

Distress, Fatigue, and Sexuality

Understanding and treating concerns and symptoms in patients with multiple myeloma

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BACKGROUND: The psychological needs of patients and caregivers may be inadvertently overlooked, contributing to the patient's distress and possibly compromising outcomes. Untreated, these psychological needs may impair the patient's ability to make decisions and adhere to treatment.

OBJECTIVES: This article aims to present consensus statements to guide oncology nurses in the recognition and management of distress, fatigue, and sexual dysfunction in patients with multiple myeloma (MM).

METHODS: Members of the International Myeloma Foundation Nursing Leadership Board reviewed the current literature and clinical experience regarding interventions related to distress, fatigue, and sexual dysfunction in patients with MM.

FINDINGS: Ongoing patient education and attention to medical and psychological care is important to assess and address patients' needs, such as cancer-related fatigue, sexual dysfunction, and distress.

KEYWORDS

multiple myeloma; anxiety; distress; psychosocial; fatigue

DIGITAL OBJECT IDENTIFIER

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ACROSS AMBULATORY AND INPATIENT SETTINGS, AN ESTIMATED 47% of patients with cancer have a psychiatric disorder, 68% of which are classified as an adjustment disorder related to some aspect of the cancer illness (Derogatis et al., 1983). The true incidence of psychiatric disorders is unknown because healthcare providers do not routinely assess patients for them. With complex cancer therapies moving away from inpatient to ambulatory settings, identifying psychiatric disorders has become more problematic.

In 1997, a multidisciplinary panel of the National Comprehensive Cancer Network (NCCN) developed consensus guidelines for treating the emotional and psychological effects of cancer (Holland & Bultz, 2007). The panel concluded that the term *distress* was less stigmatizing and more acceptable to patients and oncologists than *psychological*, *psychiatric*, or *emotional disorder*. The term continues to lack a clear definition despite wide use (Phillips, 2009).

The Institute of Medicine identified quality psychological care as a vital component of comprehensive cancer care (Adler & Page, 2008). In collaboration with the NCCN panel, the American College of Surgeons (2012) Commission on Cancer developed a new accreditation standard for assessing and treating the psychological concerns of patients with cancer. Cancer centers seeking accreditation are required to assess these concerns at least once during cancer treatment.

Distress in Patients With Multiple Myeloma

Stress is defined as a feeling of being overwhelmed, worried, or run down as a result of responses to one's internal or external environment (Schneiderman, Ironson, & Siegel, 2005). When these responses are no longer effective in maintaining health or are counterproductive, stress can become distress (Weisman & Worden, 1977).

Distress, however, is more difficult to define than stress (Horwitz, 2007; Phillips, 2009). It consists of a collection of symptoms and not a specific diagnosis and is closely associated with many psychiatric disorders. Distress-related functional impairment in patients without a clinical psychiatric disorder (non-disordered people) and individual psychopathology are often

treated as mental disorders (Horwitz, 2007; Phillips, 2009). One point of view is that distress arises in non-disordered people when psychological mechanisms allow them to respond appropriately to stressful circumstances, whereas mental disorders reflect dysfunctional and perhaps deeper internal mechanisms that create problems for affected individuals and those around them (Horwitz, 2007). In any case, distress and psychopathology

affect several dimensions of quality of life, which independently predicts overall survival, making mental health assessments an important part of cancer care (Strasser-Weippl & Ludwig, 2008).

Unmet Mental Health Needs

The most prevalent patient needs in cancer care are the lack of disease-related information and social and psychological support (Husson et al., 2013; Lamers et al., 2013; Swash, Hulbert-Williams, & Bramwell, 2014; Zabora et al., 2015). The experience of disease-related distress depends not only on the severity and frequency of its symptoms, but also on the meanings and expectations that patients attach to their symptoms (Husson et al., 2013). Therefore, ongoing patient education and attention to medical and psychological care is fundamentally important to reducing disease burden (Sherman, Simonton, Latif, Spohn, & Tricot, 2004).

In patients with multiple myeloma (MM), unmet mental health needs appear to be the highest and most varied during treatment. Some patients express these needs at diagnosis, but most only after treatment (Swash et al., 2014). Although many patients accept treatment and are satisfied with the physical aspects of their care, many are reluctant to discuss their feelings and fears with their health-care team, particularly if providers appear to be busy. Willingness of healthcare professionals to listen is one of the most positive and helpful aspects of patient care. Assessing the need for psychosocial care is paramount in all patients with cancer, particularly in the early phases of diagnosis and treatment, but the best time for such assessment may vary according to disease stage (Harrison, Young, Price, Butow, & Solomon, 2009). For example, a mental health assessment should be a priority if the disease relapses or requires a change in therapy (Cormican & Dowling, 2016; Maher & de Vries, 2011).

Studies have reported that patients with MM believe their cancer is rarer than other malignancies (Kelly & Dowling, 2011). Many patients had never heard of the disease before their diagnosis (Stephens, McKenzie, & Jordens, 2014). Providing information about MM and its personal and social implications is important but often does not occur. The causes and risk factors of MM are unknown, and information on symptom management is often inconsistent. This uncertainty contributes to distress. In addition, family members are often shocked by the diagnosis and by the patient's frequent encounters with physicians for treatment of chronic pain, infections, and bone fractures (Vlossak & Fitch, 2008).

