

# Sleep Disorders, Fatigue, and Cognitive Function in Cancer Survivors: A Plenary Session

Presented by Kristin Dickinson, PhD, RN; Halle C.F. Moore, MD; Jennifer Schmitz, MSN, APRN, FNP-C; Eric S. Zhou, PhD; and moderated by Andrew T. Day, MD, MPH

## ABSTRACT

For many patients, sleep disorders (particularly insomnia), cancer-related fatigue, and cancer-related cognitive impairment are common and distressing symptoms of cancer and its treatment. At the NCCN 2023 Annual Conference, a panel of experts began with a personal account of a cancer survivor's experience and discussed approaches to assess and manage these adverse effects of cancer and its treatment.

*J Natl Compr Canc Netw* 2023;21(5.5):1-4  
doi: 10.6004/jnccn.2023.5022

**Sleep disorders** (particularly insomnia), cancer-related fatigue, and cancer-related cognitive impairment are common and distressing symptoms of cancer and its treatment. A plenary discussion on this topic at the NCCN 2023 Annual Conference, moderated by Andrew T. Day, MD, MPH, Assistant Professor of Otolaryngology - Head and Neck Surgery at UT Southwestern Medical Center, member of the Population Science and Cancer Control Program at the Harold C. Simmons Comprehensive Cancer Center, and Vice Chair of the NCCN Survivorship Panel, began with a personal account of one cancer survivor's experience.

### From Survivor to Thriver: One Woman's Story

Jennifer Schmitz, MSN, APRN, FNP-C, Instructor, College of Nursing, Fred & Pamela Buffett Cancer Center, University of Nebraska Medical Center, was 38 years old and a full-time nurse practitioner, wife, and active mother of 2 when she began experiencing recurrent infections. The infections led to constant fevers, bone pain, and mouth sores, and eventually fatigue. However, because of her atypical presentation, it took about a year from the onset of these symptoms to a diagnosis of acute lymphoblastic leukemia.

She was immediately started on a regimen of hyperfractionated cyclophosphamide + vincristine + doxorubicin + dexamethasone. During her 6-month inpatient stay in the hospital, she experienced a multitude of sleep issues in addition to extreme fatigue. "Your brain really starts to play tricks on you, and it's like living in a fog," she explained. "You're kind of an observer, to a certain extent. I like to think of it as self-preservation, but it's a very strange experience."

"My fatigue didn't just go away because I was out of the hospital, or because my chemo treatments weren't

quite as harsh anymore," she said. "It got worse for a little while. And that continued for almost a year." However, her cancer journey was far from over, and adverse effects persisted. "Going into treatment I knew I was probably going to have some long-term issues, but it's not something that anyone talked to me about," she recalled.

She hopes her story can inform better approaches to survivorship care in oncology. "I'm hoping that as practitioners and providers in the oncology world, we'll get better at that, because there are a lot more people like me out there."

### Sleep Disorders in Cancer Survivors

According to Eric S. Zhou, PhD, Faculty Member, Division of Sleep Medicine, Assistant Professor of Pediatrics, Harvard Medical School; Staff Psychologist, Dana-Farber Cancer Institute and Boston Children's Hospital; and member of the NCCN Cancer-Related Fatigue Panel, it's important to hear stories like Jennifer's to remind oncology providers that statistics about sleep disorders, fatigue, and cognitive dysfunction come from real people dealing with the life-altering effects of cancer and its treatment.

According to *The International Classification of Sleep Disorders—Third Edition*, there are more than 80 different sleep disorders, falling into 7 distinct categories: insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, parasomnias, sleep-related movement disorders, and those falling under "other." However, research investigating sleep disorders in cancer survivors has mostly relied on fairly limited tools (eg, a short self-report survey), so the true prevalence of sleep disorders in people with cancer cannot be accurately ascertained.

Despite this research limitation, “sleep is probably one of the biggest issues your patients and survivors will face,” stated Dr. Zhou.

