The Cancer Patient with Anxiety and Chronic Pain

Clinicians working with patients with chronic cancer-related pain are familiar with the experience of pain having both somatic sensory and psychological components. With adequate pain management, we often see a lessening of anxiety and a return to emotional equilibrium, which allows patients to process the loss inherent in the cancer experience. But in some of our patients we see persistence of psychological suffering and of a maladaptive anxious response that interrupts this processing and worsens outcome. While most anxiety develops after the onset of cancer, a smaller subset of patients with anxiety represent those with preexisting conditions. This issue of Pain: Clinical Updates addresses the complex and bidirectional relationship of chronic pain and anxiety in cancer patients, the dilemmas inherent in adequately diagnosing the underlying cause of this prolonged suffering, and the multimodal treatment approach necessary to improve adaptation and quality of life.

Anxiety

Anxiety can be described as an emotional state characterized by feelings of unpleasant anticipation and a sense of imminent danger. Anxiety has both physiological and psychological components. Autonomic hyperarousal with acceleration of heart rate and respiration, tremor, sweating, muscle tension and gastrointestinal changes are common physiological experiences. Apprehension, feeling powerless, and fearing loss of control are psychological aspects. There are many types of anxiety disorders, and all are relatively common in the population, with prevalence data varying from 7% to 18%. Anxiety is a common, though not universal, symptom that affects 13–16% of patients with cancer. The high prevalence of anxiety disorders in those with chronic pain is also well documented, with prevalence data of 20–40%. Characteristics of anxiety disorders are listed in the American Psychiatric Association’s Diagnostic and Statistical Manual (DSM) and include acute stress disorder, post-traumatic stress disorder (PTSD), generalized anxiety disorder, obsessive compulsive disorder, panic disorder, and phobias. PTSD occurs in 25% of the general population after exposure to a traumatic event that threatens an individual’s life and causes intense fear and helplessness. The American Psychiatric Association expanded its DSM criteria for a PTSD stressor to include diagnosis with life-threatening illness in 1994. PTSD can thus exist prior to cancer and its treatment and can also be caused or exacerbated by cancer and its treatment. Acute stress disorder and PTSD involve re-experience of trauma in the form of intrusive thoughts or nightmares, efforts to avoid reminders of the trauma, and increased arousal that causes disturbances in sleep and attention. When the disorder lasts 2–4 weeks and resolves, it meets the criteria for acute stress disorder; when these symptoms persist for more than 1 month, they meet the criteria for PTSD. Essential to both acute stress disorder and PTSD is impaired functioning at home and work. Other anxiety disorders include generalized anxiety disorder, which involves excessive worry along with motor...
tension and restlessness, irritability, autonomic hyperarousal, sleep disturbance, and inattention, with onset typically in early adult life. Panic disorder involves episodes of sudden high anxiety accompanied by fear of loss of control, by activation of the sympathetic nervous system, and by the urge to escape, which can result in abrupt termination of cancer treatment. Phobias usually have a childhood onset and are characterized by extreme anxiety when exposed to a feared situation or object and by efforts to avoid them. Phobias involving exposure to the medical environment (needles, blood, enclosed spaces found in the intensive care unit, diagnostic scanners, and radiation therapy devices) are common.

**Anxiety in Pain Research**

Modern concepts of chronic pain incorporate more than just an understanding of transduction, transmission, and modulation effects of direct tissue damage or invasion. Pain perception also involves genetics, psychological state, social situation, cognitive variables such as expectations and memories, personality, and culture. Keefe found in 1987 that coping variables powerfully predict perception of and adjustment to pain. The 1980s also brought exciting research into the cognitive-behavioral model of disease-related pain and new roles for intervention involving altering one’s thoughts, beliefs, expectations, and behavioral patterns to enhance adjustment to pain. More recently, studies involving brain imaging and psychosocial aspects of pain and its psychological adjustment to chronic pain have provided new findings indicating that cognitions, emotions, and behaviors can influence pain.

