[News * Analysis * Commentary * Controversy]

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Fatigue: The Forgotten Symptom?

BY HEATHER LINDSEY

A new study shows that few oncologists are following the National Comprehensive Cancer Network guidelines for treating cancer-related fatigue in their patients with advanced disease. Here's the surprising news about the probable reasons. *Page 26*

ASH Annual Meeting: Highlights & Perspective pp.10,20,23,29

Remembering Pioneering Hematopathologist Costan Berard p.5

Pancreatic Cancer Advances from the GI Cancers Symposium pp.6,8

[ALSO]

PERIODICALS

Fatigue: The Forgotten Symptom?

BY HEATHER LINDSEY

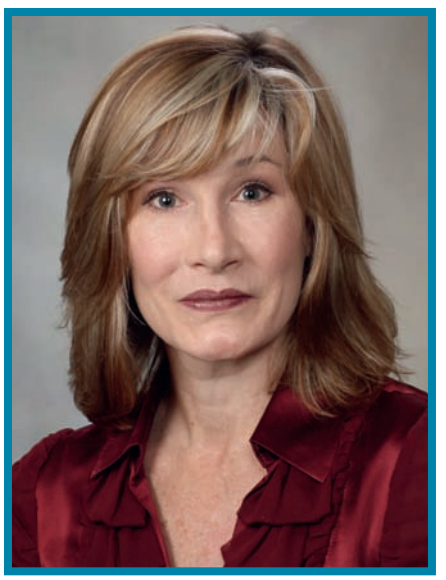
"The undertreatment of fatigue may mirror the undertreatment of pain and functional problems, which has consistently been documented in cancer populations."

Few oncologists are recommending the National Comprehensive Cancer Network (NCCN) guidelines for cancer-related fatigue to their patients with advanced disease, according to a new study (***Supportive Care in Cancer 2013;21:229-233***), which the authors believe is the first such assessment.

"A lot of my work over the years has looked at the adequacy of rehabilitation and supportive care, in general, provided to patients with cancer and survivors," said the lead author, Andrea Cheville, MD, Associate Professor and Director of Cancer Rehabilitation and Lymphedema Services at the Mayo Clinic. "I and many others have consistently found that this type of care overall remains limited at best, particularly in community settings."

While the fatigue guidelines recommend interventions such as increasing exercise, seeking psychosocial and behavioral help, and prescribing appropriate medications, some physicians say these approaches are not particularly helpful. "Oncologists are very attuned to the NCCN guidelines, and when they sense the recommendations are appropriate and effective, they indeed interface with them," Larry Gluck, MD, Medical Director of the Greenville Hospital System's (GHS) Cancer Center in South Carolina, explained. But the cancer-related fatigue guidelines, he said, lack strength of efficacy, and medical management recommendations are not especially helpful because available pharmaceuticals do not adequately address fatigue.

Mellar P. Davis, MD, of the Harry R. Horvitz Center for Palliative Medicine at the Taussig Cancer Institute at Cleveland Clinic Some agreed: "Some of the recommendations in the NCCN guidelines—for example, to conserve your energy by having others help you do things—don't have much of an evidence base to them," he said.



ANDREA CHEVILLE, MD: "The low rates of guideline-congruent treatment reported are concerning, particularly since the better validated behavioral treatments were the least prescribed."

LARRY GLUCK, MD, pointed to ongoing research showing that cancer patients with fatigue are aerobically deconditioned and theorized that chemotherapy may cause toxicity leading to dysfunction at the mitochondrial level.

Overall, oncologists do not have much in their toolbox to help patients with fatigue, said Amy P. Abernethy, MD, Director of the Duke Cancer Care Research Program, who has sat on the NCCN cancer-related fatigue guidelines panel since 2006. "As a result, we spend a lot of time deciding whether we should be measuring and assessing it."

Study Details

The prospective, cross-sectional study by Cheville and her colleagues (supported by a grant from the U.S. Department of Defense) surveyed 160 patients with stage IV lung, breast, colon, or prostate cancers who had moderate to severe fatigue (5 or more on an 10-point scale). Participants had attended a follow-up outpatient appointment at the Mayo Clinic Cancer Center over a two-month period beginning in June 2010.

