■ PRACTICE GUIDELINES

Anesthesiology
1996; 84:1243–57

Practice Guidelines for Cancer Pain Management

A Report by the American Society of Anesthesiologists Task Force on Pain Management, Cancer Pain Section

Practice guidelines are systematically developed recommendations that assist the practitioner and patient in making decisions about health care. These recommendations may be adopted, modified, or rejected according to clinical needs and constraints.

Practice guidelines are not intended as standards or absolute requirements. The use of practice guidelines cannot guarantee any specific outcome. Practice guidelines are subject to revision from time to time as warranted by the evolution of medical knowledge, technology, and practice. The guidelines provide basic recommendations that are supported by analysis of the current literature and by a synthesis of expert opinion, open forum commentary, and clinical feasibility data (Appendix 1).

A. Definition of Cancer Pain. For these guidelines, cancer pain is defined as pain that is attributable to cancer or its therapy. The Task Force has not given preference to literature based on any particular system of definition or classification of cancer pain.

B. Purpose of Guidelines for Cancer Pain Management. The purpose of these guidelines is to: (1) optimize pain control; (2) minimize side effects, adverse outcomes, and costs; (3) enhance functional abilities and physical and psychological well-being; and (4) enhance the quality of life for cancer patients.

C. Focus. These guidelines focus on the knowledge base, skills, and range of interventions that are the essential elements of effective management of pain and pain-related problems in patients with cancer. The guidelines recognize that the management of cancer pain occurs within the broader context of supportive care, which also encompasses other quality of life concerns (*e.g.,* functional status, psychosocial well-being).

The guidelines recognize that comprehensive pain management by anesthesiologists may not be feasible in every clinical setting. However, aspects of these guidelines may be useful when comprehensive pain management cannot be offered.

The Task Force recognizes that therapies used to modify the underlying cause of pain may improve analgesia and outcome. Commonly used approaches include radiotherapy, surgery, and chemotherapy. The decision to implement primary therapy should be based on a comprehensive assessment of risks and benefits and are outside the scope of these guidelines.

D. Application. The guidelines are intended for use by anesthesiologists and individuals who deliver care under the direct supervision of anesthesiologists. The guidelines apply to patients of all ages and with all types of cancer.

I. Comprehensive Evaluation and Assessment of the Patient with Cancer Pain

The literature suggests that a comprehensive cancer pain evaluation is associated with improved analgesia. The Task Force and panel of consultants support the conduct of a comprehensive pain evaluation. In the opinion of the Task Force and consultants, effective cancer pain management requires a clear understanding of the etiology and pathophysiology of the pain.

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Submitted for publication November 28, 1995. Accepted for publication December 1, 1995. Supported by the American Society of Anesthesiologists, under the direction of James F. Arens, M.D., Chairman of the Ad-Hoc Committee on Practice Parameters. Approved by the House of Delegates, October 22, 1995. A list of the articles used to develop these guidelines is available by writing to the American Society of Anesthesiologists.

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Key words: Pain: cancer. Practice guidelines: cancer pain management. Cancer: supportive care; symptom management.

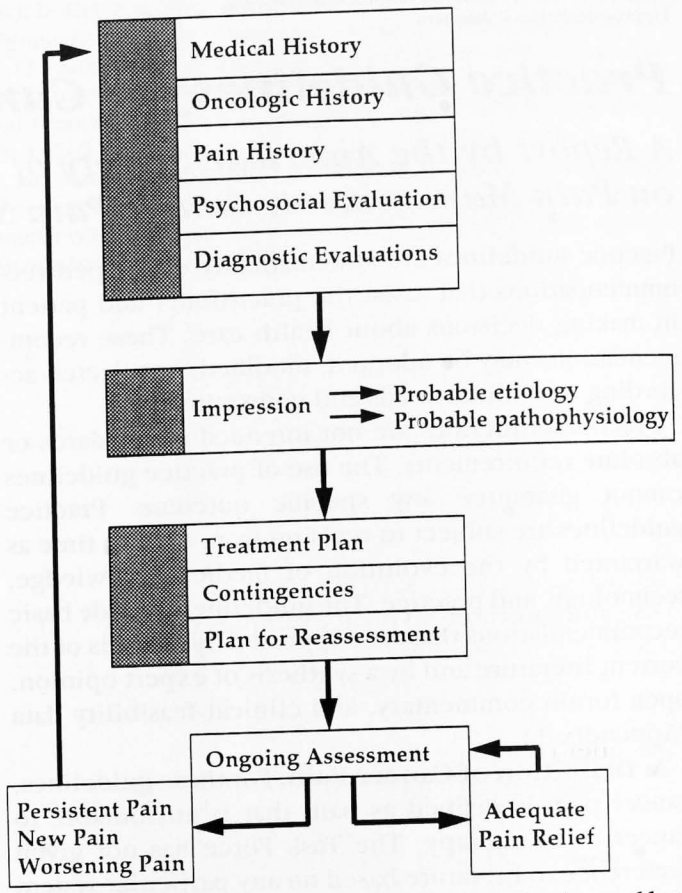
Recommendations:

1. General Constructs. The Task Force identifies four fundamental features that should guide the comprehensive evaluation of the patient with cancer pain.

a. The patient's general medical condition and the extent of disease must be assessed.
b. A knowledge of common pain syndromes is a prerequisite for conducting a cancer pain evaluation. Common pain syndromes include but are not limited to bone metastases, abdominal (visceral) pain, neuropathic pain (*e.g.,* peripheral neuropathies, acute herpes zoster and postherpetic neuralgia, plexopathies), and mucositis.
c. A knowledge of oncologic emergencies (*e.g.,* hypercalcemia, spinal cord compression, cardiac tamponade, superior vena cava syndrome) is also required to conduct a comprehensive cancer pain evaluation.
d. A thorough knowledge of the modalities that can be employed in the treatment of painful crisis (*i.e.,* pain emergency) is also necessary.

2. Elements. The Task Force identifies six essential features of a comprehensive evaluation and treatment plan. These features are outlined below (template 1).

a. History: A complete history includes a general medical and oncologic history with a description of the extent of disease and prognosis. A pain history should include: (1) the quality of the pain (*e.g.,* "burning", "aching"), (2) pain intensity (*i.e.,* numeric, categorical, or visual analog scales), (3) spatial relationships of the pain (*i.e.,* location, areas of radiation), (4) factors that palliate or provoke pain, (5) temporal characteristics of the pain (*i.e.,* continuous, episodic), (6) duration of the pain, (7) course of the pain (*e.g.,* stable, progressive, "crescendo"), and (8) associated features of the pain (*e.g.,* numbness, weakness, vasomotor changes).
b. Psychosocial evaluation: A psychosocial evaluation should include: (1) the presence of psychological symptoms (*e.g.,* anxiety, depression), (2) indicators of psychiatric disorder (*e.g.,* delirium, major depression), (3) investigation of the "meaning" of the pain to the patient and his or her significant others, (4) changes in mood state, (5) premorbid and current coping mechanisms, (6) family function, (7) the availability of psychosocial support systems, and (8) assessment of the patient's expectations and preconceptions regarding pain management (*e.g.,* fear of addiction surrounding opioids, psychostimulants).



