

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 neuroablation (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 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, $S_{av} = 0.46$, $\text{Var}(S_{av}) = 0.008$; (2) analysis, $S_{av} = 0.63$, $\text{Var}(S_{av}) = 0.006$; (3) linkage identification, $S_{av} = 0.64$, $\text{Var}(S_{av}) = 0.005$; and (4) literature database inclusion, $S_{av} = 0.53$, $\text{Var}(S_{av}) = 0.030$. 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.

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.

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.

Template 3. Drug Delivery Systems	
Method of Access to the "Receptor"	
Indirect (<i>via</i> blood-borne carriage, <i>i.e.</i> , systemic analgesia)**	Direct***
Via systemic absorption	Neuraxial drug delivery
Oral, buccal	Epidural
Sublingual, intranasal	Subarachnoid
Rectal	Intraventricular
Via depot formation	Neuroablation
Transdermal	Chemical
Intramuscular	Thermal
Subcutaneous	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.

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. Used as a single entity for severe pain. Sustained release form is available.
Fentanyl	Sublimaze	Intravenous	0.1	Minimal experience outside the hospital setting
Fentanyl	Duragesic	Transdermal	45-134 mg	Used around-the-clock for stable pain, especially with GI dysfunction
			oral morphine	
			~25 micrograms/h fentanyl	
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.

Template 7. Commonly Used Adjuvant Analgesics	
Class (examples)	Usual Indications
Anticonvulsants	
Phenytoin	Neuropathic pain, particularly lancinating or paroxysmal pain
Carbamazepine	
Clonazepam	
Valproate	
Antidepressants	
Amitriptyline	Neuropathic pain
Nortriptyline	
Imipramine	
Desipramine	
Trazodone	
Local anesthetics	
Lidocaine	Neuropathic pain
Mexiletine	
Corticosteroids	
Dexamethasone	Tumor invasion of neural tissue, elevated intracranial pressure, spinal cord compression, additional effects (mood elevation, antiemesis, appetite stimulation)
Prednisone	
Antihistaminics	
Hydroxyzine	Coanalgesic, antiemetic
Muscle relaxants	
Orphenadrine	Occasionally useful for musculoskeletal pain
Carisoprodol	
Methocarbamol	
Chlorzoxazone	
Cyclobenzaprine	
Neuroleptics	
Methotrimeprazine	Neuropathic pain
Fluphenazine	
Other drugs for neuropathic pain	
Baclofen	Neuropathic pain
Clonidine	
Calcitonin	
Capsaicin, topical	
Drug action on bone	
Biphosphonates (pamidronate)	Bone pain
Calcitonin	
Radiopharmaceuticals (Strontium 89)	
Anticholinergics	
Scopolamine	Visceral pain due to bowel obstruction
Glycopyrrolate	
Psychostimulants	
Caffeine	Decrease sedation due to opioid analgesia
Methylphenidate	

Dextroamphetamine

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		

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

Linkages	Analgesic Benefit	Reduced Risk	Improved Symptoms	Improved Quality of Life	Important Topic
	(%Supportive)	(%Supportive)	(%Supportive)	(%Supportive)	(%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