Evaluation and Management of Sleep and Circadian Rhythm Disturbance in Cancer

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Opinion statement

Sleep and circadian rhythm disturbance are among the most commonly experienced symptoms in patients with cancer. These disturbances occur throughout the spectrum of cancer care from diagnosis, treatment and long into survivorship. The pathogenesis of these symptoms and disturbances is based on common inflammatory pathways related to cancer and cancer treatments. The evaluation of sleep and circadian disorders requires an understanding of how these symptoms cluster with other cancer-related symptoms and potentiate each other. A thorough evaluation of these symptoms and disorders utilizing validated diagnostic tools, directed review of clinical information, and diagnostic testing is recommended. Treatment of sleep and circadian disturbance in cancer patients should be based on findings of a detailed evaluation and include specific treatment of primary sleep and circadian disorders and integrative and personalised of management of cancer-related symptoms through multiple pharmacologic and non-pharmacologic modalities. Recognition, evaluation and treatment of sleep and circadian rhythm disturbance in cancer may lead to improved symptom management, quality of life and outcomes.

Introduction

Sleep is a fundamental active physiological process in humans and a paramount determinant of health and wellbeing (1). The alternation of sleep (rest) and wakefulness (activity) cycles along the 24-hour span constitutes a biological rhythm coordinated by a hierarchical circadian timing system, whose disturbance has a negative impact on human health. (2, 3) Thus, both disrupted circadian rhythms and sleep disorders have been found to be associated with poor outcomes in oncology. (4-6)

Globally, sleep disorders are among the most frequently experienced symptoms by patients with advanced cancer, with an estimated prevalence of up to 2 out of 3 patients experiencing sleep disruption during their cancer journey including at the time of diagnosis, treatment, and into survivorship. (7, 8) Understanding the nature of primary sleep disorders and their incidence and presentation in cancer patients is essential for management. Sleep disturbance often manifests in cancer patients in conjunction with other cancer-related symptoms and understanding how these symptoms cluster and share common etiologies and inflammatory pathways will help to mitigate the effects of sleep and circadian disturbance in cancer patients and improve quality of life.

Objective signs of circadian disruption are less common in cancer patients, with a prevalence of about 1 in 2. (9) Nonetheless, the choice of the diagnostic procedure (objective biosensors or subjective questionnaires) and the threshold for “abnormality” in each domain, alongside other demographical and clinical determinants, heavily impacts the exact occurrence rate. (10)

The pathogenesis of these disturbance can be multifactorial (including physical and psychological components) and their impact on health broad and deep (including an array of complaints associated with jet lag and shift work) (11, 12). Altogether, sleep and circadian rhythms have effects on and are affected by multiple other physiological functions. (13, 14) Indeed, strikingly, shift work and the associated circadian disruption are considered as carcinogenic by the World Health Organisation (15). This determination, which has profound social impact, was based on experimental, genetic and epidemiological evidence linking circadian disruption to increased risk of cancer (16). As for the impact of poor sleep on cancer risk, the current data remains mixed. In a recent meta-analysis short sleep duration was found

to be strongly associated with increased breast cancer incidence in Asian participants but not in American and European participants.(17) It was suggested that this discrepency may be due to differences in melatonin secretion patterns between Asians and Americans or may be due to differences in sleep patterns (e.g. daytime naps, the use of sleep medication, and sleeping alone or with a partner) across different countries.(18, 19) The review, however, reported significant heterogeneity between studies and further investigation on this topic is therefore warranted. These data suggest that alterations in circadian and sleep functions are pervasive in cancer processes and in the clinical course of the disease.

