Cancer-related fatigue in palliative care: a global perspective

VILCHYNSKA, Tetyana and BEARD, Barbara

Cancer-Related Fatigue in Palliative Care - a Global Perspective

Tetyana Vilchynska, Director of Patient Services, Clinic of Children's Supportive and Palliative Care

Radyanska str.1, Pirnovo, Vyshgorod district, 07342, Kyiv, Ukraine, Tel +380 50 331 31 29

Correspondence to: Tetyana Vilchynska, b3047061@my.shu.ac.uk

Barbara Beard, Senior Lecturer, Sheffield Hallam University

Room F428, Robert Winston Building, S10 2BP, Sheffield, Great Britain**,** Tel +44 0114 225 5617

Abstract

Cancer–related fatigue (CRF) in a palliative care setting is a distressing symptom which can have a negative impact on a patient's quality of life. A range of setting and disease specific factors, unknown etiology and absence of unilateral guidelines makes CRF treatment a challenge for clinicians. In the absence of high-quality evidence in favour of any pharmacological and non-pharmacological measures, except exercise, cognitive behavioural therapy and psychosocial interventions, a personalized integrative oncology approach can lead to effective management. Findings suggest a severity-based symptom-stage adjusted CRF management care pathway, highlighting best practices to illustrate the lived experience of this symptom. Overcoming barriers by staff training, patient education, facilitating communication and patients' self-care, will increase CRF management effectiveness. Future CRF multi-symptomed or multidimensional nature investigation trials of its underlying mechanisms and new pharmacological and non-pharmacological strategies applied separately or in combination, will allow revealing the best approach to CRF diagnosis, assessment and management.

Key Words

Cancer-related fatigue (CRF), cancer-related fatigue (CRF) assessment, cancer-related fatigue (CRF) management, cancer-related fatigue (CRF) guidelines, palliative care

Introduction

Cancer-related fatigue (CRF) experienced by patients in a palliative care setting is a severe symptom, with complexity of its assessment and management being stipulated by a range of setting- and disease-specific factors including lack of precise guidelines and insufficient evidence. A careful analysis of existing CRF assessment models, with application of integrative oncology methods, can ensure both ethical and professional approaches and effective palliation. This article proposes solutions for an optimal CRF care pathway in palliative setting and reveals the areas for future research to optimize current CRF treatment strategies.

Prevalence

The discrepancies in the reported prevalence rates of cancer-related fatigue (CRF) range from 33 to 99% (Peters et al., 2014). Although many patients are either too weak for participation in studies (O'Regan, 2008), or deem CRF "untreatable" (Borneman, 2013), all of them rank it as one of the most distressing symptoms, severely affecting their quality of life (QOL) (Peters et al., 2014).

Definition

There is no commonly agreed definition of fatigue and CRF in particular (Donovan et al., 2012). It fits neither in the available chronic fatigue nor in psychogenic fatigue syndrome (ICD-10, 2010) definitions as a separate disease with its own etiology and pathogenesis (Raaf et al., 2013). The core features of CRF derived from different definitions are its subjectivity, the degree of impairment it implies and its abnormally high level and negative QOL effect (ICD-10, 2010; NCCN 2014). Subjectivity remains the main problem as no individuals experience CRF in the same way and clinicians should rely entirely on patients' description (Borneman, 2013).

Assessment

Apart from acknowledged physical and cognitive dimensions of fatigue, there is still a dilemma whether CRF is a multidimensional or multi-symptomed notion (Donovan et al., 2012). If physical and mental fatigues are different symptoms, each having their own pathogenesis, the clinician should assess and treat them differently (Raaf et al., 2013). The range of setting- and disease-specific factors contributes to the definition of CRF rather as a complex syndrome, than an isolated symptom. Lack of recognition and knowledge to treat CRF makes assessment a challenge (Borneman, 2013). The patients should always be asked about fatigue and what the symptom means to them as they may fail to report this due to religious beliefs (deeming it essential for fighting spirit,) or to fear of affecting medical treatment if reported (Borneman, 2013).

