CHAPTER 30

Pain

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INTRODUCTION

Pain is perhaps among the most prevalent and distressing symptoms encountered in patients with cancer. Psychiatric and psychological consultation in the psycho-oncology setting must take into account the important relationships between pain and psychological and psychiatric morbidity. Uncontrolled pain can mimic psychiatric disorders, so mental health clinicians must be knowledgeable about pain and its appropriate management to recognize cancer-related pain when it is present. In addition, psychiatrists and psychologists can play a vital role in the multidisciplinary approach to managing cancer pain at all stages of disease. This chapter reviews the prevalence of pain in cancer, pain syndromes, and pain assessment issues, as well as pharmacologic and nonpharmacologic interventions for cancer-related pain. Psychiatric and psychological interventions in the treatment of cancer pain have now become an integral part of a comprehensive approach to pain management, and these are highlighted in this chapter.

PREVALENCE OF PAIN

Pain is a common problem for cancer patients, with approximately 70% of patients experiencing severe pain at some time in the course of their illness.[1] It has been suggested that nearly 75% of patients with advanced cancers have pain,[2] and that 50% of terminally ill patients are in moderate to severe pain.[3] It is also estimated that 25% of cancer patients die in severe pain.[4] There is considerable variability in the prevalence of pain among different types of cancer. For example, approximately 5% of leukemia patients experience pain during the course of their illness, compared to 50%–75% of patients with tumors of the lung, gastrointestinal (GI) tract, or genitourinary system. Patients with cancers of the bone or cervix have been found to have the highest prevalence of pain, with as many as 85% of patients experiencing significant pain during the course of their illness.[5] Despite the high prevalence of pain, however, studies have shown that it is frequently underdiagnosed and inadequately treated.[4] It is important to remember that pain is frequently only one of several symptoms that occur as part of a "cluster" of physical and psychological symptoms.[6] With disease progression, the number of distressing physical and psychological symptoms increases so that patients with advance disease report an average of 11 symptoms. A global evaluation of the symptom burden allows for a more complex understanding of the impact of pain.[7]

PAIN TYPES AND SYNDROMES IN CANCER

The International Association of Pain has defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[8] This definition of pain has disconnected the concept of pain intensity being directly proportional to the objectively observable tissue damage, emphasizing the subjective nature of the pain experience. In cancer pain patients however, there is typically dramatic evidence of tissue damage that is etiologically related to the pain complaint. This definition, particularly the component which emphasizes pain as an emotional experience as well as a sensory one, clearly demonstrates the need for psychosocial involvement in pain assessment and management.

Pain is often characterized by type on the basis of temporal factors as well as pathophysiology. Pain is often subtyped as acute pain or chronic pain based on temporal characteristics. A well-defined temporal pattern of onset and termination characterizes acute pain. Generally, it is associated with subjective and objective physical or behavioral signs (e.g., grimacing, guarding, restlessness) and evidence of hyperactivity of the autonomic nervous system (e.g., rapid pulse, sweating). In contrast, chronic pain is pain that is experienced for longer than 3–6 months, or pain that persists beyond evidence of tissue damage healing. Patients with chronic pain often do not "look as if they are in pain" because adaptation of the autonomic nervous system occurs, and acute pain behaviors become replaced by depression, disability, and dysfunction. Chronic cancer pain can lead to significant changes in mood, personality, quality of life, relational problems, and functional ability.[1] As such, this type of pain requires an approach that includes treatment of the cause of the pain as well as treatment of its psychological and social consequences.[9]

Table 30–1. Classification of pain

Nociceptive pain
Results from stimulation of intact "nociceptors" (pain receptors)
Includes somatic pain (involving skin, soft tissue, muscle, bone); visceral pain (involving internal organs, hollow viscera)
Responds to opioid and nonopioid analgesics
Neuropathic pain
Results from stimulation of damaged or compromised nerve tissue
Responds to opioid and nonopioid analgesics AND adjuvant medications

Pain can be further classified into two major categories based on pathophysiology: *nociceptive* and *neuropathic* pain (Table 30–1).[10] Nociceptive pain derives from the stimulation of intact "nociceptors" or pain receptors in afferent nerves and is further subdivided into *somatic pain* (involving skin, soft tissue, muscle, and bone) and *visceral pain* (involving internal organs and hollow viscera). Nociceptive pain may be well-localized (common in somatic pain) or more diffuse (common in visceral pain), and may be sharp, dull, aching, gnawing, throbbing, constant, or spasmodic, with varying intensity. Neuropathic pain involves stimulation of damaged or compromised nerve tissue, and may be burning, tingling, stabbing, shooting, with a sensation of electric shock, or allodynia (the sensation of pain or discomfort produced by a minimal stimulus such as light touch to the skin). The differentiation of pain into one of these subtypes (particularly nociceptive vs. neuropathic) can help in determining appropriate therapy, as discussed below.

Foley[1] has categorized cancer pain syndromes based on temporal, etiologic, and contextual factors (Table 30–2). This approach to understanding cancer pain syndromes provides clinicians with a useful classification when considering therapeutic approaches.

MULTIDIMENSIONAL CONCEPT OF PAIN IN TERMINAL ILLNESS

Pain, and especially pain in cancer, is not a purely nociceptive or physical experience but involves complex aspects of human functioning, including personality, affect, cognition, behavior, and social relations.[11] It is important to note that the use of analgesic drugs alone does not

Table 30–2. Types of patients with pain from cancer

1. Patients with acute cancer-related pain
   Associated with the diagnosis of cancer
   Associated with cancer therapy (surgery, chemotherapy, or radiation)
2. Patients with chronic cancer-related pain
   Associated with cancer progression
   Associated with cancer therapy (surgery, chemotherapy, or radiation)
3. Patients with preexisting chronic pain and cancer-related pain
4. Patients with a history of drug addiction and cancer-related pain
   Actively involved in illicit drug use
   In methadone maintenance programs
   With a history of drug use
5. Dying patients with cancer-related pain

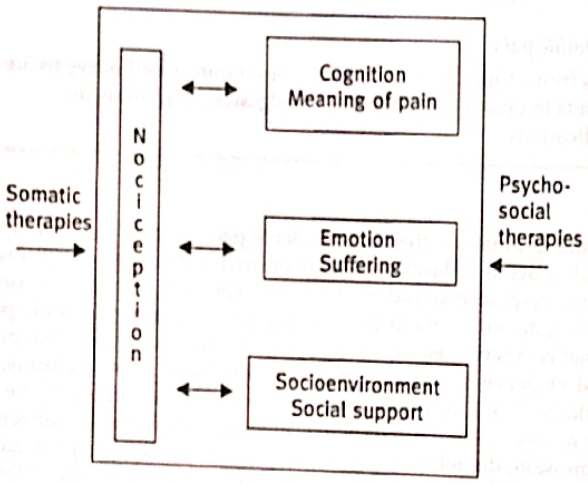

Fig. 30–1. The multidimensional nature of pain in cancer.

always lead to pain relief and that the psychological factors play a modest but important role in pain intensity.[12] The interaction of cognitive, emotional, socio-environmental, and nociceptive aspects of pain shown in Fig. 30–1 illustrates the multidimensional nature of pain in terminal illness and suggests a model for multimodal intervention.[13] The challenge of untangling and addressing both the physical and the psychological issues involved in pain is essential in developing rational and effective management strategies. Psychosocial therapies directed primarily at psychological variables have profound impacts on nociception, while somatic therapies have beneficial effects on the psychological aspects of nociceptive pain. Ideally, such somatic and psychosocial therapies are used simultaneously in a multidisciplinary approach to pain management in the cancer patient.[14]

PSYCHOLOGICAL FACTORS IN THE CANCER PAIN EXPERIENCE

Among the many stressors faced by patients with cancer are dependency, disability, and fear of painful death. Such fears are universal; however, the level of psychological distress is variable and depends on medical factors, social support, coping capacities, and personality.

Cancer pain and distress. Cancer-related pain has profound effects on psychological distress; and psychological factors such as anxiety, depression, and the meaning of pain for the patient can intensify the cancer pain experience. Daut and Cleeland[15] demonstrated that cancer patients who attribute a new pain to an unrelated benign cause report less interference with their activity and quality of life than patients who believe their pain represents progression of disease. Spiegel and Bloom[9] found that women with metastatic breast cancer experience more intense pain if they believe their pain represents spread of their cancer and if they are depressed. Belief about the meaning of pain and the presence of a mood disturbance were better predictors of pain level than number or site of metastases.

Cancer pain and quality of life. In an attempt to define the potential relationships between cancer pain and psychosocial variables, Padilla et al.[16] found that there were pain-related quality-of-life variables in three domains: physical well-being; psychological well-being (consisting of affective factors, cognitive factors, spiritual factors, communication skills, coping skills, and meaning attribute to pain or cancer); and interpersonal well-being (focusing on social support or role functioning). The perception of marked impairment in activities of daily living has been shown to be associated with increased pain intensity.[17] Measures of emotional disturbance have been reported to be predictors of pain in the late stages of cancer, and cancer patients with less anxiety and depression are less likely to report pain.[18] In a prospective study of cancer patients, it was found that maladaptive coping strategies, lower levels of self-efficacy, and distress specific to treatment or disease progression were modest but significant predictors of reports of pain intensity.[12]

Psychological variables, such as the amount of control people believe they have over pain, emotional associations and memories of pain, fear of death, depression, anxiety, and hopelessness, contribute to the experience of pain and can increase suffering. Singer and colleagues[19] reported an association among the frequency of multiple pains, increased disability, and higher levels of depression. All too frequently, psychological variables are proposed to explain continued pain or lack of response to therapy when in fact medical factors have not been adequately appreciated. Often, the psychiatrist is the last physician to consult on a cancer patient with pain. In that role, one must be vigilant that an accurate pain diagnosis is made and must be able to assess the adequacy of the medical analgesic management provided. Personality factors may be quite distorted by the presence of pain, and relief of pain often results in the disappearance of a perceived psychiatric disorder.[20]

CANCER PAIN AND PSYCHIATRIC DISORDERS

There is an increased frequency of psychiatric disorders in cancer patients with pain. In the Psychosocial Collaborative Oncology Group Study[21] on the prevalence of psychiatric disorders in cancer patients, 39% of the patients who received a psychiatric diagnosis (Table 30-3) reported significant pain, whereas only 19% of patients without a psychiatric diagnosis had significant pain. The psychiatric disorders in cancer patients with pain primarily included adjustment disorder with depressed or anxious mood (69%) and major depression (15%). This finding of increased frequency of psychiatric disturbance in cancer pain patients also has been reported by other investigators.[22] The incidence and patterns of psychiatric disorders may vary systematically in subgroups of patients. For example, Steifel et al.[23] described the psychiatric complications seen in cancer patients undergoing treatment for epidural spinal cord compression (ESCC), which may include high-dose dexamethasone (as much as 96 mg/day for up to a week, followed by a tapering course for up to 3 or 4 weeks). Twenty-two percent of patients with ESCC had a major depressive syndrome diagnosed as compared to 4% in the comparison group. Also, delirium was much more common in the dexamethasone-treated patients with ESCC, with 24% diagnosed with delirium during the course of treatment as compared to only 10% in the comparison group.