Research into the psychological factors associated with chronic pain has blossomed in the past two decades. The fear-avoidance model, as proposed by Vlaeyen, incorporates learning theory and cognitive-behavioral perspectives to explain how pain-related fear can lead to chronic disability. Pain-related fear can produce avoidance of movement and activity in a misguided attempt to preempt further pain. These avoidance behaviors occur in anticipation of pain and can ultimately lead to disuse syndromes and depression, further lowering pain tolerance and promoting pain-related disability. Asmundson and others have described the phenomenon of “anxiety sensitivity.” Anxiety sensitivity has to do with fear as a consequence of feeling the physical manifestations of anxiety. It is a trait that involves interpreting anxiety as having to do with an underlying danger or threat (e.g., cancer recurrence). Asmundson looked at 259 patients with chronic pain and found that anxiety sensitivity led to an increase in pain avoidance behavior. Anxiety sensitivity has been a fruitful area of research, and evidence has mounted to show that it may be a cognitive vulnerability factor for negative pain experiences. Keogh found that subjects who are highly fearful of pain exhibit a selective attentional bias toward pain-related stimuli compared with those with low fear of pain. Further, those with high anxiety sensitivity misinterpret innocuous body sensations as threatening.

In a review of studies of patients with arthritis, Keefe found three variables in pain coping that predicted improved adjustment to chronic pain: (1) pain control and rational thinking (the perception that one has control over pain); (2) self-efficacy (confidence in one’s ability to cope with pain); and (3) helplessness (the perception that one lacks control over outcome). Psychological distress and perception of pain were greater in those with lower scores on measures of helplessness and higher scores on measures related to self-efficacy and rational thinking. Keefe has found that interventions that teach coping skills and enhance patients’ perception of control over their pain lessen psychological distress and lower perception of pain. Sullivan, Keefe, and others have done much to further the understanding of catastrophizing and its contribution to pain-related fear avoidance and enhanced disability. Catastrophizing is a cognitive style that incorporates excessive focus and worry about negative aspects of pain, underestimation of ability to cope effectively with pain, and helplessness in the face of pain. Catastrophizers report more negative pain-related thoughts, enhanced emotional distress, and greater pain intensity.

**Anxiety in Cancer**

For most patients, cancer requires facing uncertainty, worries about cancer treatment effects, fear of cancer progression and death, guilt, and spiritual questioning. In the cancer treatment trajectory, anxiety tends to increase at nodal crisis points: initial diagnosis, initiation of cancer treatment, cancer recurrence, failure of treatment, and perception of dying. Massie and Holland have described a “normal” response to cancer diagnosis and recurrence that resolves in days to weeks and is characterized by a period of initial shock and disbelief as well as emotional distress with anxiety, irritability, sadness, and disturbed appetite and sleep. Concentration impairment often temporarily reduces function at home and work. Patients can describe ruminative worry and fear about the future. This type of short-term anxiety reaction can facilitate a patient’s anticipation and preparation for what is to come, motivate a patient to seek support, and mobilize previously successful coping strategies, thus lessening the likelihood of sustained helplessness. Maladaptive, pathological, and persistent anxiety responses exist as well. While less common, these responses can precipitate anxiety disorders characterized by persistent social and/or occupational functional impairment and helplessness.

The Psychosocial Collaborative Oncology Group looked at the prevalence of psychiatric disorders in adult cancer patients in all stages of disease receiving treatment at three major cancer centers and found pre-existing anxiety disorders to be present in 4% of these patients. More common were psychiatric disorders that developed after the cancer diagnosis. In studies of women with breast cancer, rates of psychiatric disorders after diagnosis and at the time of recurrence range between 14% and 38%. The prevalence of PTSD in all stages of breast cancer is reported to be between 3% and 19%. Research has supported the clinical finding that precancer mental disorders worsen cancer-related distress. Smith et al. conducted a review of published studies of PTSD in cancer patients and found that a prior history of trauma, low levels of social support, and prior history of a psychiatric disorder to be predictive of PTSD occurrence following cancer diagnosis and treatment.