Setting-specific. At the advanced disease stage, CRF can arise from clusters of poorly managed symptoms (pain, dyspnoea, cachexia), effects of multiple drugs interaction (steroids, benzodiazepines, opioids) and their fatigue-enhancing side effects on central nervous system (Bower, 2014). It's worth analyzing all the co-morbidities as each of them can lead to a vicious circle where CRF enhances other symptoms and increases its severity. Still, the separate effect of these co-morbidities in patients requiring palliative care can be difficult to assess (Raaf et al., 2013) as few comparative studies show the precipitating and perpetuating factors for fatigue are different at different cancer stages. Treatment duration and the time spells\overlaps between different treatment stages should be considered, as CRF increases in subsequent treatment lines, being one of long-lasting (5-10 years) side effects of previous treatments (Bower, 2014).

Disease-specific. Increased immune and pro-inflammatory response in patients with advanced cancer plays a core role in CRF pathogenesis (Bower, 2014). The changes in the immune system are enhanced by immunosuppressive tumor microenvironment with increased release of pro-inflammatory IL-family cytokines. Serotonin disregulation, dopamine alterations in the brain, HPA

axis activation are other CRF-enhancing factors (Bower, 2014). CRF severity is closely associated with cancer-specific co-morbidities (anaemia, paraneoplastic processes, sepsis) increasing during the disease trajectory (Bower, 2014; Peters et al., 2014). Psychological factors such as fear of recurrence, cognitive dysfunction, disrupted sleep\activity patterns, anxiety and depression are of core importance (Bower, 2014).

Multiple patho-psychological and patho-physiological mechanisms of disease (Mustian et al., 2007) play a unique a role for each patient, with the etiology of the majority being unknown (Peters et al., 2014). The holistic approach thus becomes an integral part of patient assessment. The critical evaluation of each specific factor's weight should be made based on the patient's medical history, socio-demographic characteristics, religious and spiritual beliefs, physical and mental status (O'Regan, 2008) (Table 1). NCCN (2014) recommends a multifaceted assessment to be held at the patient's initial clinic visit and at regular intervals afterwards (evidence level 2A) (Table 2) depending on the patient's health status.

Fatigue assessment tools and models. There is a variety of fatigue assessment tools in clinical practice, but no tool of choice exists. The most popular multidimensional tools are Multidimensional Fatigue Inventory Multidimensional Fatigue Symptom Inventory, Fatigue Questionnaire, Fatigue Assessment Questionnaire, Cancer Fatigue Scale, and Revised Piper Fatigue Scale (Raaf et al., 2013). Each of these questionnaires is proven useful to assess CRF by a number of studies (Raaf et al., 2013), but their use is associated with certain limitations. They are hardly comparable both in the same CRF-measuring aspects (e.g. "mental" as concentration and "mental" as memory\slips of tongue) (Donovan et al., 2012; Raaf et al., 2013) and in the subscales for physical and mental fatigue dimensions (Raaf et al., 2013). Only a few studies describe use of these tools to assess fatigue in advanced cancer and there are no studies comparing the effectiveness of each tool (Donovan et al., 2012). Both UK and other available fatigue assessment models and guidelines are either not disease-specific (NHSS, 2013) or not setting-specific (CPAC, 2011), or contain only specific guidance

(NICE CG81, 2014). NCCN (2014) are the only guidelines where a chapter is dedicated to CRF in a palliative care setting. However some patients may have problems with the NCCN (2014) numerical scale, finding it difficult to assign numbers or needing lengthier expressions (Donovan et al., 2012). NHSS (2013) suggests alternative verbal staging (mild, moderate, and severe) but is not specifically designed for oncology. Therefore, there is a clear need for a tool adjusted for the patients with advanced cancer.

Although NCCN (2014) is the only disease stage-based guideline, the CPAC (2011) approach with its three-staged pathway (screening, comprehensive and focused assessment) is recommended (Donovan et al 2012; Borneman 2013) as a basis of assessment. It gives the most comprehensive picture of patient's conditions, symptoms and prognosis (Table 3), enhancing the particular importance of referral possibilities and appropriate clinical knowledge and professionalism of MDT assessors (CPAC, 2011). However CPAC (2011) needs more precision in the assessment criteria (e.g. "regular intervals"). Peters et al., (2004) stress that the effects of dynamic changes over the disease trajectory also need to be integrated within the model.

