Fatigue and Disrupted Sleep-Wake Patterns in Patients With Cancer: A Shared Mechanism

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Cancer-related fatigue (CRF) is a significant clinical problem that occurs across the spectrum of cancer diagnoses, major cancer therapies, and the entire illness trajectory. CRF is highly prevalent not only among patients undergoing cancer treatment but also cancer survivors (Alexander, Minton, Andrews, & Stone, 2009; Barbera et al., 2010; Byar, Berger, Bakan, & Cetak, 2006; Curt et al., 2000; Davidson, MacLean, Brundage, & Schulze, 2002; Flechtner & Bottomley, 2003; Fleming, Gillespie, & Espie, 2010; Johansson, Wilson, Brunton, Tishelman, & Molassiotis, 2010; Kirkova et al., 2010; Langeveld, Grootenhuis, Voute, de Haan, & van den Bos, 2003; Quick & Fonteyn, 2005; Reinertsen et al., 2010). Disrupted sleep patterns often are concurrent with fatigue in cancer; an estimated 31% of fatigued patients with cancer experience frequent insomnia (Sarna, 1993). Fatigue and disrupted sleep affect all aspects of life for patients with cancer (Alexander et al., 2009; Byar et al., 2006; Davidson et al., 2002; Fleming et al., 2010; Fortner, Stepanski, Wang, Kasprowicz, & Durrence, 2002; Grunfeld & Cooper, 2010; Redeker, Lev, & Ruggiero, 2000; Rosedale & Fu, 2010; Scott, Lasch, Barsevick, & Piault-Louis, 2011). Their coexistence heightens symptom distress (Sarna, 1993) and further decreases the patient’s ability to function. As a consequence, quality of life suffers. Fatigue and disrupted sleep are severely impairing, and neither symptom has been controlled fully in patients with cancer, largely because of a lack of knowledge about the underlying mechanisms.

The growing recognition of symptom clusters (Cleeland et al., 2000; Dodd, Miaskowski, & Lee, 2004) has led to speculation of common biologic pathways underlying some of the symptoms related to cancer (Cleeland et al., 2003; Lee et al., 2004). In addition to the frequent co-occurrence of fatigue and disrupted sleep, the two symptoms demonstrate a strong and possibly reciprocal relationship (Pud et al., 2008; Roscoe et al., 2007). Patients with CRF are more susceptible to sleep problems than their nonfatigued counterparts (Alexander et al., 2009; Davidson et al., 2002; Okuyama et al., 2001), and higher CRF levels are associated with more sleep disturbances (Alexander et al., 2009; Andrykowski, Curran, & Lightner, 1998; Berger, 1998; Berger & Farr, 1999; Berger & Higginbotham, 2000; Cheng & Lee, 2011; Davidson et al., 2002; Okuyama et al., 2001; Redeker et al., 2000).
Therefore, disrupted sleep has been suggested as one of the possible mechanisms underlying CRF (Miaskowski & Lee, 1999).

With the speculation that disrupted sleep may contribute to CRF, this article provides an overview of the biobehavioral interactions of fatigue and disrupted sleep-wake patterns in cancer. A shared physiologic pathway underlying CRF and disrupted sleep-wake circadian rhythms is presented as derived from synthesis of the literature. Based on the hypothesized neuroendocrine pathways for stress (Sephton & Spiegel, 2003; Spiegel & Sephton, 2001), cancer-associated stressors may alter the circadian function of the HPA axis and result in the symptoms of fatigue and disrupted sleep-wake patterns in cancer.

The primary databases used for the literature search were PubMed and CINAHL®. The terms, cancer, fatigue, sleep disturbance, circadian rhythms, chronic-fatigue syndrome, mechanisms, pathophysiology, biological pathway, stress, and hypothalamus-pituitary-adrenal (HPA) axis, were used separately or together for the search. Search results were limited to studies involving adults, English language, and published from 1980 to 2011. Additional articles were obtained from references, books, and book chapters. The articles retrieved for the review included studies focused on HPA axis-related fatigue mechanisms and studies that were most often cited as references across stress and chronic fatigue syndrome literature.

Disrupted Sleep-Wake Patterns and Fatigue

Current knowledge of disrupted sleep-wake patterns in patients with cancer, including difficulty falling asleep, increased amount and duration of nighttime awakenings, waking up earlier than intended, and excessive daytime sleepiness, has been obtained mainly by subjective reports from women with breast cancer who had completed (Carlson, Campbell, Garland, & Grossman, 2007; Palesh et al., 2007; Savard, Simard, Blanchet, Ivers, & Morin, 2001) or were undergoing major cancer treatment (Beck et al., 2010; Berger, 1998; Berger & Farr, 1999; Berger & Higginbotham, 2000; Enderlin et al., 2011; Fortner et al., 2002; Kuo, Chiu, Liao, & Hwang, 2006). Objective data obtained by actigraphy have shown that patients with cancer experiencing restless sleep at night were less active during the day and experienced more intense fatigue (Berger, 1998; Berger & Farr, 1999; Berger & Higginbotham, 2000; Mormont et al., 2000), and that fatigued patients experienced significantly longer sleep latency (difficulty in falling asleep) and more frequent and longer nighttime awakenings than their nonfatigued counterparts (Alexander et al., 2009). Frequent nighttime awakenings, in particular, were pervasive among women during the course of chemotherapy and were associated with more daytime napping, less daytime activity, and higher levels of CRF (Berger, 1998; Berger & Farr, 1999; Berger & Higginbotham, 2000). The actigraphy data showed about half of the patients had 10 or more awakenings per night (Beck et al., 2010).