Although there is limited information about patterns of disorders in other subpopulations, it is apparent that advanced disease itself, at least among patients with cancer, is associated with a relatively high prevalence of depression and delirium.[24] Approximately 25% of all cancer patients experience severe depressive symptoms, with the prevalence increasing to 77% in those with advanced illness. The prevalence of organic mental disorders (delirium) among cancer patients requiring psychiatric consultation has been found to range from 25% to 40% and to be as high as 85% during the terminal stages of illness.[25] Opioid

Table 30–3. Rates of DSM-III psychiatric disorders and prevalence of pain observed in 215 cancer patients from three cancer centers

Diagnostic category	*Number in diagnostic class*	*Percentage of psychiatric diagnoses*	*Number with significant pain*[a]
Adjustment disorders	69	32	68
Major affective disorders	13	6	13
Organic mental disorders	8	4	8
Personality disorders	7	3	7
Anxiety disorders	4	2	4
Total with psychiatric diagnosis	101	47	39 (39%)
Total with no psychiatric diagnosis	114	53	21 (19%)
Total patient population	215	100	60 (28%)

[a]Score greater than 50 mm on a 100 mm VAS pain severity.
ABBREVIATION: VAS, visual analogue scale

analgesics and many other drugs can cause confusional states, particularly in the elderly and terminally ill.[6]

CANCER PAIN AND SUICIDE

Uncontrolled pain is a major factor in suicide and suicidal ideation in cancer patients.[26] The majority of suicides observed among patients with cancer had severe pain, which was often inadequately controlled or tolerated poorly.[27] Although relatively few cancer patients commit suicide, they are at increased risk. Pain is both a unique and synergistic contributor to suicide risk in cancer patients. For more details on suicide and desire for hastened death in cancer patients, please refer to Chapter 43.

CANCER PAIN ASSESSMENT

The initial step in cancer pain management is a comprehensive assessment of pain symptoms. An important element in assessment of pain is the concept that assessment is continuous and needs to be repeated over the course of pain treatment. There are essentially four aspects of pain experience in cancer that require ongoing evaluation, and they include pain intensity, pain relief, pain-related functional interference (e.g., mood state, general and specific activities), and monitoring of intervention effects (e.g., analgesic drug side effects, abuse).[28] Table 30–4 outlines the principles of pain assessment as described by Foley.[1] The Memorial Pain Assessment Card (MPAC)[29] is also a helpful clinical tool that allows patients to report their pain experience. The MPAC consists of visual analog scales that measure pain intensity, pain relief, and mood. Patients can complete the MPAC in less than 30 seconds. Patients' reports of pain intensity, pain relief, and present mood state provide the essential information required to help guide their pain management. The Brief Pain Inventory[30] is another pain assessment tool that has useful clinical and research applications.

Table 30–4. Principles of pain assessment

1. Believe the patient's complaint of pain
2. Take a detailed history
3. Assess the psychosocial status of the patient
4. Perform a careful medical and neurological examination
5. Order and personally review the appropriate diagnostic procedures
6. Evaluate the patient's extent of pain
7. Treat the pain to facilitate the diagnostic work-up
8. Consider the alternative methods of pain control during the initial evaluation
9. Reassess the pain complaint during the prescribed therapy

INADEQUATE CANCER PAIN MANAGEMENT

Inadequate management of cancer pain is often a result of the inability to properly assess pain in all its dimensions.[14] All too frequently, psychological variables are proposed to explain continued pain or lack of response to therapy, when in fact medical factors have not been adequately appreciated. Other causes of inadequate pain management include lack of knowledge of current pharmacotherapeutic or psychotherapeutic approaches; focus on prolonging life rather than alleviating suffering; lack of communication between doctor and patient; limited expectations of patients regarding pain relief; limited communication capacity in patients impaired by organic mental disorders; unavailability of opioids; doctors' fear of causing respiratory depression; and, most important, doctors' fear of amplifying addiction and substance abuse. In cancer, several additional factors have been noted to predict the undermanagement of pain, including a discrepancy between physician and patient in judging the severity of pain; the presence of pain that physicians do not attribute to cancer; better performance status; age of 70 years or more; and female sex.[31]

Fear of addiction and inadequate cancer pain management. Fear of addiction affects both patient compliance and physician management of narcotic analgesics, leading to undermedication of pain in cancer patients.[32] Studies of the patterns of chronic narcotic analgesic use in patients with cancer have demonstrated that, although tolerance and physical dependence commonly occur, addiction (psychological dependence) is rare and almost never occurs in individuals without a history of drug abuse before cancer illness.[32] Studies of the patterns of chronic narcotic analgesic use in patients with cancer have demonstrated that, although tolerance and physical dependence commonly occur, addiction (psychological dependence) is rare and almost never occurs in individuals without a history of drug abuse before cancer illness[33] reported on their experience in managing cancer pain in such a population. Of 468 inpatient cancer-pain consultations, only eight patients (1.7%) had a history of intravenous (IV) drug abuse, but none had been actively abusing drugs in the previous year. All eight of these patients had inadequate pain control, and more than half were intentionally undermedicated because of staff concern that drug abuse was active or would recur. Adequate pain control was ultimately achieved in these patients by using appropriate analgesic dosages and intensive staff education.

Concerns over respiratory depression and inadequate cancer pain management. The risk of inducing respiratory depression is too often overestimated and can limit appropriate use of narcotic analgesics for pain and symptom control. Bruera et al.[34] demonstrated that, in a population of terminally ill cancer patients with respiratory failure and dyspnea, the administration of subcutaneous morphine actually improved dyspnea without causing a significant deterioration in respiratory function.

Lack of concordance between patient and caregiver assessment of pain intensity. The adequacy of cancer pain management can be influenced by the lack of concordance between patient ratings or complaints of their pain and those made by caregivers. Persistent cancer pain is often ascribed to a psychological cause when it does not respond to treatment attempts. In our clinical experience, we have noted that patients who report their pain as severe are quite likely to be viewed as having a psychological contribution to their complaints. Staff members' ability to empathize with a patient's pain complaint may be limited by the intensity of the pain complaint. Grossman et al.[35] found that, while there is a high degree of concordance between patient and caregiver ratings of patient pain intensity at the low and moderate levels, this concordance breaks down at high levels. Thus, a clinician's ability to assess a patient's level of pain becomes unreliable once a patient's report of pain intensity rises above 7 on a visual analogue rating scale of 0–10. Physicians must be educated as to the limitations of their ability to objectively assess the severity of a subjective pain experience. In addition, patient education is often a useful intervention in such cases.

PSYCHIATRIC MANAGEMENT OF PAIN IN CANCER

Optimal treatment of pain associated with cancer may require a multimodal strategy, including pharmacological, psychotherapeutic, rehabilitative, and interventional approaches. Psychiatric participation in pain management involves the use of psychotherapeutic, cognitive-behavioral, and psychopharmacologic interventions, usually in combination.

PSYCHOTHERAPY AND CANCER PAIN

The goals of psychotherapy with cancer patients with pain are to provide support, knowledge, and skills (Table 30–5). Utilizing short-term supportive psychotherapy focused on the crisis created by the medical illness, the therapist provides emotional support, continuity, information, and assists in adaptation. The therapist has a role in emphasizing past strengths, supporting previously successful coping strategies, and teaching new coping skills, such as relaxation, cognitive coping, use of analgesics, self-observation, documentation, assertiveness, and communication skills. Communication skills are of paramount importance for both patient and family, particularly around pain and analgesic issues. The patient and family are the unit of concern, and need a more general, long-term, supportive relationship within the healthcare system in addition to specific psychological approaches dealing with pain and dying, which a psychiatrist, psychologist, social worker, chaplain, or nurse can provide.

Utilizing psychotherapy to diminish symptoms of anxiety and depression, factors that can intensify pain, empirically has beneficial effects on cancer pain experience. Spiegel and Bloom[36] demonstrated, in a controlled randomized prospective study, the effect of both supportive group therapy for metastatic breast cancer patients in general and, in particular, the effect of hypnotic pain control exercises. Their support group focused not on interpersonal processes or self-exploration, but rather on a series of themes related to the practical and existential problems of living with cancer. Patients were divided into two treatment groups and a control group. The treatment patients experienced significantly less pain than the control patients. Those in the group that combined a self-hypnosis exercise group showed a slight increase, and the control group showed a large increase in pain.

Table 30–5. Goals and forms of psychotherapy for pain in patients with advanced disease

Goals	*Form*
Support—provide continuity	Individuals—supportive/crisis intervention
Knowledge—provide information	Family—patient and family are the unit of concern
Skills—relaxation cognitive coping use of analgesics communication	Group—share experiences identify successful coping strategies

Group interventions for individuals with cancer pain (even in advanced stages of disease) are a powerful means of sharing experiences and identifying successful coping strategies. The limitations of using group interventions for patients with advanced disease are primarily pragmatic. The patient must be physically comfortable enough to participate and have the cognitive capacity to be aware of group discussion. It is often helpful for family members to attend support groups during the terminal phases of the patient's illness. Interventions aimed at spouses and family members of cancer pain patients can also be beneficial (see section on Novel Psychosocial Interventions). Passik et al.[37] have worked with spouses of brain tumor patients in a psychoeducational group that has included spouses at all phases of the patient's diagnosis and treatment. They have demonstrated how bereavement issues are often a focus of such interventions from the time of diagnosis. The leaders have been impressed by the increased quality of patient care that can be given at home by the spouse (including pain management and all forms of nursing care) when the spouses engage in such support.

Psychotherapeutic interventions that have multiple foci may be most useful. On the basis of a prospective study of cancer pain, cognitive-behavioral and psychoeducational techniques based on increasing support, self-efficacy, and providing education may prove to be helpful in assisting patients in dealing with increased pain.[38] Results of an evaluation of patients with cancer pain indicate that psychological and social variables are significant predictors of pain. More specifically, distress specific to the illness, self-efficacy, and coping styles were predictors of increased pain.

