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Review Article

Cancer-Related Fatigue and Its Management

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Abstract

Fatigue is the most common symptom found in the cancer patients, with a prevalence of more than 60%, as reported in the major part of various studies. This paper mainly reviews the management of the cancer related fatigue. In this paper, various pharmacologic agents are discussed for the management of fatigue in cancer patients and these agents comprises of psychostimulants, anti-depressants, corticosteroids, and hematopoietic. There are some other therapeutic agents such as paroxetine (serotonin reuptake inhibitors), bupropion, modafinil, and l-carnitine, but these agents are less studied for cancer related fatigue and at present, these agents are focusing on different clinical trials.

Keywords: Cancer; Fatigue; Corticosteroids; Anti-Depressants; Exercise

Abbreviations

5-HT: 5-Hydroxytryptamine;
ATP: Adenosine tri-phosphate;
CI: Confidence Interval;
CNS: Central Nervous System;
CRF: Cancer-Related Fatigue;
CRH: Corticotropin-Releasing Hormone;
EGFR: Epidermal Growth Factor Receptor;
FACT-An: Functional Assessment of Cancer Therapy-Anemia;
FACIT-F: Functional Assessment for Chronic Illness Therapy–Fatigue;
FDA: Food and Drug Administration;
Hb: Hemoglobin;
HPA: Hypothalamic-Pituitary-Adrenal;
HSCS: High Sensitivity Cognitive Screen;
IL-1: Interleukin-1;
IL-6: Interleukin-6;

IL-1 RA: Interleukin-1 Receptor Antagonist;
NCCN: National Comprehensive Cancer Network;
QoL: Quality of Life;
RCT: Randomized Controlled Trial;
SOC: Standard of Care;
TGF-α : Transforming Growth Factor-Alpha;
TNF: Tumor Necrosis Factor;
VEGF: Vascular Endothelial Growth Factor

Introduction

The word fatigue comes from a Greek word, which means a lack or loss of strength of the body. Fatigue is one of the most common symptoms seen in the cancer patients. The continuous nature of the cancer treatment, their effects on physical and psychological aspects of patients' lives, and the compromised quality of the life during active treatment phase contributes to fatigue. The mechanism that underlies the onset and persistence of cancer-related fatigue has not been fully determined [1].

Fatigue is the most common symptoms in the cancer patients and it is the most stressful symptom among all the symptoms which is related to cancer treatment because it significantly destroys the ability to function daily work and quality of life of patients. The important basics of cancer related fatigue are lack of ability to be relaxed through the sleep or rest, harmful effects on the quality of life, persistence, and pervasiveness. The cancer patients should be evaluated with fatigue or its fatigue levels and its treatment option should be selected on the basis of the level of fatigue and pathology in the cancer patients. The pathology helps in examining the patients with specific causes such as metabolic disorder, depression, sleep disorder, and anemia for fatigue. There are various non-specific therapies which is useful in the management of short and long term cancer related fatigue. The anti-depressants, psychostimulants, hematopoietic, and corticosteroids are also used in the management of the cancer related fatigue [2].

According to the National Comprehensive Cancer Network (NCCN), 'Fatigue is the most common symptom, which affects cancer patients. For some of the people, it is the most stressful symptom. The worst part of cancer related fatigue is constant exhaustion and draining, which limits the capability to enjoy the life and from doing other daily activities. There are a lot of ways to manage or treat cancer related fatigue, such as medications, distraction, psychosocial measures, sleep therapy, rest, nutrition counseling, and increase in activity' [3].

A Norwegian cross-sectional study was conducted with 1,431 patients, to compare the fatigue prevalence, which are long-lasting survivors of testicular cancer and at an average of eleven years post-treatment with prevalence of fatigue in the age matched male, in the common Norwegian population (1,080 patients). The prevalence of cancer related fatigue was 17.1% (95% confidence interval [CI], 15.2–19.1%) among all the long-lasting survivors of testicular cancer, as evaluated through 9.7% (95% CI, 8.0–11.5%) in the common population. The cancer related fatigue was also related to various somatic complaints, poor quality of life, and different psychosocial problems [4].

Epidemiology/Etiology: The cancer related fatigue is described through different people. Generally, fatigue includes the feeling of exhausted, lacking energy, weak, tired, washed out, wiped out, and less able to concentrate. These feeling makes hard to do day to day work. Around one third of cancer patients have reported that, fatigue can arise either in the last months or after several years of treatment. The surgery, radiation treatment, anemia, not sleeping enough, poor nutrition's, chemotherapy treatment, and not drinking enough fluids are the main causes of cancer related fatigue [5]. Generally, fatigue is distinguished as a multidimensional phenomenon, which develops psychological condition, diminishing energy, over time, and mental capacity of the patient with cancer (Table-1) [6].

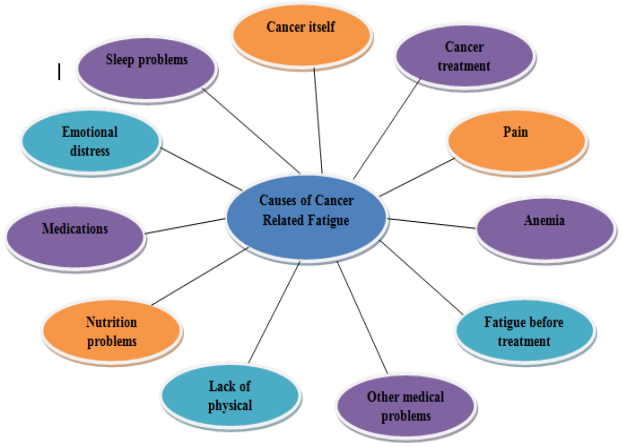


Figure 1. Cause of cancer related fatigue

Cancer related fatigue represents various etiological factors and predisposing factors (Table-2). [7]

Pathophysiology of cancer related fatigue: The risk factors and various etiological factors are not fully determined for the cancer related fatigue. There are various hypotheses, which provide the mechanism of pathophysiology of cancer related fatigue (Figure-2). These mechanisms are Growth Factor hypothesis, HPA-axis disruption hypothesis, Vagal-afferent activation hypothesis, Serotonin dysregulation hypothesis, Pro-inflammatory cytokine hypothesis, Circadian rhythm modulation hypothesis, Adenosine tri-phosphate hypothesis, and Anemia hypothesis.

