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Survivorship: Sleep Disorders, Version 1.2014

Clinical Practice Guidelines in Oncology

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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), sleep-related movement or breathing disorders, and parasomnias.[1] Sleep disorders affect 30% to 50% of patients with cancer and survivors, often in combination with fatigue, anxiety, or depression.[1–10] Improvements in sleep lead to improvements in fatigue, mood, and quality of life.[11] Most clinicians,

Abstract

Sleep disorders, including insomnia and excessive sleepiness, affect a significant proportion of patients with cancer and survivors, often in combination with fatigue, anxiety, and depression. Improvements in sleep lead to improvements in fatigue, mood, and quality of life. This section of the NCCN Guidelines for Survivorship provides screening, diagnosis, and management recommendations for sleep disorders in survivors. Management includes combinations of sleep hygiene education, physical activity, psychosocial interventions, and pharmacologic treatments. (*J Natl Compr Canc Netw* 2014;12:630–642)

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 for any cancer patient 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 consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. **The full NCCN Guidelines for Survivorship are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.**

Disclosures for the NCCN Survivorship Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Survivorship Panel members can be found on page 642. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

however, do not know how best to evaluate and treat sleep disorders.[1]

Sleep disorders are common in patients with cancer as a result of multiple factors, including biologic changes, the stress of diagnosis and treatment, and side effects of therapy (eg, pain, fatigue).[1,2] In addition, evidence suggests that changes in inflammatory processes from cancer and its treatment play a role in sleep disorders. These sleep disturbances can be perpetuated in the survivorship phase by chronic side effects, anxiety, depression, medications, and maladaptive behaviors such as shifting sleep times, excessive time in bed because of fatigue, and unplanned naps.[1,2]

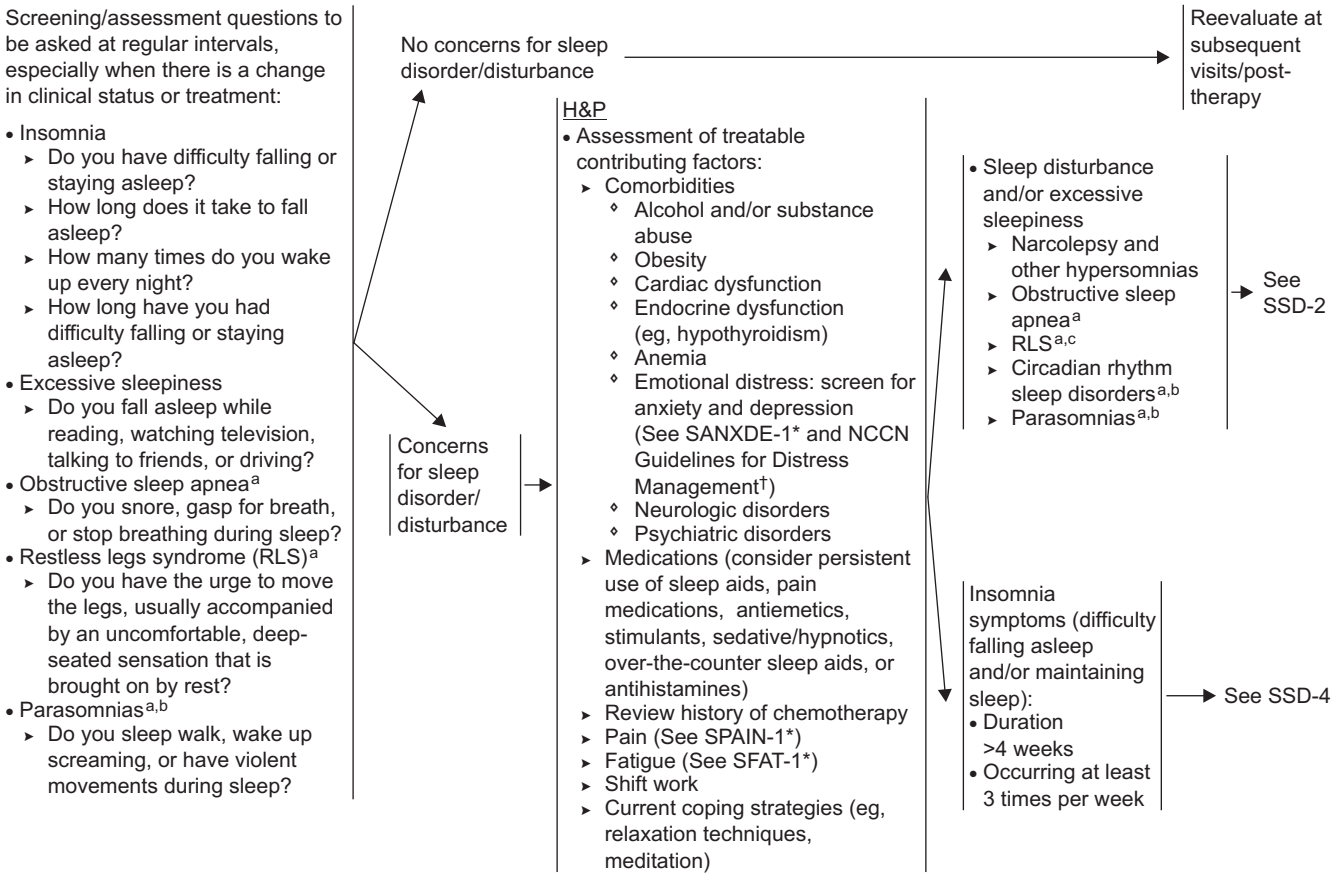
Additional information about sleep disorders in patients with cancer can be found in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Palliative Care and the NCCN Guidelines for Cancer-Related Fatigue (available at NCCN.org). These guidelines may be modified to fit the individual survivor's circumstances.