By telephone, patients (about 50% male and 50% female) were asked whether their oncology teams had mentioned any NCCN cancer-fatigue treatments, which fall into the categories of "general management, activity enhancement, psychosocial strategies, and use of pharmaceuticals." Patients were also asked about the extent of the information they had received and whether physicians had provided specific counseling, instructions, recommendations, or prescriptions.

Patients reported an average fatigue rating of 6.4. Overall, about 58 percent of participants recalled mention of treatments in one of the NCCN categories, and none recalled mention of all four. Patients also reported treatment or receipt of specific guidance in the fatigue management domains as follows: general management strategies, about 17 percent; activity enhancement, about 12 percent; psychosocial strategies, about 10 percent; and use of pharmaceuticals, about 37 percent.

"We are generally comfortable with prescribing," Cheville noted.

The study also found that most patients received what the researchers called soporifics rather than psychostimulants—i.e., "practitioners often think that helping patients with sleep quality through medication may alleviate fatigue, but there are no data to empirically support this practice," she said. "And patients aren't getting methylphenidate or modafinil, the only agents that have an evidence base suggesting some benefit for fatigue in late-stage cancer."

Commenting on the findings, the NCCN fatigue panel's team captain, Ann M. Berger, PhD, APRN, AOCNS, FAAN, Professor and Dorothy Hodges Olson Endowed Chair in Nursing, Advanced Practice Nurse, and Director of the PhD Program at the College of Nursing at the University of Nebraska Medical Center, explained that one of the advantages of nonpharmacological strategies is that they don't have side effects that exacerbate fatigue, as prescription medications do. "But in a conventional clinical setting, there's never enough time, and a prescription is a lot quicker and easier than providing a behavioral intervention."

ANN M. BERGER, PHD, APRN, AOCNS, FAAN, notes on her profile page on the University of Nebraska College of Nursing website that Florence Nightingale used to describe what is now called fatigue as a deficit of "vital force" or "vital powers."

The type of cancer patients had also appeared to make a difference in the study: Only 25 percent of lung cancer patients, 15 percent of colon cancer patients, and 17.5 percent of prostate cancer patients had their fatigue addressed, while 47.5 percent of those with breast cancer

continued on page 28

→FATIGUE

continued from page 26

Those interviewed for this article agreed that there has been nowhere near enough research into cancer-related fatigue and that the door is wide open for interested investigators.

recalled being advised about or receiving psychosocial interventions.

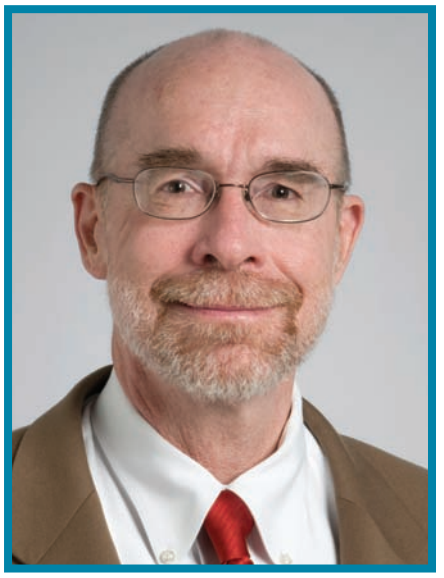
Cheville theorized that this may be because women may be more proactive in seeking treatment and more forthcoming about symptoms—"but this is purely speculative."

This theory may also explain why more women than men in the study reported receiving counseling for their fatigue, Berger noted—52.5 percent vs. 33.4 percent, respectively.

Additionally, more breast cancer patients may have received treatment for fatigue because of the established evidence-base for using exercise and erythropoietin in this population, Davis said.

The researchers also found that when patients were asked open-ended questions about strategies they used to address their fatigue, 39 percent could not recall any, 29 percent said they rested or napped during the day, nine percent said they tried to keep busy, and 10 percent said they walked or exercised.