Many studies have evaluated treatment distress in MM (Boland et al., 2014; Dahan & Auerbach, 2006; Kelly & Dowling, 2011; Potrata, Cavet, Blair, Howe, & Molassiotis, 2010, 2011; Trask et al., 2002). For example, patients have referred to the period of treatment as "looking dead" because of the difficulties in eating and weight loss (Potrata et al., 2010). However, patients report that toxicity was acceptable and quality of life was good three or more months post-transplantation (Olivieri et al., 2001). A considerable amount of patients with MM may experience several distressing symptoms before transplantation and need more immediate, intensive, and

FIGURE 1. PATIENT EDUCATION TIP SHEET: ANXIETY AND DISTRESS

Many patients experience a variety of difficult emotions. Anxiety and distress are often observed at various times during cancer screenings, diagnosis, treatment, or recurrence.

- Anxiety is fear, dread, and uneasiness caused by stress.
- Distress is emotional, mental, social, or spiritual suffering. Patients may have feelings of vulnerability, sadness, depression, panic, and isolation. For patients, anxiety may increase pain, affect sleep, and cause nausea and vomiting. Anxiety and distress may affect a patient's ability to cope with the diagnosis or treatment, which may lead to delays in treatment. Anxiety can substantially interfere with the quality of life of patients and their families.

SYMPTOMS OF ANXIETY AND DISTRESS

Uncontrolled worry, fear, or sorrow; trouble focusing or problem solving; muscle tension; trembling or shaking; restlessness; dry mouth; and irritability or anger

MANAGING THE SYMPTOMS

Do

- Remember that you are not alone.
- Take a time out—doing yoga, relaxing, and stepping back from the issue help to clear thoughts.
- Share feelings and fears.
- Caregivers should listen carefully and offer support. Do not deny or discount feelings. Encourage talking.
- It is okay to feel sad and frustrated.
- Get help through counseling and/or support groups.
- Use meditation, prayer, or other types of spiritual support if it helps.
- Exercise and walking can help, as well as yoga.
- Talk with your healthcare provider about using antidepressant medicines.
- Medications to treat myeloma, such as steroids, can make anxiety worse. Discuss your feelings with your treatment team.

Do not

- Keep feelings inside.
- Force someone to talk if they are not ready to.
- Blame yourself or another person for feeling fearful or anxious.
- Try to reason with a person whose fears and anxieties are severe; talk with the doctor about medicines and other kinds of help.

Note. Based on information from Holland & Alici, 2010; Jacobsen et al., 2006; Lamers et al., 2013; Pirl, 2004; Williams & Dale, 2006.

supportive care. In time, patients learn their limitations and develop strategies for managing fatigue, distress, pain, and neuropathy as best they can (Stephens et al., 2014).

Assessment and Interventions

The first published clinical practice guidelines for managing distress in patients with cancer were released in 1999 by the NCCN and provided a framework for assessing and managing distress (Holland, Greenberg, & Hughes, 2006). Screening tools, such as the Distress Thermometer and *NCCN Clinical Practice Guidelines in Oncology for Distress Management*, may help patients and their caregivers adjust to the stresses of living with MM. Patients with MM are generally eager to accept psychological interventions, such as relaxation techniques, psychological counseling, and peer-support groups, when provided the opportunity, even if they do not ask for them (Lamers et al., 2013).

For mild to moderate distress, interventions include cognitive behavioral therapy, psychotherapy, and medications. Exercise can be beneficial to manage distress symptoms (Holland & Alici, 2010). The results of a meta-analysis found that yoga had little benefit in managing symptoms in patients with hematologic cancers, including MM (Felbel, Meerpohl, Monsef, Engert, & Skoetz, 2014). If corticosteroids, often used with MM, are causing moderate to severe mood swings, reviewing disease status and adjusting the dosage of corticosteroids may be warranted (King & Faiman, 2017). Anxiolytics and antidepressants can be effective in treating anxiety and distress, but their side effect profiles must also be considered (Jacobsen, Donovan, Swaine, & Watson, 2006; Pirl, 2004; Williams & Dale, 2006). Access to social workers or psychologists for cognitive behavioral therapy, psychotherapy,

and medication management may be limited, but patients with moderate to severe distress should be evaluated immediately by a trained psychiatric practitioner when possible (see Figure 1).

Evidence-Based Recommendations for Distress

LEVEL OF EVIDENCE I

- The International Myeloma Foundation (IMF) Nurse Leadership Board (NLB) recommends screening for distress among all patients with MM. Distress and psychopathology affect several dimensions of quality of life, which independently predicts overall survival (NCCN, 2017b; Strasser-Weippl & Ludwig, 2008).
- Interventions, such as listening to the patient's concerns and offering cognitive behavioral therapy, may reduce distress among patients with cancer (Maher & de Vries, 2011; NCCN, 2017b).
- Patients should be made aware of the value of relaxation techniques, psychological counseling, and peer-support groups (Lamers et al., 2013).

Cancer-Related Fatigue in Patients With Multiple Myeloma

Cancer-related fatigue (CRF) is a "distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment" (NCCN, 2017a, p. FT-1). Compared to fatigue in healthy individuals, CRF is more severe and more distressing and tends to be resistant to rest. Despite being strongly related to quality of life, CRF is often underrecognized and undertreated (Mitchell, 2011). Healthcare providers may not appreciate the implications of fatigue (Mortimer et al., 2010) (see Figure 2), and patient communication with clinicians about fatigue is

FIGURE 2.

HEALTHCARE PROVIDER TIP SHEET: PREVENTING AND MANAGING FATIGUE

Cancer-related fatigue is characterized by 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 usual functioning. The symptoms affect physical, psychological, and social functioning, and can cause significant distress for patients and caregivers. Fatigue can become chronic, leading to isolation, loneliness, and deconditioning of the body.