Cognitive-behavioral techniques. Cognitive-behavioral techniques can be useful as adjuncts to the management of pain in cancer patients (Table 30–6). These techniques fall into two major categories: cognitive

Table 30–6. Cognitive-behavioral techniques used by pain patients with advanced disease

Psychoeducation
Preparatory information
Self-monitoring
Relaxation
Passive breathing
Progressive muscle relaxation
Distraction
Focusing
Controlled by mental imagery
Cognitive distraction
Behavioral distraction
Combined techniques (relaxation and distraction)
Passive/progressive relaxation with mental imagery
Systematic desensitization
Meditation
Hypnosis
Biofeedback
Music therapy
Cognitive therapies
Cognitive distortion
Cognitive restructuring
Behavioral therapies
Modeling
Graded task management
Contingency management
Behavioral rehearsal

Table 30–7. Cognitive-behavioral techniques: definitions and descriptions

Behavioral therapy	The clinical use of techniques derived from the experimental analysis of behavior, i.e. learning and conditioning for the evaluation, prevention, and treatment of physical disease or physiological dysfunction
Cognitive therapy	A focused intervention targeted at changing maladaptive beliefs and dysfunctional attitudes. The therapist engages the client in a process of collaborative empiricism, where these underlying beliefs are challenged and corrected
Operant pain	Pain behaviors resulting from operant learning or conditioning. Pain behavior is reinforced and continues because of secondary gain, i.e. increased attention and caring
Respondent pain	Pain behaviors resulting from respondent learning or conditioning. Stimuli associated with prior painful experiences can elicit increased pain and avoidance behavior
Cognitive restructuring	Redefinition of some or all aspects of the patient's interpretation of the noxious or threatening experience, resulting in decreased distress, anxiety, and hopelessness
Self-monitoring (pain diary)	Written or audiotaped chronicle that the patient maintains to describe specific agreed-upon characteristics associated with pain
Contingency management	Focusing of patient and family member responses that either reinforce or inhibit specific behaviors exhibited by the patient. Method involves reinforcing desired "well" behaviors
Grade task assignments	A hierarchy of tasks, i.e. physical, cognitive, and behavioral are compartmentalized and performed sequentially in manageable steps ultimately achieving an identified goal
Systematic desensitization	Relaxation and distraction exercises paired with a hierarchy of anxiety-arousing stimuli presented through mental imagery, or presented in vivo, resulting in control of fear

techniques and behavioral techniques. Both techniques comprise a range of techniques including passive relaxation with mental imagery, cognitive distraction or focusing, progressive muscle relaxation, biofeedback, hypnosis, and music therapy.[39] The goal of treatment is to guide the patient toward a sense of control over pain. Some techniques are primarily cognitive in nature, focusing on perceptual and thought processes, and others are directed at modifying patterns of behavior that help cancer patients cope with pain. Behavioral techniques for pain control seek to modify physiologic pain reactions, respondent pain behaviors, and operant pain behaviors (see Table 30–7 for definitions).

Relaxation techniques. Several techniques can be used to achieve a mental and physical state of relaxation. Muscular tension, autonomic arousal, and mental distress exacerbate pain.[40,41] Some specific relaxation techniques include (1) passive relaxation focusing attention on sensations of warmth and decreased tension in various parts of the body, (2) progressive muscle relaxation involving active tensing and relaxing of muscles, and (3) meditation.

Hypnosis. Hypnosis can be a useful adjunct in the management of cancer pain.[36,39,42–45] Hypnotherapy, usually involving the teaching of self-hypnotic techniques, can be used effectively in the management of pain associated with invasive procedures.[46] In a controlled trial comparing self-hypnosis with cognitive-behavioral therapy in relieving mucositis following a bone marrow transplant, patients utilizing self-hypnosis reported a significant reduction in pain compared to patients who used cognitive-behavioral techniques.[38] The hypnotic trance is essentially a state of heightened and focused concentration, and thus it can be used to manipulate the perception of pain.

Biofeedback. Fotopoulos et al.[47] noted significant pain relief in a group of cancer patients who were taught electromyographic (EMG) and electroencephalographic (EEG) biofeedback-assisted relaxation. Only 2 out of 17 were able to maintain analgesia after the treatment ended. A lack of generalization of effect can be a problem with biofeedback techniques. Although physical condition may make a prolonged training period impossible, especially for the terminally ill, most cancer patients can often use EMG and temperature biofeedback techniques for learning relaxation-assisted pain control.[48]

Novel psychosocial interventions. It should be noted that nontraditional psychosocial interventions for cancer pain hold great promise. For example, Keefe et al.[49] tested the efficacy of a partner-guided cancer pain management protocol. The partner-guided pain management training protocol was a three-session intervention conducted in patients' homes that integrated educational information about cancer pain with systematic training of patients and partners in cognitive and behavioral pain coping skills. Data analyses revealed that the partner-guided pain management protocol produced significant increases in partners' ratings of their self-efficacy for helping the patient control pain and self-efficacy for controlling other symptoms.

AROMA THERAPY

Aromas have been shown to have innate relaxing and stimulating qualities. Our colleagues at Memorial Hospital have recently begun to explore the use of aroma therapy for the treatment of procedure-related anxiety (i.e., anxiety related to magnetic resonance imaging [MRI] scans). Utilizing the scent heliotropin, Manne et al.[50] reported that two-thirds of the patients in their study found the scent especially pleasant and reported feeling much less anxiety than those who were not exposed to the scent during MRI. As a general relaxation technique, aroma therapy may have an application for pain management, but this is as yet unstudied.

PHARMACOTHERAPIES FOR PAIN

Although the management of analgesic medications is more often undertaken by the oncologist or palliative care specialist, it is essential that the psycho-oncologist have a thorough understanding of the analgesic medications most often used in the management of cancer-related pain. The World Health Organization (WHO) has devised guidelines for analgesic management of cancer pain that the Agency for Health Care Policy and Research (AHCPR) has endorsed for the management of pain related to cancer.[51] These guidelines, also known widely as the WHO Analgesic Ladder (see Fig. 30–2), have been well validated.[52] This approach advocates selection of analgesics on the basis of severity of pain. For mild to moderately severe pain, nonopioid analgesics such as nonsteroidal antiinflammatory drugs (NSAIDs) and acetaminophen are recommended. For pain that is persistent and moderate to severe in intensity, opioid analgesics of increasing potency (such as morphine) should be used. Adjuvant agents, such as laxatives and psychostimulants, are useful in preventing as well as treating opioid side effects such as constipation or sedation, respectively. Adjuvant analgesic drugs, such as the

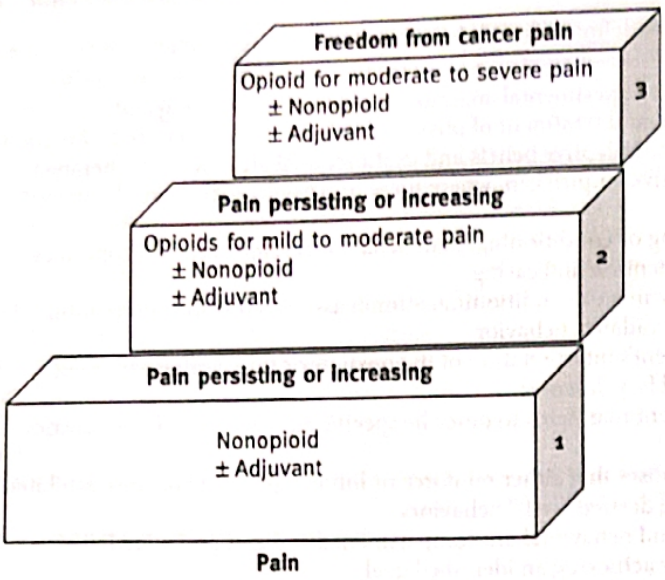

Fig. 30–2. WHO Analgesic Ladder.
SOURCE: Adapted from *Cancer pain relief, with a guide to opioid availability*. 2nd ed. Geneva: World Health Organization; 1996.

antidepressant analgesics, are suggested for considered use, along with opioids and NSAIDs, in all stages of the analgesic ladder (mild, moderate, or severe pain).

Portenoy[53] have described the indications for and the use of three classes of analgesic drugs that have applications in the management of cancer and acquired immunodeficiency syndrome (AIDS) patients with pain: nonopioid analgesics (such as acetaminophen, aspirin, and other NSAIDs), opioid analgesics (of which morphine is the standard), and adjuvant analgesics (such as antidepressants and anticonvulsants).

NONOPIOD ANALGESICS (NSAIDs)

The nonopioid analgesics (Table 30–8) are prescribed principally for mild to moderate pain or to augment the analgesic effects of opioid analgesics in the treatment of severe pain. The analgesic effects of the NSAIDs result from their inhibition of cyclooxygenase and the subsequent reduction of prostaglandins in the tissues. The concurrent use of NSAIDs or acetaminophen and opioids provides more analgesia than does either of the drug classes alone. In contrast to opioids, NSAIDs have a ceiling effect for analgesia, do not produce tolerance or dependence, have antipyretic effects, and have a different spectrum of adverse side effects.[51]

The NSAIDs' mechanisms of action, pharmacokinetics, and pharmacodynamics influence the analgesic response. The selection of the NSAID should take into account the etiology and severity of the pain, concurrent medical conditions that may be relative contraindications (e.g., bleeding diathesis), associated symptoms, and favorable experience by the patient as well as the physician. From a practical point of view, an NSAID should be titrated to effect as well as to side effects. There is also variability in patient response to both relief and adverse reactions; if the results are not favorable, an alternative NSAID should be tried.

MAJOR ADVERSE EFFECTS OF NSAIDs

The major adverse effects associated with NSAIDs include gastric ulceration, renal failure, hepatic dysfunction, and bleeding. The use of NSAIDs has been associated with a variety of GI toxicities, including minor dyspepsia and heartburn, as well as major gastric erosion, peptic ulcer formation, and GI hemorrhage. The nonacetylated salicylates, such as salsalate, sodium salicylate, and choline magnesium salicylate, theoretically have fewer GI side effects and might be considered in cases where GI distress is an issue. Prophylaxis for NSAID-associated GI symptoms includes H2-antagonist drugs (cimetidine 300 mg tid-qid or ranitidine 150 mg bid); misoprostal 200 mg qid; omeprazole 20 mg qd; or an antacid. Patients should be informed of these symptoms, issued guaiac cards with reagent, and taught to check their stool weekly. NSAIDs affect kidney function and should be used with caution. Prostaglandins are involved in the autoregulation of renal blood flow, glomerular filtration, and the tubular transport of water and ions. NSAIDs can cause a decrease in glomerular filtration, acute and chronic renal failure, interstitial nephritis, papillary necrosis, and hyperkalemia.[54] In patients with renal impairment, NSAIDs should be used with caution, since many (i.e., ketoprofen, feroprofen, naproxen, and carpofen) are highly dependent on renal function for clearance. The risk of renal dysfunction is greatest in patients with advanced age, preexisting renal impairment, hypovolemia, concomitant therapy with nephrotoxic drugs, and heart failure. Prostaglandins modulate vascular tone, and their inhibition by the NSAIDs can cause hypertension as well as interference with the pharmacologic control of hypertension.[55] Caution should be used in patients receiving β-adrenergic antagonists, diuretics, or angiotensin-converting enzyme inhibitors. Several studies have suggested that there is substantial biliary excretion of several NSAIDs, including indomethacin and sulindac. In patients with hepatic dysfunction, these drugs should be used with caution. NSAIDs, with the exception of the nonacetylated salicylates (e.g., sodium salicylate, choline magnesium trisalicylate), produce inhibition of platelet aggregation (usually reversible, but irreversible with aspirin). NSAIDs should be used with extreme caution or avoided in patients who are thrombocytopenic or who have clotting impairment.