A limited number of studies using polysomnography (PSG), the gold standard for measuring specific sleep and wake states (de Souza et al., 2003; Parker et al., 2008), further validated the aberration in sleep-wake patterns in patients with various types of cancer. The findings generally support that, although patients with cancer slept about the same amount of time as those without cancer (Parker et al., 2008; Silberfarb, Hauri, Oxman, & Schnurr, 1993), patients with cancer tended to stay in bed longer, and their sleep was characterized by prolonged sleep onset latency (X = 37–63.3 minutes), decreased sleep efficiency (the ratio of time asleep to total time in bed) (X = 76%–85%), increased proportion of light sleep (11%–21% of total sleep time [TST]), prominent decrease in delta sleep (deep slow wave sleep stage) (0.3%–4% of TST), and reduced rapid eye movement (REM) sleep (15%–18% of TST) (Parker et al., 2008; Silberfarb, Hauri, Oxman, & Lash, 1985; Silberfarb et al., 1993). The noticeable prolonged REM latency (prolonged time to reach REM sleep) of 129 minutes also was observed (Parker et al., 2008). The objective findings of being awake about 25% of the night time, with an average of six awakenings lasting at least 60 seconds, and more than 60 brief awakenings per hour (Parker et al., 2008) confirm the prominent problem in night time sleep maintenance reported by patients with cancer.

The PSG data provide an in-depth understanding of the types of disruptions in sleep-wake cycles. The frequent awakenings, increased stage 1 sleep (transition to sleep), and prolonged sleep onset latency all contribute to the subjective complaints of poor sleep quality among patients with cancer. Among the sleep stages, delta sleep mainly occurs in the first half of the sleep period in most adults (Culebras, Lee-Chiong, Sateia, & Carueadan, 2002; Parker et al., 2008). The dramatic decrease in the amount of delta sleep observed in patients with cancer, coupled with prolonged REM latency, indicates that the greatest disruption may occur during the first half of the night in which non-REM sleep predominates. Fragmented sleep can be particularly problematic during the first two nocturnal sleep cycles, as delta sleep usually disappears beyond the second sleep cycle (Culebras et al., 2002). In most adults, large amounts of growth hormone are secreted during delta sleep (Culebras et al., 2002); therefore, deprivation of delta sleep may result in growth hormone depletion and may be associated with reduced tissue growth and repair (Culebras et al., 2002) and impaired memory (Zerouali, Jemel, & Godbout, 2010). Silberfarb et al. (1985) reported that the perception of sleep quality was determined by the amount of delta sleep patients with cancer experienced. Delta sleep is believed to dissipate the need for sleep (Parker et al., 2008). Therefore, lack of delta sleep may increase the need for sleep and contribute to the subjective feeling of nonrefreshing or nonrestorative sleep, which is a prominent characteristic of CRF (Cella, Davis, Breitbart, & Curt, 2001; Portenoy & Itri, 1999; Sadler et al., 2002; Van Belle et al., 2005).

Decreased amounts of nocturnal delta sleep also were associated with increased amounts of daytime sleep (Parker et al., 2008). Patients with cancer were found to nap as much as 20% of the day with an average of more than 12 brief naps per hour (Parker et al., 2008). Although their daytime sleep was mainly stage 2 non-REM sleep, about 4% of REM sleep occurred, particularly in the midafternoon (Parker et al., 2008). Daytime REM sleep is unusual in healthy individuals, particularly in the afternoon. Deprivation of delta sleep may play a major role in fatigue in patients with cancer (Berger, 1998; Berger & Farr, 1999; Berger & Higginbotham, 2000; Mormont et al., 2000).
Whether the problem of nocturnal awakenings proportionally occurs across the night or is more frequent during a specific time period is largely unknown because of the limited PSG data in patients with cancer. The type, as well as the timing, of disruptions in sleep-wake cycles are important because they may be associated with the symptomology of CRF (i.e., physical, emotional, and cognitive fatigue); also, different disruptions require different interventions. Information on daytime sleepiness, as part of the 24-hour sleep-wake pattern, is lacking, possibly because of the difficulty in distinguishing sleepiness from fatigue.

**Altered Circadian Rhythms and Chronic Stress**

The circadian sleep-wake rhythm is a marker of circadian function (Sephton & Spiegel, 2003). Disruption in the sleep-wake cycle is indicative of a circadian aberration, which has been associated with the incidence, progression, and prognosis of cancer (Sephton & Spiegel, 2003), and may underlie some of the cancer symptoms. Disruptions in the circadian system are evident in tumor tissue, with greater disruption observed in patients with more advanced cancer (Sephton & Spiegel, 2003).

Circadian rhythm alterations manifest as a loss of regulatory competence of stress response pathways, including the HPA axis and autonomic nervous system (Sephton & Spiegel, 2003). The HPA axis is the primary neuroendocrine interface responding to a physiologic or psychological challenge and coordinates the nervous and endocrine systems to maintain homeostasis in all body systems (Payne, 2004). The HPA axis is activated by stress (Dallman, 1993) and is the long-term mediator of the stress response (Cleare & Wessely, 1996). In response to a variety of physical and psychological stressors, corticotropin-releasing hormone (CRH) is produced and released. CRH acts via adrenocorticotropic hormone (ACTH) from the anterior pituitary gland to stimulate glucocorticoid (including cortisol) secretion (Raison & Miller, 2003) from the adrenal cortex. Cortisol increases the breakdown of glycogen and tissue protein to provide energy sources and maintain homeostasis under stressful conditions (Caudaell, 2000).

Activation of the HPA axis is an adaptive response to acute stress to protect and restore the body (McEwen, 1998). In response to acute stress, the HPA axis may exhibit spontaneous changes in basal circadian rhythm, a rapid increase in activity in response to stress, and feedback regulation by adrenal corticosteroid (Dallman, 1993). In the face of prolonged stress, those characteristics may be altered and lead to adverse physiologic consequences (McEwen, 1998). The diagnosis of cancer, the physiologic and psychological adjustment to the prognosis and treatment, and the disruption of social functioning all are sources of stress that often become chronic. In addition, the cancer’s cause and its treatment directly or indirectly may alter the function of the HPA axis, resulting in changes within the neuroendocrine system. Compelling evidence exists to suggest that disruptions in HPA function induce important biologic and behavioral consequences (Spiegel & Sephton, 2001), and, in part, may be responsible for some cancer symptoms (Aists, 1987). In addition, cancer-related symptoms are likely to increase the impact of distress or induce changes in rhythms of HPA axis activity (Sephton & Spiegel, 2003; Spiegel & Sephton, 2001) and, therefore, contribute further to the cycle of deterioration.