Table 1. Criteria for cancer related fatigue [6].

Familial Renal cell carcinoma	
Renal cell tumor	**Malignant**
	· Clear cell Renal cell carcinoma
	· Multilocular clear cell renal cell carcinoma
	· Papillary renal cell carcinoma
	· Chromophobe renal cell carcinoma
	· Carcinoma of the collecting ducts of Bellini
	· Renal medulary carcinoma
	· Xp11 translocation carcinomas
	· Carcinoma associated with neuroblastoma
	· Mucinous tubular and spindle cell carcinoma
	· Renal cell carcinoma unclassified
	Benign
	· Papillary adenoma
	· Oncocytoma
Metanephric Tumor	· Metanephric adenoma
	· Metanephric adenofibroma
	· Metanephric stromal tumors
Mixed mesenchymal and epithelial tumors	· Cystic nephroma
	· Mixed epithelial and stromal tumor
	· Synovial sarcoma
Nephroblastic tumors	· Nephrogenic rests
	· Nephroblastoma
	· Cystic partially differentiated nephroblastoma
	· Neuroendocrine tumors
	· Carcinoid
Neuroendocrine carcinoma	· Primitive neuroectodermal tumor
	· Phaeochromocytom
Other tumors	· Mesenchymal tumors
	· Hematopoietic and lymphoid tumors
	· Germ cell tumors
	· Metastatic tumors

Table 2. Etiological and predisposing factors.

Column1	Column2	Column3	Column4	Column5	*Column6*
Endpoint		Avastin + IFN	Placebo + IFN	HR(Hazard ratio) (95% CI (confidence interval))	*P* value
					(probability of obtaining a result)
	Number of patients	327	322		
Primary	PFS (median)	10.2 months	5.4 months	0.60(0.49–0.72)	<0.0001
Initial primary*	OS (median)	23 months	21 months	0.86 (0.72–1.04)	0.1291
Secondary	ORR (overall response rate)	30% (n=306)	12% (n=289)		<0.0001

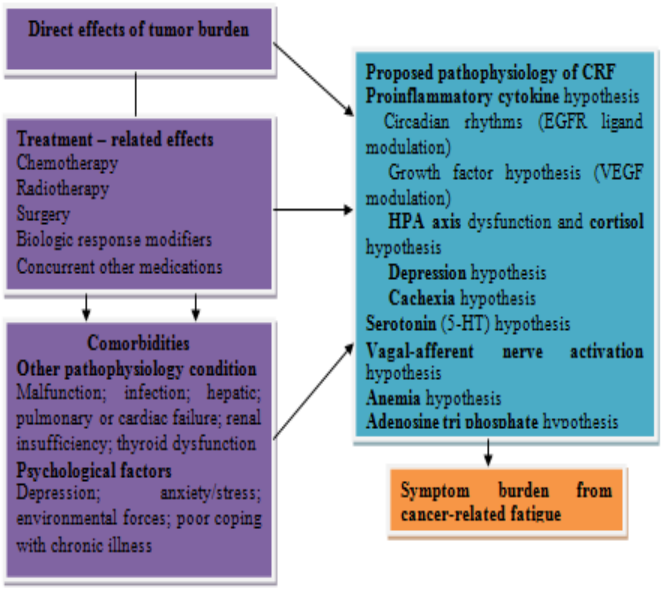


Figure 2. Causes of cancer related fatigue.

Growth Factor Hypothesis: This hypothesis states that the level of vascular endothelial growth factor (VEGF) is related to the treatment induced fatigue. The vascular endothelial growth factor (VEGF) is an angiogenic cytokine and having high significance for the cancer, and inspires the development of new blood vessels which is essential for the metastasis and growth of the tumor. [8] VEGF receptor inhibitor (Sunitinib) is hypothesized to reduce the function of thyroid through avoiding the binding of VEGF to the thyroid cells or by diminishing thyroid blood flow that results in the thyroiditis. The Sunitinib induced hypothyroidism has been detected in the gastro stromal cancer [9] and renal cell cancer patients and the thyroid hormone replacement enhanced fatigue and various other symptoms in 9 out of 17 renal cancer patients. [10]

HPA-axis disruption Hypothesis: Hypothalamic-Pituitary-Adrenal (HPA) – axis is an important system to control the delivery of stress hormone cortisol. This hypothesis states that cancer or the cancer treatment can cause directly or indirectly, the modification in the HPA function and it also leads to changes in the endocrine which either cause or add to fatigue [11,12]. The fatigue has been related to reduce function of HPA – axis, such as downregulation of corticotropin-releasing hormone (CRH) and CRH release in the response to the chronic stress, chronic fatigue syndrome, with hypocortisolemia in rheumatoid arthritis, and other cancer patients [13].

Vagal-afferent activation Hypothesis: Vagal-afferent activation hypothesis states that cancer or the cancer treatment cause peripheral discharge of a variety of neuroactive molecules such as prostaglandin, cytokines, and serotonin which may trigger the vagal – afferent nerves [14-16]. Generally, the effects may be visible as reduced somatic motor output and continued changes in the specific area of the brain which is related to the fatigue through the initiation of IL-1β sickness behavior [17,18].