Characteristics of sleep and circadian rhythm disturbance in cancer

Sleep disruption arises from both the clinical factors and comorbidities of a cancer patient prior to their diagnosis. These include age, stress, poor sleep hygiene, other medical conditions and medications. These are compounded by adjustment to cancer diagnosis and therapy.(20) Underlying sleep disorders may also contribute to sleep disruption, and these may be pre-date the cancer diagnosis or arise as a result of cancer diagnoses and cancer therapies. Sleep disruption in cancer patients often leads to other symptoms which can be coincident and comorbid including fatigue, anxiety and depression, cognitive impairment, and pain.(10) Hormonal imbalances, weight changes, and other medical conditions as a result of cancer therapies may also precipitate, and in some cases be precipitated by, sleep disruption.(8)

Analysis of sleep disorders in cancer patients revealed a high prevalence. In a large series, in all cancers, almost 44% of patients reported cancer-related fatigue. 40% had restless legs, 30% had insomnia, 28% had daytime sleepiness, 21% were on a sleep medication and about 11% had symptoms of clinical sleep apnea.(21) These results have been confirmed in other prevalence studies.(8)

One symptom of cancer that often is confused with sleep disturbance is cancer-related fatigue (CRF).(22) CRF is often coincident and clusters with sleep disturbance but does have distinct characteristics. CRF is described as a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with the usual functioning. CRF correlates with decreased daytime activity and

increased nocturnal wakefulness. Because of this, the decreased daytime activity is often confused with daytime sleepiness and increased nocturnal wakefulness with insomnia.

Along with CRF, sleep disturbance in patients with cancer is frequently associated with other distressing symptoms such as pain, shortness of breath, depression, anxiety, anorexia and decreased quality of life.(7) These symptoms co-occur in the form of symptom clusters and may share common pathophysiologic mechanisms such as dysregulation of pro-inflammatory cytokines, specifically IL-1, TNF-alpha, and IL-6 and their receptors.(23, 24) Interventions targeting the pro-inflammatory cytokines result in improvement of not only sleep disturbance but also of the symptom clusters and therefore, overall quality of life. However, there are limited studies for the alleviation of sleep disturbance, or symptom clusters which mechanistically target inflammatory cytokines, and therefore, further research is warranted. (25, 26) Moreover, poor sleep and symptom clusters persist until end of life and are associated with significant decrease in patients' functioning and quality of life, and can negatively affect patients' families. Thus, interventions which target multiple symptoms may be beneficial in improving sleep disturbance in the context of symptom clusters and are urgently needed.(27-29)

Evaluation of sleep and circadian rhythm disturbance in cancer.

Validated diagnostic tools can assist in determining whether a patient truly has sleepiness as opposed to CRF, although the two often coexist. These tools can be helpful in identifying a primary sleep disorders in cancer patients. These include insomnia, sleep-disordered breathing, sleep-related movement disorders, and hypersomnia. Circadian rhythm disturbance may further disturb sleep in cancer patients. A comprehensive algorithm for the evaluation of sleep disorders in cancer and description of the validated diagnostic tools are included in **Table 1**. Subjective tools to assess sleep-related symptoms which impact cancer patients include the Pittsburgh Sleep Quality Index, which addresses nocturnal sleep disturbance, the Epworth Sleepiness Scale Score which measures daytime sleepiness, the Insomnia Severity Score which measures insomnia, and the Brief Fatigue index which quantifies fatigue. Physical exam findings, review of medications, and diagnostic and laboratory testing should be employed in the detection and evaluation of primary sleep disorders as indicated.

Sleep Disorders in Cancer Patients

Insomnia

Insomnia is described as a subjective complaint of difficulty falling asleep or staying asleep or nonrestorative sleep associated with marked distress and significant daytime impairment.(30) Cancer patients have at least a 2-fold higher incidence of insomnia compared to the general population.(8, 31) The Speilman 3P behavioral model offers an illustrative paradigm4 for conceptualizing insomnia that can be applied to understanding and managing sleep disturbance in patients with cancer.(20, 32) The Speilman model describes factors contributing to insomnia and categorizes these into predisposing, precipitating, and perpetuating factors. In cancer patients, predisposing factors may include age, the presence of hyper-arousability, a prior personal or family history of insomnia, or a pre-existing psychiatric disorder. Precipitating factors include those factors that may cause acute symptoms of insomnia such as surgery, hospitalization, chemotherapy, radiation therapy and use of steroids medications. Hormonal therapy that may induce premature menopause and hot flashes may also disturb sleep.(33) Pain related to cancer or cancer therapy also constitutes an important cause of acute insomnia.(34) Adjustment to a new diagnosis of cancer may also be significant precipitating factor in patients with cancer.(35) Perpetuating factors are mainly split into either maladaptive sleep behaviors or faulty beliefs that accrue during the course of a cancer diagnosis or treatment. Maladaptive sleep behaviors include excessive time in bed, irregular sleep wake cycles, napping, and poor sleep hygiene. Faulty beliefs and attitudes include unrealistic sleep expectations or faulty appraisals of sleep disruption.(36-38)