**Circadian Dysregulation and Chronic Fatigue Syndrome**

In the absence of knowledge about the underlying CRF mechanisms, emerging biologic models from chronic fatigue syndrome may facilitate the initial understanding of CRF’s cause. HPA aberrations have long been associated with chronic fatigue syndrome. Symptom overlap between chronic fatigue syndrome and CRF, including disabling fatigue, unrefreshing sleep, impaired short-term memory, diminished concentration, and postexertion malaise (Cella et al., 2001; Fukuda et al., 1994; Portenoy & Itri, 1999; Sadler et al., 2002; Van Belle et al., 2005), indicates that chronic fatigue syndrome and CRF may represent symptomologic variants of the same underlying pathophysiology. Like sleep disruption, the onset and exacerbation of chronic fatigue syndrome are linked to a variety of physical or emotional stressors (Cleare & Wessely, 1996; Demitrack, 1997; Demitrack & Crofford, 1998) and HPA axis aberrations (Cleare & Wessely, 1996; Demitrack, 1997; Demitrack & Crofford, 1998). Among several competing hypotheses, hypocortisolism, in particular, is the suggested mechanism underlying chronic fatigue syndrome (Demitrack, 1997; Demitrack & Crofford, 1998, Heim, Ehlert, & Hellhammer, 2000).

In a landmark study examining HPA axis dysregulation in chronic fatigue syndrome, Demitrack et al. (1991) reported a mild glucocorticoid deficiency in patients with chronic fatigue syndrome. Evening basal total and free cortisol levels and 24-hour free cortisol urinary excretion were significantly decreased, although evening basal ACTH levels were increased. Hypocortisolism has been reported not only in individuals with chronic or acute fatigue (Potelakhoff, 1981), but also among breast cancer survivors (Bower, Ganz, Aziz, & Fahey, 2002). In contrast, some studies have shown normal or higher levels of cortisol in chronic fatigue syndrome and in patients with metastatic breast cancer when compared with healthy controls (Crofford et al., 2004; Dinan et al., 1997; Giorgio, Hudson, Jerjes, & Cleare, 2005; Scott, Medbak, & Dinan, 1998b; van der Pompe, Antoni, & Heijnen, 1996). Table 1 summarizes the studies of cortisol patterns in patients with cancer or chronic fatigue syndrome.

The discrepancies in basal cortisol levels probably reflect two major methodologic issues. First, most researchers of cancer or chronic fatigue studied patients with a heterogeneous psychiatric history and did not exclude individuals with depressive illness. Although the symptoms of depression overlap with fatigue, previous studies note hyperactivity of the HPA axis in depression and, conversely, hypofunction of the HPA axis in chronic fatigue syndrome (Griep, Boersma, & de Kloet, 1993; Scott & Dinan, 1998, 1999).

Patients with depression often show increased, rather than reduced, glucocorticoid levels (Leonard, 2010; Scott & Dinan, 1998). Neuroendocrinologic evidence from clinical trials of selective serotonin reuptake inhibitor antidepressants proved to be ineffective in improving fatigue in either patients with cancer or chronic fatigue syndrome (Morrow et al., 2003; Roscoe et al., 2005; Versouw et al., 1996), suggesting that fatigue and depression are discrete conditions and may each have a
### TABLE 1. Diurnal Cortisol Patterns in Patients With Cancer and Chronic Fatigue

