No Rest for Fatigue Researchers

By Caroline McNeil

Fatigue is the most important side effect of cancer and cancer treatment, according to a recent study of patients and professionals in major cancer centers across the United States. Led by David Cella, Ph.D., at Evanston Northwestern Healthcare and Northwestern University's cancer center in Chicago, the study confirms not only that cancer-related fatigue is common but also that it affects patients with diverse cancers. Patients undergoing treatment for nine different kinds of advanced cancer ranked it as their most important symptom or concern; patients with two other kinds of cancer ranked it among their top five concerns.

Unfortunately, fatigue is still harder to treat than other common, cancer-related symptoms such as pain and nausea. In this issue of the Journal (1155–1166), Ollie Minton, M.D., of St. George’s University of London and colleagues report their findings from a systematic review and meta-analysis of drugs targeted at cancer-related fatigue. Limiting their review to randomized controlled cancer trials that focused on cancer-related fatigue, they identified three drugs with some evidence of effectiveness.

But each of the three has important limitations. Methylphenidate (Ritalin), a psychostimulant, has been tested in only two small trials of cancer-related fatigue (most trials of the drug have focused on chronic fatigue syndrome rather than cancer-related fatigue). Also, methylphenidate is a controlled drug and has side effects, including addiction, that limit its usefulness.

The second drug, darbepoeitin alfa (Aranesp), showed only borderline superiority over placebo among anemic patients participating in four cancer trials included in the review. The third drug, epoetin alfa (Procrit and Epogen), has evidence of effectiveness in patients with chemotherapy-induced anemia but, like darbepoeitin, has not been shown to affect fatigue in nonanemic cancer patients. In fact, a public health advisory from the U.S. Food and Drug Administration, issued in March, warns that these erythropoiesis-stimulating agents have not been approved for cancer-related fatigue in nonanemic patients. The advisory was issued in the wake of recent studies showing that such drugs increase mortality and tumor progression rates in head and neck and breast cancer, as well as increasing cardiovascular risks among cancer patients and others.

Another drug, modafinil (Provigil), had some effect on severe fatigue in a randomized controlled trial reported at the annual meeting of the American Society for Clinical Oncology in June. But the drug,
now used to treat narcolepsy, had no effect on moderate or mild fatigue (rated by the patient as 6 or lower on a 10-point scale) in this trial.

Overall, the picture for patients with cancer-related fatigue remains bleak. “There are no clear precipitating factors, no clear mechanisms, no targeted therapy,” Minton said.

He and other experts said that research on fatigue has lagged behind research on other quality-of-life issues for cancer patients. Pain and nausea interventions have been studied for decades, but studies on fatigue interventions date back only to the 1990s.

One reason for the lag, Minton said, was that patients tended not to talk about fatigue, assuming that it had to be expected as part of cancer and cancer treatment.

And oncologists didn’t ask, noted Gary Morrow, Ph.D., of the University of Rochester cancer center in New York, who led the modafinil trial. “You seldom ask a question about a problem you don’t have an answer for,” he said.

New interest in cancer-related fatigue is due partly to increased awareness of its prevalence. Recent studies have found that it affects more than 60% of cancer patients; one report put its prevalence at 90% among patients receiving radiation therapy.

The growing number of cancer survivors has also raised awareness of the problem. Fatigue can continue for years after treatment and have a major effect on quality of life. Those with severe fatigue have trouble carrying out the activities of daily living, such as bathing and dressing. They often cannot return to work or take up family responsibilities. In a qualitative study at the University of Texas M. D. Anderson Cancer Center in Houston, patients who were asked to describe the condition cited a lack of energy and “a feeling of heaviness.” They said, “I don’t have a body part that is not tired,” and “I just have a weak feeling ... pretty well all over.” In this study, participants also reported a lack of motivation and decreased interest in social activities, according to Loretta Williams, Ph.D., who presented the findings at the annual meeting of the Oncology Nursing Society in May.

**Defining and Measuring**

There is no universally accepted definition of cancer-related fatigue, but most descriptions include words and phrases such as “pervasive” and “persistent” and “interferes with usual functioning.” Some note that the condition is not proportional to recent activity and is not relieved by rest or sleep.

How to assess fatigue is another area in which there is little consensus. More than 20 different measures have been used in research, according to a review last year in *The Oncologist* by Jean-Pierre Pascal, Ph.D., and colleagues at the University of Rochester. These range from single-item tools that measure fatigue severity on a scale to multi-item measures that assess the physical, cognitive, affective, and/or behavioral aspects of fatigue, with questions, for instance, on the patient’s energy levels, ability to walk around the block, or capacity for social interactions.