**Anxiety in Chronic Cancer Pain**

Patients often come to cancer with much fear about pain, and pain is common among cancer patients. In a recent review of the literature, the prevalence of pain...
in all cancer types was more than 50%.\textsuperscript{35} Cancer pain can result from direct tissue invasion, from biopsy and other diagnostic procedures, and from treatment (surgery, radiation, chemotherapy) and untoward consequences of treatment (infections, gastrointestinal tract ulcerations). Cancer pain can be treated with long-acting analgesics and shorter-acting rescue medications for breakthrough pain along with adjuvant therapies according to the World Health Organization guidelines.\textsuperscript{36} Cancer pain can be complicated by the psychological distress inherent in the experience of cancer pain itself, with its associated fear and helplessness, often precipitating mood and anxiety disturbances.\textsuperscript{37,38} Portenoy found significant pain to be a causal factor in an ovarian cancer patient’s report of increased anxiety.\textsuperscript{39} Further, cancer pain can trigger a reactivation of prior emotional trauma and can exacerbate underlying anxiety disorders.\textsuperscript{40,41} Precancer emotional trauma increases a sense of vulnerability that both cancer and pain reinforce.\textsuperscript{34} A prior history of trauma taxes the patient’s capacity to cope with illness and pain.\textsuperscript{42} More research is needed in this area because few studies in the cancer pain literature have examined pain as either a trigger or symptom of PTSD. In looking at patients with cancer of mixed etiologies, Gold found a significant association between the presence of PTSD and the degree of pain severity reported.\textsuperscript{43} As with noncancer pain, the relationship between pain catastrophizing and increased experience of pain and anxiety in cancer patients has been demonstrated.\textsuperscript{36,44–46} In addition, an enhanced sense of control over pain is associated with a reduction in cancer pain perception.\textsuperscript{44,46} Early identification and treatment of anxiety reactions, especially those involving low self-efficacy and high tendency to catastrophize, are likely have the potential to enhance cancer treatment compliance, recovery, and survival.

**Case History**

The pain and symptom management team of a large tertiary care center was asked to perform a consultation on Ms. A. She is a 35-year-old, married, successful businesswoman who 2 years previously had undergone a bilateral mastectomy with reconstruction for initial treatment of locally advanced, invasive, node-positive breast cancer. Chemotherapy followed by radiation therapy was completed, but targeted cancer therapy with monoclonal antibody treatment was terminated secondary to complaints of pain for which oxycodone was prescribed. Ms. A. also experienced persistent pain in her right axilla and across her upper back. Opioid tolerance developed, necessitating escalating doses and leading to the referral to the pain and symptom management team. On initial assessment by the team, Ms. A described her pain as continuous and interfering with most daily activities. It was not relieved by trials of physical therapy, acupuncture, or escalating doses of opioids, both with and without gabapentin. She also reported feeling highly irritable and worried, spending much of her time ruminating about the possibility of recurrence. She was unable to return to work, was unable to shop or do household chores, and isolated herself from friends and other family. Further evaluation revealed a history of early childhood abandonment by her father and neglect and emotional abuse by her mother. In her adult life, she had experienced untreated depression and anxiety as well as episodes of PTSD with hyperarousal, nightmares, avoidance, and overwhelming fear and helplessness. PTSD symptoms recurred at the time of cancer diagnosis and worsened after surgery, when she experienced severe postoperative pain. Over the 2 years since her surgery, she had had brief periods of improvement in function. Episodes of improvement ended with the onset of worsened pain, which she believed signified cancer recurrence. Much of the fear and ruminative worry she described during the day involved a hypervigilance for pain cues. She described herself as “frozen with fear,” unable to function, relentlessly pursuing reassurance from her oncology team. Despite having 2 years of being cancer free, she had been unable to recover a meaningful sense of purpose and enjoyment to her life.