Table 30–8. Oral analgesics for mild to moderate pain in cancer

Analgesic (by class)	*Starting dose (mg)*	*Plasma duration (hrs)*	*Half-life (hrs)*	*Comments*
Nonsteroidal				
Aspirin	650	4–6	4–6	The standard for comparison among nonopioid analgesics
Ibuprofen	400–600	—	—	Like aspirin, can inhibit platelet function
Choline magnesium trisalicylate	700–1500	—	—	Essentially no hematologic or gastrointestinal side effects
Weaker opioids				
Codeine	32–65	3–4	—	Metabolized to morphine, often used to suppress cough in patients at risk of pulmonary bleed
Oxycodone	5–10	3–4	—	Available as a single agent and in combination with aspirin or acetaminophen
Proxyphene	65–13	4–6	—	Toxic metabolite norpropoxy accumulates with repeated usage

The use of NSAIDs in patients with cancer and AIDS must be accompanied by heightened awareness of toxicity and adverse effects. NSAIDs are highly protein bound, and the free fraction of available drug is increased in cancer patients who are cachectic, wasted, and hypoalbuminic, often resulting in toxicities and adverse effects. Patients with cancer are frequently hypovolemic and on concurrent nephrotoxic drugs and so are at increased risk for renal toxicity related to NSAIDs. Finally, the antipyretic effects of the NSAIDs may interfere with early detection of infection in patients with cancer.

COX-2 inhibitors have an analgesic action equal to that of conventional NSAIDs, but with fewer GI complications and have been widely used for rheumatic diseases.[56] COX-2 inhibitors are associated with an increased risk of adverse cardiovascular events, including infarction, stroke and new onset or worsening of preexisting hypertension, GI irritation, ulceration, bleeding and perforation, and are contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG).

OPIOID ANALGESICS

Opioid analgesics are the mainstay of pharmacotherapy of moderate to severe intensity pain in the patient with cancer (see Table 30–9).

In choosing the appropriate opioid analgesic for cancer pain, Portenoy[57] highlights the following important considerations: opioid class, choice of "weak" versus "strong" opioids, pharmacokinetic characteristics, duration of analgesic effect, favorable prior response, and opioid side effects (Table 30–10).

Opioid classes. Opioid analgesics are divided into two classes: the agonists and the agonist-antagonists, on the basis of their affinity to opioid receptors. Pentazocine, butorphanol, and nalbuphine are examples of opioid analgesics with mixed agonist-antagonist properties. These drugs can reverse opioid effects and precipitate an opioid withdrawal syndrome in patients who are opioid tolerant or dependent. They are of limited use in the management of chronic pain in cancer and AIDS. Oxycodone (in combination with either aspirin or acetaminophen), hydrocodone, and codeine are the so-called weaker opioid analgesics and are indicated for use in step 2 of the WHO ladder for mild to moderate pain. More severe pain is best managed with morphine or another of the "stronger" opioid analgesics, such as hydromorphone, methadone, levorphanol, or fentanyl. Oxycodone, as a single agent without aspirin or acetaminophen, is available in immediate and sustained-release forms and is considered a stronger opioid in these forms. Oxymorphone, including Numorphan, Opana, and Opana ER, is a potent opioid analgesic. They act quickly when taken orally and have significantly longer half-lives than morphine. Rectal administration is an alternative for those patients unable to take oral medications. Equianalgesic dosages may be due to pharmacokinetic differences.

Pharmacokinetics. A basic understanding of the pharmacokinetics of the opioid analgesics[58] is important for the cancer and AIDS care provider. Opioid analgesics with long half-lives, such as methadone and levorphanol, require approximately 5 days to achieve a steady state. Despite their long half-lives, the duration of analgesia that they provide is considerably shorter (i.e., most patients require administration of the drug every 4–6 hours). As both methadone and levorphanol tend to accumulate with early initial dosing, delayed effects of toxicity can develop (primarily sedation and, more rarely, respiratory depression).

Duration of effects. The duration of analgesic effects of opioid analgesics varies considerably. Immediate-release preparations of morphine or oxycodone often provide only 3 hours of relief and must be prescribed on an every 3-hour, around-the-clock basis (not as needed). Methadone and levorphanol may provide up to 6 hours of analgesia. There is individual variation in the metabolism of opioid analgesics, and there can be significant differences between individuals in drug absorption and disposition. These differences lead to a need for alterations in dosing, route of administration, and scheduling for maximum analgesia in individual patients. While parenteral administration (IV, intramuscular, subcutaneous) yields a faster onset of pain relief, the duration of analgesia is shorter unless a continuous infusion of opioid is instituted. The use of continuous subcutaneous or IV infusions of opioids, with or without patient-controlled analgesia (PCA) devices, has become commonplace in caring for cancer patients with escalating pain and in hospice and home settings during late stages of disease.

Routes of administration. The oral route is often the preferred route of administration of opioid analgesics from the perspectives of convenience and cost. Immediate-release oral morphine or hydromorphone preparations require that the drug be taken every 3–4 hours. Longer-acting, sustained-release oral morphine preparations and oxycodone preparations are now available that provide up to 8–12 hours of analgesia (or longer), minimizing the number of daily doses required for the control of persistent pain. Rescue doses of immediate-release, short-acting opioid are often necessary to supplement the use of sustained-release morphine or oxycodone, particularly during periods of titration or pain escalation. The transdermal fentanyl patch system (Duragesic) also has applications in the management of severe pain in cancer. Each transdermal fentanyl patch contains a 48- to 72-hour supply of fentanyl, which is absorbed from a depot in the skin. Levels in the plasma rise slowly over 12–18 hours after patch placement, so, with the initial placement of a patch, alternative opioid analgesia (oral, rectal, or parenteral) must be provided until adequate levels of fentanyl are attained. The elimination half-life of this dosage form of fentanyl is long (21 hours), so it must be noted that significant levels of fentanyl remain in the plasma for approximately 24 hours after the removal of a transdermal patch. The transdermal system is not optimal for rapid dose titration of acutely exacerbated pain; however, a variety of dosage forms are available. As with sustained-release morphine preparations, all patients should be provided with oral or parenteral rapidly acting short-duration opioids to manage breakthrough pain. The transdermal system is convenient and eliminates the reminders of pain associated with repeated oral dosing of analgesics. In patients with cancer and AIDS, it should be noted that the absorption of transdermal fentanyl can be increased with fever, resulting in increased plasma levels and shorter duration of analgesia from the patch.

It is important to note that opioids can be administered through various routes: oral, rectal, transdermal, IV, subcutaneous, intraspinal, and even intraventricularly.[59] There are advantages and disadvantages, as well as indications, for the use of these various routes. Further discussion of such alternative delivery routes as the intraspinal route are beyond the scope of this chapter; however, interested readers are directed to the Agency for Health Care Policy and Research Clinical Practice Guideline: Management of Cancer Pain[51] available free of charge through 1-800-4 cancer.

Appropriate dosage. The adequate treatment of pain in cancer also requires consideration of the equianalgesic doses of opioid drugs, which are generally calculated using morphine as a standard. Cross-tolerance is not complete among these drugs. Therefore, one-half to two-thirds of the equianalgesic dose of the new drug should be given as the starting dose when switching from one opioid to another.[60] For example, if a patient receiving 20 mg of parenteral morphine is to be switched to hydromorphone, the equianalgesic dose of parenteral hydromorphone would be 3.0 mg. Thus, the starting dose of parenteral hydromorphone should be approximately 1.5 to 2 mg. There is also considerable variability in the parenteral-to-oral ratios among the opioid analgesics. Both levorphanol and methadone have 1:2 intramuscular/oral ratios, whereas morphine has a 1:6 and hydromorphone a 1:5 intramuscular/oral ratio. Failure to appreciate these dosage differences in route of administration can lead to inadequate pain control.

Standing dose scheduling. Regular ("standing") scheduling of the opioid analgesics is the foundation of adequate pain control. It is

Table 30–9. Opioid analgesics for moderate to severe pain in cancer patients

Analgesic	*Equianalgesic route*	*Dose (mg)*	*Analgesic onset (hrs)*	*Duration (hrs)*	*Plasma half-life (hrs)*	*Comments*
Morphine	PO IM, IV, SC	30–60*10	1–1½ ½–1	4–6 3–6	2–3	Standard of comparison for the narcotic analgesics. 30 mg for repeat around-the-clock dosing; 60 mg for single dose or intermittent dosing
Morphine	PO	90–120	1–1½	8–12	———	Now available in long-acting sustained-release forms
Oxycodone	PO PO	20–30 20–40	1 1	3–6 8–12	2–3 2–3	In combination with aspirin or acetaminophen it is considered a weaker opioid; as a single agent it is comparable to the strong opioids, like morphine Available in immediate-release and sustained-release preparation
Hydromorphone	PO IM, IV	7.5 1.5	½–1 ¼–½	3–4 3–4	2–3 2–3	Short half-life; ideal for elderly patients. Comes in suppository and injectable forms
Methadone	PO IM, IV	20 10	½–1 ½–1	4–8 ———	15–30 15–30	Long half-life; tends to accumulate with initial dosing, requires careful titration. Good oral potency
Levorphanol	PO IM	4 2	½–1½ ½–1	3–6 3–4	12–16 12–16	Long half-life; requires careful dose titration in first week. Note that analgesic duration is only 4 hrs
Meperidine	PO IM	300 75	½–1½ ½–1	3–6 3–4	3–4 3–4	Active toxic metabolite, ormeperidine, tends to accumulate (plasma half-life is 12–16 hrs), especially with renal impairment and in elderly patients, causing delirium, myoclonus, and seizures
Fentanyl Transdermal System	TD IV	0.1–01	12–18	48–72 ———	20–22 ———	Transdermal patch is convenient, bypassing GI analgesia until depot is formed. Not suitable for rapid titrationw
Oxymorphone	PO IV, IM, SC	10 mg	½–1	4–6	8	Long half-life but low oral bioavailability Rectal administration is an alternate route for patients unable to take oral medications. More frequent dosing may be required

ABBREVIATIONS: GI, gastrointestinal tract; PO, per oral; IM, intramuscular; IV, intravenous; SC, subcutaneous; TD, transdermal.

preferable to prevent the return of pain as opposed to treating pain as it reoccurs. "As needed" orders for chronic cancer pain often create a struggle among patient, family, and staff that is easily avoided by regular administration of opioid analgesics. The typical prescribing of methadone is a notable exception. It is often initially prescribed on an as-needed basis to determine the patient's total daily requirement and to minimize toxicity (due to its long half-life).

