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Title: The aetiology, impact and management of cancer-related fatigue in patients with advanced cancer

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Abstract

Cancer-related fatigue (CRF) is a distressing symptom frequently experienced by patients with advanced cancer. While there have been some advances in the understanding of the management of fatigue associated with cancer treatment, CRF associated with advanced cancer remains a phenomenon that is not well-managed. The aetiologic factors associated with CRF, the impacts of CRF and the current management of CRF are discussed in this review article in relation to patients with advanced cancer. The paper concludes that while further research is required in the area, there are several potentially effective strategies currently available that can reduce the severity of CRF in patients with advanced cancer.

Introduction

Fatigue is one of the most frequently experienced (1-3) and distressing symptoms (4, 5) reported by patients with advanced cancer. The prevalence and impact of fatigue in this population, however, is not often acknowledged or understood by health professionals (6, 7). The likely reasons for this are that health professionals tend to focus more on pain or other more obvious symptoms (8); health professionals' and patients' lack of awareness of effective treatments for this symptom (7). Over the past few decades, however, for patients at all stages of the cancer trajectory, there has been a substantial body of research that has enhanced our understanding of the pathophysiology of fatigue, patients' experiences of this symptom, and potentially effective interventions for patients who report cancer-related fatigue (CRF). It should be noted, however, that most of this research does not pertain to patients with advanced cancer (1, 2); it has focused to date largely on patients undergoing active treatment. The purpose of this paper is to review the state of knowledge regarding CRF in patients with advanced cancer. In this paper, we review the evidence pertaining to the aetiologic factors associated with fatigue, the impact of fatigue on the patient with advanced cancer and current trends in its management.

Aetiologic factors associated with fatigue in patients with advanced cancer

The aetiology of CRF is complex and remains unclear in patients with advanced cancer (9). The literature indicates that aetiologic factors associated with CRF could comprise (but are not limited to) cachexia, infection, anaemia, neurological changes, psychological distress, metabolic and endocrine disorders, over-exertion, medications, side-effects of antineoplastic treatment and paraneoplastic neurological syndromes (10). In recent years, the role of a number of biological response

modifiers (e.g. interferon, tumour necrosis factor, IL-1 and IL-6) (11, 12), and the patient's genetic makeup (13) in CRF have also been explored. Although these studies have focused on people experiencing cancer treatment-related fatigue, there is preliminary evidence to indicate relationships between genetic makeup, cytokine markers and symptoms in oncology patients and their family caregivers (13). One recent study, for example, reported an association between a functional promoter polymorphism in the TNF- α gene with the severity of both sleep disturbance and morning fatigue (13).

The evidence further indicates that the aetiologic factors associated with CRF could vary between those in the earlier stages of the cancer trajectory compared to those who are at the more advanced stage. For example, although it is repeatedly reported that anaemia is associated with fatigue in patients undergoing treatment, it is also reported that there is no association between haemoglobin levels and fatigue in patients with advanced cancer (14, 15). For another example, although fatigue is thought to be a common side effect of antineoplastic treatment in cancer patients, antineoplastic treatments received by patients with advanced cancer normally aim to improve symptom control and quality of life, and can in some cases alleviate their fatigue and other symptoms (16, 17).

One UK observational study of 122 patients with advanced cancer provided further empirical evidence of potential differences in contributors to CRF (15). The study reported no relationships between the level of fatigue and age, sex, diagnosis, presence or sites of metastases, anaemia, dose of opioid or steroid, or a range of haematological markers or biochemical indices (except urea), but did identify

significant associations between fatigue, pain and dyspnoea scores (15). Recent studies which have investigated the inter-relationship between and co-existence of fatigue and other symptoms (18, 19), similarly emphasise the greater significance of symptom burden as a contributor to fatigue in patients with advanced cancer.