Sleep Movement Disorders

Sleep movement disorders occur in patients with cancer and may be primary or attributable to chemotherapy related neuropathy from therapy regimens including platinum compounds, taxanes, vinca alkaloids, proteasome inhibitors or thalidomide based agents.(39, 40) Treatment of the resultant movement disorders is directed at the management of these neuropathic processes. The two major sleep movement disorders in cancer are restless leg syndrome and periodic limb movement syndrome. Restless leg syndrome is defined as an unpleasant tingling or creeping feeling in the legs, during inactivity or sleep accompanied by

an irresistible urge to move which improves with movement. Restless legs can be diagnosed by asking one question that encompasses the elements of RLS which are uncomfortable sensations or need to move (akathisia) that has a circadian, usually nocturnal, manifestation and is relieved by movement.(41) Periodic limb movements can be suspected based on clinical history but require diagnosis by polysomnography revealing excessive period leg movements with associated neuro-cortical arousal form sleep. These repetitive arousals from sleep precipitated by limb movements are a cause of daytime sleepiness. The diagnostic workup for a movement disorder includes evaluation of etiologies such as electrolyte abnormalities, thyroid disease, diabetes, excessive consumption of caffeine, and metabolic abnormalities such as low ferritin levels, vitamin B12, or folate deficiencies. Medications such as selective serotonin receptor inhibitors can also precipitate restless leg syndrome. Treatment may involve correcting the underlying causes, eliminating caffeine, the use of dopamine agonists, and for severe cases, narcotic medications.(42, 43)

Hypersomnolemce

Hypersomnolence or excessive daytime sleepiness is a common symptom noted among cancer patients.(44) Oftentimes, this hypersomnolence cannot be attributed to a primary sleep disorder. Hypersomnias are specific sleep disorders often with prolonged sleep times and hypersomnolence as classified by the International Classification of Sleep Disorders (Version III) which identifies multiple subtypes of hypersomnia.(45) Hypersomnia related to cancer can be often classified as either hypersomnia due to a medical condition or hypersomnia due to drug or substance, especially for those patients taking opioid or other sedative medications. The Epworth Sleepiness Scale score may be useful in identifying and stratifying daytime sleepiness in these patients and confirmation with a polysomnographic multiple sleep latency test (MSLT) can objectively quantify sleepiness.(46) These evaluations may be warranted prior to beginning therapy with stimulants such as methylphenidate, modafinil, or armodafinil. These agents have been used in multiple studies for cancer-related fatigue, which may guide the management of hypersomnolence in cancer patients as well.(47)

Sleep disordered breathing

Obstructive sleep apnea occurs in patients with cancer may be increased in patients with specific cancers such as head and neck tumors.(48) Obstructive sleep apnea is a disorder in which increased airway resistance in the upper airway leads to closure of the airway during sleep resulting in intermittent hypoxemia and neurocognitive arousal. The symptoms of sleep apnea include snoring, witnessed apneas, choking and gasping arousals, and daytime sleepiness. The diagnosis is suggested by using validated tools such as the STOP-BANG questionnaire and can be confirmed by polysomnography and increasing ambulatory sleep monitoring.(49) Treatment of sleep apnea most commonly involves the night-time administration of positive airway pressure through a nasal or oro-nasal mask which acts as pneumatic stent to prevent airway obstruction. Oral appliance therapy, positional therapy and adjunctive measures such as weight loss, and avoidance of alcohol, sedative-hypnotic and narcotic mediations are also used in the treatment of this sleep breathing disorder.(50)