Management

Two CRF care pathways approaches are proposed by CPAC\NCCN guidelines: severity-based (CPAC, 2011) or disease stage-based (NCCN, 2014) (Table 4); in practice, the combination of both is often required to individually tailor interventions (Peters et al., 2014). CRF management is a difficult task and though a causal (etiological) approach is advocated by some authors (Barnes and Bruera, 2002), all guidelines are based on holistic symptomatic management (CPAC 2011; NHSS 2013; NCCN 2014; NICE CG81 2014). Another approach is targeting specific symptoms. However, the setting where whole clusters rather than isolated symptoms are present (Roxburgh and McMillan, 2014), suggests addressing the whole chain of co-morbidities, though their interaction may not always be known (O'Regan, 2008). So the concept "treat the symptoms not the syndrome" (cluster-based) is proposed by the authors (Table 5).

General measures (GM). Energy conservation measures, daily scheduling, distraction and relaxation techniques with constant self-monitoring of fatigue levels, are the core of both CPAC and NCCN recommendations (evidence level 2A (CPAC, 2011; NCCN 2014) (Table 2). Patient education about patterns, causes, consequences and ways of CRF management aimed at self-control, are key general strategies aimed at overcoming patient barriers and identifying treatment targets (Mustian et al., 2007).

Pharmacological measures (PM). Several groups of medications have been used to treat CRF but high quality evidence in favour of any is insufficient (CPAC 2011; NCCN 2014). The Cochrane review of 50 studies of CRF pharmacological management showed contradictory results for psychostimulants, both methylphenidate (27 trials) and modafinil (4 open-label studies), due to its frequent adverse effects (anorexia, insomnia, nausea, tachycardia), with a recommendation for a large scale RCT to enable their approval for use in CRF (Minton et al., 2010). These findings are corroborated by the results of the recent large Cochrane review (45 studies, 4696 participants with advanced stage diseases, with cancer being primary diagnosis in majority of them (n =3223)) which demonstrated only some low quality evidence in favour of methylphenidate improving CRF (Mücke et al., 2015). Both CPAC (2011) and NCCN (2014) restrict the use of psycho-stimulants to when other measures failed (evidence level 2A) (Table 2). Interestingly, antidepressants- paroxetine and sertraline, did not demonstrate such positive effect as psycho-stimulants, though improved mood and depression in CRF patients was noted (Minton et al., 2010). Consequently CPAC (2011) included them only for selected patients, and NCCN (2014) approved them under a "sleep medication" label to address insomnia\anxiety. The same review recommended against the use of haematopoietic growth factors darbepoetin and erythropoietin, due to frequent adverse effects, in spite of significant reduction in the level of anemia-induced CRF (Minton et al., 2010). For safety reasons and high costs, they were finally recommended only for selected patients after careful risk-benefit analysis by NCCN 2014 (evidence level 2A) (Table 2) and recommended against by CPAC

(2011). Progestational steroids demonstrated no difference with placebo in 4 studies (Minton et al., 2010); which however was contradictory to the previous RCTs' results of significant appetite\QOL improvement (Caroll et al., 2007). NCCN (2014) allowed progestagens (megestrol acetate) for patients with CRF due to anorexia\cachexia for optimization of nutritional deficit, but no evidence level was assigned to this recommendation. CPAC (2011) found no evidence to recommend the use of progestagens. The evidence-base for all corticosteroids was generally scarce, with short-term studies without exact dosage (Caroll et al 2007; Lai and Shung 2011). However, their ability to improve QOL in CRF was recognized. NCCN (2014) approved dexamethasone\prednisolone only, while CPAC (2011) approved all of them generally (evidence level 2A) (Table 2).

New treatments of CRF suggested either lack evidence from RCT (NSAID, amantadine; L-carnitine), or were not tested in palliative care (ginseng) and did not prove effective in cancer (cholinesterase inhibitors - donepezil) populations (Minton et al., 2010; Mücke et al., 2015). That explains wide discrepancies in different guidelines (Table 4), with a general rule to apply pharmacology as a last resort (evidence level 2A) (Table 2), carefully weighing risks and benefits (CPAC 2011; NCCN 2014). Future clinical trials are necessary to justify use of different drugs classes (Mücke et al., 2015).