The impact of fatigue for patients with advanced cancer

Fatigue is associated with impaired health-related quality of life in patients with cancer at all stages of cancer, but particularly for those whose disease is more advanced (20-23). For example, a study of 40 patients with advanced cancer admitted to an academic palliative care unit reported a high correlation between fatigue within 24 hours of admission and individual quality of life scores at 7 days (23). Moreover, the experience and impact of fatigue in patients with advanced cancer is likely to have some unique characteristics that have implications for management strategies. One qualitative study of patients with advanced cancer described how fatigue affects the physical, psychological, social and spiritual aspects of their lives (24). These individuals often find that they are unable to do much and they particularly struggle to manage fatigue (8, 25, 26). The perception of “nothing can be done” for their fatigue is often shared among families and health professionals (25). As a result, the effect of fatigue on patients can be tremendous, which they express in terms of the burden they impose on others, their inability to participate in family and other social activities, and cognitive impairments such as memory loss and loss of ability to concentrate (8, 24-27). Moreover, patients with advanced cancer are more likely to associate fatigue with the process of adjusting to living with a terminal illness and ultimately death (24, 27). Individuals with advanced disease may thus perceive fatigue in different ways to those individuals who

experience fatigue primarily associated with curative treatment for their disease (28, 29).

In 1996, Sutchilffe-Chidegey and Holme's cross-sectional survey offered insights into perceived distress levels associated with fatigue in patients with advanced cancer, where 49% (n=100) of participants perceived fatigue as a distressing symptom (4). This study also reported that the level of perceived distress varied among patients, professionals and bereaved carers, with only nine per cent of professional carers (n=60) and 17% of bereaved carers (n=30) perceiving fatigue as a distressing symptom (4). Such findings suggest that people other than the patient may have limited insight into such a subjective experience.

For some patients with advanced cancer, fatigue could also be perceived as "necessary" or unavoidable in the terminal phase of life (30). Some have suggested that treatment of fatigue is no longer indicated at end-of-life as fatigue may provide protection and shielding from suffering (30). While there is some agreement that fatigue negatively influences quality of life among patients with advanced cancer, the association between fatigue and quality of life and negative emotions could change during the last days and weeks of life (31). However, while attitudes towards fatigue might change over time, it is still a burdensome symptom even during the last week of life (32) and therefore worthy of further investigation.

Other studies involving patients with advanced cancer report that the decline in performance status that is associated with advanced cancer is associated with increased fatigue levels. For example, one study reported that as performance status

declined, fatigue interfered with subjects' physical activities such as walking (36.3%, n=157), normal work (31.8%), mood (21.7%) and enjoyment of life (19.1%) (33). Other studies report that fatigue is highly and negatively correlated with performance status (34-38). One Japanese longitudinal study offered some insights into the specific physical and psychological factors correlating with fatigue in terminally ill patients with cancer over three time points (33). At time 1 (the second visit to the palliative outpatient department), greater fatigue was significantly correlated with psychological distress, lower performance status, dyspnoea and appetite loss. At time 2 (a week after time 1), greater fatigue was significantly correlated with higher psychological distress, and lower performance status at time 1. Fatigue was also positively correlated with deterioration in psychological distress, performance status, and dyspnoea severity during the period between time 1 and 3. Another study that attempted to differentiate factors that affected fatigue and physical function in lung cancer patients did so cross-sectionally (39). Using multiple regression analysis, the researcher identified that performance status scores, weakness and depression scores were correlated independently with fatigue. Hence, while studies report that CRF is almost universally a distressing and disruptive symptom, the experience and impact of fatigue for people with advanced cancer as compared to early stage cancer has some unique dimensions. These unique features are associated with the particular meanings and declining performance characteristic of progressive and life-limiting disease.

