Anxiety and sleep disorders in cancer patients

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1. Introduction

Even though most cancer patients do not meet diagnostic criteria for any specific mental disorder [1], many experience symptoms such as anxiety and sleep disturbances that may interfere with their overall adjustment to their disease. Anxiety is a common reaction to a cancer diagnosis and a normal response to perceived threats like loss of body functions, alterations in appearance, family disruption, death, etc. Anxiety may persist throughout the disease process, affecting the patient's quality of life significantly, and often coexists with depression in cancer patients. Anxiety tends to appear or worsen at critical points during the course of the illness (diagnosis, beginning and end of treatment, recurrence, survival and terminal stage).

Sleep disorders are frequently associated with the psychological impact of cancer as well as with the physical illness itself, pain, hospitalisation and specific medical treatments. Altered sleep adversely affects emotional wellbeing and daytime performance, and may be an early sign of delirium in the oncology setting. In the general population, persistent insomnia has been associated with a higher risk of developing clinical anxiety or depression [2].

To effectively adjust patient needs to optimal treatment interventions, health-care professionals must be able to distinguish normal adjustment to cancer from altered reactions to the disease. This paper will focus on anxiety and sleep disorders in the oncology setting and will describe their clinical presentation, assessment, aetiology and treatment.

2. Anxiety in the cancer setting

2.1. *Description and prevalence*

Anxiety is defined as the apprehensive anticipation of future danger or misfortune accompanied by feelings of dysphoria or somatic symptoms of tension [3]. Classification systems used in psychiatry – such as the World Health Organization International Classification of Disorders [4] – require (a) a core of anxiety symptoms such as palpitation or tremor, manifesting the presence of autonomic overactivity, and (b) anxiety to be abnormal, in order to fulfil a diagnosis of anxiety disorder [5].

While anxiety is a normal reaction to threats such as cancer, some patientU:/ES/DTD520/EJCSUP/204s exhibit an overwhelmingly anxious response that impairs their day-to-day functioning. Frequently, anxiety increases as the disease progresses or as treatment becomes more aggressive [6], as well as at transition points that represent threatening events throughout the course of the disease. Patients receiving a cancer diagnosis, learning about a recurrence, or hearing that treatment has been ineffective usually experience initial shock or disbelief followed by emotional turmoil, anxiety and depressive symptoms [7]. Inability to concentrate, diminished sleep, loss of appetite, irritability and intrusive thoughts about the future are also frequent at these times. However, these symptoms tend to decline gradually and resolve within the first 7–10 days after confirmation of cancer diagnosis [8].

Anxiety may affect a person's behaviour regarding his/her health, contributing to a delay in or neglect of measures that might prevent or treat cancer adequately. Anxiety can lead to an overestimation of negative prognosis. For example, women with high levels of anxiety who learn that they have a genetically higher level of risk of breast cancer than they had previously believed might perform breast self-examinations less frequently [9]. A longitudinal study of women with breast cancer found that anxiety was the factor that was most consistently and strongly associated with an inaccurate perception of and an overestimation of future breast-cancer-related risk [10]. Anxiety may also delay or interfere with the seeking of medical care once symptoms have developed, adversely influencing – in this case – prognosis.

As mentioned already, in most cases the anxious reactions are time-limited and may motivate patients and families to take steps to reduce the reactions, such as seeking medical advice, which may assist in adjusting to the illness. Anxiety may also be part of a normal adaptation to cancer. Normal or successful adjustment is indicated in patients who are able to minimise disruptions to life roles, regulate emotional distress and remain actively involved in aspects of life that con-

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1359-6349/$ - see front matter
http://dx.doi.org/10.1016/j.ejcsup.2013.07.009

tinue to hold meaning and importance for them [11]. Clinical practice shows that anxiety may also decrease as patients accept and come to terms with their medical situation, despite disease progression.