SYMPTOMS OF FATIGUE

- **Physical:** An unrelenting feeling of tiredness or exhaustion that is not relieved by sleep
- **Psychological:** Absentmindedness, forgetfulness, difficulty communicating, unpleasant emotions, mental exhaustion, and impaired concentration and memory
- **Social:** Fatigue that limits ability to socialize, impairs relationships, and leads to feeling isolated or lonely

Always report your symptoms to your healthcare team.

ASSESSMENT

Check vital signs, testosterone levels, thyroid levels, complete blood count with differential, electrolytes, and liver and kidney function; check for hyponatremia and other signs of dehydration (skin turgor); assess for depression, general appearance, and affect; check for cognitive impairments and infection; assess for muscle weakness; and involve caregivers and/or family members with assessments and interventions.

MANAGING THE SYMPTOMS

The following nonpharmacologic suggestions may help with symptoms of fatigue: Exercise, cognitive behavioral interventions, sleep interventions, ginseng, management of other symptoms, massage/aromatherapy, mindfulness-based stress reduction, multicomponent rehabilitative intervention, psychoeducational interventions, and yoga.

Note. Based on information from Oncology Nursing Society, 2017.

often inadequate. Patients may be reluctant to discuss their fatigue because they perceive it as untreatable or are unaware of treatment options. They may be reluctant to take additional medications or are concerned that they will be seen as complaining (Horneber, Fischer, Dimeo, Rüffer, & Weis, 2012; Mitchell, 2011) (see Figure 3).

Characteristics

CRF is a personal experience, so its characteristics are often subjective and vary by individual. Some patients describe mental fog-giness, inertia, or loss of efficiency, whereas others may describe it as an excessive need to rest, the inability to recover promptly from exertion, or muscle heaviness and weakness (Mitchell, 2011). Disruptive symptoms of chronic fatigue may persist for months to years after cancer therapy is completed (Horneber et al., 2012).

At least two dimensions of CRF have been described: mental and physical (Horneber et al., 2012). Mental fatigue includes dif-

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FIGURE 3. PATIENT EDUCATION TIP SHEET: PREVENTING AND MANAGING FATIGUE

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Always report your symptoms to your healthcare team.

MANAGING THE SYMPTOMS

The following suggestions may help with symptoms of fatigue. Always check with your healthcare provider before taking new medications or starting an exercise program.

- Nonpharmacologic: Exercise, cognitive behavioral interventions, sleep interventions, ginseng, management of other symptoms, massage/aromatherapy, mindfulness-based stress reduction, multicomponent rehabilitative intervention, psychoeducational interventions, and yoga
- Pharmacologic: Corticosteroids (low doses) and erythropoiesis-stimulating agents
- Other: Blood transfusions

Note. Based on information from Oncology Nursing Society, 2017.

iculties with cognition, concentration, and speed of information processing. Patients with mental fatigue may have difficulty understanding simple instructions or completing a to-do list. They may describe absentmindedness, forgetting important appointments or to take medications, or difficulties in communicating with healthcare providers and family members. Patients may also report negative or unpleasant emotions, mental exhaustion, and impaired concentration and memory (Mitchell, 2011).

Symptoms of physical fatigue include exhaustion, weakness, and tiredness (Horneber et al., 2012). Patients may report having heavy limbs or feeling slow, weary, sluggish, or unable to carry out activities of daily living. Patients commonly report limited energy and an inability to complete routine tasks, such as housecleaning, cooking, or recreational hobbies. Even routine activities, such as getting dressed, require more effort than usual. Mental and physical fatigue may prevent patients from participating in relationships and limit socialization, leading to isolation and loneliness (NCCN, 2017a).

Causes

Contributors to CRF in MM are multidimensional. They are thought to involve anemia, pain, reduced activity, insomnia, therapy toxicity, and myeloid suppression (Coleman et al., 2011; Smith et al., 2015; Stone & Minton, 2008). Other contributors include infection, malnutrition, cachexia, and medication side effects. Hypothyroidism and cardiac, pulmonary, hepatic, and renal impairment can contribute to profound fatigue, which can become more severe during cancer treatment (Mitchell, 2011). Fatigue is also commonly reported after autologous stem cell transplantation (Miceli et al., 2013).

Patients with MM are at risk for treatment-related fatigue, which can be short- or long-term (Miceli et al., 2013). Immunomodulators, such as thalidomide, lenalidomide, and pomalidomide, are associated with marked fatigue, as are proteasome inhibitors, such as

bortezomib and carfilzomib (Amgen, 2017; Celgene, 2016, 2017a, 2017b; Millennium Pharmaceuticals, 2017). In addition, opioids, hypnotics, anxiolytics, antihistamines, antiemetics, anticonvulsants, antihypertensives, and insomnia medications can cause medication-related fatigue and enhance the symptoms of fatigue from other causes. Corticosteroids, such as dexamethasone and prednisone, carry well-known neuropsychological effects that can lead to anxiety, distress, insomnia, mood swings, depression, and fatigue. Side effects of corticosteroids, many of which contribute to CRF, are discussed in Figure 4. Although steroids are associated with improved energy, this experience is followed by intense fatigue, called a “let-down effect,” for several days after steroid administration (King & Faiman, 2017). Steroids affect numerous body systems. Figure 5 provides a patient education tool for continuing treatment after corticosteroid side effects.

Assessment

All patients should be assessed for CRF. The NCCN (2017a) strongly encourages healthcare providers to assess fatigue at

baseline and with every major change in the patient’s care or health. CRF assessments include identifying its characteristics, its impact on quality of life, and any potential contributing factors (Mitchell, 2011). Several validated instruments are widely used to diagnose fatigue in patients with cancer, including the Functional Assessment of Cancer Therapy, Brief Fatigue Inventory, and the Fatigue Symptom Inventory (NCCN, 2017a).