Template 1. Algorithm for comprehensive evaluation and longitudinal assessment of cancer pain.

c. Physical examination: A physical examination should include general medical and neurologic examinations and a specific examination of the site of pain and surrounding anatomic regions.
d. Impression and differential diagnosis: The findings of the history and physical examination should be used to determine the probable etiology and pathophysiology of the pain.
e. Diagnostic evaluations: Additional diagnostic tests may be required to ascertain or confirm the etiology of the pain and its relationships to underlying disease processes.
f. Treatment plan: Once a definitive diagnosis has been made, a treatment plan should be formulated and discussed with the patient. The treatment plan should characterize the expected outcome, define contingencies, and outline a plan for reassessment.

II. Longitudinal Monitoring of Pain

There is insufficient literature to evaluate the efficacy of the longitudinal monitoring of pain. The Task Force

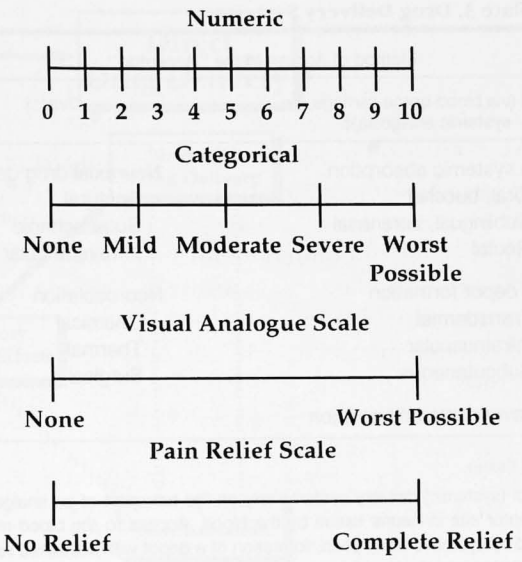
and consultants support the contention that the longitudinal monitoring of pain will result in improved pain management and reduced adverse effects from therapy (template 1).

Recommendations: The Task Force identifies three fundamental concepts in the longitudinal monitoring of pain.

1. Patient Self-report. Reports of pain made by the patient should be the primary source of pain assessment and should take precedence, whenever possible, over inferences and observations made by others. Continuous assessment over time (*e.g.,* pain diaries) is appropriate for outpatients. For some age groups and populations (*e.g.,* the cognitively or developmentally impaired), external observation may be preferable. Age-appropriate instruments should be used in children.

2. Rating Scale. The longitudinal monitoring of pain intensity should be based on rating scales that are easy to use and interpret. Typical examples of rating scales include discrete numeric scales (*e.g.,* 0–10), categorical scales (none, mild, moderate, severe, worst possible), and continuous visual analog scales of pain or pain relief (template 2).

3. Frequency of Pain Ratings. Self-report should be obtained at regular intervals. Increased frequency and evaluation of self-reports may be indicated: (1) at the onset of new pain, (2) when established pain exhibits changes in pattern and/or intensity, or (3) when a major therapeutic intervention is performed.



Template 2. Pain intensity scales.

III. Involvement of Specialists from Multiple Disciplines

The literature supports the concept that involvement of specialists from multiple disciplines results in effective analgesia and suggests that such involvement improves other health outcomes. The panel of consultants and Task Force members endorse the importance of collaboration between anesthesiologists and other health-care providers in the management of cancer pain.

Recommendations: Anesthesiologists who engage in cancer pain management should avail themselves of interdisciplinary expertise in their clinical environments. It is important to note that the patient's primary physician must be a part of the coordination of pain management. The Task Force recognizes that full interdisciplinary coordination of cancer pain treatment is not feasible in every clinical setting.

IV. Paradigm for the Management of Cancer Pain

The guidelines conceptualize the pharmacologic management of cancer pain as a continuum from indirect drug delivery (*i.e.,* systemic analgesia) to direct drug delivery (*i.e.,* neuraxial drug administration and neuroablation; template 3). *Indirect* drug delivery systems rely on blood-borne carriage of analgesic to receptors after (1) systemic absorption, (2) formation of a depot for sustained and continuous release, or (3) administration into the blood stream. *Direct* drug delivery systems involve administration of an agent to the neuraxis or in the vicinity of "target" neural tissue.

Recommendations for the oral administration of analgesics are provided by the World Health Organization (WHO) analgesic ladder (template 4). These American Society of Anesthesiologists guidelines provide evidence and recommendations for cancer pain management involving the oral and other routes of administration. The literature provides supportive evidence for specific elements of the paradigm (template 5).

A. Indirect Delivery Systems: Systemic Analgesia

a. Oral pharmacologic interventions: The literature suggests and consultant opinion supports the view that oral pharmacologic interventions applied according to the WHO analgesic ladder are associated with adequate analgesia. The literature indicates an

Template 3. Drug Delivery Systems

Method of Access to the "Receptor"*	
Indirect (*via* blood-borne carriage, *i.e.*, systemic analgesia)†	Direct‡
Via systemic absorption Oral, bucchal Sublingual, intranasal Rectal	Neuraxial drug delivery Epidural Subarachnoid Intraventricular
Via depot formation Transdermal Intramuscular Subcutaneous	Neuroablation Chemical Thermal Surgical
Intravenous administration	

* Neural tissue.

† Indirect (systemic) delivery systems rely on the transport of an analgesic to the receptor site in neural tissue by the blood. Access to the blood may be achieved by systemic absorption, formation of a depot with sustained release, and instillation into the blood.

‡ Direct drug delivery systems involve administration of an agent to the neuraxis (*i.e.*, in proximity to the receptor) or in the vicinity of "target" neural tissue.

increased risk of adverse sequelae with the use of oral opioids (Appendix 2).

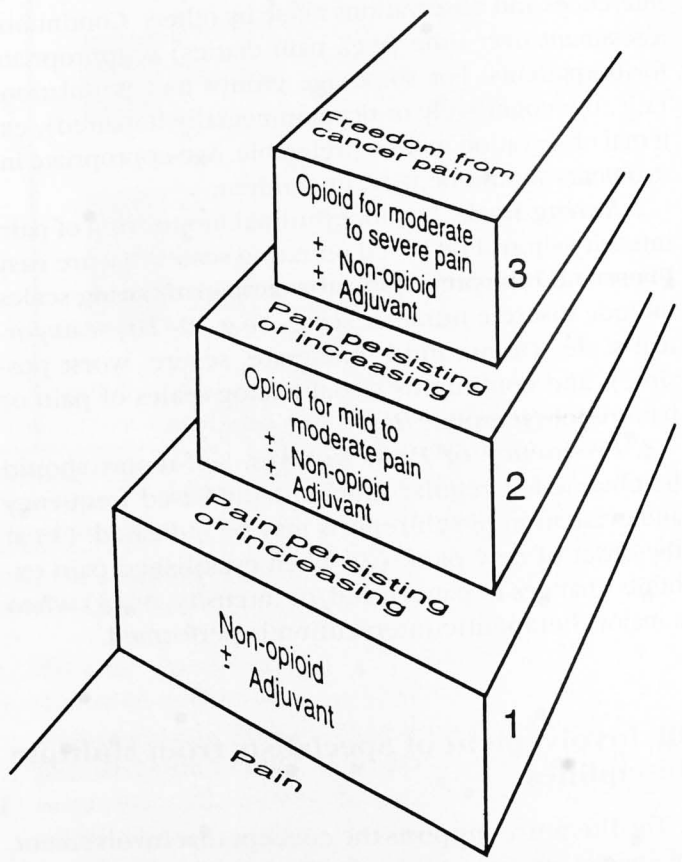
b. Rectal and transdermal analgesia: The literature suggests that rectal and transdermal modes of analgesia are effective alternatives to oral analgesics. The Task Force supports the use of these analgesic modalities, when appropriate, before employment of more invasive systemic therapies.

c. Subcutaneous and intravenous drug delivery: The literature suggests that subcutaneous or intravenous administration of opioids is effective for patients requiring continuous infusions and does not increase the risk of adverse effects. Subcutaneous administration provides blood levels similar to intravenous infusion, and the comparative risks and benefits of the continuous parenteral techniques have not been evaluated.