In the United States (US), 1-year prevalence for all anxiety disorders among adults in the general population exceeds 16% [12], and in the United Kingdom (UK) reported prevalence is between 3% and 16% [13]. Anxiety occurs to varying degrees in patients with cancer. Our limited understanding of anxiety in cancer care is illustrated by the wide range of prevalence estimates of abnormal anxiety in cancer patient populations [5]. Estimated current prevalence of anxiety disorders in oncology is within a range 15–28% [14], with variations being due to differences in research methodology. In large studies using standardised psychiatric interviews and applying research diagnostic criteria, estimates of abnormal anxiety in cancer populations ranged from 10% to 30% [4]. Some researchers have found that up to 44% of patients with cancer reported some anxiety, and 23% reported significant levels of anxiety [5,15]. Variation in reported prevalence is due largely to limitations in research methodology: differing study populations (single versus mixed cancer diagnosis, differing tumour sites, early- versus late-stage disease, outpatient versus inpatient; etc.), varying diagnostic criteria and assessment instruments and studies failing to separate anxiety from depression, etc.

Some researchers suggest that anxiety disorders are also prevalent in medically ill patients in general [16]. However, rates of anxiety disorders among primary care outpatients have ranged from 7% to 15% [17], and among general medical inpatients rates of 20% have been reported [18]. In both cases, reported rates seem to be lower than those reported in cancer patients. However, populations studied have varied widely in disease severity and prognosis [16].

In cancer patients symptoms of anxiety often coexist with depression and mixed states, and are perhaps more common than anxiety alone [1,19].

2.2. *Clinical presentation and pathological anxiety*

In order to understand anxiety we need to differentiate between anxiety as a state and anxiety as a relatively stable personality characteristic or trait (state versus trait anxiety). Patients with high levels of trait anxiety will carry their predisposition throughout the disease course, and thus it is important to identify it in an early phase.

Symptoms are similar in most patients, regardless of whether they represent acute responses to cancer or its treatment, or are part of a pre-existing anxiety disorder, exacerbated by the diagnosis of cancer [16]. Acute anxiety symptoms include:

- uneasiness, unpleasant feeling of arousal, restlessness;
- irritability;
- inability to relax; tendency to startle;
- difficulty falling asleep (leads to fatigue and low tolerance to frustration);
- recurring, intrusive thoughts and images of cancer;
- occasionally, sense of impending doom;
- distractibility;
- helplessness and a sense of loss of control over one's own feelings;
- symptoms of autonomic arousal: rapid or forceful heartbeat, sweating, unpleasant tightness in stomach, shortness of breath, dizziness;
- vegetative disturbances: loss of appetite, decreased sexual interest;
- parasympathetically-mediated symptoms: abdominal distress, nausea, diarrhoea.

Pathological anxiety can be identified because it tends to be out of proportion to the level of threat; it persists or deteriorates when no intervention is administered, the intensity of symptoms is unacceptable regardless of the intensity of the threat (these include panic attacks, severe physical symptoms, abnormal beliefs such as thoughts of sudden death), and the patients experience a disruption of their usual or desirable functioning [3,4]. However, such criteria are difficult to apply to cancer patients given that cancer is always associated with some form of threat: the threat of loss, death, body functions, roles, body image, etc. In addition, while the duration of symptoms is important in identifying abnormal anxiety, the natural history of anxiety in oncology is uncertain. Disruption of functioning is also common in cancer patients and is frequently associated with anxiety (i.e. intrusive and unpleasant thoughts regarding recurrence, disability or death can disrupt the ability to concentrate, decision-making, sleep patterns, etc.) [4].

Massie and Shakin [20] have categorised anxiety in cancer patients into three groups: reactive anxiety, pre-existing anxiety disorders and anxiety related to medical illness.

Reactive anxiety: Adjustment disorders are emotional reactions to an identifiable stressor, in this case the disease, with a degree of psychopathology that is less severe than diagnosable mental disorders such as generalised anxiety. The patient experiences significant distress that is in excess of what would be expected from exposure to the stressor and a significant impairment in functioning.