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<th>Sample</th>
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<tr>
<td>Abercrombie et al., 2004</td>
<td>Salivary cortisol on three consecutive days at four time points: waking, noon, 5 pm, and 9 pm.</td>
<td>17 female patients with metastatic breast cancer with a mean age of 57.6 years 31 healthy female controls with a mean age of 56 years All forms of psychopathology were excluded (criteria not given).</td>
<td>Patients with cancer had a flatter diurnal slope of cortisol than controls. No differences were noted between groups in cortisol levels for any time of day. Patients with more severe metastatic spread showed higher mean cortisol levels and flatter diurnal cortisol slopes. Cortisol was not related to psychological measures.</td>
<td>Metastatic disease is associated with dysregulated cortisol function. The cortisol diurnal slope may have important, but different, correlates in healthy women versus those with breast cancer.</td>
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<td>Bower et al., 2002</td>
<td>Plasma cortisol within a two-hour time period in the morning (e.g., 8–10 am)</td>
<td>40 female early-stage breast cancer survivors: 20 were fatigued women with a mean age of 57.1 years, and 20 were nonfatigued women with a mean age of 58.4 years. Psychiatric conditions were excluded (criteria not given).</td>
<td>Fatigued women had lower serum cortisol levels than the nonfatigued women.</td>
<td>Cortisol levels were lower during the typical morning peak, suggesting dysregulation of the immune system normally regulated by inhibitory mechanisms, including negative feedback by glucocorticoids in breast cancer survivors with fatigue.</td>
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<td>Bower, Ganz, Dickerson, et al., 2005</td>
<td>Salivary cortisol four times a day for two consecutive days</td>
<td>29 women with early-stage breast cancer: 13 were fatigued with a mean age of 58.2 years; 16 were nonfatigued with a mean age of 61.8 years. Psychiatric conditions were excluded (criteria not given).</td>
<td>Fatigued survivors had flatter cortisol slopes than nonfatigued survivors; fatigued survivors had high cortisol levels at 10 pm. Higher current fatigue was associated with flatter slopes. Mean daily cortisol levels as well as overall secretion of cortisol did not differ between groups.</td>
<td>Fatigued breast cancer survivors had a flatter cortisol slope that nonfatigued survivors, with a less rapid decline in evening hours. Findings suggest subtle dysregulation in HPA axis among fatigued breast cancer survivors.</td>
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<td>Crofford et al., 2004</td>
<td>24-hour urine collection for free cortisol for three days; plasma ACTH and cortisol every 10 minutes for 24 hours beginning at 9 am.</td>
<td>15 patients with CFS: 4 men and 11 women with a mean age of 35 years 12 patients with CFS and fibromyalgia: 12 women with a mean age of 37.4 years 13 patients with fibromyalgia: 13 women with a mean age of 49.8 years 39 gender and age-matched healthy controls for each patient group: 4 men and 35 women, mean age of 40.8 years Excluded patients met criteria for major axis 1 psychiatric disorder by SCID (anxiety, panic, somatoform disorders, or history of depression).</td>
<td>Higher UFC in patients with CFS compared to controls. All subjects’ ACTH and cortisol levels increased in the early morning and decreased thereafter. Patients with CFS had lower cortisol compared to controls. No significant difference in ACTH to cortisol ratios was noted between patients and controls. A significant delay in decline of cortisol was found in all patient groups compared to controls.</td>
<td>Depressed early morning cortisol levels in patients with CFS suggest hypoactive HPA axis. Patterns of basal circadian HPA hormones differ in some respects in each patient group compared with controls.</td>
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<td>Giorgio et al., 2005</td>
<td>Plasma ACTH and cortisol every hour during daytime (10 am–10 pm) and every 15 minutes (10 pm–10 am) for a 24-hour period</td>
<td>15 patients with CFS: 6 men and 9 women with a mean age of 38.7 years. 10 age-, weight-, and body mass index-matched healthy controls: 3 men and 7 women with a mean age of 38.3 years Psychiatric disorders excluded (DSM-IV).</td>
<td>Significant diurnal fluctuations existed in ACTH and cortisol levels. Patients with CFS showed reduced ACTH levels over 24 hours. Lower ACTH from 8 am–10 am or earlier meant acrophase with a phase advance of 38 hours. Higher 24-hour and overnight cortisol levels were noted in patients with CFS compared to controls.</td>
<td>Patients with CFS demonstrated subtle alternation in HPA axis characterized by reduced ACTH over a full circadian cycle and reduced levels during the usual morning physiologic peak.</td>
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AC—cyclophosphamide and doxorubicin; ACTH—adrenocorticotropic hormone; CDC—Centers for Disease Control and Prevention; CFS—chronic fatigue syndrome; CRH—corticotropin-releasing hormone; DSM—Diagnostic and Statistical Manual; HPA—hypothalamus-pituitary-adrenal; SCID—severe combined immunodeficiency disease; UFC—urinary free cortisol excretion, WHO—World Health Organization
TABLE 1. Diurnal Cortisol Patterns in Patients With Cancer and Chronic Fatigue (Continued)

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<tr>
<th>Study</th>
<th>Methods</th>
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<th>Findings</th>
<th>Conclusions</th>
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<tr>
<td>Palesh et al., 2008</td>
<td>Salivary cortisol at waking, 30 minutes after waking, noon, 5 pm, and 9 pm on 2 consecutive days</td>
<td>99 women with metastatic breast cancer: 85% were Caucasian with a mean age of 54.6 years, 39% were taking antidepressant medication, and 19% were taking sleep medication. Depression diagnosis (by the structured clinical interview for DSM-IV) was not excluded.</td>
<td>A flatter cortisol slope correlated with a longer nocturnal wake episode.</td>
<td>Association was noted between disrupted nocturnal sleep and flattened diurnal cortisol rhythm in women with metastatic breast cancer.</td>
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<td>Payne et al., 2006</td>
<td>Serum cortisol at 4 am and 7 am on cancer treatment day and the day after cancer treatment during cycle 1 and cycle 4</td>
<td>11 women with stage II breast cancer receiving AC every three weeks with a mean age of 47.4 years 11 age-, ethnicity- and menopausal status-matched cancer-free women with a mean age of 47.6 years No psychiatric screening was performed.</td>
<td>Cortisol levels decreased the day after cancer treatment in the cancer group but not in the control group. Significant differences in the cortisol levels were found between cancer and control groups on the day after chemotherapy.</td>
<td>Cortisol is a primary biomarker of the HPA axis that may alleviate stress, fatigue, and sleep disturbances.</td>
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<td>Poteliakhoff, 1981</td>
<td>Plasma cortisol measured at 9 am</td>
<td>25 fatigued patients (10 men and 15 women) with a mean age of 40 years 25 age-, gender-matched controls (10 men and 15 women) with a mean age of 40.2 years All participants were not depressed (criteria not given).</td>
<td>Cortisol levels were lower in fatigued patients compared to controls.</td>
<td>Mild adrenocortical insufficiency exists in patients with fatigue.</td>
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<td>Scott &amp; Dinan, 1998</td>
<td>24-hour urine collection period for free cortisol</td>
<td>21 patients with CFS (CDC criteria): 7 men and 14 women with a mean age of 36.1 years Five patients had major depression (DSM-IV). 10 patients with major depression (DSM-IV, melancholic subtype): 4 men and 6 women with a mean age of 43.4 years 15 healthy controls: 6 men and 9 women with a mean age of 33.4 years No past or current history of CFS or mental illness were noted.</td>
<td>High UFC values in depressed groups than controls. Low UFC values in CFS group than controls.</td>
<td>Hyperactivity of the HPA axis in depression and hyperactivity of the HPA axis in CFS exists. High cortisol in depression reflects abnormality in hypothalamus. Low cortisol of CFS results from decreased responsivity of CRH receptors and decreased ACTH production.</td>
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<td>Sephton et al., 2000</td>
<td>Salivary cortisol at 8 am, noon, 5 pm, and 9 pm on three consecutive days</td>
<td>104 women with metastatic breast cancer with a mean age of 53.2 years; most were Caucasian (90%), receiving hormonal treatment (69%), and estrogen receptor positive (78%). Depressive symptoms were not excluded.</td>
<td>37% of patients had normal diurnal rhythms, 49% had peaked diurnal cortisol rhythm, and 14% had no apparent peaks.</td>
<td>No association was found between area under the curve and survival cortisol slope. Failure of normal cortisol nadir at bedtime may disrupt sleep and cause further circadian disruption.</td>
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<td>Toutou et al., 1995</td>
<td>Plasma cortisol every 4 hours for 48 hours</td>
<td>13 women with metastatic breast cancer with a mean age of 52 years No psychiatric screenings were performed.</td>
<td>Patients with good WHO performance status or no liver metastasis displayed rhythms in cortisol. Suppressed cortisol rhythms were found in patients with liver metastasis with poor performance.</td>
<td>Patients with metastatic breast cancer who have poor prognostic factors may exhibit altered circadian rhythms.</td>
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<td>Toutou et al., 1996</td>
<td>Plasma cortisol every 4 hours for 24 hours (basal values recorded at 8 am)</td>
<td>13 women with metastatic breast cancer who had previous cancer treatment; mean age was 52 years (SD = 9), 10 women had bone metastases. 20 women with ovarian cancer; mean age was 55 years (SD = 12), cancer stage ranged from IIa–IV; 8 women had previous cancer treatment. No psychiatric screenings were performed.</td>
<td>For patients with breast cancer, 8 showed flattened profile, 5 had normal patterns, and 1 had high peak. For patients with ovarian cancer, 15 showed flattened profile and 5 had normal patterns (2 of whom had overall low cortisol concentration).</td>
<td>Altered cortisol circadian patterns are prevalent in breast and ovarian cancer, which consists of high levels along the 24-hour scale and/or erratic peaks and troughs and/or flattened profiles.</td>
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AC—cyclophosphamide and doxorubicin; ACTH—adrenocorticotropic hormone; CDC—Centers for Disease Control and Prevention; CFS—chronic fatigue syndrome; CRH—corticotropin-releasing hormone; DSM—Diagnostic and Statistical Manual; HPA—hypothalamus-pituitary-adrenal; SCID—severe combined immunodeficiency disease; UFC—urinary free cortisol excretion; WHO—World Health Organization
different pathophysiologic basis (Demitrack, 1997; Minton, Richardson, Sharpe, Hotopf, & Stone, 2008; Scott & Dinan, 1999). Therefore, the differences in the characteristics of altered HPA axis function with fatigue and depression may, in part, account for the inconsistent cortisol findings in the current literature. Second, the diverse measures of cortisol (e.g., plasma, urine, saliva) and time for samplings (e.g., morning, evening, mean 24-hour levels) also may explain inconsistent cortisol profiles in the current literature. Cortisol is regulated by an endogenously precise circadian pacemaker (Czeisler et al., 1999) and typically peaks before awakening and then decreases throughout the day (Posener, Schildkraut, Samson, & Schatzberg, 1996). Therefore, the time when cortisol is sampled must be considered, as levels of cortisol change over the 24-hour period.