Serotonin dysregulation hypothesis: Serotonin dysregulation hypothesis states that cancer or cancer treatment causes an increase 5-hydroxy tryptamine ([5-HT] or Serotonin) levels in the restricted area of the brain and also an upregulation of 5-HT receptors, which further causes decrease in the somatomotor drive, the modified function of HPA – axis, and the feeling of reduced ability to carry out other physical work [19-21]. According to an animal model, the concentration of 5-HT raised in the hypothalamus and the brain stem, through

continuous exercise, and reaches to the peak point of the fatigue [22,23]. According to numerous studies, the serotonin reuptake inhibitors administration has been indicated with the decreased ability to carry out exercise. Though, various researchers have also indicated that the concentration of central 5-HT don't affect the cancer related fatigue [24, 25].

Pro-inflammatory cytokine hypothesis: The symptoms of cancer patients throughout the treatment are usually related to the characteristics of the developing animal models of the cytokine-induced sickness behavior. [26-28] The sickness behavior specify to the array of physiological and behavioral response such as decreased activity and food ingestion, sleep disturbance, and hyperalgesia recognized in the animals after the administration of pro-inflammatory cytokines or inflammatory agents or the physical insult [29-31]. The cytokines plays a key role in the cancer related fatigue as a common biologic mechanism [32].

The insult of chemotherapy and radiation therapy as well as other cancer therapy boosts the inflammatory cytokines production, mainly TNF and IL-6 variants [33,34]. The cancer related fatigue patients, show the elevation in the TNF, IL-1, IL-1RA (IL-1 receptor antagonist), and IL-6, as well as decreased albumin [35].

Circadian rhythm modulation hypothesis: The research investigative promising links between cancers related fatigue and circadian rhythms has focused on the discharge rhythms of the stress hormone cortisol. The several preclinical studies have indicated that EGFR ligands, such as TGF-α (transforming growth factor-alpha), inhibits the hypothalamic signaling. There are various observation which shows that the elevated level of TGF- α is related to the loss of appetite, fatigue compressed circadian rhythms, & fatigue in the metastatic colorectal cancer patients [36]. A gradually decrease in the levels of the salivary cortisol is associated with improved fatigue severity and found to be detected in the cancer fatigued survivors over the treatment of the day [37]. The cancer patients are most commonly observed with the sleep disorders which may result from changed circadian rest activity rhythms. The two correlations have been reported, the positive correlation between restless sleep at night and fatigue, and an inverse correlation between levels of daily activity and fatigue [38,39].

Adenosine tri-phosphate hypothesis: The cancer patients, who have decreased capability to perform physical work, were reported as the feeling of lack of energy and weakness. [40,41] Adenosine tri-phosphate hypothesis states that cancer or cancer treatment may lead to an imperfection in the regulation of ATP and also accumulate the different metabolic byproducts in the skeletal muscle and neuromuscular junction. ATP is a most important source of energy for the skeletal muscle contraction, and the physical ability could be decrease in cancer patients due to its disturbance and this mechanism of assembling different fatigue symptoms has been known as peripheral fatigue [13].

Anemia hypothesis: The cancer related anemia has some serious affects on patients, who experience various complications of decreased cognitive function, dyspnea, dizziness, palpitations, and fatigue [42]. The delivery of oxygen to the body tissue is decreased in anemia and the body tries to compensate for the consequences of depletion in red blood cells [43] and hypoxia-related compromise is related to hemoglobin dysfunction or anemia which might cause fatigue [13].

Algorithm for the management and evaluation of Cancer Related Fatigue: A successful approach should mitigate fatigue contained by an extensive approach to the care of patients. The important characteristic of the therapy is the patient's education about the nature of fatigue, probable results, and the various options for the therapy [44]. There are following strategies which can be used in the management of the cancer related fatigue (Figure-3).

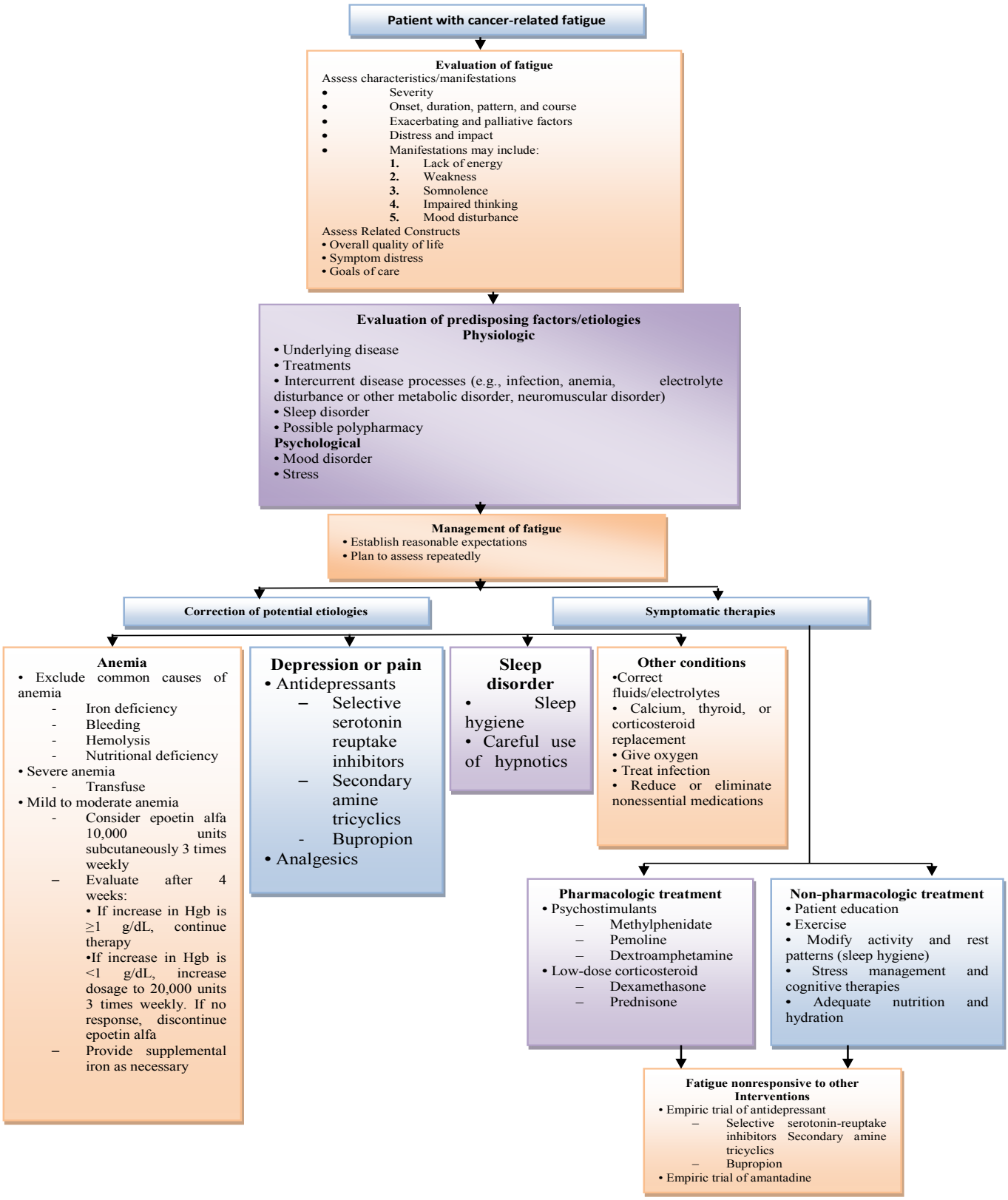
Antidepressants: Many cancer patients feel depression and the prevalence of depression disorder range from 5 to 50% and it depends on the type of the diagnostic tools