Increasing data over the last several years suggests a bidirectional relationship between cancer and sleep apnea. Patients with sleep apnea have a 5-fold increased risk of cancer-related mortality and several studies show an increased incidence of cancer in patients with severe sleep apnea.(51, 52) It is thought that both the intermittent hypoxemia and increased sympathetic tone which occurs with sleep apnea may stimulate tumor growth.(53, 54) A recent review of multiple longitudinal studies reported an up to a 2.5-fold increased risk of cancer incidence associated with obstructive sleep apnea. The incidence of cancer increased in a dose-dependent manner corresponding to the severity of oxygen desaturation. Patients with untreated sleep apnea had a higher incidence of cancer suggesting that the possibility the treatment of sleep apnea may decrease incidence of cancer.(52) More recent studies have shown conflicting data does not support an increase incidence of cancer with sleep apnea. (52, 55) Notwithstanding, there does seem to be a signal for specific cancers with higher incidences of melanoma, pancreatic and renal cancers.(56) Numerous researchers have postulated that intermittent hypoxemia potentiates tumor growth as demonstrated in animal models. Furthermore, these is an increasing realization that not only sleep apnea, but sleep disturbance, in general, may be oncogenic based on increased autonomic tone, chronic stress, variation in the pituitary-hypothalamic axis, as well as circadian mechanisms.(54) Sleep apnea which often presents with daytime sleepiness may mimic cancer-related fatigue and should

be evaluated in appropriate candidates. Moreover, opioid medications, commonly used to treat cancer related pain syndromes, may exacerbate obstructive sleep apnea or induce sleep related hypoventilation.(57)

Treatment of Sleep and Circadian Disturbance in Cancer

The basis of effective treatment of sleep and circadian disturbance in cancer patients relies on the appropriate diagnosis of the underlying sleep pathology, which in turn determines the expected benefit in terms of symptomatic relief, during both nighttime and daytime. (10) Indeed, sleep disturbance negatively impacts the wakeful period the next day and is associated with other common and bothersome psychoneuroendocrine complaints, such as fatigue, anorexia and depression. (58, 59) Overall, taking into account the diagnostic difficulties and the multiple determining and contributing factors, limited evidence-validated treatments are available for sleep disturbance. (60) Although tightly connected to sleep disorders, even less evidence is available for interventions manipulating the disrupted circadian clock of cancer patients. (61, 62)

We describe here the behavioral and pharmacological interventions developed to improve sleep and circadian physiology, and in particular, those studied in patients with cancer. For both types of interventions, and to a much greater extent than that of other diseases (63), the time of administration of the intervention is paramount for its activity or impact on sleep and circadian functions. For each treatment option, optimal timing of administration should be considered, in order to maximise the activity and/or minimise the toxicity (64). Altogether, the main aim of any treatment is to improve the restfulness from sleep, in terms of quality, duration or timing (65), and the physiological regularity of the biological cycles over 24 hours, in terms of patterns, phase or synchrony (12, 66).

Hypnotics

Treatment of insomnia often involves pharmacological therapy and sedative-hypnotics are often prescribed. Pharmacological therapies include sedative hypnotics and antidepressants.(67) There are no randomized control trials to date that describe the use of sedative-hypnotic therapies for insomnia, specifically in cancer patients. The 2016 National Comprehensive Cancer Network guidelines for the treatment of sleep disturbance

recommend sedative hypnotics for short term use and long-term use of these medication is not recommended, even though these agents are commonly used this way.(68) It is recommended that if sedative-hypnotics are employed for the treatment of insomnia, that they be used in conjunction with cognitive and behavioural therapy for insomnia (CBT-I). Furthermore, sedative-hypnotic use itself has been associated with a dose-dependent increased risk of cancer.(69)

Chronobiotics

Certain xenobiotics can produce an effect on the output phase of the circadian clock, in terms of advance or delay of the internal timing of the clock comparatively with the external time cues. Thus, they exert chronobiotic properties (11). One of the most studied chronobiotic is the pineal hormone melatonin, normally endogenously secreted during darkness at night (70, 71). However, the nocturnal secretion of melatonin can be modified by multiple medications or light exposure, leading to an alteration in the function of the body clock, usually with detrimental effects on health (72). Indeed, a decreased melatonin production has been associated with an increased risk of cancer (73, 74). Nonetheless, exogenous melatonin can be used to treat desynchronization and circadian disorders (75), and to promote sleep (76), due to its chronobiotic and hypnotic effects. Being an endogenous hormone, melatonin has minimal toxicitiey (77) and has been used in patients with cancer both to improve sleep and circadian function (78) and to increase chemotherapy efficacy (79). Additionally, melatoninergic agonists have been more developed to treat disturbed sleep and depression (80), but data in cancer patients remain scarce.

