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SPECIAL ARTICLE

Cancer-related fatigue and sleep deficiency in cancer care continuum: concepts, assessment, clusters, and management

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Abstract
Throughout the cancer continuum, patients are faced with the cancer- and treatment-related side effects that can have a negative impact on their overall quality of life. Cancer-related fatigue (CRF) and sleep deficiency are among the symptoms that patients and their caregivers most often experience. An increasing body of literature suggests that a strong correlation between CRF and sleep deficiency exists, indicating that they may be reciprocally related and that they may have similar underlying etiology. This paper aims at bringing together the opinions of leading cancer control (i.e., CRF and sleep) and oncology experts in order to increase the understanding of CRF and sleep deficiency's assessment, associated symptom clustering, symptom burden shared by caregivers, and CRF and sleep deficiency management in the cancer care context.

Keywords Sleep deficiency · Cancer-related fatigue · Symptom clusters · Caregivers

Introduction

A cancer diagnosis is one of the most common, disabling, and costly diagnoses affecting people living in the United States (US) and other developed countries [1]. Being diagnosed with cancer introduces the patient to the cancer care continuum where diagnostic, therapeutic, or palliative processes are generated. Throughout this continuum, the patients are faced with the cancer- and treatment-related side effects that can have a negative impact on their overall quality of life. Cancer-related fatigue (CRF) and sleep deficiency are among those symptoms that the patients and their family caregivers experience throughout the cancer trajectory. A strong correlation between CRF and sleep deficiency has been observed in several studies, suggesting that they may be reciprocally related and that they may have similar underlying etiology [2].

CRF is considered one of the most common and distressing symptoms in cancer patients [3]. It is estimated that the percentage of cancer patients who experience fatigue is in the range of 70–80%. CRF is reported during chemotherapy or radiotherapy and throughout the cancer care continuum, including the pre- and post-treatment phases.

Over time, a variety of biological mechanisms of CRF have been investigated including anemia, cytokine dysregulation, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and 5-hydroxytryptophan (5-HT) neurotransmitter dysregulation [4]. Although the exact mechanism of CRF is not yet fully understood, studies have suggested that the causes of CRF are multifactorial and include physiological factors (e.g., anemia and neuroendocrine changes), psychological factors (e.g., depression and anxiety), socio-cultural factors (e.g., cognitive and behavioral response), and chronobiological factors (e.g., sleep and circadian rhythms) [5].

The persistent and often overwhelming nature of CRF can have a debilitating impact on all aspects of the person's life. Studies showed that CRF interferes with daily activities and productivity, which may lead to poor compliance with

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chemotherapy regimens and discontinuation of treatment [3]. Research on family caregivers shows that CRF can be a source of anxiety, caregiving burden, and other negative outcomes.

Rates of cancer-related sleep deficiency range from 25 to 59% depending on age, disease type, gender, and treatment phase [6]. Sleep deficiency or insomnia symptoms usually present as an inability to initiate or maintain sleep lasting for > 2 weeks in response to anxiety or a stress-provoking event [6]. The onset pattern of sleep deficiency is similar to that of CRF. Therefore, sleep deficiency can occur before the diagnosis (i.e., waiting for results), continue during the post-diagnosis phase (e.g., initiation of chemotherapy treatment and associated side effects), and persist throughout the survivorship phase.

Within the cancer context, the etiological factors of sleep deficiency are multifactorial and include predisposing, precipitating, and perpetuating factors [7]. Predisposing factors include genetic factors, female gender, older age, hyperarousability as a trait, personal or family history of insomnia, and mood or anxiety symptoms or disorders. Precipitating factors include cancer treatments that alter levels of inflammatory cytokines or disrupt circadian rhythms or sleep–wake cycles, and side effects of cancer treatments. Perpetuating behavioral factors consist of excessive naps, variables sleep and wake cycles, activities that do not promote sleep such as lounging in bed, and long-term use of sleep medications among other factors [6].

Living with cancer is a life-changing experience. The experience can have a negative impact on the person diagnosed with cancer and also on the people close to them. This also includes the relatives and significant others who assume the role of the caregiver(s). Apart from cancer's physical impact, patients and their caregivers also experience high emotional and psychological burden. These problems can often be complicated with CRF and sleep deficiency making their management more challenging. Therefore, over the cancer trajectory, the patient and the caregiver can share the feelings of anxiety and depression while the caregiver can additionally face distress as a result of caregiving burden.

