

Cancer-related fatigue: a practical review

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Fatigue is an exceedingly common often treatable problem in cancer patients that profoundly affects all aspects of quality of life. Prevalence estimates have ranged from 50% to 90% of cancer patients overall. After addressing reversible or treatable contributing factors, such as hypothyroidism, anemia, sleep disturbance, pain, emotional distress, climacterium, medication adverse events, metabolic disturbances, or organ dysfunction such as heart failure, myopathy, and pulmonary fibrosis, patients may be screened with a brief fatigue self-assessment tool. All cancer patients should be screened regularly for fatigue. Those with moderate or severe fatigue may benefit from both pharmacologic and nonpharmacologic interventions, while mild fatigue that does not interfere with quality of life can be treated with nonpharmacologic measures alone. Physicians often have insufficient knowledge about fatigue and its treatments or underestimate the impact of fatigue on quality of life, while patients may consider it an unavoidable and untreatable side-effect and fear that reporting it may incite a change toward less aggressive cancer treatment. A practical review may therefore be useful to health care professionals in order to avoid the common barriers to its treatment that exist on the sides of both physicians and patients.

Key words: cancer, fatigue, review

Introduction

Fatigue is an exceedingly common often treatable problem in cancer patients that profoundly affects all aspects of quality of life [1]. Patients report fatigue as one of the most important and distressing symptoms related to cancer and its treatment [2], and it is a strong and independent predictor of decreased overall patient satisfaction and health-related quality of life [3]. While expert guidelines now recommend regular screening for cancer-related fatigue [4], the condition remains consistently underreported and often goes untreated [2]. Here, the authors assemble available literature on the treatment of cancer-related fatigue into a practical and informative review. Articles were selected for their relevance from searches of the PubMed database that combined the terms ‘cancer’ and ‘fatigue’ using both MeSH terms and keywords, with date range from the beginning of the database through 8 July 2010.

According to the guidelines of the National Comprehensive Cancer Network (NCCN), cancer-related fatigue is defined as a 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 that significantly interferes with usual functioning [4]. Prevalence estimates have varied widely, reflecting the variety of

populations in which it has been studied as well as the subjective nature of the condition and various screening methods that have been employed. Overall 50%–90% of cancer patients experience fatigue [5–9], the latter number corresponding with those undergoing active anticancer chemotherapy or radiotherapy [7]. Fatigue may persist for months or even years after cancer eradication; in one study, a third of patients who had been cured of their cancer for 5 years experienced fatigue [10], and in another, fatigue was present in 60% of Hodgkin’s disease patients who had been free of cancer for 5 years.

The pathogenesis of cancer-related fatigue is not well understood, and a variety of mechanisms may contribute to its development [11]. These involve effects of cancer or its treatment on the central nervous system, muscle energy metabolism, sleep or circadian rhythms [12], mediators of inflammation and stress [13], immune activation [14, 15], and hormonal changes related to effects on the hypothalamic–pituitary axis, premature menopause in women [16], or androgen deprivation in men [11–22]. Fatigue also common in patients undergoing radiation therapy [23] and in nearly all patients receiving the biologic modifiers interferon or interleukin 2 [24]. Care must always be taken to identify common reversible causes of fatigue such as hypothyroidism [25, 26], depression, and anemia [27].

screening and assessment of fatigue

The NCCN now suggests that all cancer patients be screened for cancer-related fatigue at the initial visit, when the diagnosis of

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advanced disease is made, and at each chemotherapy visit [4]. However, barriers to its treatment exist on the sides of both physicians and patients. Physicians may have insufficient knowledge about fatigue and its treatments or underestimate the impact of fatigue on quality of life, while patients may consider it an unavoidable and irremediable side-effect and fear that reporting it may incite a change toward less aggressive cancer treatment [6, 28, 29].

Several instruments have been validated to screen for and assess cancer-related fatigue, but no one modality is diagnostic. The diagnosis can be made through a combination of medical history and physical exam, relevant laboratory data, discussions with families and caregivers, and the use of standardized assessment tools (Figure 1). The simplest of these are the Visual Analog Scale (VAS) and Brief Fatigue Inventory (BFI) [4, 16, 30]. The Functional Assessment of Cancer Therapy instrument [31], Multidimensional Fatigue Symptom Inventory-Short Form [32], and others have also been validated in several languages, although they are more detailed and thus more utilized in clinical research. The diagnosis of cancer-associated fatigue is usually made by excluding reversible treatable contributing factors such as hypothyroidism, anemia, sleep disturbance, pain, emotional distress, climacterium, medication adverse events, electrolyte or metabolic disturbances, or organ dysfunction such as heart failure, myopathy, or pulmonary fibrosis [33, 34]. Once these potential contributing factors are addressed, or if none is present, patients should be screened for with a brief fatigue self-assessment tool, such as the VAS or BFI [34]. Those with moderate or severe fatigue may benefit from

both pharmacologic and nonpharmacologic interventions, while mild fatigue that does not interfere with quality of life can be treated with nonpharmacologic measures alone [4]. Ongoing reassessment of fatigue severity and its impact on quality of life and functioning will usually be necessary.

