NCCN National Comprehensive Cancer Network®

NCCN

Adult Cancer Pain

Clinical Practice Guidelines in Oncology

Robert Swarm, MD; Amy Pickar Abernethy, MD; Doralina L. Anghelescu, MD; Costantino Benedetti, MD; Craig D. Blinderman, MD, MA; Barry Boston, MD; Charles Cleeland, PhD; Nessa Coyle, PhD, NP; Oscar A. deLeon-Casasola, MD; June G. Eilers, PhD, APRN; Betty Ferrell, RN, PhD; Nora A. Janjan, MD, MPSA, MBA; Sloan Beth Karver, MD; Michael H. Levy, MD, PhD; Maureen Lynch, MS, APRN; Natalie Moryl, MD; Barbara A. Murphy, MD; Suzanne A. Nesbit, PharmD, BCPS; Linda Oakes, RN, MSN; Eugenie A. Obbens, MD, PhD; Judith A. Paice, PhD, RN; Michael W. Rabow, MD; Karen L. Syrjala, PhD; Susan Urba, MD; and Sharon M. Weinstein, MD

Overview

Pain, defined as "a sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage,"[1] is one of the most common symptoms associated with cancer. Cancer pain or cancer-related pain is distinct from pain experienced by patients without malignancies. Pain occurs in approximately one quarter of patients with newly diagnosed malignancies, one third of patients undergoing treatment, and three quarters of patients with advanced disease,[2–4] and is one of the symptoms patients fear most. Unrelieved pain denies patients comfort and greatly affects their activities, motivation, interactions with family and friends, and overall quality of life.

The importance of relieving pain and availabili-

NCCN Clinical Practice Guidelines in Oncology on Adult Cancer Pain

Key Words

NCCN Clinical Practice Guidelines, NCCN Guidelines, cancer, pain, malignancy, pain assessment, pain intensity rating

(JNCCN 2010;8:1046–1086)

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines™ is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

Disclosures for the NCCN Guidelines Panel for Adult Cancer Pain

At the beginning of each NCCN Guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in *JNCCN* and online. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Guidelines on Adult Cancer Pain panel members can be found on page 1086. (The most recent version of these guidelines and accompanying disclosures, including levels of compensation, are available on the NCCN Web site at www.NCCN.org.)

These guidelines are also available on the Internet. For the latest update, please visit www.NCCN.org.

ty of effective therapies make it imperative that physicians and nurses caring for these patients be adept at the assessment and treatment of cancer pain.[5–7] This requires familiarity with the pathogenesis of cancer pain; pain assessment techniques; common barriers to the delivery of appropriate analgesia; and pertinent pharmacologic, anesthetic, neurosurgical, and behavioral approaches to the treatment of cancer pain.

The most widely accepted algorithm for the treatment of cancer pain was developed by the WHO.[8,9] It suggests that patients with pain be started on acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). If this is not sufficient, patients should be escalated to a weak opioid, such as codeine, and then to a strong opioid, such as morphine. Although this algorithm has served as an excellent teaching tool, the management of cancer pain is considerably more complex than this 3-tiered "cancer pain ladder" suggests.

This guideline is unique in several important ways. First, it contains several required components:

- Pain intensity must be quantified by the patient (whenever possible), because the algorithm bases therapeutic decisions on a numerical value assigned to the severity of the pain.
- A formal comprehensive pain assessment must be performed.
- Reassessment of pain intensity must be performed at specified intervals to ensure that the therapy selected is having the desired effect.
- Psychosocial support must be available.
- Specific educational material must be provided to the patient.