Physical examination can determine contributing factors that lead to fatigue (Mitchell, 2011; NCCN, 2017a). For example, constitutional signs might identify nutritional deficiencies, whereas vital signs might indicate infection. A general assessment of appearance, mood, and manner may reveal anxiety or depression. Assessing the musculoskeletal system might reveal focal or generalized weakness, muscle mass loss, joint pain, warm or edematous joints, muscle pain, muscle twitching, limitations in range of motion, or bone pain. Abnormal skin turgor may indicate that dehydration could be contributing to CRF. Decreased or adventitious lung sounds might indicate pulmonary edema, chronic obstructive pulmonary disease, or pneumonia that reduces tolerance to activity. Abnormal

FIGURE 4.

PATIENT EDUCATION TIP SHEET: COMMON SIDE EFFECTS OF CORTICOSTEROIDS RELATED TO DISTRESS, FATIGUE, AND SEXUALITY

NEUROPSYCHIATRIC

Cognitive, behavioral, and mood changes

- Risk factors include higher doses and a history of neuropsychiatric effects from steroids and older age.
- Mania-like symptoms are more commonly associated with short-term use and depressive symptoms with long-term use.
- Hyperactivity and jitters are more closely associated with days taking steroids, and they abate on nonsteroid days.
- Steroid psychosis is rare, but patients with overt mood changes are at risk for suicide and should be monitored.
- Early recognition, diagnosis, and treatment of neuropsychiatric complications in patients receiving steroids are key to management.
- Educate patient and family to possible neuropsychiatric effects.
- Monitor patients for changes in mood, cognition, or behavior using an appropriate screening tool, such as the Hospital Anxiety and Depression Scale.
- Dose reduction or discontinuation in the presence of neuropsychiatric effects is the most effective management.
- Tapering doses can be useful to minimize the severity of mood changes (steroid “highs and lows”).
- The use of antipsychotic or mood stabilizers may be indicated.
- Avoid concomitant clarithromycin, which can increase circulating levels of corticosteroids and increase risk of neuropsychiatric effects.
- Consider referral to support groups and psychosocial services to aid coping.
- Relaxation, mindfulness techniques, and exercise may aid coping.

CONSTITUTIONAL

“Let-down effect”

- More commonly associated with days immediately after taking steroids
- Characterized by weakness and fatigue
- Tapering steroid doses may help.
- Educate patient to adapt lifestyle and activities around energy levels.

Flushing or sweating

- Assess for other causes, such as infection or cardiovascular abnormalities, and manage appropriately.
- Educate on appropriate clothing and maintaining hydration.

Insomnia

- More common on nights after taking steroids
- Educate to take dose in the morning.
- Educate patients about sleep hygiene practices (e.g., avoiding caffeine, alcohol, and electronic screens before bedtime). Establish an appropriate sleep environment, and suggest meditation or relaxation techniques.
- Consider pharmacologic interventions if insomnia is severe or ongoing.

SEXUAL DYSFUNCTION

Lowered libido

- Initiate assessments or conversations around sexual function and intimacy to help identify potential issues.
- May require dose reduction or hormone therapy

Note. From “Steroid-Associated Side Effects: A Symptom Management Update on Multiple Myeloma Treatment,” by T. King & B. Faiman, 2017, *Clinical Journal of Oncology Nursing*, 21, pp. 242–243. Copyright 2017 by Oncology Nursing Society. Adapted with permission.

heart sounds and jugular venous distension might indicate that congestive heart failure is causing fatigue (Mitchell, 2011).

Diagnosing the underlying cause of fatigue in patients with cancer is problematic because no diagnostic test is specific for it (Howell et al., 2013). However, reviewing medications, obtaining laboratory tests (e.g., complete blood counts with differential; electrolytes; renal, liver, and thyroid function tests) may help determine the cause of fatigue. Table 1 provides a framework to assess CRF in patients with MM.

Interventions

The optimal intervention for fatigue is prevention. Because so many factors may contribute to CRF, attention should focus on identifying correctable conditions. Clinical issues, such as nutritional deficiencies, anemia, pain, emotional distress, and sleep disturbances, should be evaluated and addressed to avoid their concomitant effects of CRF (Campos, Hassan, Riechelmann, & Del Giglio, 2011; NCCN, 2017a).

Managing fatigue should improve overall quality of life and physical, psychological, social, and vocational function. However, because the causes of CRF are poorly understood and are influenced by concomitant diseases and their various treatments, few specific and effective treatments exist (Campos et al., 2011). One important goal is to focus on eliminating stressors and increasing patients' resistance to stressors. Nonpharmacologic

interventions include activity enhancement, such as exercise, psychosocial interventions, integrative therapies, nutritional support, sleep therapy, and energy conservation (Campos et al., 2011; Mortimer et al., 2010; Mustian, Sprod, Janelins, Peppone, & Mohile, 2012). Managing pain, depression, infection, dehydration, insomnia, anemia, nutritional deficiencies, and electrolyte imbalances may improve fatigue and eliminate other symptoms as well (Campos et al., 2011; NCCN, 2017a).

Exercise and mobility enhancement are the most effective non-pharmacologic interventions that improve CRF (Carayol et al., 2013; Coleman et al., 2011; Mishra et al., 2012). A meta-analysis of the effect of exercise on CRF reported an overall benefit during and after cancer treatment (Carayol et al., 2013). The Oncology Nursing Society also recommends exercise to treat CRF (Mitchell, 2011). Encouraging and supporting patient activity and establishing a regular exercise program may prevent and treat fatigue (NCCN, 2017a).