Screening for and Assessment of Sleep Disorders

Survivors should be screened for possible sleep disorders at regular intervals, especially when they experience a change in clinical status or treatment. The panel lists screening questions that can help determine whether concerns about sleep disorders or disturbances warrant further assessment. Other tools to screen for sleep problems have been validated.[3,4]

Text cont. on page 639.

SCREENING



*Available online, in these guidelines, at NCCN.org.
†To view the most recent version of these guidelines, visit NCCN.org.

[a]Note that obstructive sleep apnea, RLS, circadian rhythm sleep disorders, and parasomnia may also present with symptoms of insomnia.
[b]For circadian rhythm sleep disorders and parasomnias, refer to a sleep specialist.
[c]RLS is also known as *Willis-Ekbom disease*.

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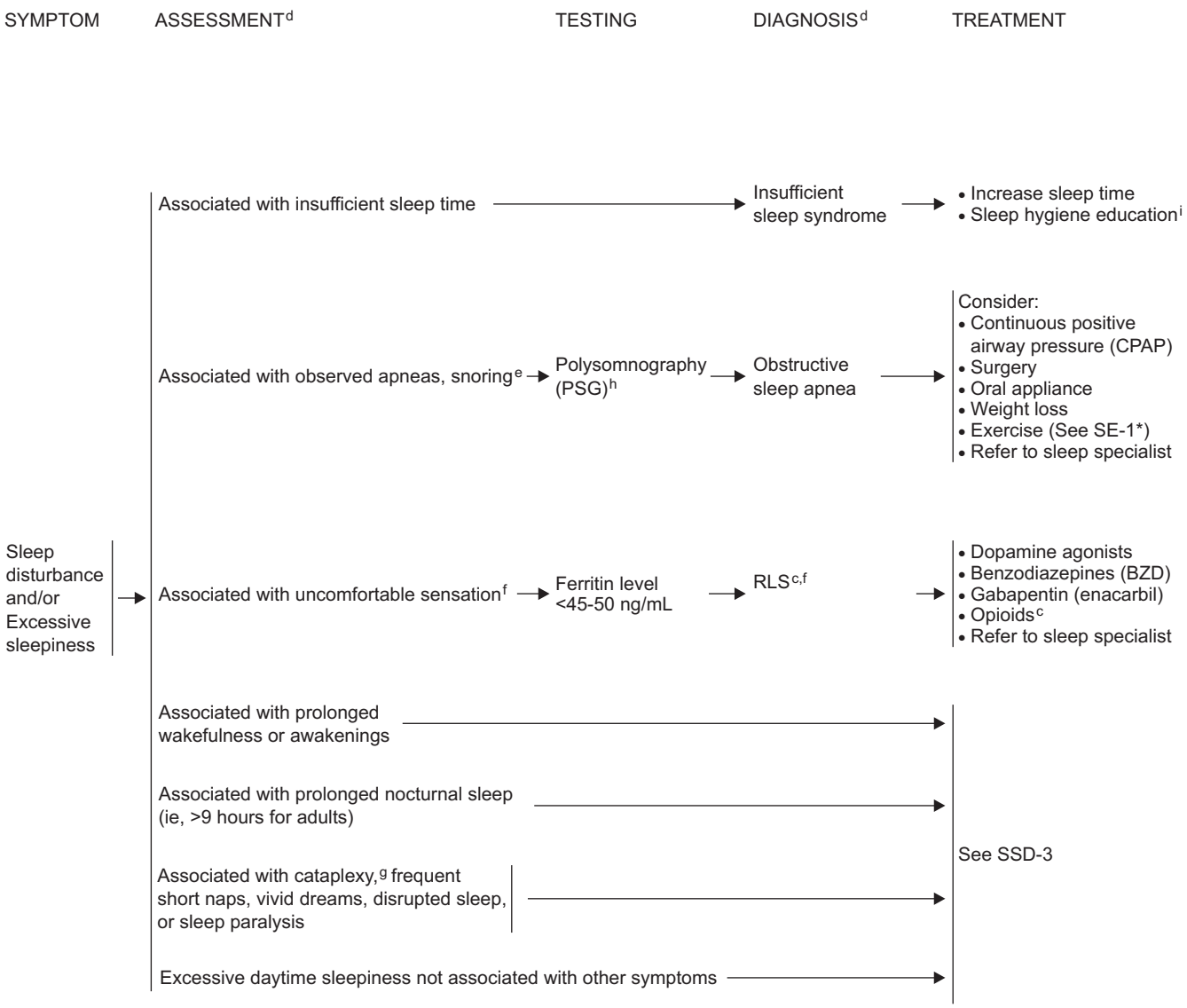
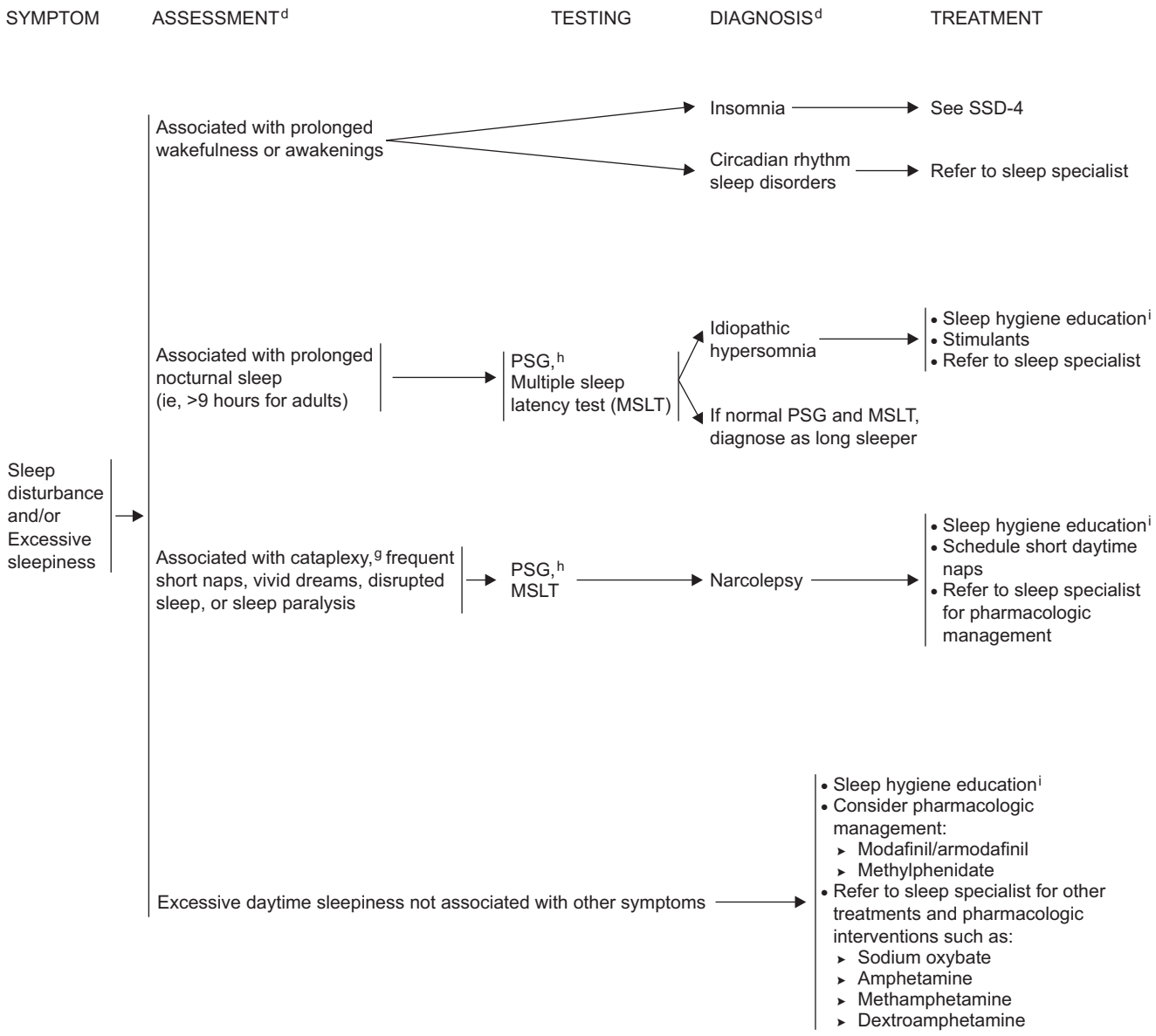