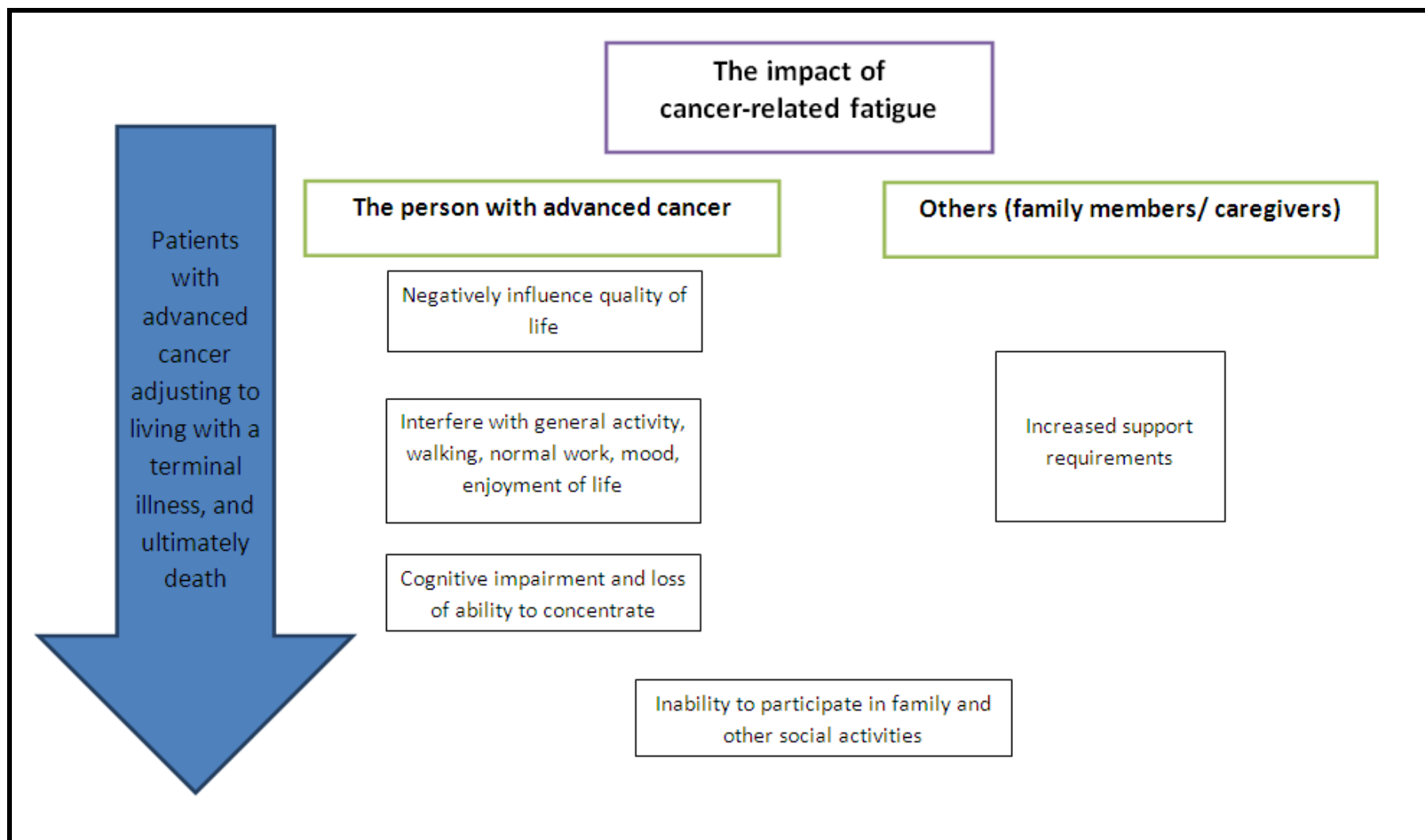


Figure 1. The impact of cancer-related fatigue on patients with advanced cancer and others.

The management of cancer-related-fatigue in people with advanced cancer

The management of CRF in patients with advanced cancer is complex and may involve a range of treatment measures associated with pharmacologic and non-pharmacologic strategies (9). These measures aim to target potentially reversible aetiologic factors that are known to contribute to CRF (9)..

Pharmacological management

A range of pharmacologic agents is used for the treatment CRF. These agents include psychostimulants (e.g. methylphenidate), paroxetine and progestational steroids (e.g. megestrol acetate). The effectiveness of each class of medication and related concerns are discussed below.

Psychostimulants

Research on symptomatic treatment of fatigue in patients with advanced cancer has concentrated on stimulant drugs such as methylphenidate and donezepil. Methylphenidate is reported as effective in several uncontrolled trials or retrospective studies that investigated fatigue in patients with advanced cancer (40-42). In 2005, one randomised placebo-controlled trial of 152 patients with breast cancer reported favourable results for methylphenidate, which was significantly more effective than placebo in improving fatigue after chemotherapy. However, this study did not report on the staging of the disease of this sample of women with breast cancer. In 2006, another randomised placebo-controlled trial of 112 patients with advanced cancer receiving palliative care reported no difference between placebo and methylphenidate (43). In light of these equivocal findings, a systematic review concluded that the two methylphenidate trials for CRF did not provide sufficient

evidence to recommend its use in practice; however a later meta-analysis favoured the use of a dose of 10 to 20 mg per day titrated to response (44). This review concluded that serious adverse effects were minimal but contra-indications should be reviewed before prescribing (44). In 2010, a retrospective analysis reported that the side effects of methylphenidate (10-20mg/d) are well tolerated in patients with advanced cancer (45). According to the information retrieved from the international trial registries, more trials are now underway to determine its effects in patients with advanced cancer.