Anxiety and depression can increase symptoms of fatigue (NCCN, 2017a). A meta-analysis reported that behavioral interventions, including behavioral therapy, cognitive therapy, education, relaxation techniques, counseling, or social support reduced fatigue among patients with breast cancer during and after treatment (Duijts, Faber, Oldenburg, van Beurden, & Aaronson, 2011).

Changes in sleep patterns, such as insomnia and hypersomnia, can disrupt sleep (Roscoe et al., 2007) and contribute to CRF. Nonpharmacologic interventions to improve sleep include

FIGURE 5.

PATIENT EDUCATION TIP SHEET: DISCUSSIONS ABOUT CONTINUING TREATMENT AFTER CORTICOSTEROID SIDE EFFECTS

Steroids commonly prescribed for multiple myeloma treatment include dexamethasone, prednisone, prednisolone, and methylprednisolone.

STRATEGIES FOR CONTINUING TREATMENT

- Steroids are commonly taken on a highly regular schedule (e.g., once per week). Side effects commonly follow a predictable pattern, particularly those affecting mood and energy.
- Maintain a symptom journal to help identify the pattern of any side effects and aid recall of side effects to discuss with your healthcare provider. Learning the pattern of side effects allows you to adapt your lifestyle to accommodate mood and energy levels.
- Patients may find that exercise or simple activities can help "burn off" the hyperactivity or jitters that steroids may cause. Relaxation, meditation, or mindfulness techniques can also help.
- Caregivers may identify mood and behavior changes in patients with multiple myeloma on steroids in advance of the patient. Caregivers should talk with the healthcare provider if they are concerned at the degree of these changes.
- Steroids should be taken with food.
- Patients should take an over-the-counter or prescription medication to prevent gastrointestinal issues.

- Steroids can cause sleeplessness and should be taken early in the morning. In some cases, the increased energy caused by taking steroids has a delayed effect. As such, taking steroids in the evening may allow improved sleep patterns.
- Be aware of symptoms of infection: a fever of more than 100.5°F (38°C), shaking chills even without fever, dizziness, shortness of breath, and low blood pressure. Contact your healthcare provider if these symptoms occur.
- Medications to prevent infection, shingles (small blister-like rash anywhere on the body; usually painful with or without rash), and thrush (white coating on tongue, bad taste, and painful swallowing) may also be prescribed.
- Know the signs and symptoms of high and low blood sugar (e.g., aggressiveness, confusion, difficulty waking, increased thirst, frequent urination). If you have diabetes, consult with your endocrinologist or diabetes educator before starting treatment with steroids.
- Always report any concerning symptoms to your healthcare team as soon as they occur.

Note. From "Steroid-Associated Side Effects: A Symptom Management Update on Multiple Myeloma Treatment," by T. King & B. Faiman, 2017, *Clinical Journal of Oncology Nursing*, 21, pp. 242–243. Copyright 2017 by Oncology Nursing Society. Adapted with permission.

cognitive behavioral therapy, patient education, and exercise. Cognitive behavioral techniques include sleep restriction, sleep hygiene, and stimulus control. Stimulus control includes going to bed and waking up at the same time each day and getting out of bed after 20 minutes if still awake. Sleep restriction in the form of avoiding long or late afternoon naps, as well as limiting total time spent sleeping, is also considered an important strategy in managing fatigue (Roscoe et al., 2007).

Sleep hygiene involves altering basic lifestyle habits that influence sleep. Examples of lifestyle changes include limiting caffeine, alcohol, and tobacco consumption; relaxing before bedtime; taking warm baths; and getting adequate exercise. Cognitive behavioral interventions include breathing control, progressive muscle relaxation, guided imagery, and complementary therapies, such as massage therapy, yoga, and stress reduction using mindfulness (Berger, Gerber, & Mayer, 2012; NCCN, 2017a). Strategies for conserving energy may also be helpful.

Nutritional consultation can help manage deficiencies caused by anorexia, diarrhea, nausea, and vomiting. Hydration and replacing deficient electrolytes, iron, and folic acid can also prevent or treat fatigue (NCCN, 2017a).

Although the use of psychostimulants, such as methylphenidate and dexamethylphenidate, can improve fatigue, treatments work better when combined with nonpharmacologic interventions, such as exercise and complementary alternative therapies (Campos et al., 2011; NCCN, 2017a). Corticosteroids can be prescribed to patients with palliative intent to treat fatigue during end-of-life care (Yennurajalingam et al., 2013). No medications specific for CRF are approved by the U.S. Food and Drug Administration (FDA). However, certain drugs are approved for treating possible concomitant, contributing diseases that affect fatigue (Minton, Richardson, Sharpe, Hotopf, & Stone, 2011). The antidepressant paroxetine, a selective serotonin reuptake inhibitor, improves depression and mood, but its effects on CRF are mixed. Other antidepressants, such as bupropion, sertraline, and venlafaxine, have also had mixed results in controlling CRF (Mitchell, 2011).

Seven meta-analyses concluded that erythropoiesis-stimulating agents may improve CRF in patients with hemoglobin concentrations of less than 10 g/dl, but the effects are small (Mitchell, 2011). Data also suggest that these agents are associated with marked risks of hypertension and thrombosis, and may reduce disease control and overall survival (Mitchell, 2011). However, treating anemia, including via transfusions in some cases, may reduce fatigue and substantially improve quality of life.