*Non-pharmacological measures (NPM).*The choice and optimal combination of NPM for CRF management in a palliative care setting is disputable due to limited and heterogeneous evidence (Sood, 2007; Borneman, 2013). Activity enhancement (exercise), psychosocial therapy such as cognitive behavioral therapy (CBT) and physical interventions (massage, yoga) can be helpful in a majority of cases where no specific CRF causes can be defined, or where other means are not effective (NCCN, 2014). The integrative oncology approach to CRF is based on the combination of conventional and complementary medicine, but harms and benefits of all complementary interventions should be determined (Bar-Sela et al., 2007) both on a general and individual level,

accounting for performance, mental and physical status, and disease trajectory of each patient (Sood, 2007).

Exercise (walking, cycling, swimming, aerobics), CBT and psychosocial interventions have the firmest evidence base (evidence level 1) (Table 2) for CRF (CPAC, 2011; NCCN, 2014) and are included in all guidelines. Available RCTs suggest exercise is well tolerated and effective in improving fitness, strength, functional capacity and emotional well-being of patients (Quist et al., 2013). Both home and supervised exercise demonstrated this, although indicating a need for tailor-made programmes, as general ones weighted effect is relatively small (ES = 0.16, 95% CI, –0.23 to 0.54 post-treatment) (Schmitz et al., 2005). Matching the exercise level to the individual patient's characteristics will require new phase III trials (Quist et al., 2013).

A specific model of CRF-perpetuating psychosocial factors tested in cancer survivors proved to be successful in advanced stage cancer in RCT (Peters et al., 2014) indicating cognitive behavioral therapy effectiveness individually and in groups, in both oral and written form and even if provided by a trained nonprofessional (Mustian et al., 2007).

Sleep therapy and nutrition consultations are supported by expert opinion (Lai and Shung, 2011) and graded evidence level 2A (NCCN 2014) (Table 2). The studies of massage, acupuncture, art, polarity therapy and yoga in cancer were sporadic, even for those demonstrating benefits (Bar - Sela et al., 2007) and neither their single effectiveness nor their most effective combination with other NPM was revealed (Mustian et al., 2007). As physical interventions have the weakest evidence (Sood, 2007) they are not covered by most guidelines, except massage\acupuncture in CPAC (2011). Future RCT should define optimal NPM dose\delivery methods, safety throughout disease progression, and their most effective combinations (Mustian et al., 2007). The integrated care pathway proposed in Table 6 based on CPAC (2011) approach combines integrative oncology strategies and general techniques, depending on CRF severity and disease stage.

Ethical, cultural issues and professional boundaries.

The principle of beneficence requires discussions with patients and their carer to find the best CRF management strategies. However, this principle may also need to be pursued in cases where fragile patients, unable to express what the symptom means to them or cannot provide information, by ascertaining this information from relatives or those close to the patient (Lai and Shung, 2011). Respecting a patient's autonomy (Beauchamp and Childress, 2013) in what the symptom means to them and how they feel needs to be satisfactorily is paramount in management. Patients also need to be supported as they work towards finding meaning in a symptom so inherently disabling (Krishnasamy, 1997). As CRF substantially affects the lives of patients' caregivers, their needs have to be regularly assessed and reviewed, with continuous support and education for them to be able to recognize health changes, to administer medicines at home (non-maleficence) and to choose either home care or consider alternatives for the patient (justice) (Connoly and Milligan, 2014). Cultural sensitivity is required to overcome patient barriers, e.g. the use of interpreters to outline "fatigue" for non-English speaking patients, respect of spiritual concepts of people of different faiths (easier acceptance of fatigue by those who place more strength on their beliefs) (Borneman, 2013) and understanding of social contexts (e.g. beliefs how they should manage suffering according to gender roles). Professional issues include the need for effective communication with the patient in boundaries of professional, not "social" presence, where a sign of particular attention to one patient (e.g. personal mobile calls) can be perceived as a permission to require it for all others (Connoly and Milligan, 2014). Such a boundary breach can be prevented by, for example, providing a 7-day a week hot-line support for patients with CRF. The general long-standing rule should be empathic understanding, effective communication with expression of general interest, without impeding professional decision-making (O'Regan, 2008).