nonpharmacologic treatment

The initial approach to treatment of cancer-related fatigue requires a comprehensive assessment, patient education, and, often, determination of an individualized treatment plan. Expectations should be addressed and reasonable achievable goals set [34].

Most fatigued patients will benefit from any of several nonpharmacologic interventions. A review of 77 heterogeneous randomized trials involving nonpharmacologic treatments of cancer-related fatigue showed some support for cognitive-behavioral interventions, exercise, hypnosis, relaxation, and psychoeducation for fatigue [35]. The major categories of nonpharmacologic treatments are reviewed below.

cognitive-behavioral interventions

Many patients with cancer-related fatigue will benefit from some type of psychological intervention, and a wide range of modalities have been studied across different populations. Interventions such as group therapy [36, 37], individual counseling [38], stress reduction and relaxation training [39–42], formal cognitive behavioral therapy [43–46], fatigue-related psychoeducation [47], and supportive

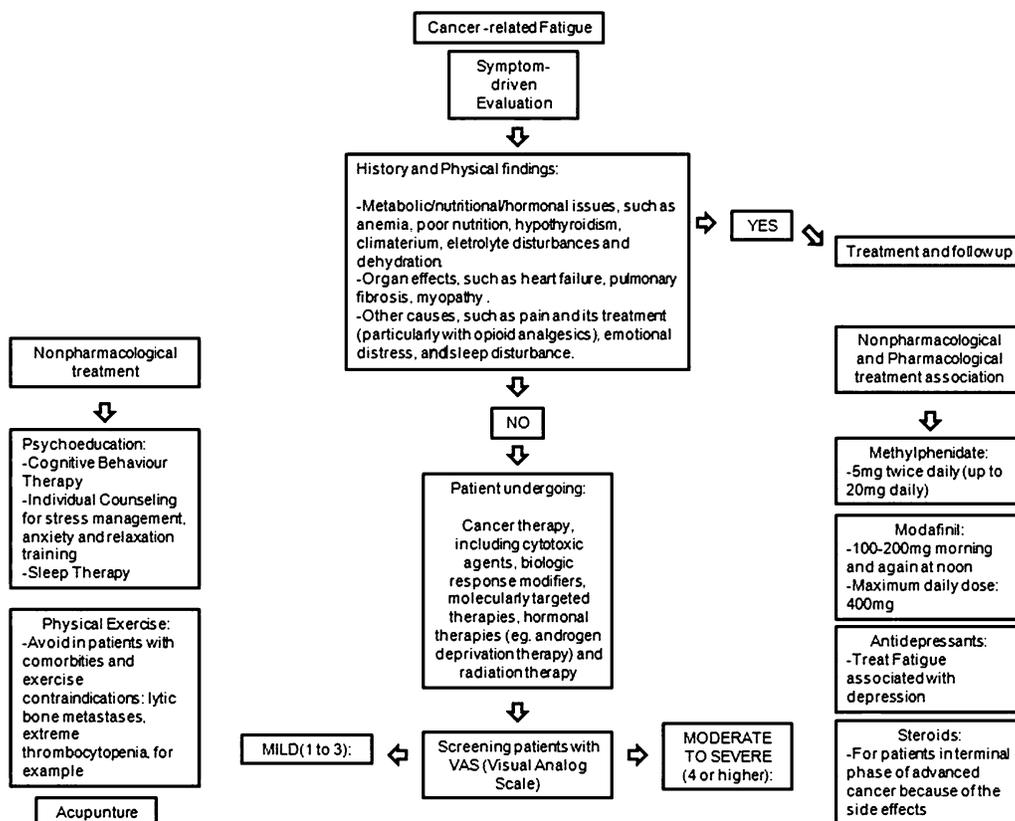


Figure 1. Algorithm: diagnosis and treatment of cancer-related fatigue.

interventions [48] have all shown promising results, mostly in patients actively undergoing cancer treatment.