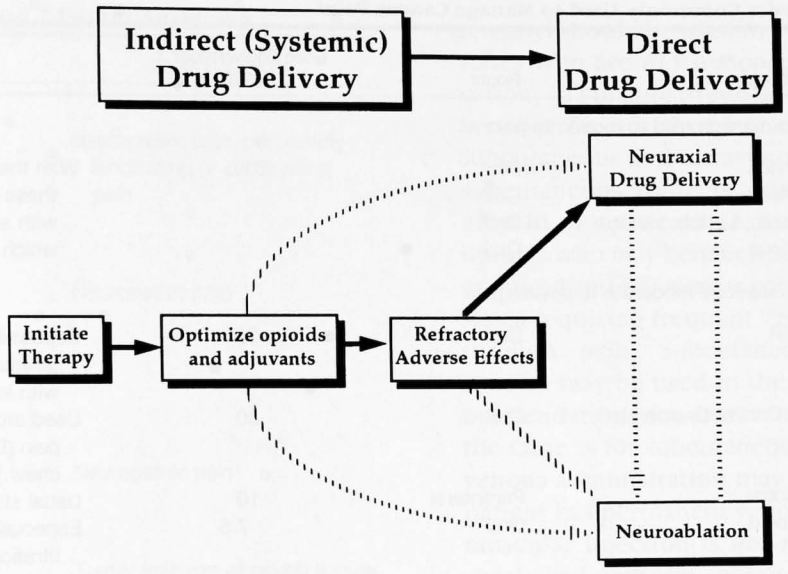
Recommendations:

1. General Recommendations. Oral medications should be used as the first line approach in most patients when initiating analgesic therapy. Because it is not effective in all patients and may not be optimal therapy in painful crisis (*i.e.*, the pain emergency), the indications, risks, and potential benefits of alternative interventions must be understood and assessed.

Any proposed systemic regimen must be individualized for the patient, and inflexible reliance should not be placed on any "standard" mixture of medications and/or dosing regimens. For patients with moderate or severe pain, opioid therapy is recommended. Once an opioid and a route of administration are chosen, the dose should be increased until a favorable response occurs or when unmanageable or intolerable adverse effects ensue. There is no predetermined maximum dose of an opioid. Dose titration may be required periodically because of the natural history of the primary



Template 4. The World Health Organization (WHO) analgesic ladder consists of a hierarchy of oral pharmacologic interventions designed to effectively treat pain of increasing magnitude. The ladder presents a framework for the rational use of oral medication before application of other techniques of drug administration. Opioid therapy is considered the mainstay approach for patients with moderate or severe pain. The type of medication administered is sequentially escalated from nonopioids (*e.g.*, nonsteroidal antiinflammatory drugs (NSAIDs) ± adjuvants to opioids used for mild to moderate pain (codeine, dihydrocodeine, oxycodone (compounded with a coanalgesic), hydrocodone, dihydrocodone) ± adjuvants to opioids commonly used for severe pain (morphine, hydromorphone, methadone, oxycodone (without compounding), fentanyl or levorphanol). Adjuvant medications are listed in template 7. (Modified with permission from WHO: Cancer pain relief and palliative care: Report of a WHO expert committee. Geneva, World Health Organization, 1990 (technical report series, no. 804).)



Template 5. Paradigm for the management of cancer pain.

disease or the development of tolerance. When pain is continuous or occurs frequently, medication generally should be administered around-the-clock with additional "rescue" doses available for breakthrough pain. The practitioner should be aware of the potential adverse sequelae of opioids and their appropriate treatment.

When considering changing opioids or routes of administration, dose adjustments should be made to correct for differences in potency. Apparent differences in potency among opioids are the result of physicochemical and pharmacokinetic differences rather than pharmacodynamic distinctions (template 6). When tolerance to a particular opioid develops, another opioid may be substituted at approximately 50–75% of the equianalgesic dose, because cross-tolerance is incomplete. The size of the reduction should be based on the severity of pain, the presence of adverse effects, and the medical status of the patient. Based on clinical observation, a switch to methadone should be done with a reduction of 75% of the equianalgesic dose.

Adjuvant agents should be used as coanalgesics (*e.g.,* corticosteroids, antidepressants) or to treat adverse drug effects. These agents may be added at any stage (template 7).

2. Specific Recommendations.

a. Oral medications: Oral medications such as acetaminophen, acetylsalicylic acid or other nonsteroidal antiinflammatory drugs (NSAIDs) should be employed first for mild to moderate pain. (Note: the simultaneous use of more than one NSAID or the concomitant use of an NSAID with a glucocorticoid is not recommended because the risk of toxicity is increased, and additional analgesia is not achieved.) If pain is not relieved or increases or if moderate pain is present at presentation, an opioid conventionally used for moderate pain (*e.g.,* codeine, dihydrocodeine, oxycodone (compounded with a coanalgesic), or hydrocodone) should be used, usually combined with a nonopioid analgesic. When increasing opioid dose, an increment of 25–50% is usually the minimum required to observe effect. If pain is not relieved, increases, or is severe at presentation, an opioid conventionally used for severe pain (*e.g.,* morphine, hydromorphone, methadone, oxycodone (not compounded with a coanalgesic), fentanyl, or levorphanol) should be selected. (Note: Besides consideration of a change in opioid, an increase in pain intensity should prompt a reevaluation of the cause of pain.)