Implications for Practice

As most countries do not have specific guidelines for CRF management in palliative care, targeting multiple barriers in CRF management should result in a clear pathway possibly similar to

other chronic fatigue guidelines (e.g. NICE CG53, 2007; NICE CG 186, 2014), but taking into consideration cancer-specific differences (Roxburgh and McMillan, 2014). The integrated care pathway proposed by the authors (Table 6) is based on the CPAC (2011) three-stage assessment with concurrent disease staging (NCCN, 2014) and treatment adjustment to patient's individual characteristics. Constant follow-up, with added frequency towards the end of life is applied to all interventions which are rescheduled as necessary in the course of the disease trajectory (Table 6). In the absence of generally aligned guidelines, the authors consider the proposed integrated care pathway a practical tool for everyday clinical practice, enhancing the MDT ability to apply effective strategies of CRF management and tailoring the approach to patients' needs. Continuous staff training and patient and carer education to recognize the symptoms and to facilitate self-care should be provided (Connoly and Milligan, 2014).

Research opportunities

Apart from clinical practice, to increase effectiveness of CRF management, new trials in the palliative care setting are recommended. They should preferably be designed as RCT\ longitudinal studies (Donovan et al., 2012; Peters et al., 2014), rigorously comply with research methodology (Mustian et al., 2007) and choose different fatigue dimensions as outcome variables to understand each intervention effectiveness (Raaf et al., 2013). They have also to focus on integrative oncology approaches identifying optimal mode, frequency, intensity, duration, delivery methods, risks and benefits of PM and NPM, both separately and in the best available combinations (Bar-Sela et al., 2007; Mustian et al 2007).

Conclusion

CRF in a palliative care setting is a widespread and a QOL-affecting symptom. It is a complex syndrome due a range of disease and setting related factors. An MDT approach can be enhanced by whole CRF multidimensional paradigm revision, defining a pathway to assess and treat different CRF domains. CRF assessment should be severity-based with use of optimal assessment

tools and simultaneous grading of the disease stage, resulting in identification of treatable symptoms and tailoring approach to the patients' needs. The proposed model of CRF care pathway is based on the principle "treat the symptoms not the syndrome". The integrative oncology approach supposes a combination of pharmacological and non-pharmacological strategies (exercise, psychosocial (evidence level 1) and physical techniques (evidence level 2A) (Table 2). The MDT should demonstrate ethical and cultural sensitivity acting within professional boundaries. In the absence of consensus on CRF management, general rules are usage of pharmacological strategies only in selected cases after careful risk-benefit analysis (evidence level 2A) (Table 2). Effects of cholinesterase inhibitors, NSAIDs, amantadine, L-carnitine are being investigated. There is a need for new complex models targeting the patient and staff barriers in CRF management as well as for new studies in search for effective treatment agents, best pharmacological and non-pharmacological strategies and combinations to refine current treatment approaches and to align existing guidelines. Finally, as was indicated several years ago by Krishnasamy (1997), as the patient approaches the end of life, there is a need to shift the focus of patients and all concerned with them, from the management of fatigue to facilitating the process of living with the fatigue of dying.

Conflicts of Interests

The authors declare no conflict of interests.

Tables

Table 1. Factors making CRF a complex syndrome

Barriers to target
Setting-specific
Multiple factors overlap in palliative setting
Precipitating and perpetuating factors different from other disease stages
Lack of research for palliative population
Absence of guidelines for palliative population
Disease-specific
Cancer-induced changes in immune and other systems
Cancer-specific symptoms\comorbidities increasing during disease trajectory
Cancer-related psychological factors

Source: *Mustian et al (2007); Bower (2014); Raaf et al (2013); Peters et al (2014)*

Table 2. Levels of Evidence

1A	Systematic review (with homogeneity) of RCTs
1B	Individual RCT (with narrow confidence intervals)
1C	All or none study
2A	Systematic review (with homogeneity) of cohort studies
2B	Individual Cohort study (including low quality RCT, e.g. <80% follow-up)
2C	"Outcomes" research; Ecological studies
3A	Systematic review (with homogeneity) of case-control studies
3B	Individual Case-control study
4	Case series (and poor quality cohort and case-control study
5	Expert opinion without explicit critical appraisal or based on physiology bench research or "first principles"

Source: CEBM (2015)

Table 3. Comparative table of CRF assessment approaches in different national guidelines.