Text continues on p. 1077

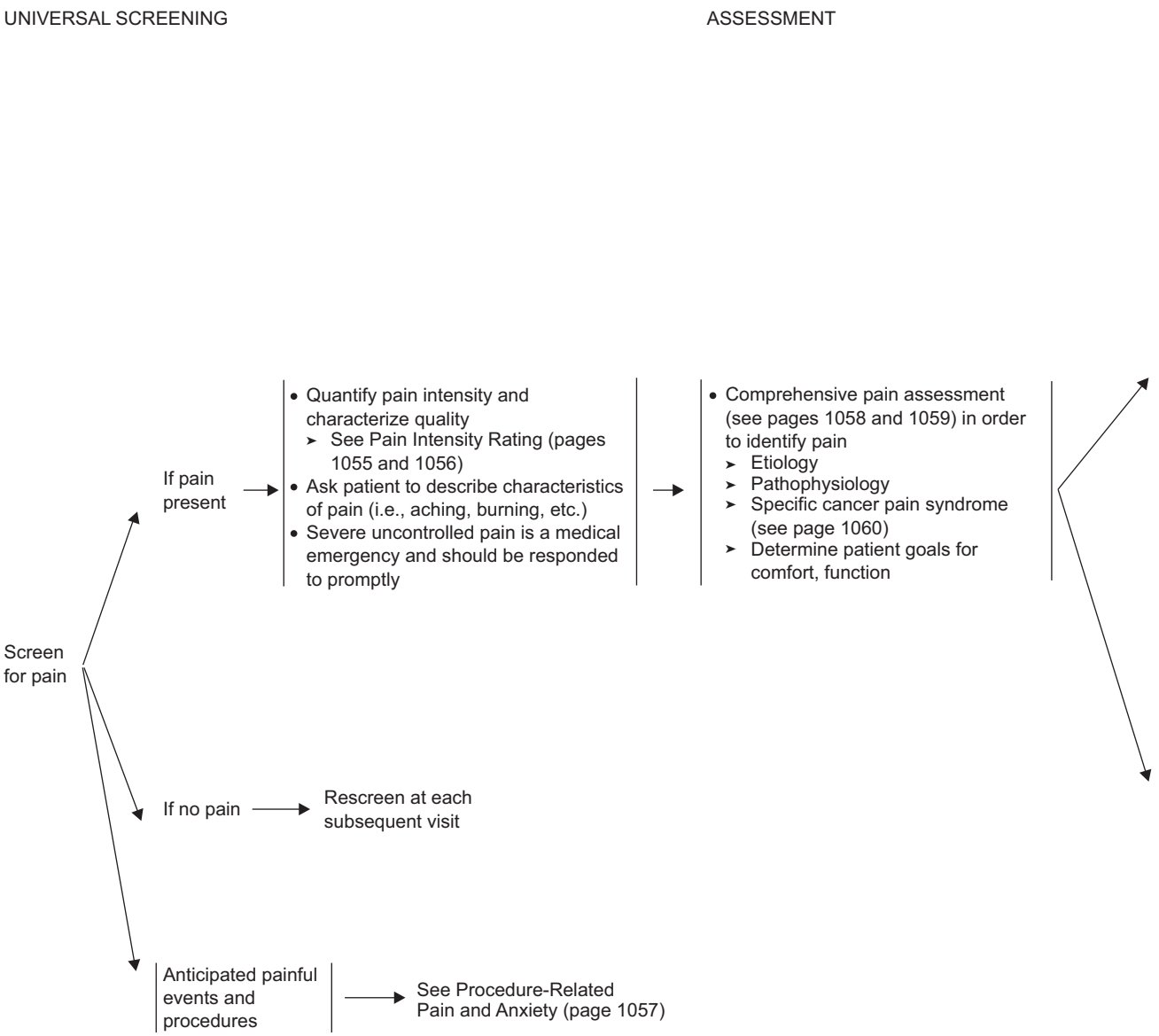
NCCN Adult Cancer Pain Panel Members

*Robert Swarm, MD/Chairϕ£
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine
Amy Pickar Abernethy, MD†£
Duke Comprehensive Cancer Center
Doralina L. Anghelescu, MDϕ
St. Jude Children's Research Hospital/ University of Tennessee Cancer Institute
Costantino Benedetti, MDϕ£
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute
Craig D. Blinderman, MD, MAÞ£
Massachusetts General Hospital Cancer Center
Barry Boston, MD£†
St. Jude Children's Research Hospital/ University of Tennessee Cancer Institute
Charles Cleeland, PhDθ
The University of Texas MD Anderson Cancer Center
Nessa Coyle, PhD, NP£#
Memorial Sloan-Kettering Cancer Center
Oscar A. deLeon-Casasola, MDϕ£
Roswell Park Cancer Institute
June G. Eilers, PhD, APRN#
UNMC Eppley Cancer Center at The Nebraska Medical Center
Betty Ferrell, RN, PhD£#
City of Hope Comprehensive Cancer Center
Nora A. Janjan, MD, MPSA, MBA§
The University of Texas MD Anderson Cancer Center
Sloan Beth Karver, MD£
H. Lee Moffitt Cancer Center & Research Institute
Michael H. Levy, MD, PhD£†
Fox Chase Cancer Center
Maureen Lynch, MS, APRN£#
