Treating Fatigue in Cancer Patients

ANN BERGER

Warren Grant Magnuson Clinical Center, National Institutes of Health, Bethesda, Maryland, USA

Key Words. Fatigue · Neoplasms · Depression · Anemia · Sleep disorders

ABSTRACT

Possible causes of cancer-related fatigue include depression, pain, sleep problems, anemia, deconditioning, metabolic abnormalities, infection, dietary problems, hypoxia, and side effects of medication. Although treatments are available for each of these conditions, there are no generally accepted treatments available for the whole fatigue syndrome. There are also very few studies on the treatment of cancer-related fatigue—only 10 randomized controlled trials. Health care providers have begun to understand that, just as the treatment of pain requires attention to imbalances in mind, body, and spirit, the treatment of fatigue will require such an approach. The Oncologist 2003;8(suppl 1):10-14

INTRODUCTION

Effective treatment strategies for cancer-related fatigue are still evolving. Although it is possible to treat the anemia and depression associated with cancer, there are no treatments available for the whole fatigue syndrome. There are also very few clinical studies on fatigue—only 10 randomized controlled trials; however, most trials are small, nonrandomized trials with inadequate sample sizes.

The first steps in treating a cancer patient’s fatigue are to determine the patient’s expectations and to set realistic goals. Expectations and goals may differ depending on the patient’s position on the disease trajectory. Those of a patient requiring end-of-life hospice care, for example, are likely to be different from those of a patient in the early stages of disease. In addition, the options available to someone in a hospice unit may be different from those available to someone in the initial stages of chemotherapy. So it is important to look at the nature of the fatigue.

ETIOLOGY OF FATIGUE

Possible causes of fatigue include depression, pain, sleep problems, anemia, deconditioning, metabolic abnormalities, infection, dietary problems, hypoxia, and side effects of medication. In fact, people who are undergoing active treatment may be receiving chemotherapy, radiotherapy, and many different medications that may make them
tired. Those medications most likely to cause fatigue include hypnotics, anti-anxiety medicines, antihistamines, analgesics, and opiates.

**Depression and Pain**

If a patient is experiencing fatigue because of depression, the clinician may administer an antidepressant, and some antidepressants have sedative side effects. Indeed, because fatigue is one of the symptoms of depression, the clinician may hope that reducing the depression will reduce the fatigue.

A patient in protracted pain is also going to be fatigued, and the administration of analgesics can cause more fatigue. Conversely, fatigue may cause a pain syndrome, much like chronic fatigue syndrome. Many patients actually have fatigue, but many of them develop a fibromyalgia-like picture with pain in different areas of the body.

Therefore fatigue and pain, with depression, cluster together not only for patients with cancer, but also for patients with chronic pain problems. It is likely that they are causally related through hormonal or other factors, but these are as yet unknown.

**Sleep Disorders**

Most cancer patients get up in the morning to find that they are just as tired as they were the night before. So the suggestion is that treating sleep disorders will help cancer patients who experience fatigue. One expert recommended a whole sleep protocol (which needs to be tailored to each individual). Sleeping too much or staying in bed too long can actually be counterproductive [1].

Under the sleep protocol, the patient arises at about the same time each day, goes to bed at about the same time each night, and limits the time spent in bed each night to a normal length of time. A normal time is defined as being between 6 and 8 hours of sleep, depending on the patient’s age and his or her habits before the problem arose. It is also wise to limit or discontinue the intake of drugs such as caffeine, nicotine, and alcohol, as these substances can actually increase fatigue the following day. Daytime naps should last no longer than 15-20 minutes. Many patients complain of severe fatigue, but then stay in bed all day. Clearly, this may lead to physical deconditioning, which also accompanies fatigue.

Patients who are having trouble sleeping should avoid evening stimulation. They need an environment where there is relaxation, music, and a daily routine. If they cannot fall asleep within 20 minutes of their nightly relaxation routine, they should get up and try some form of relaxation before they get back into bed. Many people lie in bed, sometimes for 2 hours, trying to fall asleep. The more frustrated a person becomes, however, the less likely it is that he or she will finally fall asleep.

**Anemia**

Anemia is often an important clinical problem in patients with cancer-related fatigue. The clinician who is treating anemia in a cancer patient with fatigue must first investigate the causes, such as bleeding or iron deficiency. Patients may need a blood transfusion, supplemental iron, or recombinant human erythropoietin, followed by a reevaluation of their anemia after 4 weeks.