CASE: Ms E, a 56-year-old woman recently diagnosed with colon cancer, was referred to the Psycho-Oncology Unit because of increased anxiety that interfered with her ability to decide whether to receive treatment with chemotherapy (CT) or not. Ms E had cared for her mother, who had died of ovarian cancer 2 years earlier after suffering severe treatment toxicity. Psychotherapy focused, among other things, on improving coping skills, deconstructing myths about cancer and its treatment, strengthening supports and introducing the patient to others that had successfully undergone cancer treatment, as well as practicing relaxation techniques in the oncology clinic where treatments were administered. Once her anxiety was significantly reduced, the patient decided to undergo treatment, which ended successfully.

Of hospitalised and ambulatory cancer patients, 32% were found to meet diagnostic criteria for an adjustment disorder [1]. In patients with advanced cancer, prevalence ranges from 14% to 35% [21], and in terminally ill patients rates range from 11% to 16%. Variability in prevalence rates is due to different factors such as differences in stage of disease, type of cancer or diagnostic procedures used for anxiety. The difference between an adjustment disorder and a normal reaction to cancer is based primarily on the duration and intensity of symptoms, as well as on the degree of functional impairment.

Pre-existing anxiety disorders: Panic disorders, phobias, generalised anxiety disorders and post-traumatic stress disorder are distinguished from other anxiety disorders as being long-lasting, often preceding the diagnosis of cancer. They are characterised by the extreme fear of losing control and of being overwhelmed by various circumstances:

Panic attacks are sudden, extreme anxiety reactions accompanied by sympathetic nervous system arousal and an overwhelming urge to escape. Intense anxiety is usually accompanied by severe somatic symptoms such as shortness of breath, dizziness, palpitations, trembling, diaphoresis, nausea, tingling sensations and fears of going crazy or having a heart attack. Panic attacks may be re-experienced when the patient is exposed to medical procedures, treatment toxicity, etc.

CASE: Ms. A, a 35-year-old woman diagnosed with breast cancer requested psycho-oncological consultation for recurring panic attacks that developed shortly after ending cancer treatment. Ms A described herself as a very controlling, perfectionist, anxious and self-demanding woman for whom the disease was not a logical consequence of her previous behaviour, which had focused on healthy eating habits, reduced alcoholic intake, no smoking and almost daily exercise. She was experiencing between one and three panic attacks per week. Psychotherapy focused on helping the patient regain a sense of control over her life, focusing on the here-and-now while accepting her cancer risk, and developing more efficient ways of handling her anxiety, together with cognitive-behavioural techniques (i.e. training in relaxation, deep breathing techniques, etc.). Pharmacological treatment with benzodiazepines contributed to making the panic attacks disappear.

Phobias are persistent fears, intense anxiety or avoidance of a circumscribed object or situation. Phobias are experienced by cancer patients in a number of ways, the most common of which are fears of witnessing blood or tissue injury (also known as needle phobia) or claustrophobia (fear of closed places). Phobias may interfere with the administration of cancer treatment with patients refusing medical treatment or necessary tests [22], and may lead to anticipatory anxiety [16].

Mr E was a 28-year-old male with testicular cancer who had a needle phobia. Each time the patient had to undergo blood tests or receive IV chemotherapy treatment, his anxiety escalated to the point where, on one occasion, his treatment had to be postponed to the following day. Training in relaxation as well as in deep breathing techniques alternated with techniques to help him regain control over the situation. For example, it was himself who counted to three before the nurse administered the procedure, which increased his perception of control over the situation. Mr E was trained to do breathing exercises with the use of a party blower. In addition, he learned to identify a positive thought for each negative thought he had, prior to the procedure. For example, '*This is really going to hurt*' was accompanied by '*Feeling the needle is not going to be very pleasant, but it will help cure my disease*'. Mr E was able to undergo treatment with reduced levels of anxiety.