used for the diagnosis. [46] Bupropion is an anti-depressant drug which is not related to the tricyclic anti-depressants or the serotonin reuptake inhibitor. Bupropion has been used to treat fatigue related multiple sclerosis and chronic fatigue syndrome in the human being. [47-49]

Hematopoietic: Anemia is a result of either anti-cancer treatment or disease related process in the cancer patients. [50] The dar- bepoetin alfa or epoetin alfa is used 1 to 3 times in a week for up to six months in the treatment of the anemia. These drugs increase 1.8– 2.6 g/dl hemoglobin concentration in the treatment. [51-53] These drugs also improve quality of life, activity level, energy level, and fatigue reduction in the cancer patients. [54, 53]

Corticosteroids: There are three main clinical trials of glucocorticoids, such as megestrol acetate, prednisone, and methylprednisolone. [55, 56] All these studies indicates, different improvements in several symptoms, particularly pain, and also indicated enhanced quality of life and decrease fatigue in the metastatic cancer patients. [55, 57] According to Bruera and colleagues, methylprednisolone extensively reduces the pain in the terminal cancer patients as compares to placebo after the continuous treatment of 14 days. [55] The megestrol acetate was established to reduce fatigue and also enhance the levels of energy, feelings of comfort, and appetite in the cancer patients. [56]

Figure 3. Management and evaluation of Cancer Related Fatigue [45].



Drug	No. of Patients	Study Design	Duration	Cancer	Result	Reference
Epoetin alfa	354	Open-label clinical RCT; epoetin alfa, 40,000 U qw versus SOC	12 wks	Breast Cancer	FACT-An and FACT-An/Fatigue significantly improved in epoetin alfa group	Chang et al. 2005
Epoetin alfa	2,342	Prospective, multisite, open label nonrandomized study; 150 U/kg tiw titrated to 300 U/kg tiw as needed	Maximum 16 wks	Mixed Cancer	2,030 patients had evaluable data; 1,047 patients completed the 4 months of therapy; epoetin alfa associated with significant improvement in energy level, activity level, and overall QoL	Glaspy et al. 1997
Epoetin alfa	375	Multicenter (15 countries), placebo-controlled, double- blind RCT; epoetin alfa, 150–300 IU/kg tiw	Maximum. 28 wks	Mixed Cancer	Epoetin alfa more effective than placebo in improving QoL; change in Hb correlated with change in QoL	Fallowfield et al. 2002
Darbepoetin alfa	1,173	Multicenter open-label prospective study to test 2-weekly dosing	16 wks	Mixed Cancer	Fatigue improved by 26% (FACIT-F)	Vadhan-Raj et al. 2003
Darbepoetin alfa	344	Multinational, placebo-controlled, double-blind RCT; darbepoetin alfa, 2.25 µg/kg/wk	12 wks	Lymphoma or Myeloma	Improvements in Hb, fatigue, QoL	Hedenus et al. 2003; Littlewood et al. 2006
Epoetin beta (rHuEPO)	349	RCT; epoetin beta, 150 IU/kg tiw	16 wks	NHL, MM, CLL	QoL significantly improved in epoetin beta group, which correlated with improved Hb	Osterborg et al. 2002
Darbepoetin alfa versus epoetin beta (rHuEPO)	127	RCT; 4 groups with variable, staged up-titration of rHuEPO and darbepoetin alfa doses	12 wks	Mixed Cancer	Hb concentration increased more in darbepoetin group; also early and maintained reduction in CRF	Glaspy et al. 2003
Methylphe-nidate	152	Double-blind, placebo-controlled RCT; methyl-phenidate, 10–50 mg/day	2 mos	Mixed; mostly breast and ovarian	Fatigue (FACIT-F) significantly improved; memory (HSCS) improved	Lower et al. 2005
Bupropion	21	Prospective open-label study; bupropion, 10–300 mg daily	4 wks	Mixed Cancer	Significant improvement in depression	Moss et al. 2006
Paroxetine	122	Double-blind, placebo-controlled RCT; paroxetine, 20 mg/day	2 mos	Breast Cancer	Depression decreased; no effect on fatigue	Roscoe et al. 2005
Corticosteroid (prednisone)	37	Prospective, open-label study; corticosteroid, 7.5–10 mg/day	Not stated	Metastatic prostate cancer	38% had improvement in pain; pain improvement was associated with improvements in other dimensions (QoL, well-being)	Tannock et al. 1989