Opioid rotation is a useful strategy to improve pain management, especially in long-term treatment. Accumulation of toxic metabolites can lead to the development of symptoms that include hallucinations,

Table 30–10. Principles of opioid analgesic use

1. Choose an appropriate drug
2. Start with lowest dose possible
3. Titrate dose
4. Use "as needed" doses selectively
5. Use an appropriate route of administration
6. Be aware of equivalent analgesic doses
7. Use a combination of opioid, nonopioid, and adjuvant drugs
8. Be aware of tolerance
9. Understand physical and psychological dependence

myoclonus, nausea and vomiting, and persisting pain. Several strategies of opioid rotation using equianalgesic doses have been reported to be useful in managing pain while decreasing the tolerance as well as the frequency and severity of opioid toxicity.[60]

Side effects. While the opioids are extremely effective analgesics, their side effects are common and can be minimized if anticipated in advance. Sedation is a common central nervous system (CNS) side effect, especially during the initiation of treatment. Sedation usually resolves after the patient has been maintained on a steady dosage. Persistent sedation can be alleviated with a psychostimulant, such as dextroamphetamine, pemoline, or methylphenidate. All are prescribed in divided doses in early morning and at noon. In addition, psychostimulants can improve depressed mood and enhance analgesia.[61] Delirium, of either an agitated or a somnolent variety, can also occur while the patient is on opioid analgesics and is usually accompanied by attentional deficits, disorientation, and perceptual disturbances (visual hallucinations and, more commonly, illusions). Myoclonus and asterixis are often early signs of neurotoxicity that accompany the course of opioid-induced delirium. Meperidine (Demerol), when administered chronically in patients with renal impairment, can lead to a delirium resulting from accumulation of the neuroexcitatory metabolite normeperidine.[62] Opioid-induced delirium can be alleviated through the implementation of three possible strategies: lowering the dose of the opioid drug presently in use, changing to a different opioid, or treating the delirium with low doses of high-potency neuroleptics, such as haloperidol. The third strategy is especially useful for agitation and clears the sensorium.[63] For agitated states, IV haloperidol in doses starting at between 1 and 2 mg is useful, with rapid escalation of dose if no effect is noted. Gastrointestinal side effects of opioid analgesics are common. The most prevalent are nausea, vomiting, and constipation.[64] Concomitant therapy with prochlorperazine for nausea is sometimes effective. Since all opioid analgesics are not tolerated in the same manner, switching to another narcotic can be helpful if an antiemetic regimen fails to control nausea. Constipation caused by narcotic effects on gut receptors is a problem frequently encountered, and it tends to be responsive to the regular use of senna derivatives. A careful review of medications is imperative, since anticholinergic drugs such as the tricyclic antidepressants (TCAs) can worsen opioid-induced constipation and can cause bowel obstruction. Respiratory depression is a worrisome but rare side effect of the opioid analgesics. Respiratory difficulties can almost always be avoided if two general principles are adhered to: start opioid analgesics in low doses in opioid-naive patients; and be cognizant of relative potencies when switching opioid analgesics, routes of administration, or both.

PSYCHOTROPIC ADJUVANT ANALGESICS

The patient with advanced disease and pain has much to gain from the appropriate and maximal utilization of psychotropic drugs. Psychotropic drugs, particularly the TCAs, are useful as adjuvant analgesics in the pharmacological management of cancer pain and neuropathic pain. Table 30–11 lists the various psychotropic medications with analgesic properties, their routes of administration, and their approximate daily doses. These medications are not only effective in managing symptoms of anxiety, depression, insomnia, or delirium that commonly complicate

Table 30–11. Psychotropic adjuvant analgesic drugs for pain in patients with advanced disease

Generic name	*Approximate daily dosage range (mg)*	*Route*
Tricyclic antidepressants		
Amitriptyline	10–150	PO, IM
Nortriptyline	10–150	PO
Imipramine	15.5–150	PO, IM
Desipramine	10–150	PO
Clomipramine	10–150	PO
Doxepin	12–150	PO, IM
Heterocyclic and noncyclic antidepressants		
Trazodone	125–300	PO
Maprotiline	50–300	PO
Serotonin-reuptake inhibitors		
Fluoxetine	20–80	PO
Paroxetine	10–60	PO
Sertraline	50–200	PO
Citalopram	10–40	PO
Escitalopram	10–20	PO
Newer agents		
Nefazodone	100–500	PO
Venlafaxine	75–300	PO
Duloxetine	20–90	PO
Mirtazapine	7.5–60	PO
Psychostimulants		
Methylphenidate	2.5–20 bid	PO
Dextroamphetamine	2.5–20 bid	PO
Pemoline	13.75–75 bid	PO
Modafinil	100–400	PO
Phenothiazines		
Fluphenazine	1–3	PO, IM
Methotrimeprazine	10–20 q6h	IM, IV
Butyrophenones		
Haloperidol	1–3	PO, IV
Pimozide	2–6 bid	PO
Antihistamines		
Hydroxyzine	50 q4h–q6h	PO
Anticonvulsants		
Carbamazepine	200 tid–400 tid	PO
Phenytoin	300–400	PO
Valproate	500 tid–1000 tid	PO
Gabapentin	300 tid–1000 tid	PO
Oxcarbazepine	300 bid–1800 daily	PO
Pregabalin	50 tid–150 bid	PO
Oral local anesthetics		
Mexiletine	600–900	PO
Corticosteroids		
Dexamethasone	4–16	PO, IV
Benzodiazepines		
Alprazolam	0.25–2.0 tid	PO
Clonazepam	0.5–4 bid	PO

ABBREVIATIONS: PO, per oral; IM, intramuscular; IV, intravenous; q6h, every 6 hrs; Bid, twice a day; tid, three times a day; qid, four times a day.

the course of advanced disease in patients who are in pain, but also potentiate the analgesic effects of the opioid drugs and have innate analgesic properties of their own.[61] A common use of adjuvant analgesics is to manage neuropathic pain. In this population, nonopioid adjuvant drugs that are neuroactive or neuromodulatory may be needed to complement opioid therapy. The primary adjuvant analgesics are anticonvulsant and antidepressant medications but a variety of other drugs are used.[65]

ANTIDEPRESSANTS

The current literature supports the use of antidepressants as adjuvant analgesic agents in the management of a wide variety of chronic pain syndromes, including cancer pain.[66]

Tricyclics. Amitriptyline is the TCA most studied, and proven effective as an analgesic, in a large number of clinical trials, addressing a wide variety of chronic pains.[67] Other TCAs that have been shown to have efficacy as analgesics include imipramine,[68] desipramine,[69] nortriptyline,[70] clomipramine,[71] doxepin,[72] and sertraline.[73] In a placebo-controlled double-blind study of imipramine in chronic cancer pain, Walsh[74] demonstrated that imipramine had analgesic effects independent of its mood effects, and was a potent co-analgesic when used along with morphine. Sertraline has been showed to reduce hot flashes in early stage breast cancer patients taking tamoxifen; however, compared to a placebo the reduction was not significant.[75] In general, the TCAs are used in cancer pain as adjuvant analgesics, potentiating the effects of opioid analgesics, and are rarely used as the primary analgesic.[76] Ventafridda et al.[76] reviewed a multicenter clinical experience with antidepressant agents (trazodone and amitriptyline) in the treatment of chronic cancer pain that included a deafferentation of neuropathic component. Almost all of these patients were already receiving weak or strong opioids and experienced improved pain control. A subsequent randomized double-blind study showed both amitriptyline and trazodone to have similar therapeutic analgesic efficacy.[76] Magni et al.[77] reviewed the use of antidepressants in Italian cancer centers and found that a wide range of antidepressants were used for a variety of cancer pain syndromes, with amitriptyline being the most commonly prescribed, for a variety of cancer pains. In nearly all cases, antidepressants were used in association with opioids. There is some evidence that there may be a subgroup of patients who respond differentially to tricyclics and therefore if amitriptyline fails to alleviate pain, another tricyclic should be tried. The TCAs are effective as adjuvants in cancer pain through a number of mechanisms that include (1) antidepressant activity, (2) potentiation or enhancement of opioid analgesia,[78] and (3) direct analgesic effects.[79]

The heterocyclic and noncyclic antidepressant drugs such as trazodone, mianserin, maprotiline, and the newer SSRIs, fluoxetine, and paroxetine may also be useful as adjuvant analgesics for cancer patients with pain; however, clinical trials of their efficacy as analgesics have been equivocal. There are several case reports that suggest that fluoxetine may be a useful adjuvant analgesic in the management of headache,[80] fibrositis,[81] and diabetic neuropathy.[82] In a recent clinical trial, fluoxetine was shown to be no better than placebo as an analgesic in painful diabetic neuropathy.

SSRIs. Paroxetine is the first SSRI shown to be a highly effective analgesic in the treatment of neuropathic pain,[83] and may be a useful addition to our armamentarium of adjuvant analgesics for cancer pain. Although it has not been tested on cancer pain, SSRI such as citalopram has also been shown to help with neuropathic pain.[84] Escitalopram, a newer SSRI, has advantages over other SSRIs; it has the highest selectivity in its class, no active metabolite, and does not significantly affect the CYP450 isoenzyme.[85] While Escitalopram has not been tested on cancer pain, it has been shown to lessen both depression and anxiety.[86] SSRIs may offer greater benefit to these patients as evidenced by greater improvements in quality-of-life measures.[87]

Newer antidepressants as analgesics. Newer antidepressants such as sertraline, venlafaxine, nefazodone, and duloxetine also appear to be clinically useful as adjuvant analgesics. Nefazodone, for instance, has been demonstrated to potentiate opioid analgesics in an animal model[88] and venlafaxine has been shown by Tasmuth et al.[89] to decrease the maximum pain intensity following treatment of breast cancer. Duloxetine, a dual reuptake inhibitor of serotonin and norepinephrine, has been shown to be an effective treatment for depression and for neuropathic pain[90]; however, there are no trials in cancer patients. At this point, it is clear that many antidepressants have analgesic properties. There is no definite indication that any one drug is more effective than the others, although the most experience has been accrued with amitriptyline, and most recently with duloxetine.

In a small sample, mirtazapine has been shown to improve, though not statistically significant, pain, nausea, appetite, insomnia, and anxiety. Gains were small, but one must consider that patients left untreated are likely to show decline in these symptoms, not improvement.[91] Freynhagen et al.[92] has shown that in a large sample of 594 patients, from baseline to endpoint (a 6-week period), mirtazapine significantly improves pain, sleep disturbances, irritability, and exhaustion.

Appropriate dosage of antidepressant adjuvant analgesics. In terms of appropriate dosage, there is evidence that the therapeutic analgesic effects of amitriptyline are correlated with serum levels just as the antidepressant effects are, and analgesic treatment failure is due to low serum levels.[93] A high-dose regimen of up to 150 mg of amitriptyline or higher is suggested.[94] As to the time course of onset of analgesia or with antidepressants, there appears to be a biphasic process that occurs with immediate or early analgesic effects that occur within hours or days[71] and later, longer analgesic effects that peak over a 4- to 6-week period.[67]

Treatment should be initiated with a small dose of amitriptyline; for instance, that is, 10–25 mg at bedtime especially in debilitated patients, and increased slowly by 10–25 mg every 2–4 days toward 150 mg with frequent assessment of pain and side effects until a beneficial effect is achieved. Maximal effect as an adjuvant analgesic may require continuation of drug for 2–6 weeks. Serum levels of antidepressant drug, when available, may also help in management to assure that therapeutic serum levels of drug are being achieved.