A few studies considered the rhythms and attempted to measure cortisol across an entire 24-hour period to better project the HPA activity. Altered HPA axis patterns, in particular, flat diurnal cortisol rhythms and have been found in either patients with breast cancer, being fatigued, or living with chronic stress. Unlike healthy adults who typically show marked diurnal cortisol variation, patients treated for metastatic breast cancer had significantly flatter diurnal cortisol rhythms (Abercrombie et al., 2004; Sephton, Sapolsky, Kraemer, & Spiegel, 2000; Touitou, Bogdan, Levi, Benavides, & Auzepy, 1996). Similar flattened cortisol profiles also were observed in breast cancer survivors (Bower et al., 2005). Compared to nonfatigued breast cancer survivors, fatigued survivors exhibited a slower decline in salivary cortisol during the evening hours (Bower et al., 2005). Those who reported the worst fatigue had the flattest cortisol profiles (Bower et al., 2005). In addition, a flattened diurnal cortisol rhythm was associated with the accumulated effects of chronic stressors (Abercrombie et al., 2004). Premenopausal, middle-aged women living with chronic stress had elevated evening salivary cortisol relative to nonstressed women (Powell et al., 2002). Flatter diurnal cortisol rhythms were associated with higher marital distress, more nocturnal awakenings, and earlier mortality in patients with metastatic breast cancer (Sephton et al., 2000). The failure of a normal cortisol nadir at bedtime may have disrupted sleep and, therefore, caused further circadian disruption, resulting in long-term health consequences (Sephton et al., 2000).

Although the cortisol rhythm is closely related to ACTH rhythm (Touitou et al., 1996), even less evidence exists regarding basal ACTH patterns. An overall reduction in ACTH release with reduced amplitude has been found in studies of chronic fatigue syndrome (Giorgio et al., 2005). The altered ACTH circadian pattern was characterized by a blunting of the typical morning surge (Crofford et al., 2004; Giorgio et al., 2005) and an earlier circadian peak (Giorgio et al., 2005). Together, the studies revealed a robust aberration in the circadian rhythm of pituitary and adrenal gland secretion, indicating a subtle, central dysregulation in the HPA axis (Giorgio et al., 2005).

To specify the locus of the disruption in adrenal glucocorticoid secretion, studies have used experimental stressors (endocrine or behavioral challenges) to stimulate HPA reactions (see Table 2). The findings generally support attenuated cortisol responses following ACTH or CRH administration (Scott et al., 1998a, 1998b) or a blunted ACTH in response to exogenous CRH or its agonist in patients with chronic fatigue syndrome or with breast cancer (Demitrack et al., 1991; Dinan et al., 1997; Scott et al., 1998a; van der Pompe et al., 1996). Fatigued breast cancer survivors demonstrated a pronounced deficit in cortisol response to an experimental psychological stressor, whereas nonfatigued survivors had a fourfold increase in salivary cortisol (Bower, Ganz, & Aziz, 2005). Lower basal cortisol levels and blunted cortisol response to exogenous stimulation may be explained by lower cortisol reserve and synthesis resulting from adrenal gland atrophy, possibly caused by prolonged reduction in ACTH. Tomographic evidence has revealed a more than 50% reduction in adrenal gland bodies in patients with chronic fatigue syndrome with abnormal endocrine parameters (Scott et al., 1999) as a result of either pituitary or hypothalamic defects (Sternberg, 1993).