When analgesia with acceptable adverse effects is no longer attained with the oral route of administration or when oral administration is no longer viable (inability to swallow and/or absorb medication), an alternate systemic route of administration should be chosen. (Note: The enteral route should be used in patients with percutaneous feeding tubes and inability to swallow, as long as absorption still

Template 6. Opioid Analgesics Commonly Used to Manage Cancer Pain*

Generic Name	Proprietary Name	Route	Dose Equivalence†,‡ (mg)	Comments
Opioids conventionally used to manage mild to moderate pain				
Codeine	Various	Oral	200	With the exception of codeine, these opioids are compounded with aspirin or acetaminophen, which imposes a dosage ceiling.
Dihydrocodeine	Various	Oral		
Hydrocodone	Vicodin, Lortab, various	Oral		
Oxycodone	Various	Oral		
Opioids conventionally used to manage moderate to severe pain				
"Immediate release" morphine	MSIR	Oral	30	Especially useful for initial dose titration and prn supplementation with long-acting opioids
Controlled release morphine	MS Contin, Oramorph	Oral	30	Used around-the-clock for basal pain (Do not break, crush, or chew.)
Morphine	Various	Parenteral	10	Usual standard for comparison
Hydromorphone	Dilaudid	Oral	7.5	Especially useful for initial dose titration and prn supplementation with long-acting opioids
Hydromorphone	Dilaudid	Parenteral	1.5	Often used subcutaneously
Oxycodone	Various	Oral	20–30	Often compounded with adjuvants for moderate pain
Fentanyl	Sublimaze	Intravenous	0.1	Used as single entity for severe pain Sustained release form is available Minimal experience outside the hospital setting
Fentanyl	Duragesic	Transdermal	45–134 mg oral morphine ~25 μg/h fentanyl	Used around-the-clock for stable pain, especially with GI dysfunction
Methadone	Dolophine	Oral	20	Inexpensive, but long, variable half-life may complicate titration and predispose to toxicity
Methadone	Dolophine	Parenteral	10	Inexpensive, but long, variable half-life may complicate titration and predispose to toxicity
Levorphanol	Levodromoran	Oral	4	Long half-life with much shorter dosing interval
Levorphanol	Levodromoran	Parenteral	2	Long half-life with much shorter dosing interval

* This list is partial and based on commonly used U.S. formulations. Meperidine and the agonist-antagonist opioids are not included in the table. Meperidine may produce seizures because of accumulation of the normeperidine breakdown product during chronic administration. This is of particular importance in the elderly and in patients with abnormal renal function. The agonist-antagonist opioids have ceiling and dysphoric effects and may precipitate withdrawal in patients chronically receiving pure agonist opioids.

† Dose equivalencies are approximate.

‡ When converting between drugs or routes of administration, it is recommended to reduce the calculated dose by 25–50% to account for incomplete cross-tolerance. (Based on clinical observation, methadone dose should be reduced by 75%.) Appropriate titration of dosage should then be performed as clinically indicated.

occurs.) If dose-limiting toxicity precludes effective therapy, a trial of a different opioid, a reduction of adverse effects by optimization of adjuvants, neuraxial drug delivery, or neuroablative therapy should be considered.

b. Rectal and transdermal: Use of an alternative route of administration, specifically rectal or transdermal, should be chosen before use of invasive therapies. Rectal administration usually is considered when oral therapy is temporarily unavailable (*e.g.*, nausea and vomiting refractory to therapy), although long-term use is effective in some patients. Transdermal

Template 7. Commonly Used Adjuvant Analgesics

Class (examples)	Usual Indications
Anticonvulsants	
Phenytoin Carbamazepine Clonazepam Valproate	Neuropathic pain, particularly lancinating or paroxysmal pain
Antidepressants	
Amitriptyline Nortriptyline Imipramine Desipramine Trazodone	Neuropathic pain
Local anesthetics	
Lidocaine Mexiletine	Neuropathic pain
Corticosteroids	
Dexamethasone Prednisone	Tumor invasion of neural tissue, elevated intracranial pressure, spinal cord compression, additional effects (mood elevation, antiemesis, appetite stimulation)
Antihistaminics	
Hydroxyzine	Coanalgesic, antiemetic
Muscle relaxants	
Orphenadrine Carisoprodol Methocarbamol Chlorzoxazone Cyclobenzaprine	Occasionally useful for musculoskeletal pain
Neuroleptics	
Methotrimeprazine Fluphenazine	Neuropathic pain
Other drugs for neuropathic pain	
Baclofen Clonidine Calcitonin Capsaicin, topical	Neuropathic pain
Drug action on bone	
Biphosphonates (pamidronate) Calcitonin Radiopharmaceuticals (Strontium 89)	Bone pain
Anticholinergics	
Scopalamine Glycopyrrolate	Visceral pain due to bowel obstruction
Psychostimulants	
Caffeine Methylphenidate Dextroamphetamine	Decrease sedation due to opioid analgesia

fentanyl should be used in patients with stable pain states who are (1) noncompliant with oral medication, (2) unable to swallow or absorb, or (3) may benefit from a trial of fentanyl.

c. Subcutaneous and intravenous administration: The subcutaneous route of administration should be used in (1) patients unable to swallow or absorb opioids who may benefit from a continuous infusion of opioid and (2) similar patients with dynamic pain states requiring frequent "rescue" doses for breakthrough pain. Subcutaneous administration of opioids may be used in the home setting. The recommendations for intravenous administration are the same as for subcutaneous administration. Intravenous administration may be preferred when the patient has permanent venous access. (Note: Intramuscular injection is not recommended as either short- or long-term therapy for cancer pain management because of the attendant discomfort, variable blood concentrations, and fluctuating levels of analgesia.)

B. Direct Delivery Systems: Neuraxial Drug Delivery and Neuroablation

Opioids and local anesthetics can be delivered directly to the vicinity of neural tissue, obviating the need for systemic absorption as a means to reach receptor sites. Other potential agents for neuraxial drug delivery are under development. Neuroablation refers to the chemical, thermal, or surgical destruction of neural tissue.

Neuroablation is preceded by diagnostic neural blockade. Regional analgesic techniques are referred to in these guidelines as neural blockade (*e.g.*, intercostal blocks, celiac plexus blocks) and are distinct from neurolytic blocks. Neural blockade is used alone for short-term pain management with specific indications (see below). The Task Force is supportive of the efficacy of neural blockade for prognostic purposes. (Note: Sufficient literature is not available to assess the effectiveness of neural blockade as either a prognostic procedure or a long-term analgesic modality for the treatment of cancer pain.)

a. Neuraxial drug delivery: The literature is supportive of the efficacy of neuraxial analgesic delivery (*i.e.*, epidural, subarachnoid, intraventricular). Epidural or subarachnoid drug administration may be performed by either percutaneous catheterization, reservoir, or implantation of a catheter and pump. Al-

though the literature suggests that neuraxial techniques are not associated with an increased incidence of adverse effects, the Task Force and consultants suggest that adverse effects may be possible (*e.g.*, catheter-site infections).

b. Neuroablation: The literature suggests and consultants and Task Force members support the view that neuroablation by chemical and thermal neurolysis or surgery can provide long-term control of severe cancer pain without a substantial incidence of adverse effects. Examples of chemical neuroablative procedures include but are not limited to intercostal neurolysis, neurolytic celiac plexus block, neurolytic superior hypogastric plexus block, neurolytic ganglion impar (ganglion of Walther) block, craniofacial neurolytic techniques, and subarachnoid rhizolysis. Examples of thermal neuroablative techniques include radiofrequency ablation (heat) and cryoanalgesia (cold).