Dexamethasone may improve CRF (Yennurajalingam et al., 2013). A randomized trial of 84 patients tested dexamethasone for treating CRF. At day 15, the mean score of the 13-item Functional Assessment of Chronic Illness Therapy–Fatigue instrument was significantly better in the dexamethasone group than in the placebo group (9 versus 3.1 on a scale of 1–13, where 13 is no fatigue). The improvement in total quality of life was also significantly

higher in the dexamethasone group. However, dexamethasone is associated with side effects, such as hyperglycemia, avascular necrosis, muscle weakness, emotional lability, inattention/hyperactivity, mania, psychosis, and altered sleep patterns (King & Faiman, 2017; Yennurajalingam et al., 2013).

Evaluating fatigue in patients with MM, particularly those with known treatable factors as described previously, is essential at each clinic visit and after each intervention (NCCN, 2017a). Fatigue occurs in the context of multiple symptoms, and these symptoms may act synergistically to increase symptomatology (NCCN, 2017a). Fatigue may improve as the disease becomes better controlled, a relationship that can help patients better understand the symptoms and management of CRF.

Evidence-Based Recommendations for Fatigue
LEVEL OF EVIDENCE I

- Routinely evaluate patients for fatigue (NCCN, 2017a).
- If fatigue is present, rule out and correct other organic causes of fatigue, such as anemia, thyroid dysfunction, sleep apnea, or vitamin deficiencies.
- Exercise is effective in the nonpharmacologic management of fatigue.
- Effective interventions include establishing adequate nutrition, reducing stress, and adopting sleep hygiene techniques.

TABLE 1.
MULTIPLE MYELOMA FATIGUE ASSESSMENT

LABORATORY TEST/ CONSIDERATION	EXPECTED RESULT IF CAUSE OF FATIGUE
Perform complete blood count.	Assess for low hemoglobin (anemia) and low white blood cell count (leukopenia).
Perform complete metabolic panel.	Assess for electrolyte abnormalities (hypokalemia, elevated creatinine, hypercalcemia), liver function (elevated transaminases), uncontrolled hyperglycemia, and dehydration.
Assess level of thyroid stimulating hormone.	Thyroid stimulating hormone can be high with hypothyroidism.
Assess sleep quality and duration.	Does the patient get adequate rest/sleep? Does the patient snore, have morning headaches, or have signs of sleep apnea? Does the patient experience frequent nighttime urination (nighttime diuretic use, enlarged prostate in men)?
Assess exercise patterns.	Does the patient exercise? Is exercise timed to be not too close to bedtime?
Assess for signs of infection.	Assess bladder and bowel habits, fever, and night sweats.
Evaluate disease markers.	Assess for multiple myeloma markers (SPEP, UPEP, serum free light chain assay) to rule out disease progression as a cause of fatigue.

Note. Based on information from National Comprehensive Cancer Network, 2017a.

- Pharmacostimulants, such as methylphenidate and dexamethylphenidate, can improve severe fatigue and work better when combined with nonpharmacologic interventions, such as exercise and complementary alternative therapies (Campos et al., 2011; NCCN, 2017a).
- Corticosteroids can be used with palliative intent among patients with severe fatigue and during end-of-life care (Yennurajalingam et al., 2013).

Sexual Dysfunction

Sexual dysfunction in patients with cancer may be caused by the disease, chemotherapeutic agents, surgical procedures, hormonal therapy, medications, and comorbid conditions and can interfere with intimate relationships (Richards, Bertolotti, Doss, & McCullagh, 2011). Providers should routinely ask patients with MM about sexual function and dysfunction because patients usually do not volunteer information about these topics despite citing sexuality as a major concern (Goncalves & Groninger, 2015; Osborne et al., 2014) (see Figures 6 and 7). Sexual dysfunction is an issue only if the patient regards it as one. Sexual dysfunction is not a part of normal aging. Therefore, once a problem with sexual function has been identified, possible causes should be investigated.

FIGURE 6.

PATIENT EDUCATION TIP SHEET: TALKING ABOUT SEXUALITY AND INTIMACY

Sexual dysfunction is not the result of normal aging. Rather, it occurs because of physical illness, medications, psychological factors, or some combination of these conditions. After discussing these topics and questions with your healthcare provider, be sure to seek appropriate referrals.

TOPICS TO DISCUSS WITH YOUR HEALTHCARE PROVIDER

It is important to discuss sexual concerns with your healthcare provider. The following are several topics to discuss if you are having difficulties engaging in sexual activity:

- I am not interested in having sexual intercourse but would like to be.
- Vaginal dryness
- Fearful of being touched by your partner
- Inability to obtain or maintain an erection during sexual intercourse
- Inability to achieve an orgasm
- Pain associated with intercourse

QUESTIONS TO DISCUSS WITH YOUR HEALTHCARE PROVIDER

- How will my treatment affect my sexual activity?
- Are these changes in my sexual function normal?
- What precautions do I need to take while I am on treatment for multiple myeloma or after stem cell transplantation?
- Is oral sex safe while on therapy? What precautions should I take?

Note. Based on information from Clayton & Ramamurthy, 2008.

Sexual Dysfunction in Men

Sexual dysfunction in men includes erectile dysfunction, changes in libido, premature ejaculation, and delayed or inhibited ejaculation (Cunningham & Khera, 2014). Erectile dysfunction has been reported in about 50% of otherwise healthy men aged 40–70 years (Patel, Halls, & Patel, 2012). In 10%–20% of men with erectile dysfunction, the cause is thought to be solely psychological. How many men with MM experience erectile dysfunction is unknown (Sadovsky et al., 2010).

