

FAST FACTS AND CONCEPTS #173
CANCER-RELATED FATIGUE**Gary M Reisfield MD and George R Wilson MD**

Background While several studies have found fatigue to be the single most prevalent, severe, and disabling symptom in cancer patients – exceeding even pain – it remains both underrecognized and poorly treated by physicians (1). This *Fast Fact* reviews diagnostic and treatment approaches in the palliative care setting.

Characteristics of Cancer Related Fatigue (CRF) CRF is a persistent sense of tiredness/diminished energy related to cancer and/or its treatment, which is not relieved by rest, and which causes diminution in functional capacity and quality of life. Additional proposed ICD-10 features include: diminished concentration; diminished motivation; insomnia or hypersomnia; nonrestorative sleep; short-term memory deficits, and marked emotional reactivity to fatigue that are not primarily consequences of depression.

Causes CRF is often multifactorial, with biochemical, physiological, psychological, and behavioral dimensions that remain poorly defined. Assessment is aimed at identifying correctable causes and determining the impact of CRF on both patients and caregivers. Common causes of CRF include:

- Direct effect from cancer and/or treatments
- Sedating medications
- Deconditioning
- Psychiatric co-morbidities (e.g. depression, anxiety)
- Hypoxemia, or severe anemia (Hb ≤ 8 g/dL) and possibly moderate anemia (Hb ≤ 11 g/dL)
- Systemic infection and/or or significant organ dysfunction (e.g. heart, liver, kidney, lung)
- Electrolyte abnormalities (e.g. $\downarrow\text{Na}^+$, $\downarrow\text{K}^+$, $\downarrow\text{Mg}^{++}$, $\uparrow\text{Ca}^{++}$)
- Nutritional imbalance/impairment
- Sleep disturbance
- Uncontrolled pain (2)

Specific Treatments should be directed toward correcting identifiable causes, e.g. elimination of sedating drugs, correction of anemia or electrolyte imbalance.

Non-Specific Treatments may help in reduce fatigue, optimize function, and promote adaptation.

- **Education:** Educate patient/family about CRF in order to normalize the symptom and promote adaptation/adjustment through setting realistic goals; modifying and prioritizing activities; and planning activities around diurnal variations in energy levels.
- **Exercise:** A meta-analysis suggested that aerobic exercise can improve cancer-related fatigue symptoms (3). Aerobic exercise (low to moderate intensity; progressive) is ideal, but benefits may also be realized with resistance training (4). A reasonable goal is 20-30 minutes of (cumulative) exercise per day, at least 3 days per week.
- **Drug Therapy:** There is little good data for non-specific drug therapy in CRF. The following drugs have been used with variable success:
 - **Psychostimulants:** While there is a growing literature on the use of psychostimulants for CRF, there is a lack of good controlled trials. *Methylphenidate:* a meta-analysis indicated superiority of methylphenidate over placebo for treatment of CRF (6). Start with 2.5-5 mg and titrate as necessary to 15-30 mg po at 08:00 and noon. *Modafanil:* pilot studies indicated efficacy in the treatment of fatigue associated with depression, multiple sclerosis, ALS, and HIV with potentially fewer side effects than other psychostimulants. However, a more recent meta-analysis showed no benefit over placebo (5). Suggested initial dosing is 50 mg po qam and titrate as necessary to 200-400 mg po qam. See *Fast Facts* #61 and 259.
 - **Corticosteroids:** These may provide a modest duration of benefit (2-4 weeks) offset by the potential for significant toxicity (6). Reported regimens have included prednisone 7.5-10 mg po qday; dexamethasone 1-4 mg po qday; methylprednisolone 32 mg po qday.
 - **Megestrol acetate:** Two double-blind, crossover studies showed reduction in CRF with doses of 160 mg by mouth three times a day (7,8).

- **Dietary Supplements:** Ginseng: A randomized trial of 2000 mg of daily oral ginseng vs placebo showed significant improvement in cancer-related fatigue at 8 weeks with no adverse effects (9). L-carnitine has been investigated for CRF in a non-controlled fashion, but the quality of these studies have been suboptimal.
- **Complementary Therapies:** Acupuncture: a systemic review indicated potential benefit in CRF, but also cited a need for more rigorously designed trials before conclusions may be drawn (10).

References

1. Morrow GR, Shelke AR, Roscoe JA. Management of cancer-related fatigue. *Cancer Investigation*. 2005; 23:229-239.
2. Fatigue PDQ. National Cancer Institute. Available at: <http://www.cancer.gov/about-cancer/treatment/side-effects/fatigue/fatigue-pdq>.
3. Tian L, Hui JL, Lin L, Hu Y. Effects of aerobic exercise on cancer-related fatigue: a meta-analysis of randomized controlled trials. *Support Care Cancer*. 2015. Epub ahead of print.
4. Mock V. Evidence-based treatment of cancer-related fatigue. *J Natl Cancer Inst Monogr*. 2004; 32:112-118.
5. Qu D, Zhang Zm Yu X, et al. Psychotropic drugs for the management of cancer-related fatigue: a systematic review and meta-analysis. *Eur J Cancer Care*. 2015. Epub ahead of print.
6. Yennurajalingam S, Frisbee-Hume S, Palmer JL, et al. Reduction of cancer-related fatigue with dexamethasone: a double-blind, randomized, placebo-controlled trial in patients with advanced cancer. *J Clin Oncol*. 2013; 31(25):3076-3082.
7. Bruera E, Macmillan K, Hanson J, et al. A controlled trial of megestrol acetate on appetite, caloric intake, nutritional status, and other symptoms in patients with advanced cancer. *Cancer*. 1990; 66:1279-1282.
8. Bruera E, Ernst S, Hagen N, et al. Effectiveness of megestrol acetate in patients with advanced cancer: a randomized, double-blind, crossover study. *Cancer Prev Control* 1998; 2:74-78.
9. Barton DL, Liu H, Dakhil SR, et al. Wisconsin ginseng (*Panax quinquefolius*) to improve cancer-related fatigue: a randomized, double-blind trial, N07C2. *J Natl Cancer Inst*. 2013; 105(16): 1230-1238.
10. Posadzki P, Moon TW, Choi TY, et al. Acupuncture for cancer-related fatigue: a systematic review of randomized clinical trials. *Support Care Cancer*. 2013; 21(7):2067-2073.

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