Although hypocortisolism is evident, the therapeutic effects of glucocorticoid agonists on fatigue are contradictory. Sternberg (1993) suggested that a higher origin of CRH deficiencies, rather than glucocorticoid deficiencies, result in fatigue states. CRH is a behaviorally-active neurohormone that serves as a principle stimulus not only to HPA activation but also for arousal and vigilance regulation (Sternberg, 1993). Central administration of CRH was shown to induce physiologic and behavioral arousal in animals (Brown et al., 1982). A subtle CRH deficiency theoretically can produce profound fatigue and exhaustion (Demitrack, 1997; Demitrack & Crofford, 1998; Sternberg, 1993) either through direct effects on the central nervous system or indirectly by causing a glucocorticoid deficiency (Demitrack, 1997; Scott & Dinan, 1999). In addition, CRH influences sleep-wake cycles (Vgontzas & Chrousos, 2002) by impairing sleep and elevating vigilance (Steiger, 2002). Peripheral administration of CRH significantly increased wakefulness and suppressed delta sleep during the first half of the night in middle-aged men (Vgontzas et al., 2001). Although speculation exists about the role of CRH in fatigue and disrupted sleep, no conclusion can be drawn from the literature.

Altered HPA rhythms have been observed among patients with breast cancer and chronic fatigue syndrome. Hypofunctioning of the HPA axis is being suggested as one of the potential pathophysiologic pathways for chronic fatigue in patients with breast cancer. The HPA axis alteration may be, in part, the result of a reduction in hypothalamic output of CRH or other secretagogues resulting from an impaired central nervous system drive (Demitrack, 1997; Demitrack & Crofford, 1998). The adaptive down-regulation of pituitary CRH receptors may fail to normalize, either as a consequence of prolonged stress (McEwen, 1998) or the subsequent reduction in CRH (Scott et al., 1998b). As a result, ACTH secretion is diminished and, ultimately, cortisol production is reduced (Heim et al., 2000).

Central Serotonin Dysregulation

A central serotonin dysregulation, in part from central nervous system impairment, also may be responsible for the abnormal HPA axis profiles observed in patients with chronic fatigue syndrome (Demitrack, 1997). A neurotransmitter family, including serotonin and melatonin, has been associated with a cluster of cancer symptoms (Payne, 2004). Melatonin and serotonin are critical for the regulation of the wake and sleep.
TABLE 2. Studies of Experimental Stressors to Stimulate HPA Axis Reactions

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<tr>
<td>Bower, Ganz, &amp; Aziz, 2005</td>
<td>TSST</td>
<td>Salivary cortisol</td>
<td>27 breast cancer survivors: 11 were fatigued with a mean age of 55.6 years and 16 were nonfatigued with a mean age of 61.7 years. Patients with current depression were excluded.</td>
<td>Adrenal: Salivary cortisol in fatigued patients showed a negligible change, whereas nonfatigued patients had a significant increase after the TSST. <strong>Autonomic:</strong> All participants showed increases in blood pressure and heart rate to TSST.</td>
<td>Fatigued survivors showed blunted cortisol/HPA response to psychological stress. The responsiveness of HPA axis may be altered among fatigued breast cancer survivors.</td>
</tr>
<tr>
<td>Bower et al., 2007</td>
<td>TSST</td>
<td>Salivary cortisol, serum monocytes, and lymphocytes</td>
<td>25 early-stage breast cancer survivors: 10 fatigued women with a mean age of 55 years, and 15 nonfatigued women with a mean age of 61.7 years. No psychiatric screening</td>
<td>Adrenal: Salivary cortisol in fatigued patients showed a negligible change, whereas nonfatigued patients had significant increase in response to TSST. <strong>Inflammatory cytokines:</strong> Changes in cortisol levels were negatively associated with interleukin-6 production.</td>
<td>Inadequate secretion of cortisol to stress may lead to exaggerated inflammatory response to challenge.</td>
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<tr>
<td>Demitrack et al., 1991</td>
<td>ACTH, ovine CRH</td>
<td>Basal: plasma ACTH and cortisol Adrenal: plasma cortisol Pituitary: plasma ACTH and cortisol Hypothalamus: cerebrospinal fluid, CRH, and ACTH</td>
<td>30 patients with chronic fatigue: 12 men and 18 women with a mean age of 36.9 years 6 or 12 patients, based on two different diagnostic criteria, had a lifetime history of major depression. 72 age-matched healthy controls: 43 men and 29 women with a mean age of 32.5 years Healthy controls had no history of chronic fatigue or current or past psychiatric illness.</td>
<td>Basal function: Patients with CFS showed significant reduction in basal total plasma cortisol, higher CBG binding and reduced free cortisol index. <strong>Adrenal:</strong> Low-dose ACTH groups showed significant cortisol responses, with attenuated responses to higher doses of ACTH. <strong>Pituitary:</strong> Net cortisol was slightly lower in patients with CFS binding capacity decreased, with dramatic increase in free cortisol index in both groups. <strong>Hypothalamus:</strong> No difference in CFS, CRH, and ACTH between patients and controls</td>
<td>Mild hypocortisolism was found in patients with CFS. Enhanced adrenocortical sensitivity to exogenous ACTH and blunted release of ACTH in response to CRH suggest a second glucocorticoid deficiency in CFS. CFS could be associated with impaired activation of hypothalamic CRH.</td>
</tr>
<tr>
<td>Dinan et al., 1997</td>
<td>Ipsapirone</td>
<td>Basal: plasma ACTH and cortisol Pituitary and adrenal: plasma ACTH and cortisol</td>
<td>14 patients with CFS: 6 men and 8 women with a mean age of 38 years 14 age- and gender-matched healthy controls with a mean age of 36.5 years No patients currently showed or had past history of major depressive disease.</td>
<td>Basal: Patients with CFS had normal, but slightly lower, baseline cortisol levels than controls. Patients had normal, but slightly lower, baseline ACTH levels than controls. <strong>Pituitary and adrenal:</strong> Patients showed lower ACTH and lower cortisol than controls. <strong>Cortisol feedback:</strong> Basal cortisol was correlated with ACTH changes in both groups.</td>
<td>Lower cortisol released in response to ACTH indicates a reduced adrenocortical secretory reserve. A reverse relationship exists between basal cortisol, suggesting super sensitivity of adrenocortical receptors to circulating ACTH, secondary to mild ACTH deficiency.</td>
</tr>
<tr>
<td>Griep et al., 1993</td>
<td>Human CRH, DXM</td>
<td>Basal: plasma ACTH and cortisol Pituitary: plasma ACTH and cortisol Cortisol feedback: fasting plasma cortisol</td>
<td>10 female patients with fibro-myalgia with a mean age of 38.4 years 10 matched healthy controls with a mean age of 36.9 years No screening for psychiatric illnesses</td>
<td>Basal function: No difference was found in ACTH and cortisol between groups. <strong>Pituitary:</strong> Patients had a significant release of ACTH post pituitary challenge, with no change in cortisol levels between groups. <strong>Cortisol feedback:</strong> All participants showed a cortisol value lower than 60 nmol/l (cortisol feedback was suppressed).</td>
<td>Hyper-reactive pituitary ACTH release and adrenal hyporesponsiveness were noted in reaction to post pituitary challenge tests. Enhanced ACTH response by post pituitary tests suggests hyperactive hypothalamic CRH.</td>
</tr>
</tbody>
</table>