Recommendations:

1. General Recommendations. When adequate analgesia cannot be achieved or intolerable side effects occur with indirect methods of drug delivery, direct drug delivery systems should be considered. In certain specific circumstances, neuraxial drug delivery or neuroablative therapies should be considered at the initiation of therapy or early in the natural history of the pain (see below). Neuraxial drug delivery and neuroablative therapies should not be used: (1) in individuals who are unmotivated or noncompliant or do not possess the cognitive functioning necessary to understand the risks and benefits and (2) when an appropriate logistical system does not exist. Patients must have access to a logistical system that provides the resources and availability of personnel to respond to patient needs on an around-the-clock basis. The establishment of an office or network with professional support may be necessary. For long-term therapies, appropriate home care must be available and functionally integrated into the office, hospital, and community.

2. Specific Recommendations.

a. Neuraxial drug delivery: Neuraxial drug delivery should be used: (1) when severe pain cannot be controlled with systemic drugs because of dose-limiting toxicity, (2) when there is immediate need for local anesthetic (some neuropathic pains), (3) after failed neuroablation, or (4) patient preference indicates its use. The choice between epidural or subarachnoid catheterization is determined in part by patient life expectancy. When extended life expectancy is anticipated, subarachnoid catheter placement should be considered because epidural catheters may become obstructed. The presence of epidural metastases necessitates subarachnoid catheterization.

Before insertion of an indwelling neuraxial drug delivery system, efficacy and appropriate dose range should be ascertained by trial injection or use of a temporary delivery system. Patients should have access to "rescue" doses for breakthrough pain. "Rescue" doses may be given by any route of administration as deemed appropriate by the practitioner.

Intraventricular administration of opioids may be considered in patients with head and neck cancer and Ommaya reservoirs. (Note: Neural blockade should be used before neuraxial drug delivery because of (1) the presence of pain therapeutically amenable to neural blockade (*e.g.*, myofascial pain, sympathetically-maintained pain, pain of acute herpes zoster); or (2) patient preference, when appropriate.)

b. Neuroablation: Neuroablative techniques should be initiated (1) when systemic therapies have failed to provide adequate pain control or when adverse side effects from systemic therapies are unacceptable; (2) after failure of neuraxial drug administration; (3) early in the natural history of the cancer pain in the presence of selected focal somatic lesions (*e.g.*, rib metastases), visceral (*e.g.*, cancer of the pancreas), or neuropathic (*e.g.*, craniofacial) pain that is believed to be highly responsive to neuroablation with limited risk; or (4) patient preference indicates use of neuroablative techniques, if appropriate. Except for the aforementioned specific indications, chemical, radiofrequency (thermal), and surgical neuroablation should be deferred until anticipated life expectancy is short-term, thereby minimizing the potential for deafferentation pain. On the other hand, consideration of life expectancy is moot with cryoanalgesia because of the potential for nerve regeneration associated with the technique. The cryoanalgesic procedure often must be repeated because the endoneurium is spared, allowing regrowth over time. After performance of successful chemical, thermal, or surgical neurolysis, opioid administration should not be immediately curtailed to avoid precipitation of withdrawal. Dos-

age should be immediately reduced, and opioids should be weaned to avoid respiratory depression, which may occur in the setting of abrupt pain relief.

Neural blockade should be used prognostically to determine the possible efficacy of neuroablation. However, even with proper needle placement under fluoroscopic guidance, successful neural blockade does not ensure the subsequent success of a neurodestructive procedure. Neural blockade should be performed at the time of potential neuroablation and should not be performed as a separate procedure. If analgesia is not achieved with neural blockade or significant adverse sequelae result, neuroablation should be reconsidered.

Definitive neuroablation should be performed with the aid of imaging techniques when feasible or with direct visualization of the intended neural target in the case of open surgical ablation.

V. Management of Cancer-related Symptoms and Adverse Effects of Pain Therapy

The literature supports the efficacy of interventions designed to manage symptoms related to primary disease and its treatment. In addition, the literature suggests that specific interventions used to treat the adverse effects of pain therapy are efficacious. Adverse drug effects directly resulting from cancer pain therapies include but are not limited to sedation, nausea and vomiting, pruritus, constipation, urinary retention, and respiratory depression. (Note: Respiratory depression is rare in the cancer patient receiving chronic opioid therapy (Appendix 2)).

The literature does not suggest that management of symptoms or adverse effects has an effect on analgesia.

The Task Force and consultants are supportive of the value of managing cancer-related symptoms and adverse drug effects as part of the comprehensive management of cancer pain.

Recommendations:

1. General Recommendations. Adverse effects should be promptly identified and assessed, and appropriate remedies should be offered. Opioids should not be withheld from cancer patients for fear of producing respiratory depression, tolerance, physical dependence, or addiction.

2. Specific Recommendations.

a. Constipation: All patients with an increased risk for constipation should receive prophylaxis (Appendix 2). Prophylactic or symptomatic therapy should involve the use of bulk agents, osmotic laxatives (*e.g.,* magnesium or sodium salts, lactulose or sorbitol), and/or stimulant cathartics (*e.g.,* senna or bisacodyl). A stool softener may be concomitantly used with the aforementioned agents. Occasionally, patients require enemas.
b. Sedation: Sedation should be treated by (1) eliminating contributory factors such as nonessential drugs and metabolic disturbances, (2) reducing the dose of an opioid by 25–50% if analgesia is satisfactory, (3) lowering the requirement for opioids by the addition of a nonopioid analgesic or adjuvant analgesic, (4) switching to another opioid, (5) the use of psychostimulants, or (6) considering more invasive modalities if sedation is refractory to therapy.
c. Nausea and vomiting: Persistent nausea is rare, and prophylactic therapy is not indicated. Transitory nausea and vomiting should be treated initially with standard antiemetics, such as promethazine, prochlorperazine, haloperidol, metoclopramide, or hydroxyzine. In some cases, ondansetron or meclizine can be helpful. Some patients may benefit from the use of low-dose corticosteroid, alternative treatment for gastroparesis (*i.e.,* cisapride), or a benzodiazepine (*i.e.,* lorazepam). Treatment of factors contributing to nausea (*e.g.,* constipation) should be considered when appropriate.
d. Mental clouding: The treatment of cognitive impairment should mirror the management of sedation. The addition of low-dose haloperidol occasionally may be necessary for confusional states induced by opioids. Psychostimulants can be administered to reverse mental clouding in the absence of sedation but should not be administered to agitated patients.
e. Myoclonus: Myoclonus is not usually a clinical problem, and reassurance should be given to patients regarding its benign nature. However, if myoclonus impairs function, prevents sleep, or increases pain, clonazepam or valproate should be administered. A reduction in opioid dose or a switch to a different opioid should be considered in the face of refractory or severe myoclonus.

f. Pruritus: Pruritus is rarely a problem with chronic opioid administration, and consideration should be given to an initial trial of diphenhydramine if it occurs.
g. Urinary retention: Urinary retention is also rare with chronic opioid administration and should be treated by administration of a direct cholinomimetic agent, such as bethanecol.
h. Respiratory depression: The least amount of naloxone should be administered to preserve analgesia and avoid withdrawal (Appendix 2). Because of the short half-life of naloxone, a continuous infusion may be necessary.