This paper aims at bringing together the opinions of leading cancer researchers and oncology experts in order to increase the understanding of CRF and sleep deficiency's assessment, associated symptom clustering, aspects pertaining to informal caregiving, and management of CRF and sleep in the cancer care context.

Cancer-related fatigue and sleep in cancer care continuum

Although various definitions can be found in the literature, this paper presents the most widely accepted. CRF is defined as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with the usual functioning [8]. Sleep deficiency is defined as the discrepancy in sleep duration and/or quality obtained compared to the amount needed for optimal health [9].

A review of the relevant literature on the frequency and severity of symptoms according to diagnoses of the sample and the phases of the treatment trajectory, including post-surgery, pre- and post- chemotherapy, radiation therapy, endocrine therapy, and survivorship allowed for the following conclusion to be drawn: CRF and sleep deficiency rank the highest in prevalence and severity at all phases of treatment and regardless of cancer site and/or stage. Symptoms most commonly reported with CRF and sleep deficiency include pain, depression/anxiety, and shortness of breath [10].

The impact of the symptoms on functioning during and following treatments is well-established in patients with lung and breast cancer. Poor sleep quality and depressive symptoms negatively affected the quality of life (QOL) at approximately one year after lung cancer surgery [11]. Impaired sleep, mood, and lower physical activity at the last treatment predicted persistent CRF one year post-treatment in patients with mixed diagnoses [12].

There has been steady development of knowledge regarding frequency and severity of symptoms, particularly CRF and sleep deficiency, and the impact of these symptoms on functioning and QOL. Weaknesses of the retrieved studies include small sample sizes, a variety of measurements (e.g., lack of objective measurement and lack of consensus on how to best assess for CRF), the omission of the impact on functioning/QOL, and lack of attention to pre-morbid risk factors. Clinical practice is not consistently integrating interventions to reduce these symptoms, possibly due to their non–life-threatening status. Therefore, there is a strong need for baseline screening, assessment, and treatment of these symptoms and subsequently improving QOL.

Screening and assessment

Although evidence-based clinical practice guidelines (CPGs) for adults with cancer are available, routine clinical screening and assessment is inadequately implemented. This can result in missing a large proportion of patients who may be in need of care, but who are either too distressed or without the resources to find their way through a confusing medical system. Unfortunately, these cancer-related symptoms are associated with financial, greater patient and caregiver burden, and poor health outcomes to report a few. Interpreting CPG recommendations for clinicians may be the first step to improve the quality of cancer care.

An ADAPTE-based [13] English language search of the national guideline clearing houses, cancer organizations, and health databases identified at least three CPGs for each symptom. Several organizations developed evidenced-based CPGs including the National Comprehensive Network (NCCN) [14],the Pan-Canadian Practice Guidelines (PCPG) [15], the Oncology Nursing Society Putting Evidence into Practice (ONS-PEP) [16], and the American Society of Clinical Oncology (ASCO) [17].

The standards of care developed by these organizations advocate for routine screening of patient symptoms at the initial visit, appropriate intervals, and when clinically indicated. If screening is positive, focused assessments and additional measures to clarify the symptom characteristics and to determine the degree to which it interferes with functioning are recommended. Focused assessments include a variety of reliable and valid measurements to evaluate symptom characteristics and etiology, co-morbid psychological disorders, and relevant comorbidities. No CPGs were found that address fatigue or, sleep, or distress in family caregivers; an important area for CPG development.

Language, ethnicity, race, and religion can affect perception of illness, provider–patient communication, and symptom expression. Thus, screening and assessments should be understandable and appropriate for the target population. Application of CPGs should take into account different health care systems and cultures [18]. Technology now permits electronic capture of patient-reported symptoms, functioning, and quality of life, which may improve the uptake of CPG recommendations.