Corticosteroid (megestrol acetate)	84	Double-blind crossover study; corticosteroid, 160 mg tid	10 days	Mixed Cancer	Improvements in fatigue (Piper Fatigue Scale), activity, appetite, and well-being	Bruera et al. 1998
l-carnitine	50	Prospective open-label study; l-carnitine, 4 g/day	1 wk	Mixed stage IV solid tumors	Fatigue improved	Graziano et al. 2002
Modafinil	51	Prospective, open-label study; modafinil, 200 mg/day	1 mo	Breast Cancer	Fatigue severity improved; patients reported beneficial effects	Morrow et al. 2005
Abbreviations:- RCT: randomized controlled trial; FACT-An: Functional Assessment of Cancer Therapy–Anemia; SOC: standard of care; QoL: quality of life; FACIT-F: Functional Assessment for Chronic Illness Therapy–Fatigue; Hb: hemoglobin; CRF: cancer-related fatigue; HSCS: High Sensitivity Cognitive Screen;						

Table 3. Under trials studies of various drugs in the management of the fatigue [76-90].

Psychostimulants: The sleep disorders as well as extreme daytime sleepiness, and insomnia are most common in the cancer patients. [58] Methylphenidate is a psychostimulant drug which could be very effective in the treatment of cancer related fatigue. Methylphenidate has been established to improve vigilance; attention, alertness, and decreased fatigue in HIV infected patient and multiple sclerosis patients. [59-61]

Modafinil: Modafinil is a FDA approved CNS stimulant drug, which is used for the treatment of shift-work sleep disorder, [62] narcolepsy, [63-65] and obstructive sleep apnea. [66] There were some short-term clinical studies which have indicated better wakefulness in the Parkinson's disease patients, [67, 68] major depression patients, [69, 70] and multiple sclerosis patients. [71, 72]

L-carnitine: There are several chemotherapeutic drugs, which can affect badly to the levels of l-carnitine. L-carnitine is a micronutrient, which is significant to manage long chain fatty acids and the production of energy in the mammalian cells. There are three studies of l-carnitine in the treatment of cancer related fatigue. [73-75] The cancer patients treated with l-carnitine for 1 to 4 weeks, but lacking of anemia improved plasma free carnitine concentrations and considerably enhanced fatigue and the quality of life measures.

There are various drugs which are under clinical trials and these drugs are evaluated by the researchers in different ways to treat or manage cancer related fatigue (Table-3).

Conclusion

The evaluation and management of cancer related fatigue needs a broad spectrum initial approach due to different etiological factors and various probable contributing factors. Currently, there are various therapeutic options which include-treatment as well as assessment of any underlying causes, such as depression and anemia. Numerous pharmacological pathway or approaches are present, which have possible ability to make availability of relief for the patient with cancer related fatigue. There are plentiful severely intended clinical trials to date, which have been conducted with darbepoetin alfa and epoetin alfa; numerous studies have indicated its efficacy in treating cancer related fatigue, in anemia patients. Additional medications such as CNS stimulants and psychostimulants have indicated assurance in the open label probable designs, but the evidence is absent in the placebo-controlled randomized trials. The future development of pharmacologic treatment or management of cancer related fatigue requires, proving the effects of encouraging open-label studies through a double-blind randomized design. Additionally, the relative profiles of side-effects and benefits must be evaluated through head-to-head randomized studies analyzing several classes of medications, including single agent drugs versus drugs in combination with hopeful behavioral and non-pharmacologic interventions such as patient's education and exercise for the management of the cancer related fatigue.

References

1. Borneman T, Piper BF, Koczywas M, Munevar CM, Sun V et al. A qualitative analysis of cancer-related fatigue in ambulatory oncology. Clin J Oncol Nurs. 2012, 16(1): E26-E32.

2. Morrow GR, Shelke AR, Roscoe JA, Hickok JT, Mustian K. Management of cancer-related fatigue. Cancer Invest. 2005, 23(3): 229-239.

3. Fatigue. National Comprehensive Cancer Network.

4. Fatigue. National Cancer Institute.

5. Managing cancer-related fatigue. Dana Farber Cancer Institute.

6. Cella D, Peterman A, Passik S et al. Progress toward guidelines for the management of fatigue. Oncology. 1998, 12: 1-9.

7. Portenoy RK, Miaskowski C. Assessment and management of cancer-related fatigue. In: Berger A, Portenoy RK, Weissman DE, eds. Principles and Practice of Supportive Oncology. Philadelphia: Lippincott-Raven, 1998, 109-118.

8. Boudreau N, Myers C. Breast cancer-induced angiogenesis: multiple mechanisms and the role of the microenvironment. Breast Cancer Research. 2002, 5: 140–146.

9. Rini BI, Tamaskar I, Shaheen P, Salas R, Garcia J et al. Hypothyroidism in patients with metastatic renal cell carcinoma treated with sunitinib. Journal of the National Cancer Institute. 2007, 99(1): 81–83.

10. Desai J, Yassa L, Marqusee E, George S, Frates MC, Chen MH et al. Hypothyroidism after sunitinib treatment for patients with gastrointestinal stromal tumors. Annals of Internal Medicine. 2006, 145: 660–664.