This case highlights the reactivation of underlying psychopathology linked to earlier emotional trauma by postoperative pain in the context of high-risk cancer. The patient experienced fear, terror, helplessness, and anticipation of doom, which she linked to her current condition but which was probably fueled by her past trauma experience. The resulting disabling anxiety affected all aspects of her functioning, including her interpersonal relationships and her work, and interfered with her cancer treatment. She became overwhelmed, unable to cope, and unable to process and adapt to the loss, the fear, and the uncertainty she was facing. In patients like Ms. A., pain can trigger a flashback to an earlier trauma. We can suspect that Ms. A.’s hypervigilance with respect to her pain is in part a sign of PTSD and that her attentional bias toward pain cues links the present and past traumas and taxes her underdeveloped and insufficient capacity to cope with the emotional fallout of cancer.

**Diagnosis**

Diagnosis of anxiety in the context of cancer and chronic pain is difficult for many reasons. First, there is an overlap of anxiety symptoms, cancer symptoms, and adverse effects of cancer treatment. Problems with concentration, fatigue, shortness of breath, sleep, and appetite are common and nonspecific. All can be caused by anxiety, and all can be worsened by anxiety. Second, any medication or other organic factors producing an ongoing anxiety state must be identified (e.g., involvement of the central nervous system; systemic factors such as anemia, abnormal glucose levels, or atrial fibrillation; endocrine factors such as thyroid, pituitary, and parathyroid abnormalities; medications such as corticosteroids and interferon-\textsuperscript{\alpha}; withdrawal syndromes; and substance abuse). Third, one must differentiate an acute anxiety reaction associated with pain from a more maladaptive anxiety reaction that may become chronic. Psychiatric symptoms in patients

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<th>Table I</th>
<th>Key components of anxiety evaluation in cancer patients</th>
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<tr>
<td><strong>1.</strong></td>
<td>Obtain history of precancer anxiety disorder (generalized anxiety disorder, panic disorder, phobias, post-traumatic stress disorder, obsessive compulsive disorder)</td>
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<td><strong>2.</strong></td>
<td>Rule out drug effects (corticosteroids, interferon-\textsuperscript{\alpha} and underlying medical conditions (brain metastasis, pulmonary embolism, hypoxia, delirium, electrolyte disturbances, anemia, hormone-secreting tumors))</td>
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<tr>
<td><strong>3.</strong></td>
<td>Treat pain adequately</td>
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<td><strong>4.</strong></td>
<td>Once pain is controlled, reassess for anxiety disorder</td>
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with severe pain must be considered a direct result of pain and must be treated before an accurate psychiatric assessment can be made. Once pain is adequately addressed, psychopathology can be assessed. Table I outlines the key components of the psychiatric evaluation of patients with persistent cancer pain.

Several scales have been used to detect pathological anxiety states: The Hospital Anxiety and Depression Scale (HADS), the Hamilton Rating Scale for Anxiety, and the State-Trait Anxiety Inventory. Payne and others at Memorial Sloan Kettering Cancer Center found the HADS to be an easy, inexpensive, and convenient scale for use in the clinic setting, with a high predictive value when screening breast cancer patients for anxiety and mood disorders. The HADS is a 14-item self-report scale designed for use in the medically ill. It eliminates the somatic symptoms of anxiety and depression, which are poor indicators of psychological distress in this population. Each item is rated from 0 (“not at all”) to 3 (“very much”). A score greater than 13 has a positive predictive value of 75%.

### Treatment

The complexity of cancer patients with chronic pain underscores the potential benefit of a multidisciplinary approach, with psychiatry and psychology assuming major roles within the treatment team. However, many cancer treatment settings cannot offer this breadth of service within their own facility. Health care professionals should be aware of local and wider community resources available for psychoeducation, psychotherapy, and psychopharmacology interventions aimed at enhancing compliance with cancer treatment, coping, function, and quality of life. Hutchinson and colleagues have developed a tiered model of psychosocial intervention for cancer patients incorporating referral to community-based clinical interventions based on the level of the patient’s distress. Patients with mild distress (difficulty coping emotionally, social isolation, and problem-solving and decision-making issues) are referred for supportive care through cancer support websites, organizations that