Generalised anxiety disorder is characterised by ongoing, unrealistic and excessive anxiety and worry that the patient finds difficult to control. The worry is pervasive and does not respond to either reassurance or contrary evidence. Symptoms do not have either the sudden onset or intensity of panic attacks and include restlessness, muscle tension, being easily fatigued, irritability, difficulty concentrating and sleep disturbance. Cancer patients with generalised anxiety disorder may, for example, worry or fear that no one will care for them, even though they have adequate social support, or they tend to anticipate medical complications.

Post-traumatic stress disorder (PTSD) develops when a person is exposed to a mentally stressful event that involved actual death or the threat of death, serious injury or a threat to oneself or others, and responds with intense fear, helplessness or anxiety. The person with PTSD re-experiences the traumatic event persistently in the way of recurrent and intrusive distressing images or thoughts, dreams of the event, avoids situations associated with the trauma, and experiences persistent symptoms of increased arousal that were not present prior to the trauma. To be diagnosed with PTSD, these symptoms must last for at least 1 month and cause significant problems in the patient's personal relationships, employment or other important areas of daily life [3]. For the person who has experienced a diagnosis of cancer, the specific trauma that triggers PTSD is unclear. It may be the actual diagnosis of a life-threatening illness, certain aspects of the treatment process, test results, information given about recurrence or some other aspect of the cancer experience. Because the cancer experience involves so many upsetting events, it is much more difficult to single out one event as a cause of stress than it is for other traumas, such as a natural disaster or rape. PTSD has been studied in long-term non-Hodgkin's lymphoma survivors who had participated in an earlier survey and were at least 7 years post-diagnosis [23]. Although half of the respondents reported no PTSD symptoms and 12% reported a resolution of symptoms, more than one third (37%) reported persistence or worsening

of symptoms over 5 years. Those who had a low income, more advanced illness at diagnosis (stage ⩾2), aggressive lymphoma, having received chemotherapy and greater impact of cancer at the initial survey had more PTSD symptoms at follow-up. Cancer survivors with PTSD may relive the cancer experience in nightmares or flashbacks and by continuously thinking about it; they may avoid places, events and people associated with the cancer experience, and may tend to be continuously overexcited, fearful, irritable and unable to sleep.

Mr K was a war veteran who underwent a bone marrow transplantation for leukaemia. During hospital isolation, Mr K started re-experiencing the time when he was imprisoned and placed in a cell, isolated for a prolonged period of time, during the war. In the hospital he had recurrent and intrusive images and thoughts about the war episode, frightening dreams of the event, and flashback episodes that gave him a sense of reliving the traumatic event. Other symptoms he exhibited included hypervigilance, insomnia, difficulty concentrating and avoidance of conversations related to the war episode when he was imprisoned. Benzodiazepines were administered. In addition, he was trained in different video games that provided him with cognitive distraction. In the evenings, when other patients were asleep and visitors had left the hospital, Mr K had to be walked in a wheelchair, the appropriate protective measures having been taken, up and down the hallways of the hospital floor to alleviate his sense of being 'locked up'.

Obsessive-compulsive disorder is characterised by: (a) recurrent, persistent thoughts, ideas or images (obsessions) that cause marked anxiety or distress, and are experienced as intrusive and inappropriate, and (b) repetitive, purposeful and intentional behaviours (compulsions) that the patient performs in response to an obsession in an attempt to reduce his/her distress. In order to diagnose an obsessive-compulsive disorder, the obsessions or compulsions should cause marked distress, should be time-consuming (take more than an hour a day) and interfere with the person's normal routine or functioning [3].

Ms T was a 34-year-old woman who had been treated for skin melanoma. Her skin was extremely white and full of freckles all over her face, body and extremities. Ms T was referred to the Psycho-Oncology Unit by her dermatologist, whom she visited frequently and unnecessarily. The patient would spend more than 2 h daily observing her freckles and trying to identify changes in any one of them. She involved her husband in helping her with this task, as she couldn't view her back. This habit became increasingly incapacitating for the patient, and a source of irritation for her husband. The patient was treated with antidepressant medication and initiated psychotherapy sessions that helped reduce her distress as well as confront her underlying fear of death and other internal conflicts she had.