Dana-Farber/Brigham and Women's Cancer Center
Natalie Moryl, MDÞ£
Memorial Sloan-Kettering Cancer Center
Barbara A. Murphy, MD£†
Vanderbilt-Ingram Cancer Center
Suzanne A. Nesbit, PharmD, BCPS∑
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
Linda Oakes, RN, MSN#
St. Jude Children's Research Hospital/ University of Tennessee Cancer Institute
Eugenie A. Obbens, MD, PhD£Ψ
Memorial Sloan-Kettering Cancer Center
Judith A. Paice, PhD, RN£#
Robert H. Lurie Comprehensive Cancer Center of Northwestern University
Michael W. Rabow, MD£
UCSF Helen Diller Family Comprehensive Cancer Center
Karen L. Syrjala, PhDθ
Fred Hutchinson Cancer Research Center/ Seattle Cancer Care Alliance
Susan Urba, MD£†
University of Michigan Comprehensive Cancer Center
Sharon M. Weinstein, MD£Ψ
Huntsman Cancer Institute at the University of Utah

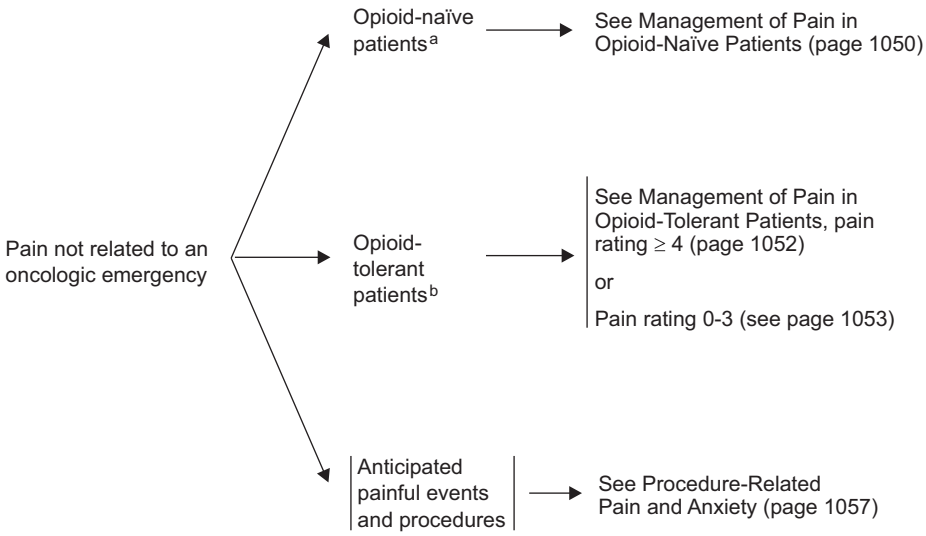
KEY:

*Writing Committee Member

Specialties: ϕAnesthesiology; £Supportive Care, Including Palliative, Pain Management, Pastoral Care, and Oncology Social Work; †Medical Oncology; ÞInternal Medicine; θPsychiatry, Psychology, Including Health Behavior; #Nursing; §Radiotherapy/Radiation Oncology; ∑Pharmacology; ΨNeurology/Neuro-Oncology