Both pain and depression in cancer patients often respond to lower doses (25–100 mg) of antidepressant than are usually required in the physically healthy (100–300 mg), most probably because of impaired metabolism of these drugs.

Choosing the appropriate antidepressant adjuvant analgesic drug. The choice of drug often depends on the side-effect profile, existing medical problems, the nature of depressive symptoms if present, and past response to specific antidepressants. Sedating drugs like amitriptyline are helpful when insomnia complicates the presence of pain and depression on a cancer patient. Anticholinergic properties of some of these drugs should also be kept in mind. Occasionally, in patients who have limited analgesic response to a tricyclic, potentiation of analgesia can be accomplished with the addition of lithium augmentation.[95]

Tricyclic antidepressants have been shown to be as effective as analgesics for mucositis when compared to opioids and for patients for whom opioids are contraindicated TCAs may be used.[96]

MONOAMINE OXIDASE INHIBITORS

Monoamine oxidase inhibitors (MAOIs) are less useful in the cancer setting because of dietary restriction and potentially dangerous interactions between MAOIs and narcotics such as meperidine. Amongst the MAOI drugs available, phenelzine has been shown to have adjuvant analgesic properties in patients with atypical facial pain and migraine.[97]

ANTICONVULSANTS

Selected anticonvulsant drugs appear to be analgesic for the lancinating dysesthesias that characterize diverse types of neuropathic pain.[64] Clinical experience also supports the use of these agents in patients with paroxysmal neuropathic pains that may not be lancinating and, to a far lesser extent, in those with neuropathic pains characterized

solely by continuous dysesthesias. Although, in the past, practitioners used carbamazepine because of the good response rates observed in trigeminal neuralgia, it is, generally, not currently perceived as a first-line anticonvulsant analgesic. Carbamazepine must be used cautiously in patients with thrombocytopenia, those at risk for marrow failure, and those whose blood counts must be monitored to determine disease status. Several newer anticonvulsants are now commonly used in the treatment of neuropathic pain, particularly in cancer patients with chemotherapy-induced neuropathic pain syndromes. These drugs include gabapentin, pregabalin, oxcarbazepine, lamotrigine, and felbamate. Of these anticonvulsants, anecdotal experience has been most favorable with gabapentin, which is now being widely used by pain specialists to treat neuropathic pain of various types. Gabapentin has a relatively high degree of safety, including no known drug–drug interactions and a lack of hepatic metabolism.[64] Treatment with gabapentin is usually initiated at a dose of 300 mg per day and then gradually increased to a dose range of 900–3200 mg per day in three divided doses. Pregabalin is Food and Drug Administration (FDA)-approved for neuropathic pain associated with diabetic neuropathy as well as for postherpetic neuralgia. A randomized placebo-controlled trial reported by Dworkin et al.[98] demonstrated that pregabalin at doses of 300 mg or 600 mg daily, significantly reduced pain by 30% after 8-week treatment. Oxcarbazepine has shown in small clinical trials to be effective in the management of trigeminal neuralgia and diabetic neuropathy.[99]

PSYCHOSTIMULANTS

The psychostimulants dextroamphetamine and methylphenidate are useful antidepressant agents prescribed selectively for medically ill cancer patients with depression.[99] Psychostimulants are also useful in diminishing excessive sedation secondary to narcotic analgesics, and are potent adjuvant analgesics. Bruera et al[69] demonstrated that a regimen of 10 mg methylphenidate with breakfast and 5 mg with lunch significantly decreased sedation and potentiated the analgesic effect of narcotics in patients with cancer pain. Dextroamphetamine has also been reported to have additive analgesic effects when used with morphine in postoperative pain.[100]

In relatively low dose, psychostimulants stimulate appetite, promote a sense of well-being, and improve feelings of weakness and fatigue in cancer patients. Treatment with dextroamphetamine or methylphenidate usually begins with a dose of 2.5 mg at 8 a.m. and at noon. The dosage is slowly increased over several days until a desired effect is achieved or side effects (overstimulation, anxiety, insomnia, paranoia, confusion) intervene. Typically, a dose greater than 30 mg per day is not necessary although occasionally patients require up to 60 mg per day. Patients usually are maintained on methylphenidate for 1–2 months, and approximately two-thirds will be able to be withdrawn from methylphenidate without a recurrence of depressive symptoms. Those who do recur can be maintained on a psychostimulant for up to 1 year without significant abuse problems. Tolerance will develop and adjustment of dose may be necessary. A strategy we have found useful in treating cancer pain associated with depression is to start a psychostimulant (starting dose of 2.5 mg of methylphenidate at 8 a.m. and at noon) and then to add a TCA after several days to help prolong and potentiate the short effect of the stimulant.

Modafinil is a wakefulness agent, FDA approved for the treatment of excessive daytime sedation secondary to sleep disorders (e.g., narcolepsy, sleep apnea), but often used clinically in the palliative care setting as a mild psychostimulant.[101] A study by DeBattista et al.[102] tested modafinil on subjects with major depression and partial response to antidepressants, and found that adjunctive treatment with modafinil significantly improved fatigue and depressive symptoms. Furthermore, modafinil was found to increase attention, concentration, and cognitive functioning. Fatigue is a common symptom of cancer and cancer treatment, and modafinil has been shown to improve fatigue in patients with multiple sclerosis and in cancer populations.[103] Modafinil, in doses ranging from 50 to 400 mg, is used in the palliative care settings to treat fatigue as well as to counteract the sedation caused by opioids in the setting of pain management. Modafinil is not a sympathomimetic agent, and its mechanism of action is distinct from classic psychostimulants, suggesting that issues of dependence, tolerance, and abuse may be significantly less of a concern with modafinil than with agents such as dextroamphetamine or methylphenidate.[104]

NEUROLEPTICS AND ANTIPSYCHOTIC AGENTS FOR CANCER PAIN

Methotrimeprazine is a phenothiazine that is equianalgesic to morphine, has none of the opioid effects on gut motility, and probably produces analgesia through α-adrenergic blockade.[105] In patients who are opioid tolerant, it provides an alternative approach in providing analgesia by a nonopioid mechanism. It is a dopamine blocker and so has antiemetic as well as anxiolytic effects. Methotrimeprazine can produce sedation and hypotension and should be given cautiously by slow IV infusion. Unfortunately, methotrimeprazine has limited availability (e.g., unavailable in the United States, but available in Canada). Other phenothiazines such as chlorpromazine and prochlorperazine (Compazine) are useful as antiemetics in cancer patients, but probably have limited use as analgesics.[106] Fluphenazine in combination with TCAs has been shown to be helpful in neuropathic pains.[107] Haloperidol is the drug of choice in the management of delirium or psychoses in cancer patients, and has clinical usefulness as a co-analgesic for cancer pain.[106] Pimozide (Orap), a butyrophenone, has been shown to be effective as an analgesic in the management of trigeminal neuralgia, at doses of 4–12 mg per day.[105]

Atypical antipsychotics, such as olanzapine, risperidone, quetiapine, apiprazole, and ziprasidone are primarily used to treat delirium in the palliative care setting. Boettger and Breitbart[106] suggest that olanzapine and risperidone are the atypical antipsychotics with the most demonstrated efficacy for managing the symptoms of delirium; however, smaller studies and case series reports suggest potential benefit for quetiapine,[108] ziprasidone,[109] and apiprazole.[110] Olanzapine[111] has been used to treat unmanaged pain in the context of anxiety and mild cognitive impairment. Patients received 2.5–7.5 mg of olanzapine daily. Daily pain scores decreased; anxiety and cognitive impairment resolved. Aripiprazole has been shown to be potentially beneficial in reducing bone pain.[112]

ANXIOLYTIC AGENTS AND CANCER PAIN

Hydroxyzine is a mild anxiolytic with sedating and analgesic properties that are useful in the anxious cancer patient with pain.[113] This antihistamine has antiemetic activity as well. One hundred milligrams of parenteral hydroxizine has analgesic activity approaching 8 mg of morphine, and has additive analgesic effects when combined with morphine. Benzodiazepines have not been felt to have direct analgesic properties, although they are potent anxiolytics and anticonvulsants.[114] Some authors have suggested that their anticonvulsant properties make certain benzodiazepine drugs useful in the management of neuropathic pain. Recently, Fernandez et al.[115] showed that alprazolam, a unique benzodiazepine with mild antidepressant properties, was a helpful adjuvant analgesic in cancer patients with phantom limb pain or deafferentation (neuropathic) pain. Clonazepam (Klonopin) may also be useful in the management of lancinating neuropathic pains in the cancer setting, and has been reported to be an effective analgesic for patients with trigeminal neuralgia, headache, and posttraumatic neuralgia.[116] With the use of midazolam by IV in a patient-controlled dosage, there was no reduction in the use of postoperative morphine requirements or in the patient's perception of pain.[117] Intrathecal midazolam in animal models, however, has been shown to potentiate morphine analgesia.[118]

CORTICOSTEROIDS

Corticosteroid drugs have analgesic potential in a variety of chronic pain syndromes, including neuropathic pains and pain syndromes resulting from inflammatory processes.[64] Like other adjuvant analgesics, corticosteroids are usually added to an opioid regimen. In patients with advanced disease, these drugs may also improve appetite, nausea,

malaise, and overall quality of life. Adverse effects include neuropsychiatric syndromes, GI disturbances, and immunosuppression.

ORAL LOCAL ANESTHETICS

Local anesthetic drugs may be useful in the management of neuropathic pains characterized by either continuous or lancinating dysesthesias. Controlled trials have demonstrated the efficacy of tocainide and mexiletine, and there is clinical evidence that suggests similar effects from flecainide and subcutaneous lidocaine.[64] It is reasonable to undertake a trial with oral local anesthetic in patients with continuous dysesthesias who fail to respond adequately to, or who cannot tolerate, the TCAs and with patients with lancinating pains refractory to trials of anticonvulsant drugs and baclofen. Mexiletine is preferred in the United States.[18]

PLACEBO

A mention of the placebo response is important to highlight the misunderstandings and relative harm of this phenomenon. The placebo response is common, and analgesia is mediated through endogenous opioids. The deceptive use of placebo response to distinguish psychogenic pain from "real" pain should be avoided. Placebos are effective in a portion of patients for a short period of time only and are not indicated in the management of cancer pain.