Anticancer and Support Medications

Systemic anticancer treatment and its support medications (such as antiemetic or antiallergic drugs) have a potential impact on sleep function and on the circadian clock at various levels (61). In general, the repercussions of chemotherapy are considerably detrimental to the quality of sleep and to circadian robustness, and invariably there are unwanted side effects rather than the desired therapeutic outcomes. (81) The synchronising effect of glucocorticoids could be one of the few exceptions; (82) yet the other immunologic, metabolic and general reactions to the steroids have arguably a heavier impact than the chronobiotic effect on cancer patients (83).

Non-pharmacological therapies

Cognitive and behaviour therapy (CBT-I) is considered the gold standard non-pharmacological treatment of insomnia.(84). CBT-I is a multi-modal intervention which includes elements of sleep restriction (consolidating sleep by limiting time in bed), stimulus control (restricting behaviours incompatible with sleep to re-associate the bedroom environment with sleep) and cognitive restructuring (redirecting maladaptive thoughts and beliefs about sleep) to promote and re-establish correct sleep patterns. CBT-I is recommended and commonly used to treat insomnia in cancer patients. (68) Recent meta-analyses provide data to support a strong recommendation to utilize CBT-I for cancer survivors.(84, 85) The availability of qualified personnel to administer CBT-I is a barrier to therapy. Novel delivery systems using brief behavioral therapy, video and app-based delivery of CBT-I may make this treatment modality more readily and universally accessible.(37, 86, 87)

Other therapies such as exercise, movement, yoga and tia-chi have also shown benefit in reducing sleep disturbance often in conjunction with reduction in CRF and other cancer-related symptoms.(88, 89). Light therapy to improve daytime alertness and entrain circadian rhythms has also had some success in improving sleep disturbance in cancer.(90, 91) Novel multimodal protocols involving therapy with pharmacotherapy, light therapy and melatonin for sleep disturbances in cancer are ongoing and may synergistically impact these symptoms.(92)

Future Directions

A major advantage of behavioral coaching is the paucity of side effects, permitting the development of integrative approaches including several simultaneous behavioral interventions.(93) Indeed, the circadian human clock can be entrained by environmental cues, whose exposure is dependent on behavioral factors. (66) Thus, behavioral approaches require patient engagement and ownership of their own sleep and circadian health, in a tailored personalized manner. Moreover, the personalization of interventions to restore proper sleep and circadian functions in patients with cancer relies on the prevention of alterations induced by the disease, its treatments and the psychological stress associated with such diagnosis (81, 94). In order to provide adequate customized proactive interventions, precise prediction of the trajectory of the deterioration in sleep and circadian functions is

required. Hence, we anticipate the future approaches of treatment of sleep disturbances and circadian disruption in patients with cancer to be fully integrated within the patient-centric paradigm of P4 systems medicine (95, 96).

Another foreseeable aspect of forthcoming interventions on sleep and circadian functions involves the use of internet of things to sense longitudinally the whole-body physiology (97, 98). Thus, off-the-shelf sleep and activity wellbeing trackers, widely used in the general and cancer population alike, can be exploited to passively and unceasingly collect real-world physiological data in order to tailor and optimize treatment interventions for the restoration of sleep and for circadian entrainment (99, 100).

Additionally, another broader therapeutic approach could involve the use of circadian-based anticancer treatments, which accounting for temporal oscillations in pharmacological and physiological determinants of drug effects aim at reducing toxicity and enhancing activity (101). However, despite the extensive experimental evidence showing a marked impact of time of administration of various class of anticancer drugs on their tolerance or efficacy (102), and trials supporting its clinical relevance as well (103, 104), cancer chronotherapy is not yet routinely applied (105). Nonetheless, translational research avenues identifying determinants of personalised and precise chronotherapeutic schedules warrant dedicated novel trials to be developed with timing of drug administration as a fundamental aspect to optimize and improve patient outcomes (63).

