil is reasonable in select survivors or certain clinical scenarios, although data informing the efficacy of these agents are lacking.[81,82]

Panel Discussion and Recent Updates

The NCCN Guidelines have included the recommendation that cognitive concerns be screened for and assessed using self-report. In this year's panel discussion, it was

noted that self-report of cognitive concerns is not the same as a measurement of cognitive function. It was further noted that there is a weak association between objective measures of cognitive function and subjective self-report of cognitive concerns.[83–85] However, the panel also noted that no effective brief screening tool for cancer-associated cognitive dysfunction has been identified. Existing tools lack adequate sensitivity to detect the subtle decline in cognitive performance seen in most cancer survivors. Therefore, the panel continues to recommend self-report for initial screening and assessment, but they added a note to alert providers that self-report of cognitive concerns, or the lack thereof, is not a surrogate for measurement of the presence or absence of impairment in cognitive function (see SCF-1, page 798).

Another point discussed by the panel was the recommendation to consider referral to a "memory clinic" for survivors who continue to have memory problems after rehabilitation. This term was considered too vague by some on the panel, and it was acknowledged that there is heterogeneity among clinic staffing and approaches. The neuropsychological profile of memory disorders due to cancer and cancer therapy does not necessarily suggest a progressive neurodegenerative condition or memory disorder such as those commonly seen and treated at memory clinics. There was thus concern that such clinics may not offer much help to survivors with continued memory problems after medical and neuropsychological workup and treatment and cognitive rehabilitation. The panel agreed that specialty care in cancer neurology would be ideal, but its availability is likely limited and varied across the United States. The panel consensus was thus to remain nonprescriptive about the type of clinical referral for individuals experiencing persistent cognitive concerns due to different availability of clinical resources, while still ensuring that survivors can get specialized care when needed. They therefore changed "memory clinic" to "a clinician with expertise in memory or cognitive concerns" (see SCF-4, page 799).

Conclusions

Poor sleep, fatigue, and cognitive difficulties are common and distressing long-term effects in cancer survivors. They can have a large negative impact on function and QoL. The NCCN Survivorship Panel emphasizes the importance of identifying and managing these problems so that cancer survivors can fully participate in the roles and activities that bring joy and meaning to their lives.

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