*To view the most recent version of these guidelines, visit NCCN.org.

[c]RLS is also known as *Willis-Ekbom disease*.
[d]For other less frequent syndromes, refer to sleep specialist.
[e]See STOP Questionnaire: A Tool to Screen Patients for Obstructive Sleep Apnea (SSD-A).
[f]See Essential Diagnostic Criteria for Restless Legs Syndrome (SSD-B).
[g]Cataplexy: Sudden loss of muscle tone. Typically triggered by strong emotions, such as laughter or anger. Cataplexy is the most specific diagnostic feature of narcolepsy.
[h]Sleep studies can be done as laboratory PSG or as home sleep study.
[i]See General Sleep Hygiene Measures (SSD-C).



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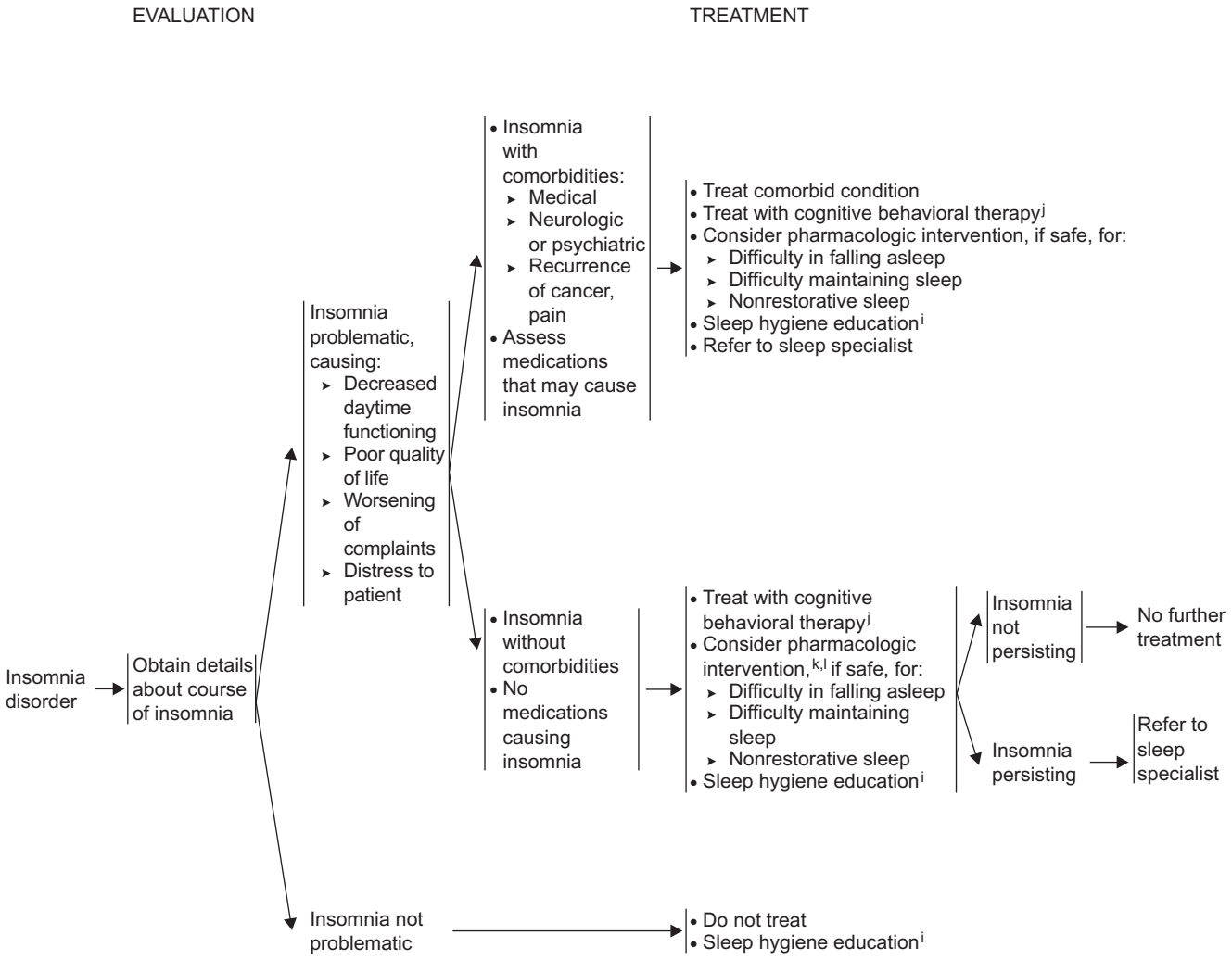

[i]See General Sleep Hygiene Measures (SSD-C).
[j]See Cognitive Behavioral Treatments (SSD-D).
[k]See Principles for Choosing an FDA-Approved Hypnotic (SSD-E).
[l]See Other Commonly Used Medications For Insomnia (SSD-F).