Anxiety related to medical illness uncontrolled pain, metabolic causes, medication side effects, withdrawal states and hormone-producing tumours may result in increased anxiety levels in the cancer patient. Patients with severe pain are usually anxious, and anxiety in turn can potentiate the pain sensation. Consequently, it is important to treat anxiety in order to adequately manage pain [24]. Anxiety may be the first sign of a change in metabolic state. Sepsis accompanied by chills and fever is often associated with anxiety. Delirium may cause symptoms of anxiety, restlessness and increased agitation. Certain drugs used in cancer, such as corticosteroids, are frequently a cause of anxiety symptoms such as restlessness and agitation. Akathisia is a side effect of several neuroleptic drugs that are frequently used for control of emesis. Withdrawal states from alcohol, narcotic analgesics and sedative hypnotics are often overlooked as causes of anxiety [20]. This is an especially important issue in head and neck cancer patients who often have histories of heavy alcohol and tobacco consumption that place them at increased risk for withdrawal states. Hormone-secreting tumours such as thyroid and parathyroid tumours may be associated with anxiety symptoms.

2.3. *Variables associated with anxiety in the cancer setting*

Cancer is usually an emotionally stressful event in the lives of patients. In addition to physical discomfort, patients typically face dysfunction, alterations in appearance, changes in family and social roles, disruption of work activities and other complex situations. Various factors have been associated with anxiety in cancer patients. Among them are:

- history of anxiety disorders: premorbid anxious tendencies such as elevated trait anxiety and obsessive personality traits [25,26]; helplessness, fatalism and anxious preoccupation have also been correlated with anxiety in breast cancer patients [27];
- psychological variables such as anxiety at the time of diagnosis [28] and history of trauma [29].

Previously discussed factors have been associated with anxiety in cancer patients and include history of anxiety disorders [25–27] and psychological variables such as anxiety at the time of diagnosis [28] and history of trauma [29]. In addition, medical/physical variables such as functional limitations, pain (described earlier) and advancing disease [6] have been associated with increased levels of anxiety in cancer patients. Cancer treatments, specifically the type of treatment administered and tumour response, have also been associated with elevated anxiety [30]. Anxiety is experienced by patients with anticipatory nausea and vomiting (ANV), a phenomenon that results from a classical conditioning process by which stimuli repeatedly associated with chemotherapy end up producing nausea and emesis prior to treatment administration. Anxious patients seem to develop anticipatory nausea and vomiting more frequently than non-anxious patients [31]. In these cases, patients may feel nauseous or vomit the week/day before treatment, as they approach the clinic, or even just thinking about chemotherapy.

2.4. *Screening and assessment*

Optimal management of anxiety disorders requires a comprehensive assessment and an accurate diagnosis. The distinction between normal fears and more severe fears that reach criteria for an anxiety disorder is not always clear in the cancer setting. According to Nicholas [32], patients with normal worry compared to those with more serious symptoms of anxiety disorders have only some difficulty concentrating, are able to 'turn off thoughts' most of the time, have occasional trouble falling asleep, and crying spells that seem to provide relief, and have few, if any, physical symptoms such as dry mouth, restlessness or racing heart. Worry comes and goes in this group of patients. On the other hand, patients with severe anxiety symptoms are unable to concentrate and to 'turn off thoughts' most of the time, have sleep problems most nights as well as crying spells that interfere with daily activities, experience constant worries and have few ways of reducing anxiety. It is important to understand the extent to which anxiety interferes with daily living and quality of life.