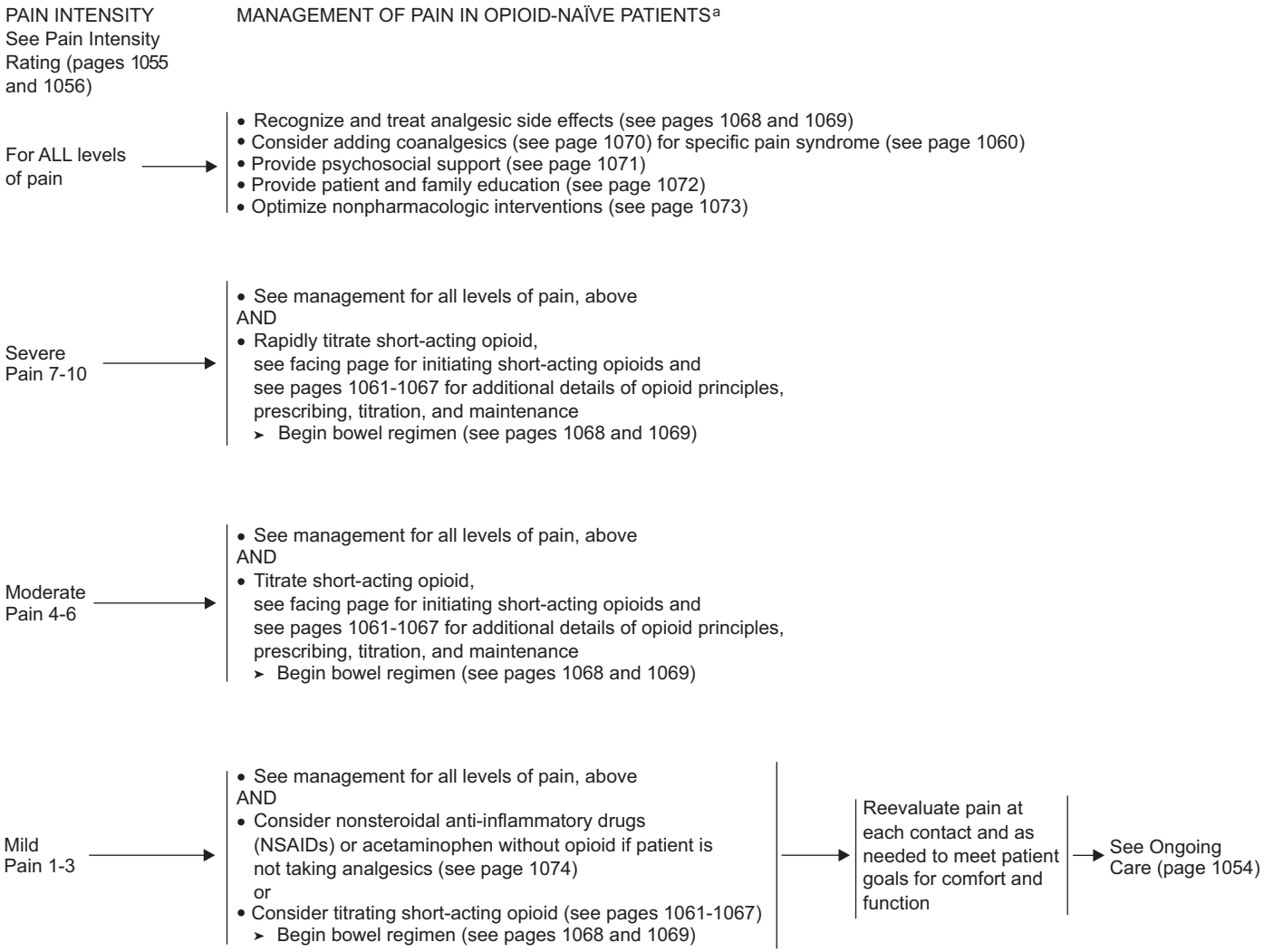
MANAGEMENT OF PAIN



Pain related to an oncologic emergency:
- Bone fracture or impending fracture of weight-bearing bone
- Brain metastases
- Epidural metastases
- Leptomeningeal metastases
- Pain related to infection
- Obstructed or perforated viscus (acute abdomen)

→ Analgesics as specified by above pathway in addition to specific treatment for oncologic emergency (e.g., surgery, steroids, RT, antibiotics)