With respect to donezepil, the effects are still not certain in patients with advanced cancer. Although donezepil was reported as effective in the treatment of opioid-induced sedation in an uncontrolled trial (46), one recent randomised placebo-controlled trial of 142 patients with advanced cancer also reported that it was not superior to placebo (47). Another recent randomised, double-blinded, placebo-controlled trial conducted with 39 patients with advanced cancer reported potential benefits of using dexamphetamine (48). Specifically, the use of 10mg twice daily for eight days was well tolerated with minimal side effects and improved fatigue levels on day two, but not at the end of the study. These results suggest uncertainty about the effectiveness of dexamphetamine beyond day two. With the consideration that the current tested dosing was well tolerated, further investigations with higher dosing may be warranted.

Paroxetine, progestational steroids and Acetyl-L-Carnitine

In 2010, two meta-analysis were conducted in a Cochrane systematic review (49). The meta-analysis of two studies (n=625) was conducted for paroxetine and

indicated no difference between paroxetine and placebo for the treatment of CRF in patients with advanced cancer (49). Similarly, the meta-analysis of four studies (n=587) investigating the effect of progestational steroids on CRF also reported that it was not superior to placebo (49). Acetyl-L-Carnitine was compared against placebo in a double-blind randomised-controlled trial (RCT) with patients with advanced cancer and was not superior to placebo (50).

Non-pharmacological management

A range of non-pharmacological management strategies are used in the management of CRF (51). This section discusses the evidence base for each of the non-pharmacologic management strategies as recommended by the National Comprehensive Cancer Network (NCCN), and their potential application for patients with advanced cancer (52). Due to the lack of direct evidence for patients with advanced cancer, some of the recommended strategies in the NCCN guidelines are based primarily on evidence for patients with early stage cancer (52), and their application to patients with advanced cancer is yet to be tested in randomised trials. The key strategies reviewed in this section include exercise, sleep and rest, energy conservation, complementary therapies and psychosocial interventions.

Exercise

A Cochrane review by Cramps and Daniel (2008) of 28 RCTs that studied patients with cancer of all stages concluded that moderate exercise appears to have benefit in the management of CRF both during and after active cancer treatment (53), particularly in patients with breast cancer and prostate cancer. However, there is not sufficient evidence to determine the best type or intensity of exercise for reducing

CRF (53). Further, this review only identified few studies that included samples with patients who had advanced cancer (53).

The few available studies suggest that at least some groups of patients with advanced cancer may also benefit from exercise based interventions. One Norwegian study of 63 patients with advanced cancer receiving palliative care pilot-tested an exercise program and reported that the exercise participants had significantly less physical fatigue and increased walking distance (54). This program consisted of two 50-minute sessions twice a week for 6 weeks. A combination of strength building, standing balance, and aerobic exercise was used in this program. Another small pilot study was conducted by Porock and her research team to evaluate an exercise program for nine patients with advanced cancer who were enrolled in a home hospice program (55). In this intervention, a physical therapist guided participants to perform a range of strategies throughout the day (e.g. walking, performing arm exercises with resistance, marching in place, and dancing). All participants were able to increase their activity level over a 2-week period without increased fatigue. There was also a trend toward increased quality of life and decreased anxiety. In 2003, a 12-week exercise program was tested in 82 men with locally advanced/ metastatic prostate cancer receiving androgen deprivation therapy, as compared to a wait-list control group (56). Patients who were in the exercise group reported less interference of fatigue with daily activities ($p=0.002$) and better quality of life ($p=0.001$). In addition, they also demonstrated high levels of upper body ($p=0.009$), and lower body ($p<0.001$) muscular fitness than men in the control group.