Some agents used to treat MM may lead to sexual dysfunction (Celgene, 2017b; Sadovsky et al., 2010). Alkylating agents, such as melphalan (particularly in high doses) and cyclophosphamide, may decrease semen production, contribute to erectile dysfunction, and reduce desire (Sadovsky et al., 2010; Thygesen, Schjødt, & Jarden, 2012). Peripheral neuropathy is one of the more common side effects of thalidomide and bortezomib, and both drugs may damage small nerve fibers, causing erectile dysfunction (Delforge et al., 2010). In addition, lenalidomide has been associated with erectile dysfunction in clinical trials (Celgene, 2017a). In addition to erectile dysfunction, bortezomib may cause testicular swelling, pain, and peripheral neuropathy (Richards et al., 2011). Steroid therapy used to treat MM may reduce desire and cause erectile dysfunction (Kalantaridou, Calis, et al., 2006; Kalantaridou, Naka, et al., 2006). Steroid therapy may also cause hyperglycemia, which can also reduce sexual function (Faiman, Bilotti, Mangan, & Rogers, 2008; Richards et al., 2011). In men without prostate cancer, comorbid conditions, such as diabetes, hypertension, thyroid disorders, renal disease, cardiovascular disease, pain, and disturbances in body image, may reduce sexual function (Richards et al., 2011).

Sexual Dysfunction in Women

About half of women with MM report sexual dysfunction lasting more than a month, but only about 20% seek treatment for it (Srivastava, Thakar, & Sultan, 2008). Women may experience hypoactive arousal, painful intercourse, loss of desire, and difficulties having an orgasm. The most common report of sexual dysfunction is loss of desire (Fourcroy, 2003; Srivastava et al., 2008).

In women, sexual dysfunction may be caused by medications, hormonal therapy, ovarian failure, pain, body image changes, and changes in interpersonal relationships. Treatments, such as stem cell transplantation, alkylating agents, steroids, and the use of birth control, may reduce sexual function. The effect of new agents, such as pomalidomide, carfilzomib, ixazomib, daratumumab, elotuzumab, and panobinostat, on sexual function is unknown. In stem cell transplantation, women tend to not recover baseline sexual function, whereas men return to baseline function within two to three years after transplantation (Li et al., 2015). Alkylating agents may cause ovarian failure, leading to vaginal dryness, decreased desire, and painful intercourse (Sadovsky et al., 2010). Several factors increase the risk for sexual dysfunction

in men and women after stem cell transplantation, including graft-versus-host disease, cardiac complications, and prescription medications (Li et al., 2015).

Assessment

Properly assessing sexual function is difficult, given the reluctance of patients and caregivers to discuss the topic and a lack of provider training and standardized questionnaires on sexual function. Two questionnaires have been validated in patients with cancer that could be relevant to patients with MM, the International Index of Erectile Function and the Female Sexual Function Index (Bober & Varela, 2012). In addition, reviewing medications and comorbid conditions to determine whether they may be contributing to the dysfunction is essential (McVary, 2007; Richards et al., 2011; Srivastava et al., 2008).

Treating Male Sexual Dysfunction

Erectile dysfunction may be reversed with phosphodiesterase type-5 inhibitors. However, these medications are contraindicated in men receiving nitrate therapy because they may cause hypotension (McVary, 2007). Nonpharmacologic interventions for erectile dysfunction include testosterone replacement, vacuum devices, surgery, and psychotherapy (Bruner & Calvano, 2007; McVary, 2007; Richards et al., 2011). The use of testosterone therapy in men with hypogonadism is controversial and is contraindicated in men with a history of prostate cancer (Hackett, 2016). The risks and benefits should be discussed with the patient before starting therapy (Hackett, 2016). Although intracavernous and transurethral injections are used to treat erectile dysfunction, their use in men with MM is contraindicated by the risk of priapism (i.e., prolonged erection) (McVary,

FIGURE 7.

HEALTHCARE PROVIDER TIP SHEET: DISCUSSING SEXUAL DYSFUNCTION

When discussing sexual dysfunction, it is important to remember that it is only a problem if the individual defines it as one. In addition, sexual activity is not required for a person or relationship to be normal.

USE OPEN-ENDED QUESTIONS

When discussing a patient's sexual function, a relaxed, nonjudgmental, and professional conversation can make an awkward topic easier to approach.

- "Patients with cancer may have problems with intercourse. Have you experienced sexual problems?"
- "Are you having any difficulties participating in sexual intercourse?"
- "Are you concerned about your sexual response?"
- "Has your level of sexual activity decreased or changed?"
- "Has your cancer diagnosis or treatment affected how you feel about yourself?"
- "Have you discussed your feelings with your partner?"
- "Do you have any questions or concerns about your sexual function?"

MANAGEMENT STRATEGIES

When managing sexual dysfunction, it is important to address other conditions, such as thyroid dysfunction, renal dysfunction, diabetes, cardiovascular disease, or depression, that may affect sexual function. In addition, the underlying causes of sexual dysfunction must be thoroughly assessed, including nerve root compression, peripheral neuropathy, opioid therapy, treatment effects, and medication side effects.

PHYSIOLOGIC INTERVENTIONS

- Vaginal dryness and dyspareunia: For first-line treatment, use nonhormonal vaginal moisturizers and lubricants. For second-line treatment, use vaginal estrogen replacement (low-dose estradiol rings or creams).
- Testosterone replacement (remains controversial)
- Erectile dysfunction: Use oral PDE-5 inhibitors (e.g., sildenafil), vacuum erection devices, and penile prosthesis.
- Avoid sexual intercourse if neutropenic (absolute neutrophil count less than

1,000) or thrombocytopenic (platelet count less than 50,000) to minimize risk of infection or bleeding.

