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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].

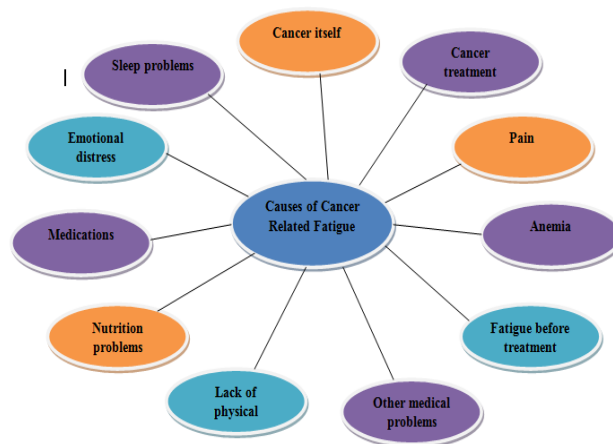


Figure 1. Cause of cancer related fatigue

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

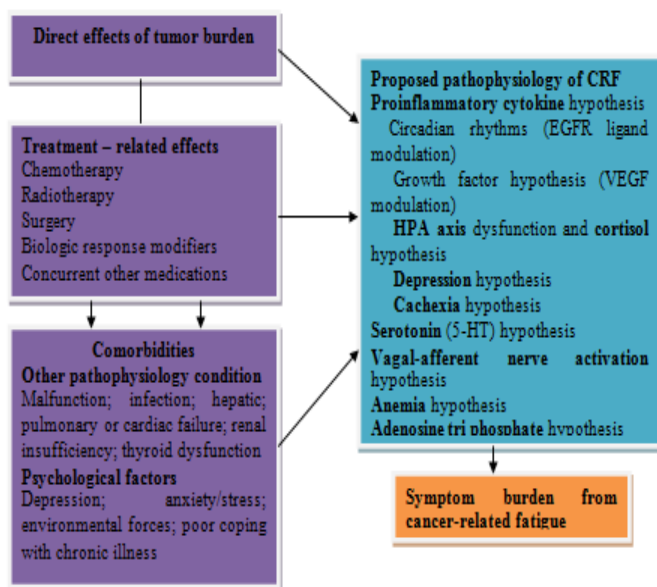
Pathophysiology of cancer related fatigue: The risk factors and various etiological factors are not fully determined for the cancer related fatigue. There are various hypotheses, which provide the mechanism of pathophysiology of cancer related fatigue (Figure-2). These mechanisms are Growth Factor hypothesis, 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))	<i>P</i> 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-1 β 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).

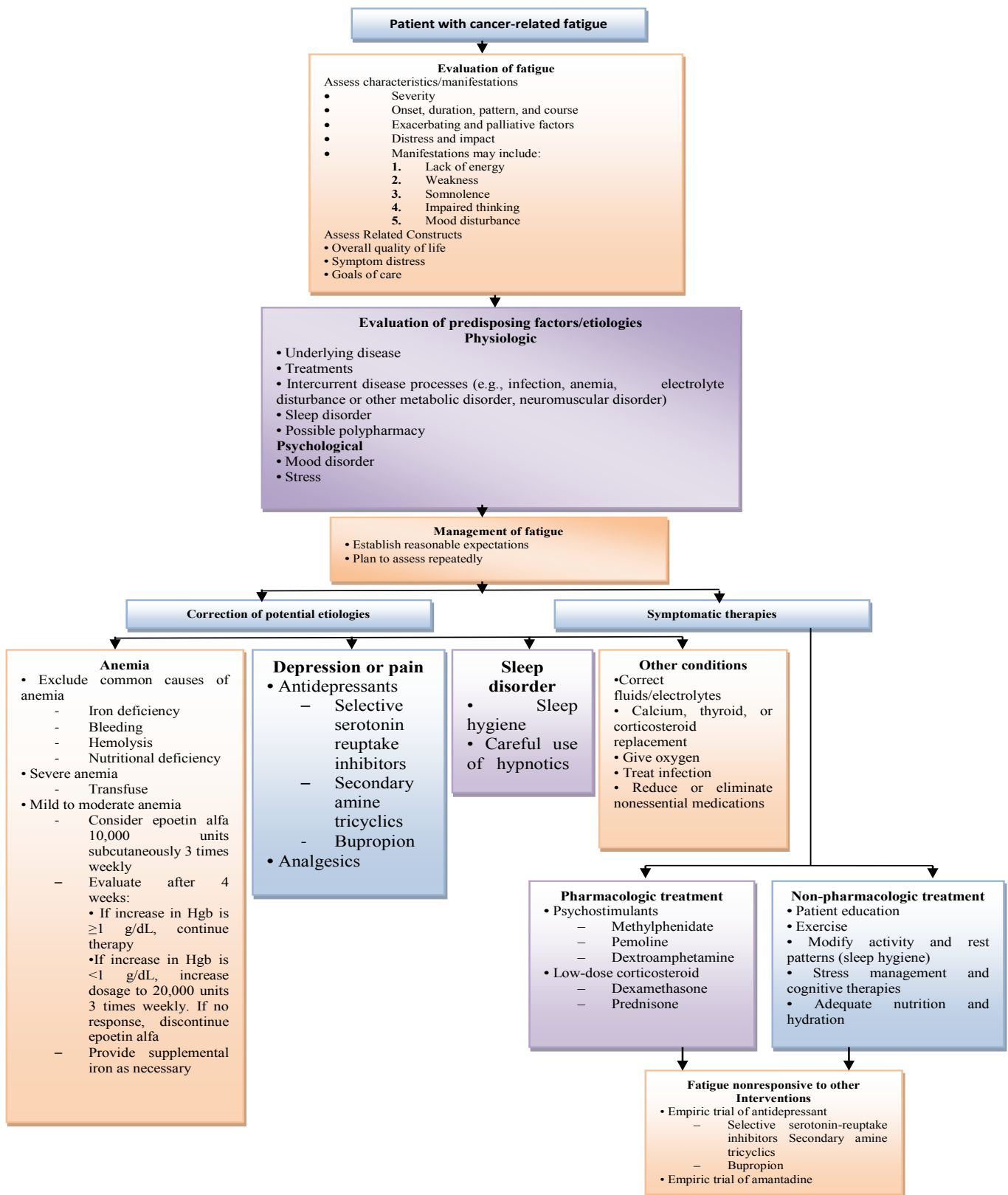
Antidepressants: Many cancer patients feel depression and the prevalence of depression disorder range from 5 to 50% and it depends on the type of the diagnostic tools

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 darbepoetin 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
Methylphenidate	152	Double-blind, placebo-controlled RCT; methylphenidate, 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 etio-

logical 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.

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