REFERENCES

1. Foley KM. The treatment of cancer pain. *N Engl J Med.* 1985 Jul 11;313(2):84–95.
2. Fitzgibbon DR. Cancer pain: management. In: Loeser JD, Butler SH, Chapman CR, Turk DC (eds). *Bonica's management of pain.* Philadelphia, PA: Lippincott Williams & Willkins; 2001:659–703.
3. Weiss SC, Emanuel LL, Fairclough DL, Emanuel EJ. Understanding the experience of pain in terminally ill patients.[see comment]. *Lancet.* 2001 Apr 28;357(9265):1311–1315.
4. Twycross RG, Lack SA. *Symptom control in far advanced cancer: Pain relief.* London: Pitman Brooks; 1983.
5. Foley KM. Pain syndromes in patients with cancer. In: Bonica JJ (ed). *Advances in pain research and therapy.* New York: Raven Press; 1975:59–75.
6. Grond S, Zech D, Diefenbach C, Bischoff A. Prevalence and pattern of symptoms in patients with cancer pain: a prospective evaluation of 1635 cancer patients referred to a pain clinic. *J Pain Symptom Manage.* 1994 Aug;9(6):372–382.
7. Achte KA, Vanhkonen ML. Cancer and the psych. *Omega.* 1971;2:46–56.
8. IASP Subcommittee. Taxonomy pain terms: a list with definitions and notes on usage. *Pain.* 1979;6:249–252.
9. Spiegel D, Bloom JR. Pain in metastatic breast cancer. *Cancer.* 1983;52:341–345.
10. Doyle D, Hanks GWC, MacDonald N. *Oxford textbook of palliative medicine.* 2nd ed. New York: Oxford University Press; 1998.
11. Breitbart W, Stiefel F, Kornblith A, Pannulo S. Neuropsychiatric disturbances in cancer patients with epidural spinal cord compression receiving high dose corticosteroids: a prospective comparison study. *Psychooncology.* 1993;2:233–245.
12. Syrjala K, Chapko M. Evidence for a biopsychosocial model of cancer treatment-related pain. *Pain.* 1995;61:69–79.
13. Breitbart W, Holland J. Psychiatric aspects of cancer pain. In: Foley KM (ed). *Advances in pain research and therapy.* Vol 16. New York: Raven Press; 1990:73–87.
14. Breitbart W. Psychiatric management of cancer pain. *Cancer.* 1989;63: 2336–2342.
15. Daut RL, Cleeland CS. The prevalence and severity of pain in cancer. *Cancer.* 1982;50:1913–1918.
16. Padilla G, Ferrell B, Grant M, Rhiner M. Defining the content domain of quality of life for cancer patients with pain. *Cancer Nurs.* 1990;13:108–115.
17. Payne D, Jacobsen P, Breitbart W, Passik S, Rosenfeld B, McDonald M. Negative thoughts related to pain are associated with greater pain, distress, and disability in AIDS pain. Presented at: *American Pain Society;* 1994; Vol Miami, FL.
18. McKegney FP, Bailey LR, Yates JW. Prediction and management of pain in patients with advanced cancer. *Gen Hosp Psychiatry.* 1981;3(2):95–101.
19. Singer EJ, Zorilla C, Fahy-Chandon B, Chi S, Syndulko K, Tourtellotte WW. Painful symptoms reported by ambulatory HIV-infected men in a longitudinal study. *Pain.* 1993;54(1):15–19.
20. Cleeland CS, Tearnan BH. Behavioral control of cancer pain. In: Holroyd D, Turk D (eds). *Pain mangement.* New York: Pergamon Press; 1986:93–202.
21. Derogatis LR, Morrow GR, Fetting J, et al. The prevalence of psychiatric disorders among cancer patients. *JAMA.* 1983 Feb 11;249(6):751–757.
22. Ahles TA, Blanchard EB, Ruckdeschel JC. The multi-dimensional nature of cancer related pain. *Pain.* 1983;17:277–288.
23. Stiefel FC, Breitbart W, Holland J. Cortico-steroids in cancer. neuropsychiatric complications. *Cancer Invest.* 1989;7:479–91.
24. Bukberg J, Penman D, Holland JC. Depression in hospitalized cancer patients. *Psychosom Med.* 1984 May-Jun;46(3):199–212.
25. Massie MJ, Holland JC, Glass E. Delirium in terminally ill cancer patients. *Am J Psychiatr.* 1983;140:1048–1050.
26. Breitbart W. Suicide in cancer patients. *Oncology.* 1987;1:49–53.
27. Bolund C. Suicide and cancer: II. Medical and care factors in suicide in cancer patients in Sweden, 1973–1976. *J Psychosoc Oncol.* 1985;3:17–30.
28. Elliot K, Foley KM. Pain syndromes in the cancer patient. *J Psychosoc Oncol.* 1990;8:11–45.
29. Fishman BB, Pasternak SS, Wallenstein SL, Houde RW, Holland JC, Foley KM. The Memorial Pain Assessment Card. A valid instrument for the evaluation of cancer pain. *Cancer.* 1987;60(5):1151–1158.
30. Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other disease. *Pain.* 1983;17:197–210.
31. Cleeland CS, Gonin R, Hatfield AK, et al. Pain and its treatment in outpatients with metastatic cancer. *N Engl J Med.* 1994 Mar 3;330(9):592–596.
32. Kanner RM, Foley KM. Patterns of narcotic use in a cancer pain clinic. *Ann N Y Acad Sci.* 1981;362:161–172.
33. Macaluso C, Weinberg D, Foley KM. Opioid abuse and misuse in a cancer pain population (Abstract). *Second International Congress on Cancer Pain.* Vol.
34. Bruera E, MacMillan K, Pither J, MacDonald, RN. Effects of morphine on the dyspnea of terminal cancer patients. *J Pain Symptom Manage.* 1990;5:341–344.
35. Grossman SA, Sheidler VR, Sweden K, Mucenski J, Piantadosi S. Correlations of patient and caregiver ratings of cancer pain. *J Pain Symptom Manage.* 1991;6:53–57.
36. Spiegel D, Bloom JR. Group therapy and hypnosis reduce metastatic breast carcinoma pain. *Psychosom Med.* 1983;4:333–339.
37. Passik S, Horowitz S, Malkin M, Gargan R. A psychoeducational support program for spouses of brain tumor patients (Abstract). Presented at: Symposium on New Trends in the Psychological Support of the Cancer Patient, American Psychiatric Association Annual Meeting; 1991; New Orleans, LA.
38. Syrajala K, Cummings C, Donaldson G. Hypnosis or cognitive behavioral training for the reduction of pai and nausea during cancer treatment: a controlled trial. *Pain.* 1992;48:137–146.
39. Tan SY, Leucht CA. Cognitive-behavioral therapy for clinical pain control: a 15-year update and its relationship to hypnosis. *Int J Clin Exp Hypn.* 1997 Oct;45(4):396–416.
40. Cleeland CS. Nonpharmacologic management of cancer pain. *J Pain Symptom Manage.* 1987;2:523–528.
41. Loscalzo M, Jacobsen PB. Practical behavioral approaches to the effective management of pain and distress. *J Psychosoc Oncol.* 1990;8:139–169.
42. Douglas DB. Hypnosis: useful, neglected, available. *Am J Hosp Palliat Care.* 1999 Sep-Oct;16(5):665–670.
43. Levitan A. The use of hypnosis with cancer patients. *Psychiatr Med.* 1992;10:119–131.
44. Montgomery GH, DuHamel KN, Redd WH. A meta-analysis of hypnotically induced analgesia: how effective is hypnosis? *Int J Clin Exp Hypn.* 2000 Apr;48(2):138–153.
45. Rajasekaran M, Edmonds PM, Higginson IL. Systematic review of hypnotherapy for treating symptoms in terminally ill adult cancer patients. *Palliat Med.* 2005 Jul;19(5):418–426.
46. Montgomery GH, Weltz CR, Seltz M, Bovbjerg DH. Brief presurgery hypnosis reduces distress and pain in excisional breast biopsy patients. *Int J Clin Exp Hypn.* 2002;50(1):17–32.
47. Fotopoulos SS, Graham C, Cook MR. Psychophysiologic control of cancer pain. In: Ventafridda JJBaV (ed). *Advances in pain research and therapy.* Vol 2. New York: Raven Press; 1979:231–244.
48. Kazak AE, Penati B, Brophy P, Himelstein B. Pharmacologic and psychologic interventions for procedural pain. *Pediatrics.* 1998;102(1 pt 1):59–66.
49. Keefe FJ, Ahles TA, Sutton L, et al. Partner-guided cancer pain management at the end of life: a preliminary study. *J Pain Symptom Manage.* 2002 Mar;29(3):263–272.
50. Manne S, Redd W, Jacobsen P, Georgiades I. Aroma for treatment of anxiety during MRI scans. (Abstract) Presented at: Meeting APAA (ed). Symposium on new trends in the psychological support of the cancer patient; 1991; New Orleans, LA.

51. Jacox A, Carr D, Payne R, Berde CB, Breitbart W (ed). Clinical Practice Guideline Number 9: Management of Cancer Pain. In: U.S. Department of Health and Human Services PHS, Agency for Health Care Policy and Research, ed. Publication No. 94-0592. AHCPR 1994:139-141.

52. Fotopoulos SS, Graham C, Cook MR. Psychophysiologic control of cancer pain. In: Bonica JJ, Ventafridda V (eds). *Advances in pain research and therapy.* Vol 2. New York: Raven Press; 1979:231-244.

53. Portenoy RK. Pharmacologic approaches to the control of cancer pain. *J Psychosoc Oncol.* 1990;8:75-107.

54. Murray MD, Brater DC. Adverse effects of nonsteroidal anti-inflammatory drugs on renal function. *Ann Intern Med.* 1990;112:559-560.

55. Radack K, Deck C. Do nonsteroidal anti-inflammatory drugs interfere with blood pressure control in hypertensive patients? *J Gen Intern Med.* 1987;2(2):108-112.

56. Bolten WW. Symptomatic therapy of rheumatic diseases. How they reduce pain and thereby save costs. *MMW Fortschr Med.* 2002 Aug 22;144(33-34):30-36.

57. Portenoy RK. Acute and chronic pain. In: Lowinson J, Ruiz P, Millman R (eds). *Comprehensive textbook of substance abuse.* Baltimore: William and Wilkins; 1992:691-721.

58. Bruera E, Chadwick S, Brennels C, Hanson J, MacDonald RN. Methylphenidate associated with narcotics for the treatment of cancer pain. *Cancer Treat Res.* 1987;71:67-70.

59. Lefkowitz M, Newshan G. An evaluation of the use of analgesics for chronic pain in patients with AIDS (Abstract #684). Preented at: Proceedings of the 16th annual scientific meeting of the American Pain Society; 1997:71.

60. Freye E, Anderson-Hillemacher A, Ritzdorf I, Levy JV. Opioid rotation from high-dose morphine to transdermal buprenorphine (Transtec) in chronic pain patients. *Pain Pract.* 2007 Jun;7(2):123-129.