PSYCHOLOGICAL INTERVENTIONS

- Cognitive behavioral stress management, relaxation training, sexual education, or sexual counseling
- Partner participation in therapy may improve intimacy and body image.
- To improve intimacy between partners, one technique is to redefine sexual activity as a continuum between no intercourse and intercourse. The purpose is to allow partners to become familiar with one another's sexual changes.

REFERRALS

Several areas of the health profession are concerned with sexuality and sexual function, including mental health professionals, sex therapists and counselors, gynecologists, urologists, endocrinologists, sperm banks, infertility clinics, and genetic counselors.

ADDITIONAL RESOURCES

CancerCare

- www.cancerca.org

Cancer Survival Palace

- www.cancersurvivorsplace.org

Livestrong Fertility

- www.livestrong.org/we-can-help/livestrong-fertility

National Cancer Institute Office of Cancer Survivorship

- <http://dcccps.nci.nih.gov/ocs>

National Coalition for Cancer Survivorship

- www.canceradvocacy.org

Oncolink: Oncolife survivorship care plan

- www.oncolink.org/oncolife

Note. Based on information from Goncalves & Groninger, 2015; Richards et al., 2011; Tomlinson, 1998.

2007; Richards et al., 2011). Healthcare providers may refer patients to specialists in erectile dysfunction (see Figure 8).

Treating Female Sexual Dysfunction

Options to treat female sexual dysfunction are limited. Medications as treatment include flibanserin. Approved by the FDA in 2015, flibanserin is a treatment for premenopausal women reporting a low desire for sex (Valent Pharmaceuticals, 2016). Potential side effects include low blood pressure or fainting, nausea, dizziness, and headache. Women taking flibanserin must avoid alcohol. Bremelanotide is a cyclic 7 amino acid melanocortin receptor agonist with high affinity for the type 4 receptor and the potential to modulate brain pathways involved in sexual response. Women taking bremelanotide in a randomized placebo-controlled study had a greater number of satisfying sexual events and improved sexual desire and arousal than that of women receiving placebo (Clayton et al., 2016). This drug is not yet approved by the FDA (Safarinejad, 2008).

FIGURE 8. SPECIALIST REFERRAL NETWORK FOR SEXUAL DYSFUNCTION

The oncologist and healthcare team should build a referral network of specialists for the treatment of sexual dysfunction. The type of referral will depend on the problem with which the patient presents. A comprehensive referral network should include the following:

- A mental health professional who provides sex therapy and sexual counseling
- A gynecologist who has expertise in assessing and treating pain with sexual activity or one who can help women make decisions about hormone replacement therapy after cancer
- An urologist who has specialized knowledge and skill regarding problems of the male and female urinary tract and the male reproductive organs, and who provides medical treatment for loss of sexual desire and erectile dysfunction
- An endocrinologist who treats the deficiency or excess production of hormones causing diseases such as diabetes, thyroid diseases, and menopause
- A sperm bank that can store semen samples for men about to begin cancer treatment that could potentially damage fertility
- An infertility clinic offering in vitro fertilization and donor gamete programs that has a good success rate and staff who are familiar with cancer-related infertility in men and women
- A genetics clinic that can counsel cancer survivors regarding their concerns about birth defects or cancer risks in their offspring

Note. From "Sexual Dysfunction in Multiple Myeloma: Survivorship Care Plan of the International Myeloma Foundation Nurse Leadership Board," by T.A. Richards, P.A. Bertolotti, D. Doss, & E.J. McCullagh, 2011, *Clinical Journal of Oncology Nursing*, 15, p. 62. Copyright 2011 by Oncology Nursing Society. Adapted with permission.

IMPLICATIONS FOR PRACTICE

- Assess anxiety, distress, and fatigue at every visit because these symptoms are often interrelated and can be debilitating.
- Address patients' sexual needs to improve quality of life.
- Provide routine assessment of psychological health to gauge need for interventions, including relaxation, stress management, or counseling.

Vaginal lubricants are recommended for the initial treatment of vaginal dryness (Goncalves & Groninger, 2015). Women should be encouraged to discuss vaginal dryness with their gynecologist to determine the best treatment for their sexual dysfunction (Goncalves & Groninger, 2015).

Evidence-Based Recommendations for Sexual Dysfunction LEVEL OF EVIDENCE I

- Routinely assess patients for sexual dysfunction.
- For men, evidence supports the use of nonpharmacologic interventions, such as vacuum devices, surgery, and psychotherapy (Bruner & Calvano, 2007; McVary, 2007; Richards et al., 2011).
- The use of testosterone therapy in men with hypogonadism is controversial and contraindicated in men with a history of prostate cancer (Hackett, 2016). The risks and benefits should be discussed.
- The evidence also supports the use of phosphodiesterase type-5 inhibitors in men experiencing erectile dysfunction (McVary, 2007).
- Flibanserin is approved for use in premenopausal women who experience a lack of desire, and the drug can be recommended (Valent Pharmaceuticals, 2016).

Conclusion

Patients with MM will often receive several treatment regimens throughout their illness. The aims of anti-MM therapy are to control the disease, prolong survival, and increase quality of life. However, appropriate management of patients with MM requires ongoing assessment of several concurrent symptoms caused by the disease, its treatment, or both. Distress, fatigue, and sexual dysfunction have been reported to adversely affect psychosocial quality of life. If untreated, they may lead to unnecessary suffering, family burden, frequent visits to the healthcare provider, added stress on the healthcare team, and difficulties in treatment decision making and adherence. Nursing and clinical care can benefit patients and caregivers through critical assessment and interventions.

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