ACTH—adrenocorticotropic hormone; CBG—corticosteroid-binding globulin; CFS—chronic fatigue syndrome; CRH—corticotropin-releasing hormone; DXM—dexamethasone; HPA—hypothalamus-pituitary-adrenal; TSST—Trier Social Stress Test

(Continued on the next page)
### TABLE 2. Studies of Experimental Stressors to Stimulate HPA Axis Reactions (Continued)

<table>
<thead>
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<th>Study</th>
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<td>Powell et al., 2002</td>
<td>DXM</td>
<td>Basal: salivary cortisol, urine cortisol, catecholamine, and testosterone</td>
<td>40 women with stress who had a mean age of 46.1 years. 20 age-, ethnicity-, and education-matched nonstressed women with a mean age of 45.3 years Patients with a history of psychiatric disorders were excluded.</td>
<td>Basal: Stressed women had higher levels of salivary cortisol, lower urinary cortisol, higher urinary catecholamine, and higher testosterone than controls. <strong>Post challenge:</strong> Stressed women had higher salivary cortisol than controls. Baseline cortisol of stressed women reduced by 31%, compared to 56% in controls.</td>
<td>Stress with elevated cortisol is a promising marker of chronic stress. Stressed women showed less suppression of salivary cortisol in response to cortisol challenge.</td>
</tr>
<tr>
<td>Scott et al., 1998a</td>
<td>Oxine CRH</td>
<td>Basal: plasma ACTH and cortisol Pituitary and adrenal: plasma ACTH and cortisol</td>
<td>14 patients with chronic fatigue: 6 men and 8 women with a mean age of 38.7 years No patients had current major depressive disorder; four had past history of depression. 14 age- and gender-matched healthy controls with a mean age of 33.1 years Healthy controls had no history of fatigue or psychiatric illness.</td>
<td>Basal: Patients with chronic fatigue exhibited higher baseline cortisol levels, but lower ACTH levels, than controls. <strong>Pituitary and adrenal:</strong> Patients with chronic fatigue showed lower ACTH and cortisol in response to pituitary challenge than controls. Change in ACTH levels was associated with cortisol controls. <strong>Cortisol feedback:</strong> Basal cortisols were inversely correlated with ACTH in patients and controls.</td>
<td>Patients with chronic fatigue released less ACTH in response to exogenous cortisol-releasing hormone. Prolonged ACTH reduction resulted in hypoplasia of adrenal gland and diminished adrenocortical secretory reserve.</td>
</tr>
<tr>
<td>Scott et al., 1998b</td>
<td>ACTH</td>
<td>Basal: plasma cortisol Adrenal: plasma cortisol</td>
<td>20 patients with chronic fatigue: 7 men and 13 women with a mean age of 32.9 years 3 patients with chronic fatigue had comorbid major depressive disease. 20 age-, gender-, and weight-matched healthy controls with a mean age of 28.2 years Healthy controls had no current or past history of fatigue or psychiatric illness.</td>
<td>Basal: Patients with chronic fatigue had higher baseline cortisol levels than controls. <strong>Adrenal:</strong> Patients with chronic fatigue showed lower cortisol changes when tested with ACTH than controls. <strong>Cortisol feedback:</strong> Patients with chronic fatigue had basal cortisol levels that were inversely correlated with change in cortisol after challenge test. In controls, basal cortisol levels were positively correlated with cortisol challenge test.</td>
<td>Lower cortisol release in response to ACTH indicates a reduced adrenocortical secretory reserve. A reverse relationship existed between basal cortisol and suggests supersensitive adrenocortical receptors to circulating ACTH, secondary to mild ACTH deficiency.</td>
</tr>
<tr>
<td>van der Pompe et al., 1996</td>
<td>Behavioral challenge test</td>
<td>Plasma cortisol, ACTH, prolactin</td>
<td>23 patients with early-stage breast cancer with a mean age of 60.5 years 8 patients with metastatic breast cancer with a mean age of 54.76 years 25 age-matched healthy controls with a mean age of 55.69 years All participants were included in analysis after effective state was measured.</td>
<td>Baseline: Patients with breast cancer had significant elevation in cortisol levels compared to controls. Patients with metastatic cancer had higher baseline cortisol than those with early-stage cancer. No differences were found in basal ACTH or prolactin between patients and controls. <strong>Behavioral challenge:</strong> Decreases in cortisol levels were induced in all three groups. Patients with metastatic cancer showed a blunted ACTH response and had faster cortisol decline compared to healthy controls. ACTH response was negatively correlated with basal cortisol in patients with metastatic cancer only.</td>
<td>Hyperactive adrenal gland suggests higher basal cortisol levels in patients with breast cancer. Blunted ACTH response might be related to hypercortisolemia, suggesting pituitary corticotroph cell is appropriated by negative feedback effects of chronic cortisol elevations.</td>
</tr>
</tbody>
</table>