**Deconditioning**

Fatigue associated with deconditioning is a problem for many people with cancer. Despite some interest in the value of conserving the energy of cancer patients, there is no clinical evidence that energy conservation helps them. Resting in naps of 15-20 minutes a day may have some benefit, but these patients really need increased physical function. Appropriate exercise usually includes some kind of aerobic work, such as walking or cycling. Such exercise has been shown to help some patients with fatigue.

**Interventions**

Both pharmacologic and nonpharmacologic interventions are available to help cancer patients with fatigue; however, currently, there are not many effective pharmacologic interventions.

**Pharmacologic Interventions**

The psychostimulants available include methylphenidate, pemoline, and dextroamphetamine. There is some thought that modafinil, a new medication for the treatment of narcolepsy, may help fatigue in cancer patients. None of these has been shown to have efficacy in cancer-related fatigue on the basis of randomized controlled trials. The clinical trials that have been done on these medications have involved small case studies.

Anorexia, severe insomnia, anxiety or agitation, heart disease, and advanced age are contraindications to the use of psychostimulants. The potential toxicities of the psychostimulants can even promote anorexia, which can lead to further fatigue. Psychostimulants should not be administered to patients in the morning and then at night; rather, they should receive these medications once in the morning and again at about 2 p.m., as they will stimulate the patient and keep him or her awake at night if given after 2 p.m. Furthermore, there is evidence that most of the psychostimulants can cause tachyphylaxis, meaning that it is necessary to increase the dosage within a short period of time.
Corticosteroids are clinically useful for fatigue in patients with advanced cancer, usually during end-of-life hospice care. One of the reasons for this somewhat limited use is that steroids have many complications. Leaving patients on steroids long enough, sometimes even 4 or 5 months, may lead to the development of myopathy, and patients will not be as physically active as they could be. The inactivity increases their fatigue; therefore, most clinicians reserve the use of steroids as a last option, and most of the case-controlled trials have involved hospice patients.

For patients who are unresponsive to other treatments, amantadine is used as an end-of-line drug. Again, there have been no trials in cancer patients, but amantadine has been useful as treatment in multiple-sclerosis-related fatigue or as an antidepressant. Methylphenidate is also useful as an antidepressant. As it takes a few weeks for an antidepressant to become effective, a psychiatrist may start the patient on an antidepressant together with methylphenidate so that the benefit actually begins within the first few days. In many ways, this effect is diagnostic of depression.

Nonpharmacologic Interventions

Patient education is a very important component of nonpharmacologic treatment for cancer-related fatigue. Patients must understand that fatigue is normal and that their clinicians are trying to help. Those patients who must cope with pain and fatigue for long periods of time are likely to doubt that any improvement in their condition will ever occur.

Exercise (e.g., individually tailored walking, cycling, or swimming programs), modification of activity (e.g., naps during morning and early afternoon), assessment of sleep patterns, stress management and cognitive therapies, and adequate nutrition and hydration are all nonpharmacologic methods of dealing with fatigue. It is seldom one of these that produces the desired effect, but rather a combination of the many different approaches. However, no studies have yet shown what combinations of strategies are most appropriate.

Randomized Controlled Trials

The Agency for Healthcare Research and Quality in the U.S. found and analyzed all randomized clinical trials (n = 10) evaluating various treatments for patients with cancer-related fatigue [2]. Three of the trials had exercise programs, which showed promising preliminary results, and there were also positive outcomes for interventions such as support groups, relaxation, and psychotherapy. However, the only pharmacologic treatment that demonstrated significant benefit was the use of epoetin alfa in patients with anemia due to chemotherapy.

With the exception of the large randomized controlled trial of epoetin alfa that was performed for registration, many of these randomized controlled trials had problems. The sample sizes were very small, they were underpowered to detect any benefit, which was not always indicated prospectively but rather identified retrospectively. In addition, patients were not always stratified according to known risk factors, and important demographic data were omitted in some studies. One of the biggest problems encountered in clinical trials involving fatigue is the dropout rate. The scales used to measure fatigue are far too long or too numerous, and patients just cannot complete them for all the time periods.