Psychometric instruments may be used to complement the clinical interview when assessing anxiety. The scales most frequently used with cancer patients include:

- hospital anxiety and depression scale (HADS) [33], which is a 14-item scale measuring symptoms of clinical depression and anxiety;
- brief symptom inventory (BSI) [34], which is an 18-item scale measuring somatisation, depression, anxiety and general distress;
- profile of mood states (POMS) [35], which is a 65-item scale measuring six mood states: anxiety, fatigue, confusion, depression, anger, vigour;
- state-trait anxiety inventory (STAI) [36], which is a 40-item measure that indicates the intensity of feelings of anxiety; STAI differentiates between state anxiety (a temporary condition experienced in specific situations) and trait anxiety (a general tendency to perceive situations as threatening);
- distress thermometer and problem list, which consists of a 0–10 scale to measure distress that is accompanied by a problem list in which patients are asked to note the nature and source of their distress (physical, social, psychological or spiritual) [37].

Self-report screening instruments must be scored, evaluated and discussed with each patient, and are useful in providing the oncology team with notions of how anxious the patient is.

2.5. *Treatment of anxiety disorders*

Psychosocial adjustment to cancer is an ongoing process in which the patient tries to manage emotional distress, solve specific cancer-related problems, and gain control over cancer-related events [38]. The purpose of treatment for anxiety in cancer patients is to facilitate successful adjustment to the disease: i.e. to help them minimise disruptions to life roles, regulate emotional distress and remain actively involved in aspects of life that continue to hold meaning and importance to them [11]. The average patient receiving psychosocial intervention for anxiety is less anxious than those not receiving the intervention. The overall positive benefit for psychosocial interventions seems to be greater with those who seem to need it most [39].

Treatment of anxiety should be multimodal, including a combination of pharmacotherapy and different psychotherapeutic interventions. Holland et al. [40], in a randomised study, compared relaxation with alprazolam in the treatment of anxiety and distress in cancer patients. Findings demonstrated both treatments to be equally effective for mild to moderate degrees of anxiety or distress. Alprazolam was more effective for greater levels of anxiety or distress, and had a more rapid onset of the beneficial effect.

Medication is only considered when patients experience severe symptoms, when their anxiety does not respond to psychological intervention and/or when there are no psychosocial services available or the patient refuses to use them. Massie and Shakin [20] describe clear guidelines for the use of pharmacotherapy to treat anxiety in the oncology setting. The choice of benzodiazepine depends on the desired half-life, route of administration available, route of metabolism and the presence or absence of active metabolites. They suggest that drugs with shorter half-lives, multiple routes of administration and no active metabolites are preferable in the medically ill patient, as well as the use of low-dose antipsychotic medications in patients with severe anxiety when treatment with benzodiazepine has not been effective. Benzodiazepines are not indicated in patients with medical conditions such as delirium, because they may exacerbate confusion and disorientation. In any case, use of these agents should be closely monitored and anxiety symptoms re-evaluated, medication being tapered off as symptoms subside [41].

Psychological approaches in the treatment of anxiety include combinations of cognitive behavioural therapy (for example, calming self-talk), insight-oriented and supportive psychotherapy, crisis intervention, support and self-help groups, and relaxation-based interventions such as hypnosis, meditation, progressive relaxation, guided imagery and biofeedback. All have been proven to be effective in reducing anxiety in the cancer patient [42–46].

Different psycho-educational interventions are equally useful. They have aimed at replacing the sense of helplessness with a sense of control, and in the process, reducing psychological distress [16]. For example, a booklet with disease-related information was provided to patients with Hodgkin's disease, and these patients experienced more reductions in their levels of anxiety than those who did not receive the booklet [47]. Psychoeducational interventions might be provided by the physician and/or nurse, through accurate medical information and support. Anxiety related to medical procedures may be reduced by adequate preparation by a staff member, such that the patient will most likely have more realistic expectations about the procedure.

Regardless of the treatment modality employed to reduce anxiety in the cancer setting, organic causes of symptoms must be discarded prior to initiation of the intervention, and if detected, their correction should be a priority.

2.6. Sleep disorders

Sleep disorders are a common symptom of anxiety, one of the most prominent concerns of cancer patients [48], and one of the main reasons for consultation in oncology [49]. In the general population, people with insomnia report more medical problems than those without insomnia [50]. Altered sleep usually has a profound adverse effect on emotional, cognitive and physical functioning.