ACTH—adrenocorticotropic hormone; CBG—corticosteroid-binding globulin; CFS—chronic fatigue syndrome; CRH—corticotropin-releasing hormone; HPA—hypothalamus-pituitary-adrenal; TSST—Trier Social Stress Test
cycles (Fuller, Gooley, & Saper, 2006). Melatonin levels are high and serotonin levels are low at night (reversed during the day). The dysregulation of melatonin and serotonin rhythms disrupt the 24-hour sleep-wake cycle (Fuller et al., 2006). Cancer and its treatment increase serotonin (5-hydroxytryptamine [5-HT]) levels in specific brain regions and up-regulate a population of 5-HT receptors, which leads to modified HPA axis function and possible decreased somatomotor drive and physical capability (Andrews, Morrow, Hickok, Roscoe, & Stone, 2004).

The amino acid tryptophan is the precursor of 5-HT, and serotonin is a precursor of melatonin. Tryptophan competes with branch-chain amino acids (BCAA) for the same transporter into the brain. During exercise, more BCAA are transported into the active skeletal muscles, which results in more tryptophan entering the brain and leads to an increased synthesis and release of 5-HT in the brain. Evidence from human studies demonstrated that hypothalamic 5-HT receptor function was down-regulated in endurance-trained athletes (Jakeman, Hawthorne, Maxwell, Kendall, & Holder, 1994), contrasting up-regulation and hypersensitivity of hypothalamic 5-HT receptors in patients with chronic fatigue syndrome (Andrews et al., 2004). Because increased 5-HT release is associated with sleep and drowsiness, it also is believed to promote central fatigue (Fernstrom & Fernstrom, 2006).

Discussion

CRF and disrupted sleep-wake patterns are associated with each other. HPA axis dysregulation, demonstrated by altered HPA axis rhythms (e.g., flattened diurnal cortisol rhythms), may account for the symptoms of fatigue and disrupted sleep throughout cancer. Loss of normal diurnal variation (or flattened rhythms) in cortisol may reflect changes in HPA axis rhythms, including slower declines from morning to evening, abnormal elevation in afternoon or evening cortisol levels, or no peaks throughout the day (Bower, Ganz, & Aziz, 2005; Sephton et al., 2000), all of which have been associated with fatigue and sleep disturbances. Compelling evidence exists to support that dysregulation of the stress response can lead to abnormalities in HPA axis circadian rhythms and physical-behavioral adaptation that mimic the clinical observation of fatigue and disrupted sleep in cancer. CRH is the key regulator of the HPA axis circadian function (Vgontzas & Chrousos, 2002). Because CRH integrates behavioral and physiologic activities and is centrally involved in regulating the hormonal stress response (Weninger et al., 1999), a functional deficit in CRH may mediate the dysregulation of the HPA axis and result in symptoms such as fatigue and disrupted sleep-wake patterns.

Although the mechanisms underlying either fatigue or disrupted sleep in cancer are not presently known, the speculations that focus on stress responses can lead to testable scientific hypotheses and promote the initial development of targeted therapies. Placing an emphasis on the altered HPA response as a central pathophysiologic mechanism provides a better fit with the contemporary formulations of etiology. As research in endocrinology has stressed the importance of diurnal variation in hormone levels, evaluation of endocrine function at multiple points in the hormonal cascade is necessary to determine whether an abnormality exists in the HPA system and define its nature. That will require not only basal hormone measures, but also the sequential use of stimulation tests on HPA axis levels.

The article’s main argument is a centrally mediated mechanism of HPA axis inactivation underlying fatigue and disrupted sleep in cancer; however, several compelling hypotheses exist that may also be involved, such as proinflammatory cytokine and sickness behavior. Recent discovery of xenotropic murine leukemia virus-related virus infection in patients with CFS (Lombardi et al., 2009) supports the long-time view of persistent viral infection in CFS pathogenesis. As neurotransmitters can be altered by viral infection (Oldstone et al., 1982), with HPA alterations occurring secondarily, studying the HPA axis is a logistic starting point. Glucocorticoid suppressively effects proinflammatory cytokines production and activity (McEwen et al., 1997), and the HPA axis is a potent mediator of the immune system (Bower, 2007); additional work is necessary to determine the relative contribution of those or other factors on fatigue in cancer.

Knowledge of the nature of sleep problems as they relate to cancer can provide the basis for new management of sleep and CRF. The targeted management of either symptom likely may ameliorate the other.

Conclusion

Understanding the function of the HPA axis in cancer-related symptoms may ultimately lead to better understanding of the variability of HPA circadian function and lead to development of new approaches for managing the symptoms in patients with cancer. Identifying the functional deficient in the HPA axis and the associated clinical features also may promote the development of pharmacologic and nonpharmacologic therapies targeting specific function of the HPA axis. Exploring promising physiologic models can lead to a better understanding of fatigue and disrupted sleep in patients with cancer and provide the insights needed to foster hypothesis-based studies of the apparently overlapping symptoms. Oncology nurses may develop strategies to manage those two common symptoms experienced by patients with cancer.

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