PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #173
CANCER-RELATED FATIGUE
Gary M Reisfield MD, Maria F Lowry PharmD, George R Wilson MD

Background: While several studies have found fatigue to be the single most prevalent and disabling symptom in cancer patients – exceeding even pain – it remains both underrecognized and poorly treated (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 (1,2). 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 with regards to quality of life (QOL). Common causes of CRF include:

- Direct effects from cancer and/or treatments
- Deconditioning
- Nutritional imbalance/impairment
- Medications: opioids, benzodiazepines, antihistamines, hypnotics
- Psychiatric co-morbidities (e.g., depression, anxiety)
- Hypoxemia, or severe anemia (e.g., Hb ≤7 g/dL)
- Systemic infection and/or or significant organ dysfunction (e.g., heart, liver, kidney, lung)
- Electrolyte abnormalities (e.g., $\downarrow Na^{+}$, $\downarrow K^{+}$, $\downarrow Mg^{++}$, $\uparrow Ca^{++}$)
- Sleep disturbances such as insomnia or sleep apnea
- Uncontrolled pain (2)

Specific Treatments should be directed toward identifiable and modifiable causes (e.g., discontinuing sedating drugs, correcting electrolyte imbalance) as appropriate based on prognosis and goals of care.

Non-Specific Treatments may help to reduce CRF, optimize function, and promote adaptation.

- **Education:** Educate patient/family about CRF 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 exercise can improve CRF (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.
- **Pharmacotherapy:** It is important to determine time to benefit and compare to patient prognosis when considering pharmacologic agents for CRF. Some pharmacologic agents (psychostimulants) work more quickly than others (antidepressants). Most studies are limited time trials. Therefore, long-term efficacy and safety outcome data are not yet available.
    - Psychostimulants: *Methylphenidate*: Two meta-analyses indicated superiority of methylphenidate over placebo for treatment of CRF (5,6). For example, a recent randomized controlled trial (RCT) showed a significantly improvement subjective sense of tiredness which lasted up to 5 hours after the use of methylphenidate 10 mg taken on an as needed basis (7). Start with 2.5-5 mg and titrate as necessary to 15-30 mg po at 08:00 and noon. Avoid doses after noon to minimize effect on sleep at night. *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. Meta-analyses and RCTs have reached mixed conclusions: one meta-analysis and RCT concluded there is benefit over placebo specifically for CRF and QOL scores (6,8), another meta-analysis concluded that there is no benefit (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: Two RCTs showed dexamethasone 4 mg PO daily improved CRF and QOL scores, with an onset of benefit of 1-2 weeks (8,9). However, their use must be carefully weighed

with their recognized adverse effects (e.g., osteoporosis, risk of infection, proximal muscle weakness, hyperglycemia, insomnia). Reported regimens include prednisone 7.5-10 mg po qday; dexamethasone 1-4 mg po daily or -BID; methylprednisolone 32 mg po daily.
    - Megestrol acetate: A double-blind, crossover study showed reduction in CRF with doses of 160 mg by mouth three times a day (10).
    - Antidepressants: *Bupropion*: Two double-blind, RCTs demonstrated improvement in fatigue scores, functional outcomes, and QOL with doses of 150 mg/day. Time to benefit is ~4 weeks, which may be helpful if patients have prognosis of months (11,12). *Paroxetine*: Recent data from meta-analysis showed paroxetine 20 mg daily was superior to placebo, methylphenidate, and modafinil (6); time to benefit is likely several weeks to a month.
- **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 (13). L-carnitine has been investigated in a non-controlled fashion, but the data quality are suboptimal.
- **Complementary Therapies:** Acupuncture: A meta-analysis indicated that acupuncture is effective for CRF management and should be recommended as an alternative therapy. (14).

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. Chow R, Bruera E, Sanatani et al. Cancer-related fatigue-pharmacological interventions: systematic review and network meta-analysis. *BMJ Support Palliat Care.* 2021 Sep 30;bmjspcare-2021-003244.
7. Pedersen L, Lund L, Petersen MA, et al. Methylphenidate as needed for fatigue in patients with advanced cancer. A prospective, double-blind, and placebo-controlled study. *J Pain Symptom Manage*. 2020 Nov 60(5):992-1002.
8. Deb U, Mukhopadhyay S, Bhattacharya, et al. Efficacy and safety of modafinil versus dexamethasone in cancer-related fatigue: a prospective randomized controlled study. *Future Oncol*. 2021 May; 17(14):1735-1747.
9. 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.
10. 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.
11. Salehifar E, Azimi S, Janbabai G et al. Efficacy and safety of bupropion in cancer-related fatigue, a randomized double blind placebo controlled clinical trial. *BMC Cancer*. 2020 Feb 27;20(1):158.
12. Ashrafi F, Mousavi S, Karimi M. Potential role of bupropion sustained release for cancer-related fatigue: a double-blind, placebo-controlled study. *Asian Pac J Cancer Prev.* 2018 Jun 25;19(6):1547-1551.
13. Barton DL, Liu H, Dakhil SR, et al. Wisconsin gineng (Panax quinquefolius) to improve cancer-related fatigue: a randomized, double-blind trial, N07C2. *J Natl Cancer Inst.* 2013; 105(16):1230-1238.
14. Zhang Y, Lin L, Li H et al. Effects of acupuncture on cancer-related fatigue: a meta-analysis. *Support Care Cancer*. 2018 Feb; 26(2):415-425.

Conflicts of Interest: None to report

Version History: This *Fast Fact* was originally edited by David E Weissman MD and published in January 2007. Copy-edited in April 2009. Re-copy edited in November 2015 by Mary G Rhodes, MD. It then underwent a more substantial update in November 2021 by Maria F Lowry, Pharm D.

Fast Facts and Concepts are edited by Sean Marks MD (Medical College of Wisconsin) and associate editor Drew A Rosielle MD (University of Minnesota Medical School), with the generous support of a volunteer peer-review editorial board, and are made available online by the Palliative Care Network of Wisconsin (PCNOW); the authors of each individual *Fast Fact* are solely responsible for that ***Fast Fact's*** content. The full set of *Fast Facts* are available at Palliative Care Network of Wisconsin with contact information, and how to reference *Fast Facts.*

Disclaimer: *Fast Facts and Concepts* provide educational information for health care professionals. This information is not medical advice. *Fast Facts* are not continually updated, and new safety information may emerge after a *Fast Fact* is published. Health care providers should always exercise their own independent clinical judgment and consult other relevant and up-to-date experts and resources. Some *Fast Facts* cite the use of a product in a dosage, for an indication, or in a manner other than that recommended in the product labeling. Accordingly, the official prescribing information should be consulted before any such product is used.