Although there is some preliminary evidence now suggesting the benefits of exercise in patients with advanced cancer, the evidence is not yet conclusive due to the lack of RCTs. Two recent RCTs of patients with advanced cancer (57, 58) reported contradictory results with regards to the benefits of exercise for patients with advanced cancer. One possible explanation may be that the more effective intervention evaluated by Headley et al (2004) required patients to participate in a less intense program (a 30-minute seated exercise program, three times a week, with one a week break between sessions) (57), as compared to the less effective intervention of Brown et al (2006) that asked patients to perform stretching, strength, balance and gait training over eight 90 minute sessions in four weeks (58). Although it is suggested that a 30 minute seated exercise regimen is a feasible management strategy for patients with advanced cancer, further RCTs are needed to duplicate these results in the various populations of patients with advanced cancer. While health professionals need to be informed by high quality trials that can support specific effective exercise regimen for this patient group, research efforts should also be directed to understanding what patient responses are to these recommendations for exercise therapy, what are their confidence level with regards to carrying out the exercises, and the factors that may influence the use of exercise.

Sleep and rest

In general, patients with cancer can experience disruptions in both the quantity and the quality of their sleep (59, 60). Due to the close relationship between sleep disturbance and fatigue (61), health care professionals commonly recommend strategies for improving sleep quality to patients with cancer-related fatigue (62), and they may be the most frequent self-management activities patients perform (51, 63,

64). Although there is compelling evidence suggesting the effectiveness of sleep hygiene programs in insomnia (65-68), there are limited trials testing non-pharmacological strategies in managing sleep disturbance in patients with advanced cancer. In one RCT, forty-six patients with advanced cancer receiving hospice care were allocated to three groups: massage group, aromatherapy group and control group in the hospice setting in the UK (69). The results of this study demonstrated significant clinical improvements in sleep disturbance and depression scores. However, the sample was too small to detect statistically significant differences in sleep disturbance.

There is also now some preliminary evidence that shows the potential benefits of an 8 week Carlson's Mindfulness-based Stress Reduction program in patients with early stage cancer (70). The components of the program included body scan meditation, sitting, walking, meditation and hatha yoga. The number of participants with total sleep scores over eight (≥ 5 indicates sleep disturbance with the use of PSQI) was reduced from 70% at baseline to 49% post-intervention. Other than the structured programs mentioned above, the literature has documented a list of strategies undertaken by palliative/ cancer care professionals. These range from avoiding stimulating substances (such as caffeine, nicotine) before bedtime to light exercise during the day time (60, 71). These interventions have not yet been formally tested in this population, despite a prevalence of sleep alterations in patients with advanced cancer of approximately 71 per cent (72-74). A recent UK study using comprehensive patient reports and objective measures such as actigraphy reported the manifestations for patients with advanced cancer are high levels of sleep fragmentation and movement during sleep, rather than the length of sleep (75). It is

important that appropriate sleep therapies are formally evaluated in patients with advanced cancer.

Energy conservation

Energy conservation is defined as “the deliberate, planned management of an individual’s personal energy resources to prevent their depletion” (76). The goal of energy conservation is to balance rest and activity during times of high fatigue so that valued activities and goals can be maintained. Energy conservation involves a number of strategies: taking additional rest periods, priority setting, delegation, pacing oneself, and planning high-energy activities at times of peak energy. A multisite RCT of 396 patients with various cancer at different stages undergoing chemotherapy and radiotherapy reported that the intervention group using these strategies experienced a greater decrease in fatigue over time compared with the control group ($p < 0.01$) (76). A further recent study reported the experiences and outcomes of a fatigue clinic in a comprehensive cancer centre (62). This study reported that energy conservation was recommended to 98.5% of patients with CRF ($n = 260$), regardless of cancer stage. However, the authors also reported that they faced challenges in encouraging patients to delegate tasks to family or hire help. While some patients were reluctant to seek help, families were enthusiastic about participating in treatment plan recommendations (62). The NCCN guideline for Cancer Related Fatigue recommends energy conservation as a “general strategy for management of fatigue” for patients with advanced cancer and their caregivers. However, there is a lack of research suggesting its effectiveness in patients with advanced cancer who are not undergoing treatment.

Complementary therapies

Complementary therapies such as massage therapy (77, 78), yoga (79), breathing exercises (80, 81), muscle relaxation (82, 83) and mindfulness-based stress reduction (70, 84-86) have been evaluated in pilot studies. The preliminary data suggest that these therapies may have an effect in reducing fatigue in patients with cancer. These strategies have also been recommended for the management of CRF in a number of clinical guidelines for the management of CRF (9, 30, 87). However, these interventions were either supported by indirect evidence (88, 89) or a case report (90), or tested with benefits in patients who were not in their advanced stage of disease (82).