	A Pan-Canadian Practice Guideline CPAC (2011)	**National Comprehensive Cancer Network (NCCN) (2014)**	**National Health Service Scotland NHSS(2013)**	**National Institute for Clinical Excellence NICE CG81(2014)"**
Specificity				
Cancer specific	Yes	Yes	No	Yes (breast cancer only)
Palliative setting specific	No	Only in interventions choice	Yes	Yes
Screening				
Interview	Yes	Yes	Yes	Yes
Assessment Tools Usage	PFS\ ESAS*	Simple numeric rating	Severity rating or numeric	No recommendation
Comprehensive assessment				
Focused history and physical exam	Yes	Yes	Partly	No recommendation
Contributing factors, diagnosis (current status)and treatment details, comorbidities	Yes	Yes	Yes	Yes
Psychosocial factors	Yes	Only sleep patterns	Not separated as alleviating	No recommendation
Alcohol drugs abuse	Yes	Yes	No	No recommendation

Activity level current and functional status	Yes	Yes	No	No
Focused assessment				
Treatable factors identification	Yes	Yes	Yes	Yes
Need for referral identification			No	No

"only parts 1.5.8-1.5.10 dedicated to CRF

*PFS –Piper Fatigue Scale; ESAS –Edmonton Symptom Assessment System

Source: *CPAC (2011); NHSS (2013); NCCN (2014); NICE (2014)*

Table 4. Comparative table of recommended CRF interventions in different national guidelines (with evidence level where available)

	A Pan-Canadian Practice Guideline CPAC (2011)	**National Comprehensive Cancer Network (NCCN) (2014)**	**National Health Service Scotland NHSS(2013)**	**National Institute for Clinical Excellence NICE CG81 (2014)**
General				
Energy conservation measures\self-monitoring	2A	2A	Yes	No
Patients\carers education and counselling				Yes
Pharmacological				
Psychostimulants	Not recommended except in selected patients in EOL (2A)	2A*,✧	No	N\a**
Corticosteroids			N\a **	
Antidepressants		2A *,✧		
Haematopoietic growth factors	No	2A ✧		
Progestagens	No	Yes***	Yes	
Non-pharmacological				
Exercise	2A	1	Yes	Yes
Psychosocial interventions\cognitive behavioural therapy				
Sleep and nutrition counselling		2A	Yes	

Stress reduction strategies: massage, yoga, muscle relaxation, relaxation guided imagery, acupuncture		No	N\a**	N\a**
Attention-restoring therapy		2A		

"only parts 1.5.8-1.5.10 dedicated to CRF

✧ after ruling out all other possible causes

* under "sleep medication" label

** not mentioned at all

*** for optimization of nutritional deficit\imbalance treatment

Source: *CPAC (2011); NHSS (2013); NCCN (2014); NICE (2014)*

Table 5. Symptoms-based CRF management approach

	Symptoms cluster accompanying CRF		Possible ways to manage
CANCER-RELATED FATIGUE	Depression	Pain	Distraction techniques Behavioural therapies Antidepressants Opioids Corticosteroids
	Anxiety	Breathlessness\dyspnoea	Cognitive behavioral therapy Distraction techniques Sedation Opioids
	Sleep disorders	Insomnia	Sleep therapy Antidepressants
	Anaemia	Muscle loss	Exercise Erythropoietins L-Carnitine*
	Anorexia\Cachexia	Dehydration	Nutrition counselling Progestagens Biphosphonates**
	Infection, sepsis, fever		Antibiotics Sleep therapy
	Pulmonary and cardiac disorders, renal and hepatic failure, paraneoplastic neurological syndromes		Drugs per related guidelines Other integrative therapies

	Endocrine abnormalities, hypothyroidism or hypogonadism	Hormone replacement therapy Nutrition counselling

***** experimental treatment

** for electrolytes imbalance

Source: *Barnes and Bruera (2002); O'Regan (2008); Lai and Shung (2011); Bower (2014)*

Table 6. Integrated care pathway proposed for CRF management in a palliative care setting