Sleep consists of two phases: rapid eye movement (REM) sleep and non-REM (NREM) sleep [51]. REM sleep is the active or paradoxical phase of sleep in which the brain is active. It is also known as dream sleep. NREM sleep is the restful phase of sleep. Both phases alternate in a repeated pattern or cycle of NREM followed by REM, with each cycle lasting approximately 90 min. The sleep–wake cycle is dictated by an inherent biological clock or circadian rhythm. Disruptions in individual sleep patterns can disrupt the circadian rhythm and impair the sleep cycle [52].

2.7. Categories of sleep disorders

The American Academy of Sleep Medicine [53] has defined five categories of sleep disorders:

- disorders of initiating and maintaining sleep: insomnias;
- sleep-related breathing disorders: sleep apnoea;
- disorders of excessive somnolence: hypersomnias;
- disorders of the sleep–wake cycle: circadian rhythm sleep disorders;
- dysfunctions associated with sleep, sleep stages, or partial arousals: parasomnias.

2.8. Sleep disorders in cancer patients

Sleep disturbances occur in about 10–15% of the general population [54] and are often associated with situational stress, disease, ageing and drug treatment [55]. Between one third and one half of cancer patients experience sleep disorders [56]. These are usually associated with pain, hospitalisation, medication, recurring thoughts about the disease and cancer-related fears. Anxiety and depression have been found to be highly correlated with insomnia [56]. Alterations in the sleep–wake cycle can be early signs of delirium.

However, insomnia is often under-recognised and undertreated, partly because it has been seen as a normal and transient reaction to cancer and cancer treatment, and partly because sleep disturbances are under-reported by patients [57]. Patients with cancer report insomnia, poor sleep quality and short sleep duration [58]. Sleep disturbances can persist in time, with a significant number of cancer survivors reporting them as one of the most pervasive problems they face.

Reports over the past 20 years have begun to shed light on the putative relationship between cancer-related sleep disorders and cancer-related fatigue. While most of the studies in this area are correlative in nature, it is generally the case that sleep disturbance is: (a) positively correlated with fatigue, (b) more severe in fatigued than in non-fatigued patients and (c) a significant predictor of fatigue [58–60]. Current understanding of the possible link between cancer-related fatigue and sleep disturbances suggests that interventions targeting sleep disorders and daytime sleepiness could provide promising potential treatments for cancer-related fatigue. Targeted treatment of either symptom may possibly affect the other, given the emerging data suggesting that sleep disturbance is common in patients with cancer and that it may be both a cause and an effect of fatigue [58].

The following risk factors have been described for sleep disorders in cancer patients [61]:

- disease factors, including paraneoplastic syndromes with increased steroid production, and symptoms associated with tumour invasion (i.e. pain, fever, shortness of breath) [62];
- treatment-related factors, including symptoms associated with surgery (i.e. pain, use of opioids and frequent monitoring) [62];
- chemotherapy administration (i.e. exogenous corticosteroids);
- medications such as opioids, sedatives/hypnotics, steroids, some antidepressants and dietary supplements [63];
- environmental factors (i.e. hospital routines and roommates, environmental noise) [64];
- physical and/or psychological stressors [57];
- anxiety and depression [56];
- delirium.

In addition to considering the above risk factors, an adequate assessment of sleep disorders should evaluate the usual patterns of sleep, including usual bedtime, routine before retiring, length of time before onset of sleep and duration of sleep (waking episodes during the night, ability to resume sleep and usual time for awakening). Characteristics of disturbed sleep (changes following diagnosis, treatment and/or hospitalisation), perception of significant others as to quantity and quality of patients' sleep, and family history of sleep disorders should be taken into account, together with emotional status, exercise and activity levels, diet and care-giver routines [53].

Some studies link sleep with natural killer cell activity [65] and conclude that sound sleep may be important for immune defence against tumour cells [66].

