

Issue Stories

Focus on Fatigue

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by Greg Thompson

Sonia Ancoli-Israel, PhD, assumes nothing in her search to discover the real causes of fatigue among cancer patients.

After speaking with Sonia Ancoli-Israel, PhD, you get an undeniable sense that this Southern California-based professor will not rest until she has found new ways to help cancer sufferers. In focusing her keen eye on the often-overlooked area of fatigue, Ancoli-Israel demonstrates an awareness that energy is an essential ingredient for quality of life.

While acknowledging that oncology clinicians do a good job of fighting cancer, Ancoli-Israel goes one step further and asks a basic question: What is the patient's quality of life? Whether the patient is winning or losing the war against cancer, the question of fatigue is all too commonly overlooked. In a wide-ranging conversation with *Sleep Review*, Ancoli-Israel offers a glimpse of her research and makes a compelling argument for a renewed focus on cancer-related fatigue.

Sleep Review: How prevalent is fatigue in cancer patients, and what is the relationship between cancer and fatigue?



Sonia Ancoli-Israel, PhD, professor of psychiatry and director of the Gillin Sleep and Chronomedicine Research Center, Department of Psychiatry, University of California, San Diego: The prevalence of fatigue in cancer patients is extremely high. Studies have shown that between 75% and 90% of cancer patients experience some fatigue. What is not known is what is causing that fatigue. Is the cancer itself causing fatigue? Is the chemotherapy causing the fatigue? Is poor sleep contributing to fatigue? Is lack of exercise making fatigue worse? We just don't have all the answers yet.

We published some studies, as have others, that showed that many cancer patients, at least in breast cancer, complain of fatigue before they even begin chemotherapy. We don't know, of course, what they experienced before they actually got cancer since we can only begin studying them once they have the diagnosis. We don't know therefore how much of the cancer itself is causing the fatigue. We do know that it is not all chemotherapy-related, which is what many people think.

The more fatigued you are before chemotherapy, the worse the fatigue gets during chemotherapy. We looked at a symptom cluster of poor sleep (subjective poor sleep), fatigue, and depression. The more symptoms the patient had before chemotherapy, the worse they were during chemotherapy—the worse sleep was, the worse fatigue was, and the worse quality of life was.

SR: A 2001 *British Medical Journal* article by Gregory A. Curt said, “Both patients and physicians may view cancer-related fatigue as something to be endured, rather than a symptom amenable to differential diagnosis and treatment. Research currently underway should begin to change this perspective and offer effective approaches to treatment.” Since 2001, has the perspective changed?

Ancoli-Israel: I think Curt is absolutely right. Many oncologists still do not pay attention to cancer-related fatigue. One reason is they are busy dealing with a lot of other fundamental problems that patients are having, such as cancer and survival. The other reason is that they do not know what to do about fatigue. It is the same issue we have with sleep. A lot of physicians do not ask about sleep, because they do not know what to do about it. There are not a lot of options for treating fatigue, and so physicians do not like to ask about it.

Oncologists are more sensitive to fatigue than most physicians. Patients do complain about fatigue affecting their quality of life. There have not been a lot of studies examining new treatments for cancer-related fatigue, but there have been a few with positive results. As of about a year ago, seven studies had showed that exercise reduced insomnia, fatigue, and emotional disorders. You would think it is almost counterintuitive, because patients may be so tired that they find it difficult to get moving, but the more you sit around, the worse the fatigue gets—and so it makes sense that the exercise would help. There may also be other behavioral treatments. We recently completed a study funded by the California Breast Cancer Research Program and Litebook Inc, not yet published, that suggests that bright light therapy may reduce fatigue. And if women are exercising outside, then that might be one reason why fatigue would also be improved.

There have also been studies using cognitive behavioral therapy for insomnia that have shown that not only does that improve insomnia, but fatigue is also improved. But these treatments have not been integrated into oncological practices.

As far as pharmacologic interventions, there have been studies using hematopoietics to improve anemia. And while the anemia improved along with energy levels and quality of life, fatigue itself did not.

There have been a few controlled studies looking at psycho stimulants, but again they improved mood but not fatigue. There has been one antidepressant study using Pamelor, and it was the only one that was a randomly controlled trial—it showed an improvement in depression but not an improvement in fatigue.

There have been a couple of studies using corticosteroids, which showed some improvement in fatigue, but they were all short-term studies with metastatic cancer. Given the side effect profile of corticosteroids, long-term studies in nonmetastatic cancer are needed.