<table>
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<th>Medication</th>
<th>Starting Dose</th>
<th>Daily Dose</th>
<th>Positives</th>
<th>Possible Side Effects</th>
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<tr>
<td><strong>ANTIDEPRESSANTS</strong></td>
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<tr>
<td><em>Selective Serotonin Reuptake Inhibitors (SSRIs)</em></td>
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<tr>
<td>Citalopram</td>
<td>10 mg q.a.m.</td>
<td>20–40 mg</td>
<td>Few side effects</td>
<td>All SSRIs: Gastrointestinal stimulation, sleep disruption, sexual dysfunction, restlessness (uncommon), headache, increased risk of bleeding; paroxetine is also anticholinergic</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>5–10 mg q.a.m.</td>
<td>10–20 mg</td>
<td>Few side effects</td>
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<tr>
<td>Sertraline</td>
<td>25 mg q.a.m.</td>
<td>50–100 mg</td>
<td>Few side effects</td>
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<tr>
<td>Paroxetine</td>
<td>10 mg q.h.s.</td>
<td>20 mg</td>
<td>Generic</td>
<td></td>
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<tr>
<td>Fluoxetine</td>
<td>5–10 mg q.a.m.</td>
<td>20–40 mg</td>
<td>Stimulating</td>
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<tr>
<td><em>Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)</em></td>
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<tr>
<td>Venlafaxine</td>
<td>37.5–75 mg q.a.m. or q.h.s.</td>
<td>150–300 mg</td>
<td>Neuropathic pain</td>
<td>All SNRIs: Blood pressure elevation, constipation, nausea, withdrawal reactions, sedation</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>20 mg q.a.m. or q.h.s.</td>
<td>40–60 mg</td>
<td>Neuropathic pain</td>
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<tr>
<td><em>Tricyclic Antidepressants (TCAs)</em></td>
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<tr>
<td>Amitriptyline</td>
<td>25–50 mg q.h.s.</td>
<td>50–100 mg</td>
<td>Neuropathic pain</td>
<td>All TCAs: Sedation; anticholinergic, α₁-adrenergic, and antihistaminic effects; prolonged QT</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>25–50 mg q.h.s.</td>
<td>50–100 mg</td>
<td>Less sedating than amitriptyline</td>
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<tr>
<td><strong>Other Antidepressants</strong></td>
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<tr>
<td>Mirtazapine</td>
<td>7.5–15 mg q.h.s.</td>
<td>30–45 mg q.h.s.</td>
<td>Increased appetite; improved sleep; antinausea</td>
<td>Oversedation; weight gain</td>
</tr>
<tr>
<td>Bupropion</td>
<td>150 mg q.a.m.</td>
<td>300–450 mg q.a.m.</td>
<td>Stimulating; no sexual dysfunction; smoking cessation</td>
<td>Lowers seizure threshold; occasional overstimulation</td>
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<tr>
<td><strong>BENZODIAZEPINES</strong></td>
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<tr>
<td>Lorazepam</td>
<td>0.25–0.5 mg b.i.d.–t.i.d.</td>
<td>1–2 mg per day</td>
<td>Anti-nausea; no active metabolites</td>
<td>All benzodiazepines: Sedation, anterograde memory impairment, motor impairment, high abuse potential, withdrawal reactions</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.25–0.5 mg b.i.d.</td>
<td>0.5 mg b.i.d. and 0.5–1 mg q.h.s.</td>
<td>Longer length of action</td>
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<tr>
<td><strong>ATYPICAL ANTIPSYCHOTICS</strong></td>
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<tr>
<td>Quetiapine</td>
<td>12.5–25 mg b.i.d.</td>
<td>12.5 mg b.i.d. and 50–100 mg q.h.s.</td>
<td>Low EPS</td>
<td>All atypical antipsychotics: Metabolic syndrome, sedation, quetiapine contraindicated with methadone (QT prolongation)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.25–0.5 mg b.i.d.</td>
<td>0.25 mg b.i.d. and 0.5 mg q.h.s.</td>
<td>Low EPS</td>
<td></td>
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**Abbreviations:** b.i.d. = twice a day; EPS = extrapyramidal side effects; q.a.m. = every morning; q.h.s. = at bedtime; t.i.d. = three times a day.
provide group support and psychoeducation, and tele-based cancer help lines. Those with moderate distress (high stress around adjustment to cancer) are referred for group and individual therapy by trained health professionals (e.g., a social worker, nurse counselor, or psychologist) in the community. Those with moderate to severe distress (anxiety disorders, acute stress disorder, PTSD, or mood disorders) are referred to psychologists or psychiatrists with oncology experience for psychological treatment and consideration of pharmacotherapy. It cannot be overemphasized, however, that adequate analgesia by itself can improve emotional and functional response and must be maintained in concert with any psychiatric intervention. Table II is an overview of common psychopharmacological agents helpful in the treatment of anxiety in cancer patients with pain.