A systematic review of 27 trials, most of which were of moderate quality, demonstrated that interventions specifically focused on fatigue are more effective than general interventions [49]. As an example, a strategy of energy conservation and activity management (ECAM) was studied in 396 fatigued cancer patients initiating chemotherapy or radiotherapy who were randomly assigned to spend similar nursing orientation time focused on either diet and nutrition or strategies to conserve energy and monitor the association of various activities with level of fatigue. A modest benefit in cancer-related fatigue was seen in the treatment group [50].

exercise

According to current guidelines, counseling in cancer-related fatigue should be directed primarily at activity enhancement. However, only a minority of patients receives such counseling [51]. Studies of exercise during or just after treatment in patients undergoing a variety of cancer therapies have consistently demonstrated benefits in fatigue, quality of life, functional capacity, emotional distress, and other symptoms [52–66]. Regular physical exercise may increase functional capacity, thereby reducing the effort needed to carry out daily activities [67]. The type of exercise chosen should be based on patient preference, as no specific form of exercise has been found to confer greater benefit than any other. Allowing patients to choose their own exercise regimen [53, 68], while at the same time providing printed information and motivating materials such as a step pedometer [66], may improve outcomes. A recent meta-analysis of both behavioral interventions and exercise in cancer-related fatigue pooled 56 studies and found statistically significant improvement by both interventions on fatigue [69].

sleep therapy

Sleep disturbances are common in cancer patients and may be related to the disease, its treatment [70], or emotional distress. Benefits of sleep hygiene programs have been reported on daytime functioning and sleep parameters [70] as well as on fatigue [71] in randomized trials. However, a larger randomized trial of 219 breast cancer patients did not show any benefit of an individualized sleep therapy plan over the control intervention on fatigue [72]. It is therefore clear that behavioral interventions aimed at improving sleep may be successful in their primary aim, but their impact on cancer-related fatigue is less evident.

complementary and alternative medicine

The possible benefits of alternative treatment modalities in cancer-related fatigue have not been well explored. Two clinical trials suggest a benefit of acupuncture on fatigue. In the first, 37 patients with persistent fatigue an average of 2 years postchemotherapy were treated with six to eight sessions of acupuncture, after which they were shown to have a significant mean improvement in BFI scores from baseline [73]. In another trial, 47 fatigued cancer patients were randomly assigned to acupuncture, acupressure, or sham acupressure.

A significant benefit was seen in acupuncture over acupressure and sham acupressure [74].

pharmacologic treatment

Patients suffering from moderate-to-severe cancer-related fatigue may benefit from pharmacologic treatments in addition to nonpharmacologic therapy, especially if quality of life or the ability to carry out daily activities is impaired [75].

methylphenidate/dexmethylphenidate

These psychostimulants have shown promise in the adjunctive treatment of cancer-related fatigue. Several small open-label studies have suggested that methylphenidate improves fatigue [76–79]. The trials additionally demonstrated beneficial effects on anxiety, appetite, nausea, pain, and drowsiness [76] and an improvement in cognitive and functional ability in trials of 12 patients with melanoma [78] and 30 patients with brain tumors, despite the progressive neurologic injury documented in half of the subjects [80].

Randomized trials have also been conducted using these agents. A small, randomized, double-blind crossover study suggested that methylphenidate potentiates the analgesic effects of narcotic agents and decreases their associated drowsiness [81]. However, negative results were seen in a trial in which 112 fatigued cancer patients were randomly assigned to take either methylphenidate or placebo for 7 days. Patients were telephoned daily by a research nurse until day 8, at which time fatigue was assessed by FACIT-F (the primary end point) and patients were offered open-label methylphenidate for 4 additional weeks. A significant benefit in fatigue was seen in both the treatment and placebo groups, and there was no difference between the groups. Patients in the methylphenidate arm were not more likely to choose open-label methylphenidate than those who received placebo. The trial reminds us of the therapeutic power of the placebo effect and the role of nonpharmacologic interventions such as contact with a research nurse [82].