2.9. Treatment of sleep disorders

Multiple psychological interventions – ranging from individual supportive psychotherapy to cognitive behavioural techniques (biofeedback, hypnosis, progressive muscle relaxation) – have proven to be effective in the control of anxiety and sleep disorders [67], and may be combined with pharmacological interventions. Several large randomised trials and meta-analysis have demonstrated the efficacy of cognitive behavioural therapy for insomnia in patients without cancer [68,69] as well as in the cancer population [70–72].

Components of cognitive behavioural therapy (CBT) include:

- cognitive restructuring, such as restructuring negative thoughts, beliefs and attitudes related to sleep, and preventing excessive monitoring or worrying about getting enough sleep [68];

- behavioural strategies including stimulus control and sleep restriction in order to limit the time spent in bed during which the patient does not sleep [68];
- relaxation techniques that can be combined with both cognitive and behavioural interventions are quite useful when accompanied by visual imagery;
- basic sleep hygiene education includes suggesting the following to the patient: sleeping and waking up at regular times, relaxing at least 90 min before going to bed; creating a dark, comfortable sleep environment with a cool temperature, avoiding watching television, using a laptop, or working in bed, getting ample daylight during non-sleep hours, avoiding day naps, avoiding stimulants such as caffeine, nicotine and cigarettes 2–3 h before bedtime, avoiding intake of liquids 2 h prior to sleeping, and getting regular exercise but no closer than 3 h before bedtime.

In one study, 30 cancer patients were assigned to either a three-session relaxation programme or no treatment. Patients receiving relaxation training reported reductions in sleep latency [70]. Espie et al. [72] found CBT to be associated with mean reductions in wakefulness of 55 min per night compared with no change for the care as usual group for persistent insomnia in patients with cancer. Results were sustained 6 months after treatment. Standardised relative effect sizes were large for complaints of difficulty initiating sleep, waking from sleep during the night and for sleep efficiency (percentage of time in bed spent sleeping). CBT was associated with moderate to large effect sizes for five of seven quality-of-life outcomes, including significant reduction in daytime fatigue. No significant interaction was found between any of these outcomes and baseline demographic, clinical or sleep characteristics. Savard et al. [71] studied 57 women with insomnia caused or worsened by breast cancer. Patients in the treatment group participated in CBT group sessions during eight weekly sessions of 90 min duration each, led by a psychologist. Sustained reductions in sleep latency and wakefulness were observed after CBT compared with controls. There was no increase in total sleep, but increases in sleep efficiency (proportion of time in bed spent asleep) averaged 15%.

Long-term pharmacological treatment is not desirable, especially when fatigue is an issue [73,74]. Despite this, 25% of cancer patients have been reported to take sleeping pills on a regular basis [66], and approximately 25–50% of all prescriptions written for patients with cancer are for hypnotics [75]. In cases where CBT is not available, has not been successful, or when patients have comorbidities contributing to sleep disturbances (i.e. pain, hot flashes, depression, etc.), then pharmacological treatment will be necessary. Several types of medication are used to treat disturbed sleep [61]: non-benzodiazepine benzodiazepine receptor agonists, benzodiazepines, melatonin receptor agonists, antihistamines, antidepressants and antipsychotics that have sedative effects, and melatonin. Most of the approved sleep aids have not been studied in cancer populations; therefore the risk/benefit profiles of these drugs are not delineated in this setting.

3. Conclusion

Patients with cancer report elevated levels of anxiety and sleep disturbances that may intensify throughout the disease course. Symptoms are frequently underestimated, despite the enormous adverse impact they have on patients' quality of life. Adequate assessment of symptoms is imperative and should identify medical as well as non-medical variables influencing or causing anxiety or sleep disturbance, in order to obtain optimal symptom management. Psychotherapeutic techniques such as CBT have proved to be effective in controlling both anxiety and sleep disturbances. However, the most effective intervention for both anxiety and sleep disorders is that which combines psychotherapeutic techniques with pharmacological treatment, when necessary.

Conflict of interest statement

None declared.

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