11. Swain MG, Maric M. Defective corticotropin-releasing hormone mediated neuroendocrine and behavioral responses in cholestatic rats: implications for cholestatic liver disease-related sickness behaviors. Hepatology. 1995, 22: 1560–1564.

12. Bakheit AM, Behan PO, Dinan TG, Gray CE, O'Keane V. Possible upregulation of hypothalamic 5-hydroxytryptamine receptors in patients with post viral fatigue syndrome. BMJ (Clinical Research Edition). 1992; 304: 1010–1012.

13. Ryan JL, Carroll JK, Ryan EP, Mustian KM, Fiscella K, Morrow GR. Mechanisms of cancer-related fatigue. The Oncologist. 2007, 12(Suppl 1): 22–34.

14. Blackshaw LA, Grundy D. Effects of 5-hydroxytryptamine on discharge of vagal mucosal afferent fibres from the upper gastrointestinal tract of the ferret. Journal of the Autonomic Nervous System. 1993, 45: 41–50.

15. Ek M, Kurosawa M, Lundeberg T, Ericsson A. Activation of vagal afferents after intravenous injection of interleukin-1β: Role of endogenous prostaglandins. Journal of Neuroscience. 1998, 18: 9471–9479.

16. Niijima A. The afferent discharges from sensors for interleukin-1β in the hepatoportal system in the anaesthetized rat. Journal of the Autonomic Nervous System. 1996, 61: 287–291.

17. Opp MR, Toth LA. Somnogenic and pyrogenic effects of interleukin-1β and lipopolysaccharide in intact and vagotomized rats. Life Sciences. 1998, 62: 923–936.

18. Hansen MK, Krueger JM. Subdiaphragmatic vagotomy blocks the sleep-and fever-promoting effects of interleukin-1β American Journal of Physiology. 1997, 273(4 Pt 2): R1246–R1253.

19. Andrews PLR, Morrow GR, Hickok JT, et al. Mechanisms and models of fatigue associated with cancer and its treatment: evidence of pre-clinical and clinical studies. In: Armes J, Krishnasamy M, Higginson I, editors. Fatigue in cancer. Oxford, England: Oxford University Press. 2004, 51–87.

20. Newsholme EA, Blomstrand E. Tryptophan, 5-hydroxytryptamine and a possible explanation for central fatigue. Advances in Experimental Medicine and Biology. 1995, 384: 315–320.

21. Gandevia SC, Allen GM, McKenzie DK. Central fatigue. Critical issues, quantification and practical implications. Advances in Experimental Medicine and Biology. 1995, 384: 281–294.

22. Blomstrand E, Perrett D, Parry-Billings M, Newsholme EA. Effect of sustained exercise on plasma amino acid concentrations and on 5-hydroxytryptamine metabolism in six different brain regions in the rat. Acta Physiologica Scandinavica. 1989, 136: 473–481.

23. Bailey SP, Davis JM, Ahlborn EN. Neuroendocrine and substrate responses to altered brain 5-HT activity during prolonged exercise to fatigue. Journal of Applied Physiology. 1993, 74: 3006–3012.

24. Morrow GR, Hickok JT, Roscoe JA, Raubertas RF, Andrews PL, Flynn PJ et al. Differential effects of paroxetine on fatigue and depression: a randomized, double-blind trial from the University of Rochester Cancer Center Community Clinical Oncology Program. Journal of Clinical Oncology. 2003, 21: 4635–4641.

25. Roscoe JA, Morrow GR, Hickok JT, Mustian KM, Griggs JJ, Matteson SE et al. Effect of paroxetine hydrochloride (Paxil) on fatigue and depression in breast cancer patients receiving chemotherapy. Breast Cancer Research and Treatment. 2005, 89: 243–249.

26. Lee BN, Dantzer R, Langley KE, Bennett GJ, Dougherty PM et al. A cytokine-based neuroimmunologic mechanism of cancer-related symptoms. Neuroimmunomodulation.

2004, 11: 279–292.

27. Cleeland CS, Bennett GJ, Dantzer R, Dougherty PM, Dunn AJ, Meyers CA et al. Are the symptoms of cancer and cancer treatment due to a shared biologic mechanism? A cytokine-immunologic model of cancer symptoms. Cancer. 2003, 97: 2919–2925.

28. Miller AH. Cytokines and sickness behavior: implications for cancer care and control. Brain, Behavior, and Immunity. 2003, 17(Suppl 1): S132–S134.

29. Dantzer R. Cytokine-induced sickness behavior: where do we stand? Brain, Behavior, and Immunity. 2001, 15: 7–24.

30. Hart BL. Biological basis of the behavior of sick animals. Neuroscience and Biobehavioral Reviews. 1988, 12: 123–137.

31. Kent S, Bluthé RM, Kelley KW, Dantzer R. Sickness behavior as a new target for drug development. Trends in Pharmacological Sciences. 1992, 13: 24–28.

32. Wang XS, Fairclough DL, Liao Z, Komaki R, Chang JY, Mobley GM et al. Longitudinal study of the relationship between chemoradiation therapy for non-small-cell lung cancer and patient symptoms. Journal of Clinical Oncology. 2006, 24: 4485–4491.

33. Linard C, Marquette C, Clarencon D, Galonnier M, Mathieu J, Pennequin A et al. Acute ileal inflammatory cytokine response induced by irradiation is modulated by subdiaphragmatic vagotomy. Journal of Neuroimmunology. 2005, 168: 83–95.

34. Linard C, Marquette C, Mathieu J, Pennequin A, Clarencon D, Mathé D. Acute induction of inflammatory cytokine expression after gamma-irradiation in the rat: effect of an NF-κ B inhibitor. International Journal of Radiation Oncology, Biology, Physics. 2004, 58: 427–434.