The following is a description and commentary of the 10 randomized studies performed on cancer-related fatigue: Spiegel and colleagues, in 1981, studied 86 patients with metastatic breast cancer who participated in a support group that met weekly for 1 year [3]. All study participants had equivalent amounts of chemotherapy. Fatigue increased and energy declined for the control group, but not for the treatment group. Furthermore, those in the treatment group also had significantly lower scores on the fatigue subscale. It was concluded that women with advanced breast cancer who participated in support groups experienced significantly less psychological distress. However, the investigators did not indicate in the report how they randomized or stratified patients, and the fact that the treatment group actually had a higher socioeconomic class may have had an impact on the study outcome. Only 30 subjects completed the assessment. In 1985, Forester and colleagues studied the effect of psychotherapy on 100 subjects with multiple, different cancers [4]. They assessed the level of fatigue in a therapy group and a control group at baseline, near the midpoint of radiation therapy, at the end of radiation therapy, 4 weeks after the end of radiation therapy, and 8 weeks after the end of radiation therapy. The change in baseline fatigue scores of those in the therapy group was significantly greater than the change in the scores of the control group only after 4 weeks of radiation therapy. The fact that this result occurred at only one point in time makes it impossible not to question its validity and significance and there was no power calculation. Finally, the patient population was poorly characterized.

A trial by Decker and colleagues involved 82 subjects who were “all recently diagnosed cancer patients” [5]. The study excluded patients who had previously had cancer or radiation therapy, inpatients, and those who had suicidal ideation. The treatment used was relaxation therapy. In the control group, the fatigue increased significantly; in the treatment group, there was no significant change. Decker and colleagues concluded that relaxation training had a psychological benefit. However, the report included no patient characteristics, provided only a vague description of the
randomization and selection process, and did not explain baseline differences between the control group and the treatment group on the Profile of Mood States scales. Clearly, these shortcomings have the potential to introduce several biases. In a randomized controlled trial by Mock and colleagues, 46 patients with metastatic breast cancer participated in a walking exercise program [6]. The scores of the exercise group on physical functioning were significantly higher than those of the control group at the end of the program, but the report did not include all the data gathered from the scales used. A study by Ahles and colleagues in 1999 examined treatment with massage versus quiet time in 34 patients [7]. The most significant effects in terms of fatigue occurred at the day 7 assessment point. It is difficult to determine the applicability of this study because it measured fatigue only immediately before and immediately after massage. There were no indications of how patients felt 4 hours or indeed 2 days later, nor was there any report on how long the effect lasted. In a study involving 59 subjects who performed aerobic cycling exercises, Dimeo and colleagues found no significant differences at baseline [8]. However, fatigue was greater at discharge in the control group than in the exercise group. It is very difficult to interpret this study as the arms were not really compared with one another and no statistically significant difference between the two groups was apparent at the time of discharge. In a trial involving 110 patients, Gaston-Johansson and colleagues examined the effect of a comprehensive coping strategy program on cancer-related fatigue [9]. At day 7, fatigue was significantly less in the treatment group. It was concluded that the coping strategy program reduced nausea and vomiting and may have indirectly improved other symptoms. Oyama and colleagues used virtual reality technology in an effort to counter fatigue in their study [10]. Thirty cancer patients received information through all senses; they heard music, saw pictures, smelled aromas—the strategy really made use of all the senses for relaxation. The level of fatigue was significantly lower in the treatment group than in the control group after the second treatment, but not after the first. It is not clear whether some of the parameters were considered the end point or whether they were added later. The population was small and heterogeneous, and it is difficult to know if this finding can be generalized to a larger population. Another trial on physical conditioning in 48 subjects, conducted by Mock and colleagues, showed no statistical difference in fatigue scores between exercise and control groups at the end of treatment [11]. The study did show that 50% of the people in the control group were actually exercising, while 30% of the people in the treatment group who were supposed to be exercising were not. A very well controlled trial, and the only trial involving medication, is that done in 2001 by Littlewood and associates [12]. The medication, epoetin alfa, was used in the treatment of anemia, which may be partly responsible for fatigue. An examination of the effects of a placebo versus epoetin alfa in 251 cancer patients showed a strong statistical correlation between hemoglobin and quality of life. Thus, it appears that epoetin alfa significantly improves fatigue and quality of life in the setting of anemia.

**CONCLUSION**

Health care providers have begun to understand that the symptom or syndrome of fatigue is an alert to imbalances in mind, body, and spirit. Just as the treatment of pain requires attention to all three, the treatment of fatigue will require such an approach—not only in cancer patients. As we move forward in the war against cancer, we need to move forward equally in the war against fatigue and other cancer-associated symptoms.

**REFERENCES**