61. Breitbart W. Psychotropic adjuvant analgesics for pain in cancer and AIDS. *Psychooncology.* 1998;7(4):333-345.

62. Kaiko RF, Foley KM, Grabinski PY, et al. Central nervous system excitatory effects of meperidine in cancer patients. *Ann Neurol.* 1983;13(2):180-185.

63. Breitbart W, Sparrow B. Management of delirium in the terminally ill. *Prog Pall Care.* 1998;6:107-113.

64. Portenoy RK. Adjuvant analgesics in pain management. In: Doyle D, Hanks GWC, MacDonald N (eds). *Oxford textbook of palliative medicine.* New York: Oxford University Press; 1993:187-203.

65. Farrar JT, Portenoy RK. Neuropathic cancer pain: the role of adjuvant analgesics. *Oncology.* 2001 Nov;15(11):1435-1442.

66. Onghena P, Van Houdenhove B. Antidepressant-induced analgesia in chronic non-malignant pain: a meta-analysis of 39 placebo-controlled studies. *Pain.* 1992;49(2):205-219.

67. Max MB, Culnane M, Schafer SC, et al. Amitriptyline relieves diabetic-neuropathy pain in patients with normal and depressed mood. *Neurology.* 1987;37:589-596.

68. Sindrup SH, Ejlertsen B, Frøland A, Sindrup EH, Brøsen K, Gram LF. Imipramine treatment in diabetic neuropathy: relief of subjective symptoms without changes in peripheral and autonomic nerve function. *Eur J Clin Pharmacol.* 1989;37(2):151-153.

69. Bruera E, Fainsinger R, MacEachern T, Hanson J. The use of methylphenidate in patients with incident cancer pain receiving regular opiates: a preliminary report. *Pain.* 1992;50:75-77.

70. Gomez-Perez FJ, Rull JA, Dies H, Rodriquez-Rivera JG, Gonzalez-Barranco J, Lozano-Castañeda O. Nortriptyline and fluphenazine in the symptomatic treatment of diabetic neuropathy. A double-blind cross-over study. *Pain.* 1985;23:395-400.

71. Tiegno M, Pagnoni B, Calmi A, Rigoli M, Braga PC, Panerai AE. Chlorimipramine compared to pentazocine as a unique treatment in post-operative pain. *Int J Clin Pharmacol Res.* 1987;7:141-143.

72. Hameroff SR, Cork RC, Scherer K, et al. Doxepin effects on chronic pain, depression and plasma opioids. *J Clin Psychiatry.* 1982;2:22-26.

73. Lee RA, West RM, Wilson JD. The response to sertraline in men with chronic pelvic pain syndrome. *Sex Transm Infect.* 2005;81(2):147-149.

74. Walsh TD. Controlled study of imipramine and morphine in chronic pain due to advanced cancer (Abstract). Presented at: ASCO; May 4-6, 1986; Los Angeles.

75. Kimmick GG, Lovato J, McQuellon R, Robinson E, Muss HB. Randomized, double-blind, placebo-controlled, crossover study of sertraline (Zoloft) for the treatment of hot flashes in women with early stage breast cancer taking tamoxifen. *Breast J.* 2006;12(2):114-122.

76. Ventafridda V, Bonezzi C, Caraceni A, et al. Antidepressants for cancer pain and other painful syndromes with deafferentation component: comparison of Amitriptyline and Trazodone. *Ital J Neurol Sci.* 1987;8:579-587.

77. Magni G, Arsie D, DeLeo D. Antidepressants in the treatment of cancer pain. A survey in Italy. *Pain.* 1987;29:347-353.

78. Ventafridda V, Bianchi M, Ripamonti C, et al. Studies on the effects of antidepressant drugs on the antinociceptive action of morphine and on plasma morphine in rat and man. *Pain.* 1990;43:155-162.

79. Spiegel K, Kalb R, Pasternak GW. Analgesic activity of tricyclic antidepressants. *Ann Neurol.* 1983;13:462-465.

80. Diamond S, Frietag FG. The use of fluoxetine in the treatment of headache. *Clin J Pain.* 1989;5:200-201.

81. Geller SA. Treatment of fibrositis with fluoxetine hydrochloride (Prozac). *Am J Med.* 1989;87:594-595.

82. Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med.* 1992;326:1250-1256.

83. Sindrup SH, Gram LF, Brosen K, Eshoj O, Mogenson EF. The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. *Pain.* 1990;42:135-144.

84. Sindrup SH, Bjerre U, Dejgaard A, Brosen K, Aaes-Jorgensen T, Gram LF. The selective serotonin reuptake inhibitor citalopram relieves the symptoms of diabetic neuropathy. *Clin Pharmacol Ther.* 1992 Nov;52(5):547-552.

85. Sidney H, Kennedy HFA, Lam RW. Efficacy of escitalopram in treatment of major depressive disorder compared with conventional selective serotonin reuptake inhibitors and venlafaxine XR: a meta-analysis. *J Psychiatry Neurosci.* 2006;31(2):122-131.

86. Thase ME. Managing depressive and anxiety disorders with escitalopram. *Expert Opin Pharmacother.* 2006;7(4):429-440.

87. Holland JC, Romano SJ, Heiligenstein JH, Tepner RG, Wilson MG. A controlled trial of fluoxetine and desipramine in depressed women with advanced cancer. *Psychooncology.* 1998 Jul-Aug;7(4):291-300.

88. Pick CG, Paul D, Eison MS, Pasternak G. Potentiation of opioid analgesia by the antidepressant nefazodone. *Eur J Pharmacol.* 1992;211:375-381.

89. Tasmuth T, Hartel B, Kalso E. Venlafaxine in neuropathic pain following treatment of breast cancer. *Eur J Pain.* 2002;6:17-24.

90. Goldstein DJ, Lu Y, Detke MJ, Wiltse C, Mallinckrodt C, Demitrack MA. Duloxetine in the treatment of depression: a double-blind placebo-controlled comparison with paroxetine. *J Clin Psychopharmacol.* 2004;24(4):389-399.

91. Theobald DE, Kirsh KL, Holtsclaw E, Donaghy K, Passik SD. An open-label, crossover trial of mirtazapine (15 and 30 mg) in cancer patients with pain and other distressing symptoms. *J Pain Symptom Manage.* 2002;23(5):442-447.

92. Freynhagen R, Muth-Selbach U, Lipfert P, et al. The effect of mirtazapine in patients with chronic pain and concomitant depression. *Curr Med Res Opin.* 2006;22(2):257-264.

93. McQuay HJ, Carroll D, Glynn CJ. Dose-response for analgesic effect of amitriptyline in chronic pain. *Anaesthesia.* 1993 Apr;48(4):281-285.

94. Watson CP, Evans RJ. A comparative trial of amitriptyline and zimelidine in post-herpetic neuralgia. *Pain.* 1985 Dec;23(4):387-394.

95. Tyler MA. Treatment of the painful shoulder syndrome with amitrityline and lithium carbonate. *Can Med Assoc J.* 1974;111:137-140.

96. Ehrnrooth E, Grau C, Zachariae R, Andersen J. Randomized trial of opioids versus tricyclic antidepressants for radiation-induced mucositis pain in head and neck cancer. *Acta Oncol.* 2001;40(6):745-750.

97. Anthony M. MAO inhibition in the treatment of migraine. *Arch Neurol.* 1969;21:263.

98. Dworkin RH, Corbin AE, Young JP Jr, et al. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. *Neurology.* 2003 Apr 22;60(8):1274-1283.

99. Fernandez F, Adams F, Holmes VF, Levy JK, Neidhart M. Methylphenidate for depressive disorders in cancer patients. An alternative to standard antidepressants. *Psychosomatics.* 1987 Sep;28(9):455-461.

100. Forrest WH Jr, Brown BW Jr, Brown CR, et al. Dextroamphetamine with morphine for the treatment of post-operative pain. *N Engl J Med.* 1977;296:712-715.

101. Morrow GR, Shelke AR, Roscoe JA, Hickok JT, Mustian K. Management of cancer-related fatigue. *Cancer Invest.* 2005;23(3):229-239.

102. DeBattista C, Lembke A, Solvason HB, Ghebremichael R, Poirier J. A prospective trial of modafinil as an adjunctive treatment of major depression. *J Clin Psychopharmacol.* 2004;24(1):87-90.

103. Kingshott RN, Vennelle M, Coleman EL, Engleman HM, Mackay TW, Douglas NJ. Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of residual excessive daytime sleepiness in the sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med.* 2001;163(4):918-923.

104. Maltbie AA, Cavenar JO Jr, Sullivan JL, Hammett EB, Zung WW. Analgesia and haloperidol: a hypothesis. *J Clin Psychiatry.* 1979;40:323-326.

105. Lechin F, van der Dijs B, Lechin ME, et al. Pimozide therapy for trigeminal neuralgia. *Arch Neurol.* 1989;9:960-964.

106. Boettger S, Breitbart W. Atypical antipsychotics in the management of delirium: a review of the empirical literature. *Palliat Support Care.* 2005;3(3):227-237.

107. Langohr HD, Stohr M, Petruch F. An open and double-blind crossover study on the efficacy of clomipramine (anafranil) in patients with painful mono- and polyneuropathies. *Eur Neurol.* 1982;21:309-315.

108. Sasaki Y, Matsuyama T, Inoue S, et al. A prospective, open-label, flexible-dose study of quetiapine in the treatment of delirium. *J Clin Psychiatry.* 2003;64(11):1316–1321.

109. Leso L, Schwartz TL. Ziprasidone treatment of delirium. *Psychosomatics.* 2002;43(1):61–62.

110. Alao AO, Soderberg M, Pohl EL, Koss M. Aripiprazole in the treatment of delirium. *Int J Psychiatry Med.* 2005;35(4):429–433.

111. Khojainova N, Santiago-Palma J, Kornick C, Breitbart W, Gonzales GR. Olanzapine in the management of cancer pain. *J Pain Symptom Manage.* 2002;23(4):346–350.

112. Wilson MS. Aripiprazole and bone pain. *Psychosomatics.* 2005;46(2):187.

113. Rumore MA. Clinical efficacy of antihistamines as analgesics. *Pain.* 1986;25:7–22.

114. Coda B, Mackie A, Hill H. Influence of alprazolam on opioi
gesia and side effects during steady-stage morphine infusions. *Pain.*
306–316.

115. Fernandez F, Adams F, Holmes VF. Analgesic effect of alp
in patients with chronic, organic pain of malignant origin. *J Clin Psy*
1987;3:167–169.

116. Swerdlow M, Cundill JG. Anticonvulsant drugs used in the treat
lancinating pains: a comparison. *Anesthesia.* 1981;36:1129–1134.

117. Egan K, Ready L, Nessly M, Greer B. Self administration of mid
for post-operative anxiety: a double blinded study. *Pain.* 1992;49:3–8.

118. Liao J. Quantitative assessment of antinociceptive effects of mid
amitriptyline, and carbamazepine alone and in combination with morp
mice. *Anesthesiology.* 1990;73:A753.