Evidence-based symptom guidelines are ready for dissemination and implementation in partnership with key stakeholders [19]. Over the past few years, cancer centers around the world have been exploring optimal ways to facilitate the uptake of recommended symptom screening, assessment, and management [20]. A variety of approaches including audit and feedback have been tested [21, 22]. For example, one multidisciplinary team launched an initiative to implement routine screening with the Edmonton Symptom Assessment System (ESAS) in 14 Ontario Cancer Centers [21]. The project team created a theory-based plan and evaluation framework, developed common tools, and provided expert coaching and centralized data analysis. Additional strategies included clinical champions, clearly identified aims, and monthly progress reporting. Similarly, in another project aimed at increasing distress screening and referrals in women with breast cancer, strategies included establishing administrative support and educating and engaging breast center staff [22].

Although system-wide processes and policies can facilitate the dissemination of CPGs, clinicians remain the main entry point for symptom improvement [19]. Individual clinicians are in an ideal position to screen/assess patients at high risk for specific symptoms, facilitate referrals, and assist them to select evidence-based interventions with instructions for a safe and effective application. Clinicians can advocate for the use of symptom protocols and technology to improve symptom documentation. Finally, clinicians can engage in researcher–clinician partnerships to test implementation strategies and new interventions [19].

In summary, regular screening and assessment of common symptoms will help identify adults who need effective interventions, education, or referral to specialists. Additional research to determine the most effective dissemination and implementation strategies for CPGs in a variety of settings is sorely needed.

Cancer-related fatigue, sleep, and depression cluster

Cancer-related symptoms such as CRF, sleep deficiency, and depression are common in cancer patients and impact cancer-related outcomes and quality of life. Symptom clusters (SC) are defined as a stable group of concurrent symptoms that are related to one another and distinct from other symptom clusters [23]. SC may be related through a common etiology, shared variance longitudinally, and a predictable impact on cancer outcomes.

The SC of CRF, sleep deficiency, and depression may derive from common inflammatory mechanisms previously recognized as the sickness behavior syndrome [24]. Rodent models demonstrate that there are predictable physiologic and behavioral responses after administration of inflammatory agents which trigger pro-inflammatory cytokines such as interleukin (IL)-1, tumor necrosis factor (TNF)-α, IL-6, and interferon ϒ (IFNϒ) which correspond to symptoms of illness, including sleepiness, fatigue, and depressed mood. Sleep deficiency is influenced by IL-1 and TNF-α [25]. These cytokines can have direct effects on adenosine which mediates sleepiness, as well as on GABAergic sleep pathways [26]. Two excellent reviews describe the role of inflammatory mediators on CRF [27]. Inflammatory cytokines also play an important role in mediating synaptic transmission of glutamate and monoaminergic neurotransmitters which impact mood stability. In particular, IL-6, IL-1β, TNF-α, and IFN-γ are known to mediate monoamine synthesis as well as neurotransmitter vesicular transport and release in synaptic terminals. Gene expression studies confirm the role of these inflammatory mechanisms in inducing the SC of sleep deficiency, CRF, and depression [28].

Symptom clusters have been the topic of numerous empirical studies. In a review of 36 studies, which reported cancer-related SC, 14 studies demonstrated a fatigue, sleep deficiency, and pain cluster and 15 demonstrated an anxiety–depression cluster [29]. A systematic review evaluated 26 papers of SC in cancer patients and highlighted the various statistical methods and approaches to SC measurement revealing stability across statistical methods, longitudinal covariance, and common effects on outcomes [23]. However, others suggest that SC do not always show covariance, stability, and correlation with outcomes, proposing that there may be patient clusters rather than symptom clusters which may explain the coincidence of these symptoms [30]. Correlation and covariance of SC treatment outcomes with corticosteroids has been demonstrated [31]. Trials involving cytokine-specific therapies for depression such as tocilizumab, which inhibit IL-6 signaling are being conducted currently and may show promise for treating SC [32]. The evolving field of targeting gene polymorphisms associated with SC offers yet another excited but yet untapped target for therapy. Further study is required to determine whether treating SC will improve outcomes such as cancer morbidity, mortality, and quality of life.