STOP Questionnaire: A Tool to Screen Patients for Obstructive Sleep Apnea (OSA)[1,2]

1. Snoring
   Do you snore loudly (louder than talking or loud enough to be heard through closed doors)?
   Yes No

2. Tired
   Do you often feel tired, fatigued, or sleepy during daytime?
   Yes No

3. Observed
   Has anyone observed you stop breathing during your sleep?
   Yes No

4. Blood pressure
   Do you have or are you being treated for high blood pressure?
   Yes No

PROVIDER KEY
High risk of OSA: Answering yes to 2 or more questions
Low risk of OSA: Answering yes to less than 2 questions

ESSENTIAL DIAGNOSTIC CRITERIA FOR RESTLESS LEGS SYNDROME[3]

- An urge to move the legs usually accompanied by uncomfortable and unpleasant sensations in the legs, and sometimes the arms or other body parts.
- The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting.
- The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching.
- The symptoms are more pronounced in the evening or night or may only occur in the evening or night.

[1] Reproduced and modified with permission from Chung F, Yegneswaran B, Liao P, et al. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. Anesthesiology 2008;108:812-821.
[2] This screening tool and other similar tools are not diagnostic, but have been shown to be useful to assess risk for OSA.
[3] Reproduced with permission from Allen RP, Picchietti D, Hening WA, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 2003;4:101-119.

SSD-A

SSD-B

GENERAL SLEEP HYGIENE MEASURES[1,2,3]

- Regular exercise in the morning and/or afternoon
- Increase exposure to bright light during the day
- Avoid exposure to bright light during the night
- Avoid heavy meals or drinking within 3 hours of bed
- Avoid alcohol, caffeine, nicotine too close to bedtime
- Enhance sleep environment (dark, quiet room, comfortable temperature)
- Set aside a worry time
- Avoid looking at the clock

COGNITIVE BEHAVIORAL TREATMENTS[4]

STRATEGY	GOAL
Cognitive therapy	• Challenge patient's dysfunctional beliefs and misconceptions about sleep disturbances • Promote positive thoughts
Relaxation training	• Reduce physiologic and cognitive arousal at bedtime • Techniques include progressive muscular relaxation, transcendental meditation, yoga, biofeedback
Sleep restriction	• Improve sleep continuity by limiting time spent in bed and maintaining a regular sleep schedule
Stimulus control	• Associate the bed/bedroom as a place for sleep or sexual activity only

[1] National Heart, Lung, and Blood Institute Working Group on Insomnia. Insomnia: Assessment and Management in Primary Care. 1998. Available at: https://www.nhlbi.nih.gov/guidelines/archives/insom_pc/insom_pc_archive.pdf. Accessed April 21, 2014.
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[3] Lippmann S, Mazour I, Shahab H. Insomnia: therapeutic approach. South Med J 2001;94:866-873.
[4] Data from Bootzin RR, Perlis ML. Nonpharmacologic treatments of insomnia. J Clin Psychiatry 1992;53(Suppl):37-41.

SSD-C

SSD-D

PRINCIPLES FOR CHOOSING AN FDA-APPROVED HYPNOTIC:[1]
- 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 ONSET AND MAINTENANCE
Zolpidem	+	+	–
Zolpidem CR	+	+	+
Zaleplon	+	–	–
Eszopiclone	+	+	+
Ramelteon	+	+/–	–
Temazepam	+	+	+
Doxepin (3-6 mg)	–	+	+
Lorazepam	+	–	–

OTHER COMMONLY USED MEDICATIONS FOR INSOMNIA[2]

This is a list of agents that do not have an FDA-approved indication for the treatment of insomnia and that do not have enough data to be recommended for routine use. They have none to limited efficacy or effectiveness data for the treatment of insomnia disorder.