VI. Recognition, Assessment, and Management of Psychosocial Factors

The literature suggests that psychosocial interventions are effective in improving analgesia and the quality of life for cancer pain patients. The Task Force and panel of consultants offer similar support. Psychosocial interventions for the management of cancer pain include pain diaries, hypnosis, biofeedback, relaxation training, psychotherapy, and behavior management. Recognition is given to the nonspecific effects of listening and showing concern for the welfare of the patient. Management of the psychosocial consequences of cancer pain includes the use of nonpharmacologic interventions (*e.g.,* psychotherapy and pastoral counseling), psychotropic medications, and antidepressants.

Recommendations: A psychosocial assessment should be conducted initially as an integral part of the comprehensive pain evaluation. Results of the psychosocial assessment should be considered when formulating a pain treatment plan. Pain diaries and counseling should be considered to enhance medication compliance, if needed. The anesthesiologist should recognize that pharmacologic and neurolytic techniques may not be fully effective in controlling pain and that relaxation training, hypnosis, biofeedback, and behavior therapy are important adjuncts. The anesthesiologist should collaborate with psychologists and other health professionals when psychosocial interventions are indicated. The anesthesiologist should recognize that psychosocial manifestations related to cancer (but not to cancer pain) may require referral to appropriate mental health professionals.

VII. Home Parenteral Therapy

The literature suggests that home parenteral therapy is effective for analgesia without notable risk of adverse effects. The panel of consultants and Task Force members support the importance of home parenteral therapy in increasing analgesia and enhancing patient quality of life. Home parenteral therapy provides an infrastructure for the logistical support and clinical management of complex drug delivery systems in a nonhospital setting. Home parenteral therapy includes subcutaneous, intravenous, and neuraxial drug delivery techniques, either on an outpatient basis or with the assistance of a home health-care provider. The coordination of home parenteral therapy may be accomplished by various providers (*e.g.,* hospitals, clinics, or home health-care professionals).

Recommendations: Before changing from the oral route of administration, the anesthesiologist should ascertain the availability of family and professional support systems. The patient and family must be educated in the use of the home therapy system. The anesthesiologist should determine whether the patient and/or significant others are motivated and competent to care for sophisticated delivery systems. An assessment must be made as to whether appropriate professional services and supplies are obtainable in specific locales, because special planning may be required in rural areas. Communication among the patient, the home health-care professional, and the prescribing physician must be maintained at all times.

VIII. End-of-Life Care

The need for supportive care intensifies for patients and their families at the end of life. The literature, Task Force members, and consultants are supportive of the efficacy of palliative therapies for cancer patients approaching the end of life. End-of-life care is intended to improve patient comfort and quality of life by means of palliative therapies, including but not limited to anxiolytics, skin care, mouth care, massage, and appetite stimulants. Palliative therapies may be provided in the form of comprehensive programs, such as hospice or nursing-care outreach programs.

Recommendations: The management of cancer pain must be integrated into a comprehensive care system that may include hospice and psychosocial support for patients and their families. Assessing and monitoring a patient's palliative care needs are essential parts of the

evaluative/therapeutic process. When cancer patients are approaching the end of life, the anesthesiologist should integrate pain management with palliative care needs. Collaboration with palliative care providers is recommended to maximize patient comfort and improve patient and family quality of life.

IX. Recognition and Management of Special Features of Pediatric Cancer Pain Management

The literature suggests that child-specific interventions are associated with improved analgesia and health outcomes. The Task Force and consultants are supportive of the effectiveness of pediatric cancer pain therapies in improving analgesia and quality of life. Age-appropriate assessment includes behavioral observation (*e.g.,* facial expressions, crying) and self-reports using age-appropriate scales (*e.g.,* visual analog scale, facial pain scale). Pharmacologic interventions designed for children's use include but are not limited to (1) adjustment of dosage to those levels specific for children and (2) interventions designed to be less invasive or to alleviate patient fears or anxieties about their pain therapy (*e.g.,* topical anesthetics as premedication). Psychological and other nonpharmacologic interventions include those designed specifically for children or adult interventions modified to be applicable to children.

Recommendations: The anesthesiologist should give special attention to the assessment of pain in pediatric patients. For children unable to communicate verbally, observation of patient behavior should be the primary assessment tool. For children who can communicate verbally, age-appropriate pain scales are the recommended self-report instruments when evaluating the efficacy of pain therapy. Observation should be used as an adjunct to self-report.

Administration of oral medications to children should follow the schema of the WHO analgesic ladder, with particular attention paid to age-appropriate dosing regimens. Liquids or suspensions should be employed whenever possible, because many children find them more palatable than pills. (Note: Continuous-release morphine preparations cannot be crushed and still maintain their continuous release properties.) Every attempt should be made to minimize repetitive exposure to needles, if possible. Patient-controlled analgesia (intravenous or subcutaneous) is a viable alternative when children are of sufficient cognitive age. Invasive systemic therapies and direct delivery systems should be used when oral and noninvasive analgesic deliveries do not achieve sufficient analgesia, or side effects make their continued use untenable. Psychological and other nonpharmacologic methods of pain management should be considered as adjuvants.

The Task Force thanks those who responded to surveys on cancer pain management, reviewed guideline drafts, contributed oral and written testimony to the Open Forum, and participated in tests of clinical feasibility.

The development of these guidelines included methods recommended in the following publications: (1) Committee to Advise the Public Health Service on Clinical Practice Guidelines, Division of Health Care Services, Institute of Medicine: Clinical Practice Guidelines: Directions for a New Program. Edited by Field MJ, Lohr KN. Washington, DC, National Academy, 1990, 1992; and (2) Woolf SH: Manual for Clinical Practice Guidelines Development. Washington, DC, US Department of Health and Human Services, Agency for Health Care Policy and Research, publication number 91-0007, March 1991.

Appendix 1. Assessment of Scientific Evidence and Consultant Opinion

The scientific assessment of these guidelines was based on the following statements or evidence linkages. These linkages represent directional hypotheses about relationships between cancer pain, symptom management, and clinical outcomes.

1. Comprehensive evaluation and assessment of pain (*i.e.,* history, physical examination, laboratory evaluation) improve analgesia, reduce adverse effects of pain therapy, and improve quality of life.
2. Longitudinal monitoring of pain (*e.g.,* patient self-report, rating scales, and frequency of pain ratings) improves analgesia, reduces adverse effects of pain therapy, and improves quality of life.
3. Involvement of specialists in multiple disciplines improves analgesia, reduces adverse effects of pain therapy, and improves quality of life.
4. Indirect drug delivery systems (*i.e.,* systemic analgesia: oral medications administered by application of the WHO pain ladder, rectal and transdermal analgesia, subcutaneous drug delivery, and intravenous drug delivery) improve analgesia, reduce adverse effects of pain therapy, and improve quality of life.
5. Direct drug delivery systems (*i.e.,* neuraxial drug delivery (epidural, subarachnoid, intraventricular), neural blockade (diagnostic blockade, neural blockade for pain management), and neuroabla-

tion (chemical, thermal, and surgical neurolysis)) improve analgesia, reduce adverse effects of pain therapy, and improve quality of life.