Cancer-related fatigue, sleep, and related symptoms across the cancer trajectory in patients and caregivers

The chronic and progressive nature of cancer involves major changes for the family, including the need to assume the role of the caregiver and complicated by various responsibilities and challenges. This entails responsibilities for managing the symptoms and performing medical or nursing treatments that in other cases would have been undertaken by trained health care providers [33]. In addition, family caregivers have to deal with the home, family, and economic circumstances and social and personal relationships, increasing the physical, psychosocial, and economic impact of caring [34]. As a result of their role, family caregivers of patients with chronic diseases often experience distress and psychiatric morbidity in the form of burden or depression. The main body of the literature has investigated the level, the causes, and the associated factors related with the burden and depression of family caregivers of patients with dementia and mental health illnesses [35]. Within the cancer care context, there are neither many studies about the effect of cancer on their caregivers nor any correlational studies exploring any differences among the various groups of caregivers. However, a study that explored burden and depression in three different groups of caregivers (i.e., cancer, dementia, and schizophrenia) using a descriptive/correlation approach demonstrated how the disease can alter the caregiving factors [35]. The analysis of variance in this comparative study showed significant differences ($F = 4.85$; $P = 0.008$,) between the three caregiving groups (cancer, dementia, and schizophrenia) in terms of depression, with the highest depression levels seen in cancer caregivers. It was found that cancer caregivers' depression is highly related to their burden of care. Regression analyses also showed that 17% of the variation in depression of cancer caregivers is explained by the patients' age and the caregiver's education level. Similar results were found in more recent studies who also found that depression scores were significantly positively correlated with caregiver burden scores [36]. The findings of these studies demonstrated that family caregivers are burdened with providing support to their relatives and deal with the complexities of symptom and side effect management that may result in negative outcomes for the relative and consequently for the patient. This increases the necessity to increase family education programs both in the management of cancer care and also how to cope with their own feelings. However educational material or other conventional method of patient education could be complemented by technologies that should be targeted to make the most significant improvement in the field. For example, there is evidence suggesting a positive effect on pain-related outcomes with the use of multimedia-based patient and caregiver-targeted interventions [37]. Mobile health tools to address the medical management needs by caregivers of children with cancer as well as other mobile health applications that improve health literacy and empower patients and caregivers [38] are used.

Management of symptoms in cancer patients and caregivers

Cancer-related fatigue, depression, and sleep deficiency frequently co-occur, causing distress and difficulty in managing cancer patients who already experience high pharmacological burden associated with cancer treatments. The majority of clinical research has primarily focused on understanding and reducing the high side effects burden for cancer patients. Relatively, little attention has been attributed to the caregivers' burden. Although preliminary data show that caregivers experience high burden of symptoms as well and have high rates of depression, sleep deficiency, and fatigue [39], more research is needed to develop cost-effective interventions that are focused on the patient–caregiver dyad; studies are needed to determine the risk factors for caregivers' sleep deficiencies and distress [40]. Most of the research that has been conducted to date focused on cancer patients' symptoms. Symptoms that share cancer and behavioral/psychiatric etiology (i.e., precipitated by cancer treatments and perpetuated in part by behavior such as symptoms of insomnia) respond well to behavioral interventions (e.g., cognitive behavioral therapy for insomnia and physical activity interventions). For example, insomnia is a common side effect associated with the diagnosis of cancer and treatment. While insomnia is caused by cancer and its sequela, chronic insomnia is perpetuated by maladaptive behaviors (such as napping during the day that can lead to dysregulated sleep–wake cycles and contribute to the maintenance of insomnia). The short-term efficacy of pharmacological agents for acute insomnia is well-documented, but the safety and efficacy of the long-term use of the pharmacological agents for cancer patients for management of insomnia is not well-known. In addition, the pharmacological agents are not curative of insomnia and stopping them can lead to rebound insomnia [41]. Future research should focus on trying to prevent the development of side effects and modifying/adapting behavioral interventions so that they can be feasible and acceptable to be used by cancer patients during acute care [42]. More research is also needed to better understand the long-term effects of pharmacological agents during cancer care; for the behavioral and exercise interventions determining the effective dosage of the interventions, duration, and frequency is needed [41].

Clinicians can utilize the clinical guidelines to screen for these symptoms, provide psychoeducation (e.g., encouragement of physical activity, maintenance of consistent sleep–wake cycle, and discouragement of napping on non-treatment days), and when needed refer for further evaluation and management to appropriate specialists (e.g., psychiatry, psychology, sleep medicine, and exercise physiologist).