Psychosocial interventions

The NCCN guideline for CRF management recommends that patients should be counselled about coping and educated on how to deal with anxiety and depression, which are commonly known to be associated with fatigue during cancer treatment (52). A recent Cochrane systematic review in 2009, involving 27 studies of a total of 3324 participants, reported limited evidence that psychosocial interventions are effective in reducing fatigue during active treatment in patients with cancer (91). Of these studies, only five studies were designed with the focus of fatigue, with four being effective ($p < 0.05$). The five interventions were brief, consisting of three individual sessions provided by oncology nurses. The general content of these interventions included education about fatigue, self-care or coping techniques, and learned activity management. Only three of these studies reported sustained effects at follow-up. To date, there is scant evidence suggesting the effectiveness of psychosocial interventions in patients with advanced cancer (92).

Summary

Despite the fact that many advances have been made in understanding and managing fatigue in patients with cancer, these advances have primarily been made for patients with cancer undergoing primary or adjuvant treatment. Prevalence data for CRF suggests that this symptom is not well managed in patients with advanced disease. While the evidence base relating to management of cancer treatment-related fatigue is a useful starting point for identifying strategies for managing fatigue associated with advanced cancer, differing aetiologies and experiences means that management strategies may need to be tailored for this population.

Researchers have tested a number of interventions, both pharmacological and non-pharmacological, with the aim of reducing the severity and impact of CRF. While there have been many efforts to test pharmacological agents in patients with advanced cancer in the management of CRF, a number of non-pharmacological management strategies are recommended for patients with advanced cancer, in spite of the fact that they are not well tested in patients with advanced cancer (see table 1). Most of these interventions require patients to respond with a number of health behaviours (e.g. taking medications, exercising, delegating tasks). These responses may have a direct impact on the efficacy of some of these interventions in relieving CRF. For patients with advanced cancer, further research is required to investigate the effectiveness of these interventions with good quality controlled trials and investigate how patients respond to evidence based recommendations.

Recommendations for nursing practice

- It is important for nurses to encourage patients with advanced cancer or their caregivers to openly discuss their fears, concerns and experience of CRF.
- The literature shows that patients often are not aware of treatment options. Nurses can support the self-management of patients by providing evidence-based information in relation to fatigue management.
 - Preliminary research indicates some benefits of exercise in the management of fatigue in patients with advanced cancer. Although more research is warranted to determine the most effective intensity and mode of exercise, low intensity seated exercise appears to be appropriate for this population.
 - Evidence pertaining to patients with early stage cancer indicates the potential benefits in a number of management strategies such as energy conservation and sleep hygiene behaviours. These strategies can be recommended for use in patients with advanced cancer as appropriate.
 - Although more trials are currently underway, the use of methylphenidate could be discussed with medical staff for consideration in managing CRF in some patients with advanced cancer.

Table 1. Current evidence for the management of CRF in patients with advanced cancer

Interventions	Benefits for reducing CRF in patients with advanced cancer	NHMRC Level of evidence	The directness of evidence for patients with advanced cancer	Remarks
Pharmacological				
Methylphenidate	Potential benefits	Level I	Direct evidence	A meta-analysis favoured the use of a dose of 10 to 20 mg per day titrated to response (44)
Donepezil	Not superior to placebo	Level II	Direct evidence	
Dexamphetamine	Potential benefits	Level II	Direct evidence	The results of a RCT suggest uncertainty about the effectiveness of dexamphetamine beyond day two (48)
Paroxetine	Not superior to placebo	Level I	Direct evidence	
Progestational steroids	Not superior to placebo	Level I	Direct evidence	
Acetyl-L-Carnitine	Not superior to placebo	Level II	Direct evidence	
Non-pharmacological				
Exercise	Potential benefits	Level II	Direct evidence	The most appropriate intensity of exercise yet to be determined patients with advanced cancer (57, 58)
Sleep/rest	Potential benefits	Level II	Indirect evidence	
Energy conservation	Potential benefits	Level II	Indirect evidence	
Complementary therapies	Potential benefits	Level III or level IV	Indirect evidence	
Psychosocial interventions	Potential benefits	Level I	Indirect evidence	

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