The multi-item tools are sometimes avoided because of their length, but for research purposes, they are often considered better at capturing the complexities of cancer-related fatigue. According to Cella, they can take 2–3 minutes to administer, and they “measure fatigue more precisely and address more aspects of the problem.

“All things being equal,” he said, “a more precise measure will sharpen our understanding of the symptom and reduce the sample size required for a study.”

Single-item scales are quick and easy and, according to some, quite accurate. Pascal and colleagues, in their review, say that although “multidimensional measures could add texture and relevance ... we do not believe that the subjective experience of fatigue is, in itself, complex. Patients can very reliably report its occurrence and severity.”

One of the newest tools for assessing fatigue in research studies is part of the Patient-Reported Outcomes Management Information System (PROMIS), a database of survey questions for measuring common symptoms in clinical trials (see JNCI 2008; 100(4):234–236). Now under development at the National Institutes of Health, PROMIS includes 72 questions on fatigue that have been validated in cancer patients. A 1-minute, cancer-specific form contains just seven questions that are “brief yet precise” according to Cella, who leads the PROMIS project for NIH and presented the cancer-specific fatigue short form at ASCO in June (see box). The PROMIS system can also administer a computerized adaptive version, giving precision similar to that of much longer forms with as few as four or five questions, he said.

While the debate about fatigue assessment in clinical trials continues, single-item scales are gaining ground in practice settings. The consensus-based guidelines from the National Comprehensive Cancer Network, a consortium of 21 comprehensive cancer centers in the United States, recommend screening all cancer patients in active treatment by asking them to rate their fatigue over the past 7 days by using a 0–10 rating of severity and following up with a longer assessment as needed.

**Current Options**

If that rating shows fatigue to be a problem, the patient and physician can consider the current strategies for dealing with it. The NCCN guidelines call first for an in-depth evaluation of possible contributing and treatable factors, such as pain, emotional...
distress, sleep disturbance, and chemotherapy-induced anemia.

Treatment options include a long list of nonpharmaceutical strategies, such as energy conservation and monitoring; exercise; psychosocial interventions, such as stress management and support groups; nutrition consultation; and sleep therapy.

But NCCN’s advice concerning pharmacologic options is much briefer: Consider methylphenidate and modafinil; treat for anemia if indicated; and consider sleep medication.

There is some evidence of effectiveness for a few other drugs, though not enough for anyone to recommend their use. In their review, Minton and colleagues identify two agents, both of which have reduced fatigue in one randomized controlled trial. Ibandronate (Boniva), a bisphosphonate, reduced fatigue in a study with 466 patients with advanced breast cancer. The other, etanercept (Enbrel), a psoriasis treatment that inhibits tumor necrosis factor (TNF), had a statistically significant effect on fatigue in a 12-person trial. A larger randomized trial with etanercept is now underway at the Sanchez Cancer Center at the University of Texas Health Science Center at San Antonio.

Fatigue mechanisms that have been studied in chronic fatigue syndrome and other noncancer conditions may also be implicated in cancer-related fatigue. A recent review by Morrow’s group discusses the hypothalamic–pituitary–adrenal axis, which could result in low cortisol production or other endocrine changes; a defect in the other endocrine changes; a defect in the hypothalamic-pituitary-adrenal axis, which could result in low cortisol production or other endocrine changes; a defect in the mechanism for regenerating ATP in muscle, leading to the feelings of weakness and lack of energy; and dysregulation of proinflammatory cytokines, such as TNF.

Exercise and Counseling

Although oncologists now have few pharmacologic options to offer patients, there is some evidence that exercise and psychosocial interventions may help. In a recent review, Paul Jacobsen, Ph.D., of the H. Lee Moffitt Cancer Center in Tampa, Fla., and colleagues looked at 17 studies of exercise or activity-based interventions and 24 studies of psychological interventions for fatigue, such as telephone counseling and group therapy to teach stress management. They found that 44% of the exercise trials and 50% of the psychological studies that were of good quality had “modestly positive” results.

One possible intervention may be a combination of exercise and a drug, Morrow said. Research just getting under way at the University of Rochester will randomize patients to four different arms to study exercise and modafinil. Participants will receive exercise alone, modafinil alone, exercise and modafinil combined, or neither intervention. Led by Karen Mustian, Ph.D., and funded by the Department of Defense, the trial will enroll several hundred breast cancer patients undergoing chemotherapy at the cancer center.

Fatigue researchers are also turning to pathophysiology, hoping that an understanding of underlying mechanisms will lead to better treatments. “We need to go back and look at basic science—not leap into another candidate drug,” Minton said. He and colleagues in London, with funding from Cancer Research UK, are planning to study various hypothetical mechanisms in cancer patients under study and without fatigue to see which ones are associated with the condition.