35. Meyers CA, Albitar M, Estey E. Cognitive impairment, fatigue, and cytokine levels in patients with acute myelogenous leukemia or myelodysplastic syndrome. Cancer. 2005, 104: 788-793.

36. Rich T, Innominato PF, Boerner J, Mormont MC, Iacobelli S et al. Elevated serum cytokines correlated with altered behavior, serum cortisol rhythm, and dampened 24-hour rest-activity patterns in patients with metastatic colorectal cancer. Clinical Cancer Research. 2005, 11: 1757-1764.

37. Desai J, Yassa L, Marqusee E, George S, Frates MC, Chen MH et al. Hypothyroidism after sunitinib treatment for patients with gastrointestinal stromal tumors. Annals of Internal Medicine. 2006, 145: 660–664.

38. Berger AM. Patterns of fatigue and activity and rest during adjuvant breast cancer chemotherapy. Oncology Nursing Forum. 1998, 25: 51–62.

39. Mormont MC, Hecquet B, Bogdan A, Benavides M, Touitou Y, Levi F. Non-invasive estimation of the circadian rhythm in serum cortisol in patients with ovarian or colorectal cancer. International Journal of Cancer. 1998, 78: 421-424.

40. Dimeo F, Stieglitz RD, Novelli-Fischer U, Fetscher S, Mertelsmann R, Keul J. Correlation between physical performance and fatigue in cancer patients. Annals of Oncology. 1997, 8: 1251–1255.

41. Akechi T, Kugaya A, Okamura H, Yamawaki S, Uchitomi Y. Fatigue and its associated factors in ambulatory cancer patients: A preliminary study. Journal of Pain and Symptom Management. 1999, 17: 42-48.

42. Cella D. Quality of life and clinical decisions in chemotherapy-induced anemia. Oncology (Williston Park) 2006, 20(8 Suppl 6): 25-28.

43. Hurter B, Bush NJ. Cancer-related anemia: Clinical review and management update. Clinical Journal of Oncology Nursing. 2007, 11: 349–359.

44. Vogelzang N, Breitbart W, Cella D et al. Patient, caregiver, and oncologist perceptions of cancer-related fatigue: results of a tri-part assessment survey. Semin Hematol. 1997, 34(suppl 2): 4-12.

45. Portenoy RK and Itrib LM. Cancer-Related Fatigue: Guidelines for Evaluation and Management. The Oncologist 1999, 4: 1-10.

46. Morrow GR, Shelke AR, Roscoe JA et al. Management of cancer-related fatigue. Cancer Invest. 2005, 23: 229–239.

47. Duffy JD, Campbell J. Bupropion for the treatment of fatigue associated with multiple sclerosis. Psychosomatics. 1994, 35(2): 170–171.

48. Goodnick PJ. Bupropion in chronic fatigue syndrome. Am J Psychiatry. 1990, 147: 1091.

49. Goodnick PJ, Sandoval R, Brickman A et al. Bupropion treatment of fluoxetine-resistant chronic fatigue syndrome. Biol Psychiatry. 1992, 32: 834–838.

50. Mercadante S, Gebbia V, Marrazzo A et al. Anaemia in cancer: Pathophysiology and treatment. Cancer Treat Rev. 2000, 26: 303–311.

51. Demetri GD, Kris M, Wade J et al., for the Procrit Study Group. Quality-of-life benefit in chemotherapy patients

treated with epoetin alfa is independent of disease response or tumor type: Results from a prospective community oncology study. J Clin Oncol. 1998, 16: 3412–3425.

52. Glaspy J, Bukowski R, Steinberg D for the Procrit Study Group. Impact of therapy with epoetin alfa on clinical outcomes in patients with non-myeloid malignancies during cancer chemotherapy in community oncology practice. J Clin Oncol. 1997, 15: 1218–1234.

53. Gabrilove JL, Cleeland CS, Livingston RB. Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: Improvements in hemoglobin and quality of life are similar to three-times-weekly dosing. J Clin Oncol. 2001, 19: 2875–2882.

54. Littlewood TJ, Bajetta E, Nortier JW. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving non-platinum chemotherapy: Results of a randomized, double-blind, placebo-controlled trial. J Clin Oncol. 2001, 19: 2865-2874.

55. Bruera E, Roca E, Cedaro L et al. Action of oral methylprednisolone in terminal cancer patients: A prospective randomized double-blind study. Cancer Treat Rep. 1985, 69: 751–754.

56. Bruera E, Ernst S, Hagen N. Effectiveness of megestrol acetate in patients with advanced cancer: A randomized, double-blind, crossover study. Cancer Prev Control. 1998, 2: 74-78.

57. Tannock I, Gospodarowicz M, Meakin W. Treatment of metastatic prostatic cancer with low-dose prednisone: Evaluation of pain and quality of life as pragmatic indices of response. J Clin Oncol. 1989, 7: 590–597.

58. Roscoe JA, Kaufman ME, Matteson-Rusby SE et al. Cancer-related fatigue and sleep disorders. The Oncologist. 2007, 12(suppl 1): 35-42.

59. Burks TF. New agents for the treatment of cancer-related fatigue. Cancer. 2001, 92: 1714–1718.

60. Breitbart W. Identifying patients at risk for, and treatment of major psychiatric complications of cancer. Support Care Cancer. 1995, 3: 45–60.

61. Weinshenker BG, Penman M, Bass B. A double-blind, randomized, crossover trial of pemoline in fatigue associated with multiple sclerosis. Neurology. 1992, 42: 1468–1471.

62. Czeisler CA, Walsh JK, Roth T. Modafinil for excessive sleepiness associated with shift-work sleep disorder. N Engl J Med. 2005, 353: 476-486.

63. Broughton RJ, Fleming JA, George CF. Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. Neurology. 1997, 49: 444–451.

64. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. Ann Neurol. 1998, 43: 88–97.

65. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. Neurology. 2000, 54: 1166–1175.