Insomnia is likely the most common sleep disorder and tends to persist in cancer survivors if they do not receive proper treatment.<sup>1</sup> Getting good sleep matters, and impacts far more than just how a person feels the next day. A Stanford study tracked sleep using an objective tool (actigraph) in women with advanced breast cancer; the investigators found that a 10% improvement in sleep efficiency among poor sleepers potentially leads to a 32% increase in survival time.<sup>2</sup> “The potential impact of good sleep on improving health outcomes is amazing,” he noted.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Survivorship<sup>3</sup> (available at NCCN.org) recommend cognitive-behavioral therapy for insomnia (CBT-I) before pharmacologic intervention. Dr. Zhou explained that contrary to what patients often read online, the most important components of CBT-I are sleep restriction (matching time in bed to actual sleep need) and stimulus control (using the bed for sleep only), rather than sleep hygiene.

According to Dr. Zhou, cancer centers are performing poorly when it comes to treating insomnia. A survey of National Cancer Institute–designated Comprehensive Cancer Centers revealed <50% of survivorship program directors thought they were providing adequate insomnia treatment to survivors.<sup>4</sup>

More services are required to help provide better insomnia care for survivors. For example, offering CBT-I “in house” can be important, as referral to another hospital or community-based clinic is a potential barrier for patients. “In our survey, we found that over 75% of cancer centers did not have someone at their institution to deliver CBT-I,” he noted.

Finally, provider training is desperately needed, as many medical and graduate schools do not provide formal didactic training about sleep disorders. In prior work, Dr. Zhou surveyed psychologists across North America and found that more than 90% did not have any training in their graduate program on the subject of sleep. “However, over 50% said they were confident in treating sleep disorders,” he reported. “So, there’s a mismatch here and a real issue.”<sup>5</sup>

## Fatigue in Cancer Survivors

Fatigue is a common and distressing symptom for patients throughout the cancer journey and one with potentially profound effects on quality of life. The NCCN Guidelines for Cancer-Related Fatigue<sup>6</sup> (CRF) offers a complex definition for this symptom: “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.”

Kristin Dickinson, PhD, RN, Assistant Professor, Fred & Pamela Buffett Cancer Center, University of Nebraska Medical Center College of Nursing, and member of the NCCN Survivorship Panel, explained: “Because of the complexity of CRF, it can be challenging to assess and manage in a clinical setting. CRF is often reported to be the most distressing symptom, even more so than pain and nausea.”

This is partly because many of the common side effects of cancer and its treatment can be controlled with medications, whereas clinical management of CRF remains elusive. In addition, CRF can vary from person to person, and no 2 patients experience fatigue in the same way; this adds additional challenges to assessment and emphasizes the need for tailored and individualized approaches to management.

Prevalence estimates vary based on patient population and stage of treatment/survivorship, but CRF tends to be higher among those in active treatment, affecting up to 90% of patients. However, as Ms. Schmitz pointed out, CRF does not stop when treatment does. As many as 50% of patients in short-term survivorship (within 3 years of diagnosis) report CRF, and about 30% of people in long-term survivorship (≥5 years from diagnosis) still report CRF as a distressing symptom in their life.<sup>7,8</sup>

In terms of quality of life, CRF is underreported, underdiagnosed, and undertreated. Providers may be hesitant to ask about CRF because of a lack of knowledge and confidence about its proper assessment and management. However, when ignored, CRF negatively interferes with treatment adherence and efficacy, possibly interfering with nearly every aspect of quality of life.<sup>9</sup>

In terms of screening and assessment, the NCCN Guidelines recommend that patients receive screening for CRF at their initial visit and at every recurrent clinically relevant visit thereafter. Primary CRF evaluation involves additional workup and ruling out treatable or contributing factors for fatigue that can be medically managed. If CRF persists, general management strategies can be employed. The NCCN Guidelines for the management of fatigue—as well as patient and family/caregiver education and counseling—are stratified by survivorship stage.<sup>6</sup> For patients in active treatment, recommendations for nonpharmacologic management strategies far outweigh pharmacologic strategies. “Physical activity is the most evidenced strategy we have for managing CRF,” noted Dr. Dickinson. “It’s not only highly recommended in NCCN Guidelines; it is highly recommended across all guidelines for CRF.” In addition to physical activity, other NCCN Category 1 recommendations for patients in active treatment include massage therapy and certain psychosocial interventions, such as CBT, for CRF.