Dexmethylphenidate was studied in a randomized, blinded phase II trial consisting of 154 fatigued patients who had received at least four cycles of chemotherapy for predominantly breast and ovarian cancers. Significant improvements in fatigue were seen in the treatment group over placebo, but there were also more adverse events and study drug discontinuations in the methylphenidate group [83]. A meta-analysis of both of the above-mentioned trials, however, concluded that methylphenidate or dexmethylphenidate was superior to placebo for the treatment of cancer-related fatigue [84].

modafinil

The central stimulant modafinil was studied in a phase 3, randomized placebo-controlled trial of 631 cancer patients undergoing chemotherapy and reporting a fatigue score of at least 1 on a 10-point scale. Although a significant overall effect of the drug over placebo was found, the benefit was limited to patients with severe fatigue [85]. Two nonrandomized open-label pilot studies have also suggested a possible benefit of modafinil in cancer-related fatigue [86, 87].

erythropoietin-stimulating agents

Many cancer patients develop anemia as a consequence of their malignancy, its treatment, or coexisting comorbidities. Anemia is a major reversible cause of cancer-related fatigue [27]. When anemia is present, efforts should be undertaken to identify correctable causes such as iron deficiency, B12 or folate deficiency, blood loss, or hemolysis. When none is found, or when anemia persists despite treatment of a correctable cause, erythropoietin-stimulating agents (ESAs) and blood transfusions may be considered. Guidelines on the use of ESAs were published by the American Society of Clinical Oncology and the American Society of Hematology in 2002 and updated in 2007 [88].

The guidelines recommend the use of epoetin or darbepoetin for chemotherapy-associated anemia and a hemoglobin concentration 'that is approaching, or has fallen below, 10 g/dl, to increase Hb and decrease transfusions'. They stress that red blood cell transfusion is also a therapeutic option in a variety of clinical circumstances. Among other evidence, the panel cited a meta-analysis in which the strongest evidence for the effects of epoetin on transfusion requirements and quality of life was derived from clinical trials in patients with a baseline hemoglobin of ≤ 10 g/dl [89]. According to a systematic review, no therapeutic difference existed between epoetin and darbepoetin [90]. They also recommended monitoring the serum indicators of iron balance and instituting iron repletion when appropriate [88]. In a recently published trial of 1328 patients with advanced Hodgkin's lymphoma who received epoetin alfa, 40 000 units weekly or placebo during chemotherapy, there was a reduction in the need for blood transfusions but no impact in patient-reported outcomes, including fatigue, could be shown [91].

Two important concerns exist that significantly limit the use of ESAs. First, they have been associated with an increased risk of thromboembolic events, an association supported by a 2006 Cochrane meta-analysis of 35 trials [92] but refuted by the clinical trial above [91]. Although the studies included in the analysis tended to be of low quality, the Update Committee urged caution on the use of ESAs in patients considered to be at higher risk for thromboembolic events, with special mention of patients with multiple myeloma being treated with thalidomide or lenalidomide [88].

Second, two placebo-controlled, phase III randomized clinical trials published in 2003 and several since then have shown evidence of higher mortality and shorter locoregional progression-free survival in patients treated with ESAs. More than half of these trials were conducted in patients not receiving chemotherapy, the majority of them targeted a hemoglobin >12 g/dl, and none excluded patients with a baseline hemoglobin >10 g/dl. Although these data prompted the US Food and Drug Administration to add a black-box warning to the prescribing information for epoetin and darbepoetin in March 2007, the Update Committee found difficulty in interpreting and applying them to clinical practice. Along with the guidelines from the NCCN, they recommend that ESA use be avoided in patients with anemia not related to chemotherapy and that they only be instituted in those with a hemoglobin <10 g/dl, with a target level not to exceed

12 g/dl [75, 88]. They also cite evidence that supports the use of ESAs in patients with anemia associated with low-risk myelodysplasia [88].

other pharmacologic agents

Many other pharmacologic treatments have been examined for cancer-related fatigue. Corticosteroids were shown to cause decreased depression and analgesic consumption and increased appetite and daily activity in a small, randomized placebo-controlled trial of a 14-day course of oral methylprednisolone in terminally ill cancer patients [93]. However, no larger trials involving longer courses of corticosteroids in other populations have been carried out. Donepezil was studied in one randomized trial in which there was no benefit over placebo in patients with cancer-related fatigue [94]. Trials have also failed to show any benefit of dextroamphetamine [95], multivitamins [96], or antidepressants [97, 98]. In a meta-analysis, neither progestational steroids nor paroxetine were found to be better than placebo in the treatment of cancer-related fatigue [84]. Finally, in a Cochrane systematic review published in 2008 and updated in 2010, no clinically meaningful benefit was found for agents other than psychostimulants in the pharmacologic treatment of cancer-related fatigue [99].

combined approach to cancer-related fatigue

Patients may benefit from a multimodality approach that utilizes individualized treatment plans, the most prominent example of which is the Cancer-Related Fatigue Clinic at the University of Texas M. D. Anderson Cancer Center. The clinic was established in 1998 with the purpose of improving patients' quality of life by decreasing fatigue. The purpose was to integrate the objective evaluation of fatigue with the development of an innovative treatment plan that included pharmacologic and nonpharmacologic therapies as well as education of patients, families, and health care providers [100].