Recognition of sleep and circadian rhythms disturbance in cancer patient depends on increasing awareness of these disorders. Twenty years after Stores and Crawford reported the median duration of formal teaching on sleep in medical schools was 15 minutes, a recent survey found that median duration of sleep education has risen to 1.5 hours, with half of the respondents reporting that they thought provision was sufficient.(106) The prevalence and impact of sleep and circadian rhythms disorders is growing and there is an insufficient supply of sleep specialists. It is therefore imperative to increase opportunities to educate multiple disciplines of clinicians specializing in cancer care.(107)

In conclusion, although multiple unmet needs persist in the treatment paradigm of sleep and circadian alterations along the course of cancer, and diagnostic and treatment obstacles remain, the rapid advancements in digital monitoring, in behavioral medicine and in systems

pharmacology promise a new array of more effective interventions for our patients. The widening acknowledgement in the clinical community of the importance of restful sleep and robust circadian rhythms in oncology and general medicine warrant optimism.

Table 1. Clinical algorithm for evaluation of sleep disorders in cancer patients (108-112)

Tools to evaluate sleep disorders	**Significance**
Surveys	• **Pittsburgh Sleep Quality Index Questionnaire.** A survey that measures sleep quality over the last 1 month. With a maximum score of 24, a score ≥ 5 represents disturbed sleep • **Epworth Sleepiness Scale.** An 8 question survey which measures daytime sleepiness. With a maximum score of 24, a score ≥ 10 represents increased daytime sleepiness. • **Insomnia Severity Index.** A 7 question survey with maximum score of 28 with a score ≥15 indicative of moderate clinical insomnia • **STOP-BANG Questionnaire.** An 8 question tool, incorporates symptoms (snoring, fatigue), medical history (hypertension), and anthropometric data (age, gender, body mass index, neck circumference). With a maximum score of 8, total signifies the following: a score of <3 low risk for OSA; ≥3 and <5 intermediate risk for OSA; ≥5 high risk for OSA • **Brief Fatigue Inventory.** The Brief Fatigue Inventory (BFI) is a 6-item, 10-question tool used to assess the severity and impact of fatigue on daily functioning of an individual.
Physical exam	• **BMI (kg/m2).** BMI ≥ 30 kg/m2 is considered obese and correlates with severity of OSA • **Upper airway**. Evaluate oral airway: Mallampati Class I-IV (higher number is more prevalent in OSA). Identify macroglossia or adenotonsillar hypertrophy.

	• **Neck.** Neck circumference ≥41 cm correlates with risk of OSA. Also evaluate for firmness on the neck in sites of previous radiation. Inspect neck for thyromegaly and goiter. • **Chest.** Evaluate for wheezing (obstruction, tracheobronchial disease) or dullness to percussion (mass, pleural effusion, consolidation) • **Abdomen.** Examine for hepatosplenomegaly, abdominal masses, ascites, or central obesity
Medications	• **Opiate medications** may predispose to sleep related hypoventilation or OSA**.** • **Sedative–hypnotics, stimulant, anti-epileptic medications** may increase lead to daytime drowsiness and nighttime wakefulness.
Imaging	• **Chest.** Tumor or parenchymal infiltrates, elevated lung diaphragms, cardiomegaly, pleural effusion • **Neurologic**. Brain mass or lesion, stroke, and brainstem abnormalities which may predispose to central sleep apnea
Pulmonary studies	• Evaluate for obstructive and restrictive lung defects
Echocardiography	• Evidence of cardiac dysfunction, and valvular abnormalities
Laboratory studies	• Anemia, hypothyroidism, electrolyte abnormalities • Ferritin Level <40ng/mL associated with symptoms of RLS • Daytime hypercapnia with HCO3 > 27 mEq/L and/or PaCO2 > 45 mmHg

BMI, body mass index; OSA, obstructive sleep apnea, HCO3, serum bicarbonate; PaCO2, partial pressure of carbon dioxide; RLS, restless legs syndrome

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