There is an ongoing randomized controlled trial with modafinil, but I have not yet seen the results. There are a couple of open label studies, but we need the randomized controlled trials to see if, in fact, modafinil will be effective. The bottom line is that yes, fatigue is a problem, and yes, it is being recognized. However, we do not yet have well-established ways of treating fatigue.

SR: How should fatigue in cancer be approached?

Ancoli-Israel: Physicians must recognize that fatigue is a serious problem in cancer patients, both before and after chemotherapy. They have to remember that it is not just the chemotherapy causing the fatigue, and while it may make fatigue worse, it is not necessarily the cause. Fatigue can have long-term consequences.

We have a study looking at chemobrain, which is a term coined to describe the cognitive difficulties that patients have when undergoing chemotherapy. Patients often complain of just not being as sharp as they were before. This affects their ability to work, hold down a job, and function at an optimal level.

It was thought for a while that chemotherapy was the sole cause, but nobody really knows. We are conducting a National Cancer Institute (NCI)-funded study looking at the relationship between poor sleep and fatigue and chemobrain. Preliminary data suggest that some of the chemobrain may be driven by the fatigue.

SR: Another article by Gregory A. Curt et al published in 2000 found that physicians were the health care professionals most commonly consulted to discuss fatigue. Bed rest/relaxation was the most common treatment recommendation (37%), but 40% of patients were not offered any recommendations. Is there still work that needs to be done to educate physicians about treatment recommendations? What role can sleep professionals play in the education process?

Ancoli-Israel: Yes, we need much more education. And if you look at the data, it is only between 50% and 80% of patients who will even discuss fatigue with their physician. Normally, physicians are not asking, and patients are not mentioning it. The reason that patients do not mention it is that about 80% believe that it is caused by the treatment, and don't mention it because they figure the symptoms won't last. Half do not mention it because they think the doctor can't do anything about it. Finally, about 17% feel uncomfortable discussing it, or believe that the doctor might think they are ungrateful for mentioning such a thing.

It is often the responsibility of oncologists to ask their patients about fatigue, because they are the ones most often seeing the patients. So it is really oncologists who need to be educated more about sleep and fatigue, and the relationship between the two.

Can sleep medicine specialists play a role in the education? Absolutely, once they understand what cancer-related fatigue is. Cancer-related fatigue is different than regular fatigue. And cancer-related fatigue and regular fatigue are not the same as daytime sleepiness, as our colleagues sometimes assume. Daytime sleepiness is having difficulty staying awake. Fatigue is more of an inability to move. In fact, if you look at the official definition of cancer-related fatigue, it says that cancer-related fatigue is a distressing, persistent, and subjective sense of tiredness or exhaustion related to cancer or cancer treatment. It is not proportional to recent activity and does interfere with usual functioning. It differs from fatigue of everyday life. Regular fatigue is temporary and is relieved by rest. Cancer-related fatigue is not temporary; it is more severe, more distressing, and is not relieved by rest. It is different from the daytime sleepiness that we talk about with our sleep patients.

That is the first important point that all health care professionals, and especially our sleep colleagues, need to understand. Ultimately, all of us who do education about sleep should be including education about the relationship between sleep and fatigue in this important subgroup of patients.

SR: What do we still not understand about fatigue and cancer that would really advance our knowledge about the relationship between these disorders?

Ancoli-Israel: There is a lot that we do not understand. We need to stop looking at symptoms as individual factors, and begin looking at them as symptom clusters, because everything interacts with everything else. When we think about fatigue, we need to think about sleep, mood, and pain all at the same time.

As we understand more about the interaction of these variables, we will also need to understand more about the time course. It is important when studying these symptoms that we also look at baseline levels, at least before chemotherapy—to better understand how things change over time.

We need to follow patients longitudinally to see what happens as they become survivors and move farther and farther away from their treatment. We must look at radiation therapy, and not just chemotherapy, because patients undergoing radiation also complain about severe fatigue.

There are many other questions that still need to be answered. How does fatigue differ between the different cancers? Is fatigue worse in one type of cancer? Most studies have been done with breast, lung, or colorectal cancer, but there are plenty of other cancers that we know very little about. What causes fatigue? What contributes to it? What is the best way to treat it?

SR: How do you personally hope to advance this area of research?

Ancoli-Israel: I hope to continue to do my research. The goal of all my research with cancer has been to find ways to improve the quality of life for patients. Quality of life is so directly tied in to sleep, and sleep is tied into fatigue and to circadian rhythms. We know how to treat sleep. We know how to improve circadian rhythms. We are hoping to learn more about how to improve fatigue as well. Once we then find ways to treat these symptom clusters, we can improve quality of life of these patients during the cancer treatment process.

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