**Psychopharmacology**

Benzodiazepines are potent anxiolytics and are relatively safe in the treatment of anxiety in the cancer patient. Their anxiolytic effect is an added bonus for many cancer patients. Adverse effects include dose-dependent sedation, psychomotor impairment (which can result in falling), memory deficits, and the potential for dependence. In patients with liver dysfunction, lorazepam and oxazepam are chosen over other benzodiazepines because of their lack of active metabolites.

Tricyclic antidepressants and the newer serotonin/norepinephrine reuptake inhibitors (SNRIs), duloxetine and venlafaxine, have long been used for their positive analgesic effects in neuropathic pain. They have a proven history of analgesic effects as well. Adverse effects for tricyclics include anticholinergic, histaminic, and \( \alpha \)-adrenergic reactions. Venlafaxine and duloxetine can cause strong withdrawal reactions. Selective serotonin reuptake inhibitors (SSRIs) are also efficacious in the treatment of all anxiety disorders. The literature on analgesic properties for SSRIs is less robust than for SNRIs. Side effects include gastrointestinal activation, sleep dysfunction, and appetite changes. Mirtazapine is an antidepressant particularly well suited for the cancer patient in that it has antinausea and potentially weight-promoting side effects, as well as sedating effects that are helpful in reversing sleep disturbance.

Antipsychotics are especially useful with severe anxiety when maximal doses of benzodiazepines are insufficient, with agitation related to delirium, and with patients intolerant of benzodiazepines. Atypical antipsychotics such as quetiapine and risperidone may have a better side-effect profile than older antipsychotics such as haloperidol and chlorpromazine, but they are more expensive.

**Psychotherapy**

Combining psychotherapy with medication management has been shown to be more effective than either modality alone in the treatment of anxiety disorders, but few studies have looked at combined treatment of chronic pain. Holroyd compared the separate and combined effects of cognitive-behavioral therapy and tricyclic antidepressants for the treatment of chronic tension headaches and found that the combined treatment was more likely to produce clinically significant reduction in headache pain than either treatment alone. The goal of psychotherapy is to lessen emotional distress, enhance coping ability and sense of control, and promote psychological adaptation. Psychotherapy can lessen fears about disease progression, help problem-solve associated psychosocial difficulties, and explore worries about increased dependence. Exploratory psychotherapy, especially where precancer trauma is involved, can be helpful in understanding antecedents of anxiety, in changing maladaptive coping styles, and in working through issues around grief and loss. Forming a therapeutic relationship can be invaluable in discussing existential and spiritual issues that arise around cancer as well as exploring meaning in both life and in death. Cognitive-behavioral therapy has been shown to be helpful both in chronic pain and in anxiety disorders. It helps elucidate patterns of maladaptive attitudes toward illness, encourages alternative coping strategies, and allows for earlier recognition of triggers for anxiety and somatization. Growing evidence indicates that behavioral interventions such as hypnosis, progressive muscle relaxation, and acupuncture have roles in the treatment of anxiety and chronic pain in these patients.

**Conclusions**

Anxiety in cancer patients with pain must first be regarded as a consequence of inadequate pain control. Along with adequate pain management, a multimodal approach to anxiety treatment is critical to achieving a return to function and improving quality of life. Psychological assessment and intervention with psychopharmacological and psychotherapeutic modalities is an essential part of the comprehensive treatment approach to ongoing cancer pain.

References


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