Antidepressants[3]
- Trazodone
- Amitriptyline
- Trimipramine
- Mirtazapine
- Doxepin

Antihistamines[3]
- Diphenhydramine

Antiepileptics[3]
- Gabapentin
- Tiagabine

Atypical antipsychotics[3]
- Quetiapine

Nutritional/herbal supplements
- Melatonin
- Valerian

[1] Data from the Physicians' Desk Reference. 6th ed. Montvale, NJ: PDR Network, LLC; 2012.
[2] From Neubauer, D. Evolution and Development of Insomnia Pharmacotherapies. J Clin Sleep Med 2007;3(5 Suppl):S11–16. and National Institutes of Health State of the Science Conference Statement: Manifestations and Management of Chronic Insomnia in Adults June 13-15, 2005. Sleep 2005;28:1049-1057.
[3] Although they are commonly prescribed, antidepressants, antihistamines, antiepileptics, and antipsychotics have significant risks and should be used with caution.

SSD-E

SSD-F

Text cont. from page 631.

If concerns regarding sleep are significant, the panel recommends that treatable contributing factors be assessed and managed. Comorbidities that can contribute to sleep problems include alcohol and substance abuse, obesity, cardiac dysfunction, endocrine dysfunction, anemia, neurologic disorders, 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, and antihistamines can all contribute to sleep disturbance, as can the persistent use of sleep aids.

Diagnosis of Sleep Disorders

The panel divided sleep disorders into 2 general categories: insomnia, and sleep disturbance and/or excessive sleepiness.

Insomnia is diagnosed when patients have difficulty falling asleep and/or maintaining sleep at least 3 times per week for at least 4 weeks, accompanied by distress.

Diagnosing patients with excessive sleepiness can be challenging, because it can be caused by a variety of factors. When excessive sleepiness is associated with observed apneas or snoring, the STOP questionnaire can be used as a screening tool to determine the risk of obstructive sleep apnea (OSA).[15] Other screening tools for OSA risk have also been validated.[16] Sleep studies (ie, laboratory polysomnography [PSG] or home sleep studies) can confirm the diagnosis of OSA. Multiple sleep latency tests (MSLTs) and PSG can also be useful in diagnosing narcolepsy, idiopathic hypersomnia, and parasomnias. Narcolepsy should be considered when excessive sleepiness is accompanied by cataplexy, frequent short naps, vivid dreams, disrupted sleep, or sleep paralysis.

Excessive sleepiness can also be associated with uncomfortable sensations or an urge to move the legs (and sometimes the arms or other body parts). These symptoms are usually worse at night and with inactivity, may be improved or relieved with movement such as walking or stretching, and indicate restless legs syndrome (RLS; also known as *Willis-Ekbom disease*). In these patients, ferritin levels should be checked; levels less than 45 to 50 ng/mL indicate a treatable cause of RLS.[17,18]

Management of Sleep Disorders

OSA should be treated with continuous positive airway pressure, surgery, or oral appliances.[19–21] Additionally, weight loss and exercise should be recommended, and patients should be referred to a sleep specialist.

RLS is treated with dopamine agonists, benzodiazepines, gabapentin, and/or opioids, and referral to a sleep specialist.[22–30] Two separate recent meta-analyses found dopamine agonists and calcium channel alpha-2-delta ligands (eg, gabapentin) to be helpful in reducing RLS symptoms and improving sleep in the noncancer setting.[30,31]

For other types of sleep disturbances, several types of interventions are recommended.[1,32,33] In addition, referral to a sleep specialist can be considered in most cases.

Sleep Hygiene Education

Educating survivors about general sleep hygiene is recommended, especially for the treatment of insomnia.[34–36] Key points are listed in the guidelines and include regular morning or afternoon exercise; daytime exposure to bright light; keeping the sleep environment dark, quiet, and comfortable; and avoiding heavy meals, alcohol, and nicotine near bedtime.

Physical Activity

Physical activity may improve sleep in patients with cancer and survivors.[37–43] One recent randomized controlled trial compared a standardized yoga intervention plus standard care with standard care alone in 410 survivors (75% breast cancer; 96% women) with moderate to severe sleep disruption.[40] Participants in the yoga arm experienced greater improvements in global and subjective sleep quality, daytime functioning, and sleep efficiency (all $P \leq .05$). In addition, the use of sleep medication declined in the intervention arm ($P \leq .05$).