Steps	Action plan
Screening (CPAC 2011, NCCN 2014)	Subjective (patient's narrative) Objective symptoms (physical examinations, laboratory tests) History and current disease stage\treatment status Comorbidities\ medications Physical and psychosocial conditions
Comprehensive assessment	QOL impact (CPAC, 2011) The meaning of the fatigue to the patient (Krishnasamy, 1997) Etiology (Barnes and Bruera, 2002; CPAC, 2011) CRF severity and temporal features (CPAC, 2011; NCCN 2014) Exacerbating and relieving factors (CPAC, 2011; NCCN 2014) Precipitating and perpetuating factors (Raaf et al., 2013) Scoring (Edmonton Symptom Assessment System \Piper Scale\simple numbers\verbal staging)(CPAC 2011; Donovan et al.,2012; Borneman et al., 2013; Raaf et al., 2013; NCCN, 2014)
Focused assessment	Identifying treatable factors (Mustian et al.,2007) Screening for the setting-related factors (past treatment long-lasting effects current treatment effects, drugs' overlapping side effects (polypharmacy) comorbidities inherent to diagnosis\disease stage) (O'Regan, 2008; CPAC. 2011; Bower. 2014; NCCN. 2014) Assessing psychological status (depression?) (O'Regan, 2008; NCCN. 2014) Need for referral (CPAC. 2011) Need for related guidelines use (comorbidities) (NCCN. 2011; Bower. 2014;

	NCCN. 2014; Peters et al., 2014)
Choice and implementation of care model (CPAC 2011, NCCN 2014)	Mild – education and counselling Exclude effect of past treatments If not successful -treatment as moderate, after review Moderate - education, counselling (energy and sleep, restoration, family interactions, nutritional therapy, general information and support groups) and NPM. Contributing factors\comorbidities treatment If not successful - treatment as severe, after review Severe - urgent management of contributing factors\comorbidities – PM, addressing safety issues (falls, syncope) Excluding cancer further progression
Evaluation and monitoring	Effectiveness evaluation(CPAC,2011; NCCN, 2014) Constant review and reassessment throughout disease trajectory (Donovan et al., 2012, Peters et al., 2014) Regular monitoring, with more frequent intervals up to the end of life (CPAC,2011; NCCN, 2014)

Source: *Krishnasamy (1997); Barnes and Bruera (2002); Mustian et al (2007); O'Regan (2008); CPAC (2011); Donovan et al (2012); Raaf et al (2013); Bower (2014); Peters et al (2014); NCCN (2014)*

References

Barnes EA, Bruera E (2002) Fatigue in patients with advanced cancer: a review. International Journal of Gynecological Cancer, 12(5):424-8.

Bar-Sela G, Atid L, Danos S et al (2007) Art therapy improved depression and influenced fatigue levels in cancer patients on chemotherapy. Psycho-Oncology, 16(11): 980–984.

Beauchamp, Tom L., Childress, James F. (2013) principles of biomedical ethics. 7th edn. New York, Oxford University Press.

Borneman T (2013) Assessment and Management of Cancer-related Fatigue [Internet].Journal of Hospice and Palliative Nursing, 15(2): 77-86.

Bower JE (2014) Fatigue in Cancer Patients and Survivors: Mechanisms and Treatment. Psychiatry Weekly [Internet].Available from: http://www.psychweekly.com/aspx/article/ArticleDetail.aspx?articleid=60

Canadian Partnership Against Cancer (Cancer Journey Advisory Group) and the Canadian Association of Psychosocial Oncology (CPAC) (2011) A Pan-Canadian Practice Guideline: Screening, Assessment and Care of Cancer- Related Fatigue in Adults with Cancer [Internet]. Available from: http://www.capo.ca/Fatigue_Guideline.pdf

Centre for Evidence-Based Medicine (CEBM), University of Oxford (2015) EBM Levels of Evidence [Internet]. Available from: http://www.cebm.net/

Caroll JK, Kohli S, Mustian KM, Roscoe JA, Morrow GR (2007) Pharmacologic Treatment of Cancer-Related Fatigue. The Oncologist, 12 (1 Suppl): 43-51.

Connoly J, Milligan S (2014) Knowledge and skills needed by informal carers to look after terminally ill patients at home. End of Life Care [Internet]; 4(2):1-14. Available from: http://endoflifejournal.stchristophers.org.uk/research/knowledge-and-skills-needed-by-informal-carers-to-look-after-terminally-ill-patients-at-home

Donovan KA, McGinty HL, Jacobsen PB (2012) A systematic review of research using the diagnostic criteria for cancer-related fatigue. Psycho-Oncology, 22 (4): 737-744.