The latest advances in technology in diagnosis and management of cancer-related fatigue, sleep deficiency, and depression in cancer patients and caregivers

Earlier on this paper, the authors described the many challenges of addressing simultaneously multiple symptoms and symptoms that persist over time across the cancer care continuum. Adding to the complexity of symptom management are factors such as the poor communication between patients and health professionals or communication that does not occur in “real” time [43]. This consecutively can impact adequate symptom assessment and management. Furthermore, an increasing number of patients receive treatments on an outpatient basis as a result of the new models of care that have been adopted. These models promote the delivery of health care services at a local level and the shift from inpatient to ambulatory care. However, this trend places a great responsibility on the patient and the family (informal) caregiver for the effective continuation of treatment and the management of any toxicities (side effects) at the home setting. While these new models of care place the patient at the center of the care and promote patient empowerment, this needs to be adequately supported consistently by appropriate means. The use of mobile information and communications technology as well as other system solutions may be a means to achieve high-quality clinical outcomes and patient-centered care delivery goals. Many of these technologies are patient centered and appear to complement current transitions within health care models, shifting care from the acute hospital setting to the home environment, with technology being used to rationalize and integrate services, where appropriate, based on patient need. Smartphone technology, virtual environment, actigraphy, video game (e.g., kinetic exercise), energy and sleep enhancement, internet-based, and phone-based apps are only some of the technological interventions used to manage these symptoms [44]. The technology also utilizes behavioral techniques such as guided imagery and relaxation therapy [45] to optimize symptom management. The evidence in the literature demonstrated the promising impact of specific technological interventions in combination to more traditional ones as a means to manage these symptoms effectively. As most of these symptoms are managed at home, it is important for these interventions to promote patient’s empowerment and personalized care. Despite the many available technological interventions, more emphasis needs to be placed on technologies incorporating actigraphy, smartphone technology, and phone-based apps as the most promising for achieving the most significant improvement in the field. The reasons lay in the fact that these technologies have largely been integrated in the people’s daily living and are minimally disruptive. Furthermore, these technologies can be highly personalized according to the individual’s needs and can be used both for symptom screening and management. The technology is becoming ubiquitous but few trials that can demonstrate efficacy and non-inferiority of such interventions in this context exist.

Discussion

This paper summarizes the experts’ opinions on symptom etiology, assessment, and management in cancer patients and caregivers from the Oncology Nursing Society, European Oncology Nursing Society, and MASCC. The joint session highlighted the following consensus in the field:

- Sleep deficiency, such as insomnia, and CRF are prevalent and share some of the common etiology (i.e., inflammation pathway).
- Sleep deficiency and CRF are distressing and need to be routinely assessed and managed in cancer patients and survivors. The evidence-based interventions such as prescribed physical activity and cognitive behavioral therapy for insomnia have shown to be effective for the management of CRF and insomnia in cancer. However, more research is needed to understand how to adapt and develop new interventions that are effective for patients during active treatment.
- The cancer caregivers suffer from many psychological and psychiatric symptoms that can be attributed to the burden of caregiving. The panel acknowledges that the needs of caregivers are understudied and undertreated.

- There is a promising impact of specific technological interventions in combination to more traditional ones as a means to manage sleep deficiency and CRF more effectively. However, more trials that provide efficacy and non-inferiority evidence of such interventions are needed.
- Research on the cancer caregivers' stress and symptoms is in its infancy, but preliminary findings suggest that the caregivers are disproportionally affected.

Side effects in cancer patients are multifactorial and chronic. More research is needed to come from the teams that work in diverse fields such as psychology, psychiatry, exercise physiology, nutrition, behavioral science, nursing, palliative care, and oncology to move the field forward. International and cross-disciplinary collaborations can lead to new discoveries and ideas for how to best improve QOL in cancer patients and survivors and their caregivers. Preventing the development of symptoms or treating them early might be the best approach to the management of these difficult side effects.

Future research needs to focus on managing stress and symptoms not only in cancer patients and survivors but also in their caregivers. Addressing the needs of the caregivers might have an additive or multiplicative effect on the health of cancer patients and survivors.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict(s) of interest.

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