A recent meta-analysis of randomized controlled trials in patients who had completed active cancer treatment showed that exercise improved sleep at a 12-week follow-up.[38] Overall, however, data supporting improvement in sleep with physical activity are limited in the survivorship population.

Psychosocial Interventions

Psychosocial interventions such as cognitive behavioral therapy (CBT), psychoeducational therapy, and supportive expressive therapy are recommended to treat sleep disturbances in cancer survivors.[44] In

particular, several randomized controlled trials have shown that CBT improves sleep in the survivor population.[45–48] For example, a randomized controlled trial in 150 survivors (58% breast cancer; 23% prostate cancer; 16% bowel cancer; 69% women) found that a series of 5 weekly group CBT sessions was associated with a reduction in mean wakefulness of almost 1 hour per night, whereas usual care (in which physicians could treat insomnia as they would in normal clinical practice) had no effect on wakefulness.[45]

In addition, a small randomized controlled trial of 57 survivors (54% breast cancer; 75% women) found that mind–body interventions (mindfulness meditation or mind–body bridging), decreased sleep disturbance more than sleep hygiene education did.[49]

Pharmacologic Interventions

Many pharmacologic treatments for sleep disturbances are available, including psychostimulants for narcolepsy (eg, modafinil, methylphenidate) and hypnotics for insomnia (eg, zolpidem, ramelteon).[33,50,51] In addition, antidepressants, antihistamines, antiepileptics, and antipsychotics are often used off-label for the treatment of insomnia, even though limited to no efficacy or effectiveness data are available for this use. The panel also noted that these medications are associated with significant risks and should be used with caution. One small, open-label study found that the antidepressant mirtazapine increased the total amount of nighttime sleep in patients with cancer.[52] Overall, however, data on pharmacologic interventions aimed at improving sleep in patients with cancer and survivors are lacking.[10]

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Individual Disclosures for the NCCN Sleep Disorders Panel

Panel Member	Clinical Research Support/Data Safety Monitoring Board	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
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Elizabeth Kvale, MD	None	None	None	None	10/7/13
Terry S. Langbaum, MAS	None	None	None	None	8/13/13
Kristin Leonardi-Warren, RN, ND	None	None	None	None	1/6/14
Jennifer A. Ligibel, MD	None	None	None	None	10/3/13
Mary S. McCabe, RN, BS, MS	None	None	None	None	8/12/13
Michelle Melisko, MD	Celldex Therapeutics; and Galena Biopharma	Agendia BV; Genentech, Inc.; and Novartis Pharmaceuticals Corporation	None	None	10/11/13
Jose G. Montoya, MD	None	None	None	None	12/6/13
Kathi Mooney, RN, PhD	University of Utah	None	None	None	9/30/13
Mary Ann Morgan, PhD, FNP-BC	None	None	None	None	8/19/13
Javid J. Moslehi, MD	None	ARIAD Pharmaceuticals, Inc.; Millennium Pharmaceuticals, Inc.; Novartis Pharmaceuticals Corporation; and Pfizer Inc.	None	None	1/27/14
Tracey O'Connor, MD	None	None	None	None	6/13/13
Linda Overholser, MD, MPH	None	Antigenics Inc.; and Colorado Central Cancer Registry Care Plan Project	None	None	10/10/13
Electra D. Paskett, PhD	Merck & Co., Inc.	None	None	None	6/13/13
Muhammad Raza, MD	None	None	None	None	8/23/12
Karen L. Syrjala, PhD	None	None	None	None	10/3/13
Susan G. Urba, MD	None	Eisai Inc.; and Helsinn Therapeutics (U.S.), Inc.	None	None	10/9/13
Mark T. Wakabayashi, MD, MPH	None	None	None	None	6/19/13
Phyllis Zee, MD	Philips/Respironics	Merck & Co., Inc.; Jazz Pharmaceuticals; Vanda Pharmaceuticals; and Purdue Pharma LP	None	None	3/26/14

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