International Classification of Diseases (ICD)-10: Version 2010. World Health Organization. [Internet]. Available from: http://apps.who.int/classifications/icd10/browse/2010/en

Kryshnasamy M (1997) Exploring the nature and impact of fatigue in advanced cancer. International Journal of Palliative Nursing 393: 126-131

Lai EH, Shung SC (2011) Fatigue in hospice cancer patients: how do nutritional factors contribute? In: Preedy V, eds. Diet and Nutrition in Palliative Care. CRC Press, London: 205-213.

Minton O, Richardson A, Sharpe M, Hotopf M, Stone P (2010) Drug therapy for the management of cancer-related fatigue. Cochrane Pain, Palliative and Supportive Care Group[Internet].The Cochrane Collaboration: John Wiley and Sons Ltd. Available from: http://www.update-software.com/BCP/WileyPDF/EN/CD006704.pdf

Mustian K, Morrow GR, Caroll JK, Figueroa-Moseley CD, Pascal JP, Williams GC (2007) Integrative Nonpharmacologic Behavioral Interventions for the Management of Cancer-Related Fatigue. The Oncologist, 12 (1): 52-67.

Mücke M, Mochamat CH, Peuckmann-Post V, Minton O, Stone P, Radbruch L (2015) **Pharmacological treatments for fatigue associated with palliative care.** Cochrane Database of Systematic Reviews [Internet]; 5. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006788.pub3/abstract

National Comprehensive Cancer Network (NCCN) (2014). Cancer-Related fatigue. NCCN Clinical Practice Guidelines in Oncology. Version 1:2014. [Internet]. Available from: www.nccn.org

National Health Service Scotland (NHSS) (2013) Fatigue in Palliative Care. Scottish Palliative Care guidelines Weakness/Fatigue. [Internet]. Available from: http://www.palliativecareguidelines.scot.nhs.uk/guidelines/symptom-control/weakness-fatigue.aspx

National Institute for Clinical Excellence (NICE) (2007) Chronic fatigue syndrome/myalgic encephalomyelitis(or encephalopathy): diagnosis and management of CFS\ME in adults and children. NICE Guidelines [CG53]. [Internet]. Available from: http://www.nice.org.uk/

National Institute for Clinical Excellence (NICE) (2014) Advanced Breast Cancer Update: Diagnosis and treatment. NICE Guidelines [CG81]. [Internet]. Available from: http://www.nice.org.uk/

National Institute for Clinical Excellence (NICE) (2014) Multiple sclerosis: management of multiple sclerosis in primary and secondary care. NICE Guidelines [CG186]. [Internet]. Available from: http://www.nice.org.uk/

O'Regan P (2008) Fatigue in patients with advanced cancer who are at the end of life. End of Life Care [Internet]; 2(4):35-40. Available from: http://endoflifejournal.stchristophers.org.uk/clinical-review/fatigue-in-patients-with-advanced-cancer-who-are-at-the-end-of-life

Peters ME, Goedentorp MM, Verhagen SA, van der Graaf W, Bleijenberg G (2014) Exploring the contribution of psychosocial factors to fatigue in patients with advanced incurable cancer. Psycho-Oncology, 23(10): 773–779.

Quist M, Langer SW, Rørth M, Christensen KB, Adamsen L (2013) "EXHALE": exercise as a strategy for rehabilitation in advanced stage lung cancer patients: a randomized clinical trial comparing the effects of 12 weeks supervised exercise intervention versus usual care for advanced stage lung cancer patients.B*MC* Cancer[Internet]; **13**:477. Available from: http://www.biomedcentral.com/1471-2407/13/477

Raaf PJ, Klerk C, Rijt CCD (2013) Elucidating the behavior of physical fatigue and mental fatigue in cancer patients: a review of the literature. Psycho-Oncology, 22(9): 1919-1929.

Roxburgh CS, McMillan DC (2014) Cancer and systemic inflammation: treat the tumour and treat the host. British Journal of Cancer, 110(6): 1409–1412. Epub 2014 Feb 18.

Schmitz KH, Holtzman J, Courneya KS, Mâsse LC, Duval S, Kane R (2005) Controlled physical activity trials in cancer survivors: A systematic review and meta-analysis.Cancer Epidemiology, Biomarkers and Prevention, 14(7):1588-1595.

Sood, A (2007) A Critical Review of Complementary Therapies for Cancer-Related Fatigue. Integrative Cancer Therapies, 6(1): 8-13.