6. Management of cancer-related symptoms, side effects of cancer treatment, and adverse effects from pain therapy (*e.g.,* use of antiemetics and laxatives) improves analgesia, reduces adverse effects of pain therapy, and improves quality of life.
7. Psychosocial interventions for pain management and interventions to treat psychosocial consequences from cancer pain and pain management improve analgesia, reduce adverse effects of pain therapy, and improve quality of life.
8. Home parenteral therapy improves analgesia, reduces adverse effects of pain therapy, and improves quality of life.
9. End-of-life care improves analgesia, reduces adverse effects of pain therapy, and improves quality of life.
10. Special features of pediatric cancer pain management (*i.e.,* age-appropriate assessments and dosage levels, interventions to alleviate fears and anxieties about pain therapy, less invasive routes of pharmacologic administration) improve analgesia, reduce adverse effects of pain therapy, and improve quality of life.

Scientific evidence was derived from aggregated research literature with metaanalyses when appropriate, surveys, open presentations, and other consensus-oriented activities. For purposes of literature aggregation, potentially relevant clinical studies were identified *via* electronic and manual searches of the literature. The electronic search covered a 30-yr period from 1966 through 1995. The manual search covered a 48-yr period from 1948 through 1995. More than 3,000 citations were identified initially, yielding 953 non-overlapping articles that addressed topics related to the 10 evidence linkages. After review of the articles, 603 studies did not provide direct evidence and were subsequently eliminated, yielding 350 articles containing direct evidence. Journals (n = 116) represented by the 350 articles included the following disciplines: anesthesiology, 205; oncology, 36; internal medicine, 3; neurology, 4; neurosurgery, 34; nursing, 8; palliative care, 27; pediatrics, 6; pharmacology, 9; psychology, 14; and radiology, 4.

A directional result for each study was determined initially by classifying the outcome as either supporting a linkage, refuting a linkage, or neutral. The results were summarized to obtain a directional assessment of support for each linkage. The literature relating to linkages 3 (involvement of specialists from multiple disciplines), 5a (neuraxial, *i.e.,* epidural and subarachnoid drug delivery), 6 (management of symptoms or adverse effects), and 9 (end-of-life care) contained enough studies with well defined experimental designs and statistical information to conduct formal metaanalyses.

The following terms were used in the guidelines to express the strength of the evidence relating to various interventions and their associated outcomes: (1) *insufficient* data: There is insufficient published data to provide an indication of the relationship between intervention and outcome; (2) *suggestive* data: There is qualitative evidence in the form of case reports or descriptive studies, but there is insufficient quantitative evidence to establish a statistical relationship between intervention and outcome; (3) *supportive* data: Quantitative data indicate a significant relationship between intervention and outcome ($P < 0.01$), and qualitative data are suggestive.

Combined probability tests were applied to continuous data, and an odds-ratio procedure was applied to dichotomous study results. Two combined probability tests were employed as follows: (1) Fisher's combined test, producing chi-square values based on logarithmic transformations of the reported P values from the independent studies, and (2) the Stouffer combined test, providing representation of the studies by weighting each of the standard normal deviates by the size of the sample. A procedure based on the Mantel-Haenszel method for combining study results using 2×2 tables was used when sufficient outcome frequency information was available. An acceptable significance level was set at $P < 0.01$ (one-tailed), and effect-size estimates were calculated. Interobserver agreement was established through assessment of interrater reliability testing. Tests for heterogeneity of the independent samples were conducted to assure consistency among the study results. To control for potential publishing bias, a ''fail-safe n'' value was calculated for each combined probability test. No search for unpublished studies was conducted, and no reliability tests for locating research results were done.

Results of the combined probability tests are reported in table A1. Significance levels from the weighted Stouffer combined test for clinical efficacy were significant for linkages 3 (multiple disciplines) and 5a (neuraxial drug delivery). The weighted Stouffer test for linkage

Table A1. Statistical Summary: Combined Test Results

Analgesic efficacy			
Linkage 3. Involvement of specialists in multiple disciplines			
Fisher combined test:	Chi-square = 35.83	$P < 0.001$	$df = 12$
Stouffer combined test:	Z_c (weighted) = 3.025	$P < 0.010$	
Effect size estimate:	r (weighted) = 0.13		
Fail-safe N value:	Nfs .01 = 15.7		
Linkage 5a. Epidural and subarachnoid drug delivery			
Fisher combined test:	Chi-square = 34.45	$P < 0.001$	$df = 12$
Stouffer combined test:	Z_c (weighted) = 3.742	$P < 0.001$	
Effect size estimate:	r (weighted) = 0.34		
Fail-safe N value:	Nfs .01 = 20.2		
Linkage 9. End-of-life care			
Fisher combined test:	Chi-square = 48.39	$P < 0.001$	$df = 10$
Stouffer combined test:	Z_c (weighted) = 2.286	$P = 0.011$ (NS)	
Effect size estimate:	r (weighted) = 0.20		
Fail-safe N value:	Nfs .01 = 23.1		
Beneficial outcomes			
Linkage 3. Involvement of specialists from multiple disciplines			
Fisher combined test:	Chi-square = 40.06	$P < 0.001$	$df = 10$
Stouffer combined test:	Z_c (weighted) = 3.442	$P < 0.010$	
Effect size estimate:	r (weighted) = 0.17		
Fail-safe N value:	Nfs .01 = 19.1		
Linkage 6. Management of side effects (primary disease and treatment)			
Fisher combined test:	Chi-square = 80.21	$P < 0.001$	$df = 16$
Stouffer combined test:	Z_c (weighted) = 3.650	$P < 0.001$	
Effect size estimate:	r (weighted) = 0.34		
Fail-safe N value:	Nfs .01 = 83.7		
Linkage 9. End-of-life care			
Fisher combined test:	Chi-square = 47.34	$P < 0.001$	$df = 14$
Stouffer combined test:	Z_c (weighted) = 4.147	$P < 0.001$	
Effect size estimate:	r (weighted) = 0.18		
Fail-safe N value:	Nfs .01 = 28.8		

9 (end-of-life care) was not significant. Weighted effect size estimates ranged from r = 0.13 to r = 0.34, demonstrating small-to-moderate effect size estimates. Significance levels from the weighted Stouffer combined tests for beneficial outcomes were significant for linkages 3 (multiple disciplines), 6 (symptoms or adverse effects), and 9 (end-of-life care). Weighted effect size estimates for beneficial outcomes ranged from r = 0.17 to r = 0.34. Tests for heterogeneity of statistical tests and effect size were nonsignificant in all cases, indicating that the pooled studies provided common estimates of significance and population effect sizes. Sufficient data were not available in the literature to conduct Mantel-Haenszel analyses on these linkages.

Metaanalysis was not performed on linkage 4 (indirect drug delivery systems) for either efficacy or outcomes because literature was not conducive to an appropriate assessment. The literature did not consistently report analgesic requirements of the patients studied, which may vary over time as a function of the natural history of the disease. Lack of concurrent analytical control for time-of-measurement and cohort effects preclude valid comparisons. However, subgroup analyses indicated that mild adverse outcomes were associated with the use of weak opioids in comparison to NSAID administration. Weighted Stouffer combined test results were: $Z_c = 4.69$, $P < 0.001$; the weighted effect size estimate (r = 0.32) indicated a moderate effect size. The odds of adverse effects (*e.g.,* sedation, nausea, vomiting) were greater for weak opioids *versus* NSAID groups (odds ratio 1.95, 99% confidence limits 1.45–2.46, Z = 3.10, $P < 0.001$).