## Cognitive Function in Cancer Survivors

Cancer-related cognitive impairment can present in several ways, including difficulty with attention and multi-tasking, leaving tasks incomplete, difficulty finding words or remembering things, and thinking more slowly. Patients experiencing these symptoms may feel incredibly isolated and often may worry about the potential effects on job performance, according to Halle C.F. Moore, MD, Director, Breast Medical Oncology, Department of Hematology and Oncology, Cleveland Clinic Taussig Cancer Institute; Co-Director, Cleveland Clinic Comprehensive Breast Program; Associate Professor of Medicine, Cleveland Clinic Lerner College of Medicine; Member, Population and Cancer Prevention Program, Case Comprehensive Cancer Center; and member of the NCCN Survivorship Panel.

“There are no standard diagnostic criteria for cognitive impairment related to cancer, and that can add to the challenge of studying this problem,” she said.

Although “chemo brain” has become a commonly used term to describe these cognitive changes, it is now understood that other types of cancer treatments can also impact cognition, and cognitive impairments may even be present in some patients before treatment. Thus, broader terms like “cancer treatment-associated cognitive changes” and “cancer-associated cognitive changes” may be more accurate.

Close to one-third of individuals with cancer may have cognitive deficits before chemotherapy, with potential causes including surgery/anesthesia (generally temporary), anxiety, and inflammatory processes from the cancer itself. Between 50% and 70% of patients experience cognitive changes during chemotherapy, with about 35% reporting persistent symptoms after treatment completion.<sup>10,11</sup>

Certain risk factors for cancer-related cognitive impairment exist, including age, diabetes/cardiovascular disease, genetic predisposition, and lower cognitive reserve. However, because standard diagnostic criteria are lacking, assessment is primarily conducted through self-reporting. “However, self-reporting does not always correlate with the results of formal cognitive testing, which we often use in research,” Dr. Moore said.

Of note, individuals with higher cognitive functioning at baseline may maintain excellent cognitive performance but require more effort to do so. This idea of “cognitive compensation” may help explain discrepancies between correlative tests, subjective concerns, and

formal objective testing results, Dr. Moore explained. Conversely, patients with lower baseline cognitive reserve and older patients are more likely to experience objective cognitive changes. Some patients may need to undergo formal neuropsychologic evaluation. “However, these tests don’t always correlate with the patient experience, so they need to be used selectively,” she added.

Once issues with cognition are identified, modifiable contributing factors should be addressed. These factors may include medications and supplements, alcohol or other substances, concurrent medical issues, depression/anxiety, pain, fatigue, and sleep disturbance.

In terms of management, Dr. Moore noted that reassurance and validation are important first steps in discussing cancer-related cognitive impairment with patients. She suggested reminding patients that this is a common side effect of cancer and its treatment that typically improves with time and is often marked by subtle changes, and reassuring them that this type of cognitive impairment is not the same as dementia, which tends to be progressive.

As with fatigue, exercise/physical activity may improve cognitive reserve, and cognitive rehabilitation programs may also be beneficial. In patients for whom these strategies aren’t effective, psychotherapy or CBT may also be productive.

For patients with persistent symptoms of cancer-related cognitive impairment, additional management options can be considered, including referral to a specialized memory clinic or formal testing for dementia. The NCCN Guidelines for Survivorship<sup>3</sup> suggest the consideration of trial-use of methylphenidate, modafinil, or donepezil for some patients (although evidence is still lacking, and stimulants are likely to benefit fatigue more than cognitive function). Recommended cancer-associated cognitive dysfunction interventions are included in the cognitive function section of the NCCN Guidelines for Survivorship.<sup>3</sup>

**Disclosures:** Dr. Moore has disclosed receiving grant/research support to her institution from AstraZeneca Pharmaceuticals LP, Daiichi-Sankyo Co., Roche/Genentech, Sermonix Pharmaceuticals, and SeaGen; and receiving consulting fees from Myovant Sciences GmbH. Dr. Zhou has disclosed receiving grant/research support from Jazz Pharmaceuticals and Harmony Biosciences; and receiving consulting fees from MindUp and Samsung. The remaining presenters have disclosed no relevant financial relationships.

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