Having severe fatigue (i.e., a score of 7 or more), which was reported by about 39 percent of patients, increased the likelihood that participants were instructed in ways to activity enhancement. However, it did not increase the probability of receiving specific instruction or prescriptions in other fatigue treatment domains.



MELLAR P. DAVIS, MD, said that oncologists may not be offering fatigue treatment because they aren't trained in assessing or treating the symptoms. Moreover, late-stage cancer patients often want to focus on their disease rather than their symptoms.

Berger complimented the study for evaluating the implementation of the guideline in a busy clinical setting, but said that a limitation is that the patients surveyed were undergoing active treatment, which may not always be applicable to a stage IV patient population.

Cheville also offered that although there is a question about recall bias, she and her colleagues considered the evidence, even though from only one institution to be "pretty compelling"—"A lot of the potential biases would tend to overestimate the prescription of these services rather than underestimate them."

Possible Explanations

In addition to the guidelines lacking evidence-based support, oncologists may not be offering fatigue treatment because they aren't trained in assessing or treating the symptoms, Davis said. Moreover, late-stage cancer patients often want to focus on their disease rather than their symptoms.

Gluck noted that the low rate of treatment for fatigue is comparable to the oncology community's experience with nausea and vomiting prior to the advent of effective targeted therapies: "Fatigue is something people are living with, and it will be in the foreground of all cancer practices until there is a better management strategy," he said.

Abernethy noted a possible nomenclature issue, in that if a treatment does work well for fatigue, then the symptom is often labeled as something else. For example, if patients are fatigued from lack of sleep, then they are described as suffering from insomnia; or if patients have low red cell blood counts, then the fatigue is actually anemia. "It is very difficult to have an effective solution for fatigue that doesn't have one explicit cause," she said. "I call this 'global fatigue.'"

Addressing the Problem

And while treatment is challenging, oncologists can help patients by first of all acknowledging that their fatigue exists, she said. "Even if there's not much you can do, it can be helpful to write on your scrip pad, acknowledging how miserable the symptom is."

She also advises patients not to operate at maximum capacity if they are fatigued: "On average, I tell them to function at about 70 percent of what they think they can do or else they will be flat on their backs. The consequences often come the next day." She said she also prescribes yoga, massage, visualization, and aromatherapy.

When evaluating fatigue, oncologists should be sure to assess secondary causes such as insomnia, depression, hypogonadism, anemia, and uncontrolled pain, Davis said.

Cheville said that screening patients for fatigue upon intake and using a referral algorithm would also be useful. "Oncologists are appropriately focused on treating a deadly disease with potentially toxic therapies." It is just not realistic to expect that they can also screen for functional or psychiatric problems or comprehensively manage the symptom burden

AMY ABERNETHY, MD: "Overall, oncologists don't have much in their toolbox to help patients with fatigue. As a result, we spend a lot of time deciding whether we should be measuring and assessing it."

and physical impairments associated with cancer and its treatment.

Future Research

Future research needs to determine the underlying mechanism of fatigue and then target it with pharmaceutical treatment, Davis said.

Abernethy said that although targeted treatment, whether a drug or tool addressing the underlying physiology of fatigue, would be the ultimate solution, such a magic bullet is unlikely, especially since the biobehavioral/psychological components also need to be addressed.

Gluck said that at his institution, researchers are studying the mechanisms of fatigue and have found that exercise physiology tests show that patients with this symptom are aerobically deconditioned—"even more so than what you would expect for someone who is inactive." It could be, he theorized, that chemotherapeutic agents cause toxicity at the mitochondrial level and that subsequent mitochondrial dysfunction may contribute to aerobic deconditioning.

Davis said that he and his colleagues suspect that cancer-related fatigue is central in nature: "It's the inability to activate muscle and is relatively unrelated to wasting. Patients with cancer wake up tired and go to bed tired and have rest fatigue."

Whatever the cause, he added, "there has hardly been any research in this area, leaving the door wide open for interested investigators."