Agreement among Task Force members and two methodologists was established by interrater reliability testing. Agreement levels using a Kappa statistic for two-rater agreement pairs were as follows: (1) type of study design, k = 0.37–0.67; (2) type of analysis, k = 0.47–0.72; (3) evidence linkage assignment, k =

0.47–0.96; and (4) literature inclusion for database, k = 0.35–1.00. Three-rater chance-corrected agreement values were: (1) design, S_{av} = 0.46, Var (S_{av}) = 0.008; (2) analysis, S_{av} = 0.63, Var (S_{av}) = 0.006; (3) linkage identification, S_{av} = 0.64, Var (S_{av}) = 0.005; and (4) literature database inclusion, S_{av} = 0.53, Var (S_{av}) = 0.030. These values represent moderate to high levels of agreement.

The findings of the literature analyses were supplemented by the opinions of Task Force members as well as by surveys of the opinions of a panel of consultants with expertise in cancer pain management (n = 72). The rate of return of the surveys was 81% (n = 58 of 72). The percentage of consultants supporting each linkage is reported in table A2. Consultants, in general, were highly supportive of the linkages (*i.e.,* agreed that they provided analgesic benefit, reduced risk of adverse outcomes, improved other cancer-related symptoms, improved quality of life, and were important issues for the guidelines to address).

The feasibility of implementing these guidelines into clinical practice was assessed by an opinion survey of the cancer pain consultant panel (n = 71). Rate of return of the survey was 65% (n = 46 of 71). The mean number of patients treated annually by the consultants was reported to be 557.5 (min/max = 10/5,000). Responses for feasibility of implementation of the guidelines were as follows: (1) Ninety-one percent (n = 42 of 46) of these consultants indicated that implementation of the guidelines would not result in the need to purchase new equipment, supplies, or pharmaceuticals. (2) Among the four respondents who stated that purchases would be required, the median anticipated cost was $25,000 (mean $24,625; range $13,500–35,000).

The consultants were asked to indicate which, if any, of the evidence linkages would change their clinical practices if the guidelines were instituted. The percent of consultants expecting no change associated with each linkage were as follows: comprehensive evaluation, 76%; longitudinal monitoring, 78%; multiple disciplines, 89%; administration of systemic opioids, 100%; neuraxial drug delivery, 87%; neurolytic techniques, 87%; management of symptoms/adverse effects, 89%; psychosocial factors, 89%, use of parenteral therapy, 94%, end-of-life care, 80%, and pediatric pain management, 83%.

Eighty percent of the respondents indicated that the guidelines would have no effect on the amount of time spent on a typical case. None reported that the guidelines would reduce the amount of time spent per case. For all respondents, the mean increase in the amount of time spent on a typical case was 7.1 min (range 0–120 min). Of the 20% of respondents who reported an anticipated increase in time spent on a typical case, the mean was 36.1 min (range 10–120 min).

Readers with special interest in the statistical analyses used in establishing these guidelines can receive further information by writing to the American Society of Anesthesiologists: 520 North Northwest Highway, Park Ridge, Illinois 60068-2573.

Table A2. Consultant Responses to Evidence Linkages Survey (n = 58)

Linkages	Analgesic Benefit (% Supportive)	Reduced Risk (% Supportive)	Improved Symptoms (% Supportive)	Improved Quality of Life (% Supportive)	Important Topic (% Supportive)
1. Comprehensive evaluation	98	93	90	91	98
2. Longitudinal monitoring	98	100	85	100	100
3. Involvement of specialists in multiple disciplines	83	64	90	83	79
4. Administration of systemic opioids	71	66	38	74	91
5. Neuraxial drug administration	83	64	41	69	91
6a. Management of cancer-related symptoms or side effects of cancer	81	91	—	98	93
6b. Management of side effects from pain therapy	85	—	79	100	100
7. Psychosocial interventions	83	71	79	95	98
8. Parenteral therapy	81	62	53	81	41
9. End-of-life care	85	86	97	97	95
10. Pediatric cancer pain management	93	83	67	91	98

Appendix 2. Adverse Drug Effects from Opioid Therapies

Tolerance, physical dependence, and addiction are concerns expressed by patients and physicians and must be understood to optimize therapy.

1. Tolerance refers to the progressive decline in the potency of an opioid with continued use, such that increasingly greater doses are needed to achieve the same degree of analgesia. The phenomenon is characteristic of opioids as a class of analgesics and is receptor-mediated. Clinical observations confirm that most patients with stable pain do not require dose escalation to maintain relief. Hence, tolerance is seldom the "driving force" for dose escalation.

   When tolerance to an opioid develops, incomplete cross-tolerance to other opioids concomitantly develops. In such cases, another opioid can be substituted to provide better analgesia.
2. Physical dependence does not imply addiction. Physical dependence is a physiologic state characterized by withdrawal (abstinence syndrome) after abrupt discontinuation of an opioid.
3. Addiction is a psychological and behavioral syndrome characterized by compulsive drug-seeking behavior (among other behaviors), loss of control over drug use, and continued use despite harm. Addiction implies compulsive behavior and psychological dependence. This is exceedingly rare among cancer patients who are given opioids. Tolerance (a pharmacologic property of a class of drugs) and physical dependence (a physiologic effect characteristic of this class of drugs) are conceptually and phenomenologically distinct from addiction.
4. Constipation is highly prevalent among patients receiving chronic treatment with opioids. All patients with an increased risk for constipation should receive prophylactic therapy. Clinical scenarios or syndromes with an increased risk for the development of constipation include: (1) cachexia and/or debilitation, (2) poor performance status (especially the bedridden patient), (3) intraabdominal neoplasm, (4) a history of prior abdominal radiation, (5) autonomic neuropathy, (6) poor fluid intake, and (7) the concurrent use of constipating agents. A stool softener (*e.g.,* docusate) often is used in combination with bulk, osmotic, or stimulant cathartics.
5. Sedation is a common adverse effect associated with the analgesic therapy of cancer pain.
6. Nausea and vomiting are usually uncommon and transitory in patients undergoing opioid titration. Persistent nausea is rare, and prophylaxis is not indicated.
7. Mental clouding or cognitive impairment can vary from mild mental clouding to frank delirium. Mental clouding may occur without sedation.
8. Myoclonus, pruritus, and urinary retention occur infrequently in patients receiving chronic opioid therapy.
9. Respiratory depression is rare in the cancer patient receiving chronic opioid therapy and occurs in association with obtundation and bradypnea. Respiratory depression can occur with abrupt resolution of pain and inadequate reduction of opioid dosage after successful neuroablation. If respiratory depression occurs in a patient taking stable opioid doses without abrupt resolution of pain due to a major therapeutic maneuver, an explanation other than opioid toxicity should be sought (*e.g.,* pulmonary embolism). Reversal of respiratory problems with naloxone only signifies that an opioid was contributing to the respiratory problem. Reversal of respiratory depression with naloxone does not obviate the need to consider other possible etiologies or pursue further evaluation.