Data were recently reported on 260 patients evaluated and treated at the clinic from 1998 to 2005. Before initial evaluation, patients underwent a laboratory work-up that included chemistries, a complete blood count, and thyroid-stimulating hormone. Patients also received a fatigue assessment package containing several fatigue assessment measures. On initial consult, practitioners devised an individualized treatment plan. Treatment modalities could include the treatment of reversible associated symptoms or comorbidities; education and counseling, including the provision of take-home literature; and other standard pharmacologic and nonpharmacologic therapies. Fatigue was categorized using the BFI as either severe (score 7–10) or nonsevere (score 0–6), with the latter further subcategorized into moderate (score 4–6) and mild (score 0–3). The primary end point was a reduction in fatigue to a lesser category or subcategory. The most common interventions employed were energy conservation (98.5%), sleep hygiene (97%), exercise (95%), relaxation (27%), antidepressants (27%), analgesics (25%), stimulants (22%), anxiolytics (17%), and nutritional counseling (10%) [34].

Of the 260 patients, 47% reported severe fatigue at baseline, 42% moderate fatigue, and 10% mild fatigue. Only 54% of patients attended a follow-up visit, so loss-to-follow-up bias may have significantly impacted the results. Among the patients who attended follow-up, 59% achieved fatigue reduction by at least one category on the BFI. The generalizability of the results is uncertain—many of the patients requested referrals to the clinic, demonstrating a particular degree of motivation to treat their fatigue; the majority of patients were female, Caucasian, and had a good performance status; and the most common malignancies were breast cancer and hematologic malignancies [34].

summary

Cancer-related fatigue is the most prevalent symptom of cancer, reported in 50%–90% of patients and severely impacting quality of life and functional capacity. The condition remains under-recognized. Guidelines suggest screening for fatigue at the initial visit, when the diagnosis of advanced disease is made, and at each chemotherapy visit, as well as the identification of treatable contributing factors.

Brief assessment tools such as the BFI or VAS may be appropriate in the initial scoring of fatigue severity, but the initial approach to treatment usually requires a more comprehensive assessment, education, and the determination of an individualized treatment plan. Patients with moderate or severe fatigue may benefit from both pharmacologic and nonpharmacologic interventions, while mild fatigue that does not interfere with quality of life can be treated with nonpharmacologic measures alone.

Nonpharmacologic measures that have shown promise include cognitive-behavioral interventions such as ECAM, exercise, and perhaps sleep therapy. Many other modalities may be beneficial and can be used on an individual basis, but insufficient evidence exists to promote any one treatment. Pharmacologic therapies that have shown promise include the psychostimulants methylphenidate and dexamethylphenidate, modafinil (in severely fatigued patients only), and ESAs in patients with chemotherapy-associated anemia and a hemoglobin <10 g/dl. In addition, corticosteroids may have a variety of benefits in terminally ill cancer patients.

The authors feel that fatigue should be treated more aggressively, with more liberal use of pharmacologic agents, in patients actively undergoing anticancer treatment with curative or palliative intent. It is in these patients that the best evidence exists for pharmacologic agents, and these agents have the potential for harmful side-effects when used inappropriately. Pharmacologic therapy may also be considered in terminally ill cancer patients, despite the lack of clear evidence in favor of this approach, as the improvement in quality of life in these patients usually takes precedence.

In contrast, patients cured of their cancer or in remission have fatigue that is not associated with a transient causative factor. In these patients, an initial trial of nonpharmacologic therapy might be the best approach, even in the presence of severe fatigue. If nonpharmacologic therapy fails, pharmacologic agents may then be added.

It is difficult to tailor therapy according to cancer stage or phase based on the literature. In the trials and observational studies reviewed above, there is a clear tendency to study patients actively undergoing, or immediately following anticancer treatment, especially among the pharmacologic interventions, and many of the studies do not restrict enrollment to a specific stage or phase of treatment. Finally, while it is unclear whether dedicating the resources of a clinic solely to the treatment of cancer-related fatigue is a cost-effective strategy, benefit may be derived from a multimodality approach that utilizes individualized treatment plans in the setting of a dedicated cancer-related fatigue clinic.

disclosure

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