66. Pack AI, Black JE, Schwartz JR. Modafinil as adjunct therapy for daytime sleepiness in obstructive sleep apnea. Am J Respir Crit Care Med. 2001, 164: 1675–1681.

67. Adler CH, Caviness JN, Hentz JG. Randomized trial of modafinil for treating subjective daytime sleepiness in patients with Parkinson's disease. Mov Disord. 2003, 18: 287–293.

68. Happe S, Pirker W, Sauter C. Successful treatment of excessive daytime sleepiness in Parkinson's disease with modafinil. J Neurol. 2001, 248: 632–634.

69. DeBattista C, Lembke A, Solvason HB. A prospective trial of modafinil as an adjunctive treatment of major depression. J Clin Psychopharmacol. 2004, 24: 87–90.

70. Menza MA, Kaufman KR, Castellanos A. Modafinil augmentation of anti-depressant treatment in depression. J Clin Psychiatry. 2000, 61: 378–381.

71. Rammohan KW, Rosenberg JH, Lynn DJ. Efficacy and safety of modafinil (Provigil) for the treatment of fatigue in multiple sclerosis: A two centre phase 2 study. J Neurol Neurosurg Psychiatry. 2002, 72: 179–183.

72. Zifko UA, Rupp M, Schwarz S. Modafinil in treatment of fatigue in multiple sclerosis. Results of an open-label study. J Neurol. 2002, 249: 983–987.

73. Gramignano G, Lusso MR, Madeddu C. Efficacy of l-carnitine administration on fatigue, nutritional status, oxidative stress, and related quality of life in 12 advanced cancer patients undergoing anticancer therapy. Nutrition. 2006, 22: 136–145.

74. Graziano F, Bisonni R, Catalano V. Potential role of levocarnitine supplementation for the treatment of chemotherapy-induced fatigue in non-anaemic cancer patients. Br J Cancer. 2002, 86: 1854-1857.

75. Cruciani RA, Dvorkin E, Homel P. l-carnitine supplementation for the treatment of fatigue and depressed mood in cancer patients with carnitine deficiency: A preliminary analysis. Ann N Y Acad Sci. 2004, 1033: 168–176.

76. Chang J, Couture F, Young S. Weekly epoetin alfa maintains hemoglobin, improves quality of life, and reduces transfusion in breast cancer patients receiving chemotherapy. J Clin Oncol. 2005, 23: 2597–2605.

77. Glaspy J, Bukowski R, Steinberg D, for the Procrit Study Group. Impact of therapy with epoetin alfa on clinical outcomes in patients with nonmyeloid malignancies during cancer chemotherapy in community oncology practice. J Clin Oncol. 1997, 15: 1218–1234.

78. Fallowfield L, Gagnon D, Zagari M. Multivariate regression analyses of data from a randomized, double-blind, placebo-controlled study con-firm quality of life benefit of epoetin alfa in patients receiving non-platinum chemotherapy. Br J Cancer. 2002, 87: 1341–1353.

79. Vadhan-Raj S, Mirtsching B, Charu V. Assessment of hematologic effects and fatigue in cancer patients with chemotherapy-induced anemia given darbepoetin alfa every two weeks. J Support Oncol. 2003, 1: 131–138.

80. Hedenus M, Adriansson M, San Miguel J. Efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies: A randomized, double-blind, placebo-controlled study. Br J Haematol. 2003, 122: 394–403.

81. Littlewood TJ, Kallich JD, San Miguel J. Efficacy of darbepoetin alfa in alleviating fatigue and the effect of fatigue on quality of life in anemic patients with lymphoproliferative malignancies. J Pain Symptom Manage. 2006, 31: 317–325.

82. Osterborg A, Brandberg Y, Molostova V. Randomized, double-blind, placebo-controlled trial of recombinant human erythropoietin, epoetin beta, in hematologic malignancies. J Clin Oncol. 2002, 20: 2486-2494.

83. Glaspy JA, Jadeja JS, Justice G. A randomized, active-control, pilot trial of front-loaded dosing regimens of darbepoetin-alfa for the treatment of patients with anemia during chemotherapy for malignant disease. Cancer. 2003, 97: 1312–1320.

84. Lower E, Fleishman S, Cooper A. A phase III randomized placebo-controlled trial of the safety and efficacy of d-MPH as new treatment of fatigue and "chemobrain" in adult cancer patients. J Clin Oncol. 2005, 23(16): 2000.

85. Moss EL, Simpson JS, Pelletier G. An open-label study of the effects of bupropion SR on fatigue, depression and quality of life of mixed-site cancer patients and their partners. Psychooncology. 2006, 15: 259–267.

86. Roscoe JA, Morrow GR, Hickok JT. Effect of paroxetine hydrochloride (Paxil) on fatigue and depression in breast cancer patients receiving chemotherapy. Breast Cancer Res Treat. 2005, 89: 243–249.

87. Tannock I, Gospodarowicz M, Meakin W. Treatment of metastatic prostatic cancer with low-dose prednisone: Evaluation of pain and quality of life as pragmatic indices of response. J Clin Oncol. 1989, 7: 590–597.

88. Bruera E, Ernst S, Hagen N. Effectiveness of megestrol acetate in patients with advanced cancer: A randomized, double-blind, crossover study. Cancer Prev Control. 1998, 2: 74–78.

89. Graziano F, Bisonni R, Catalano V. Potential role of levocarnitine supplementation for the treatment of chemotherapy-induced fatigue in non-anaemic cancer patients. Br J Cancer. 2002, 86: 1854–1857.

90. Morrow GR, Gillies LJ, Hickok JT. The positive effect of the psycho-stimulant modafinil on fatigue from cancer that persists after treatment is completed. J Clin Oncol. 2005, ASCO Meeting Abstract 8012.