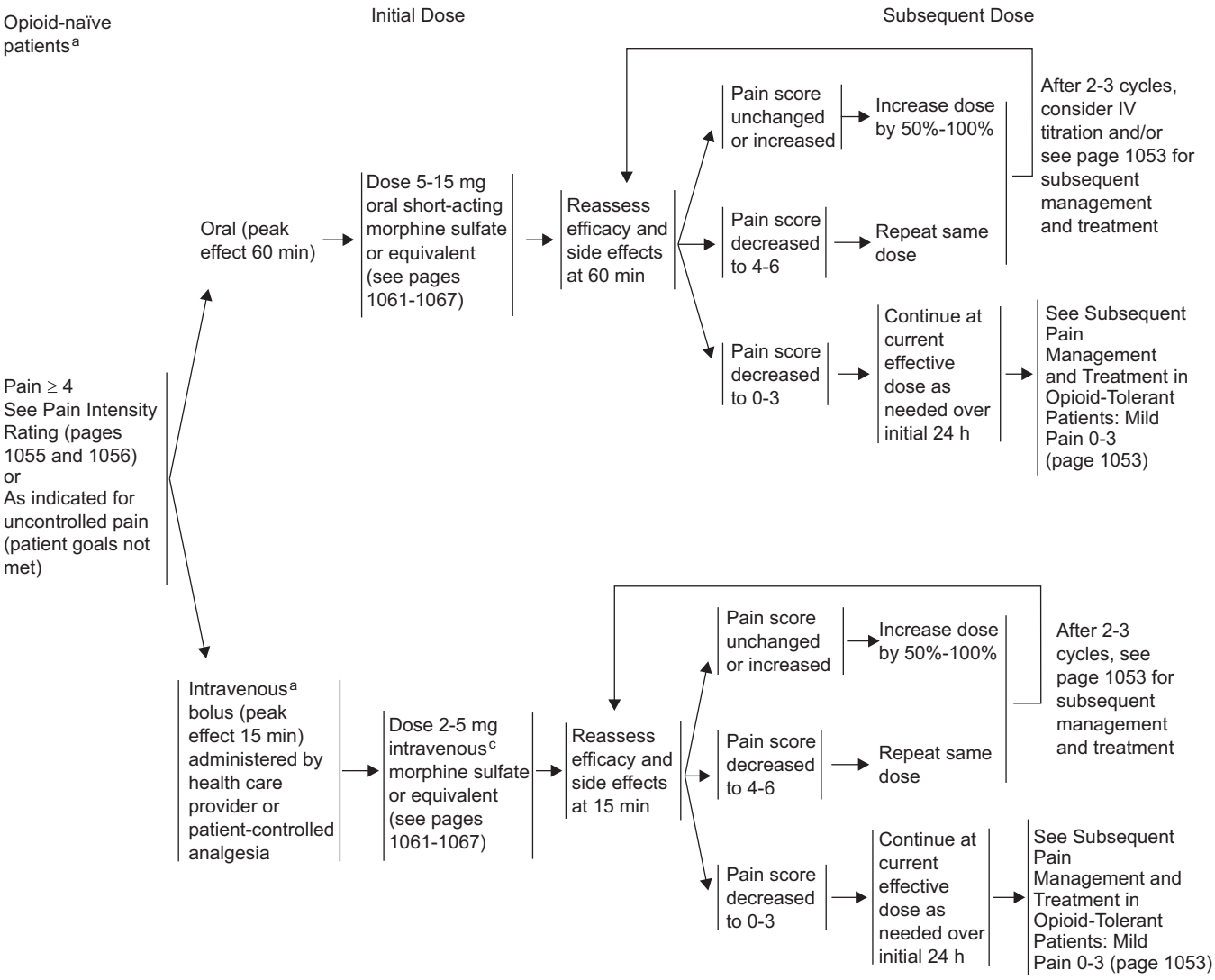
[a] Opioid-naïve patients include those who are not chronically receiving opioid analgesics on a daily basis.
[b] Opioid-tolerant patients include those who are chronically receiving opioid analgesics on a daily basis.



[a] Opioid-naïve patients include those who are not chronically receiving opioid analgesics on a daily basis.

INITIATING SHORT-ACTING OPIOIDS IN OPIOID-NAÏVE PATIENTS[a]

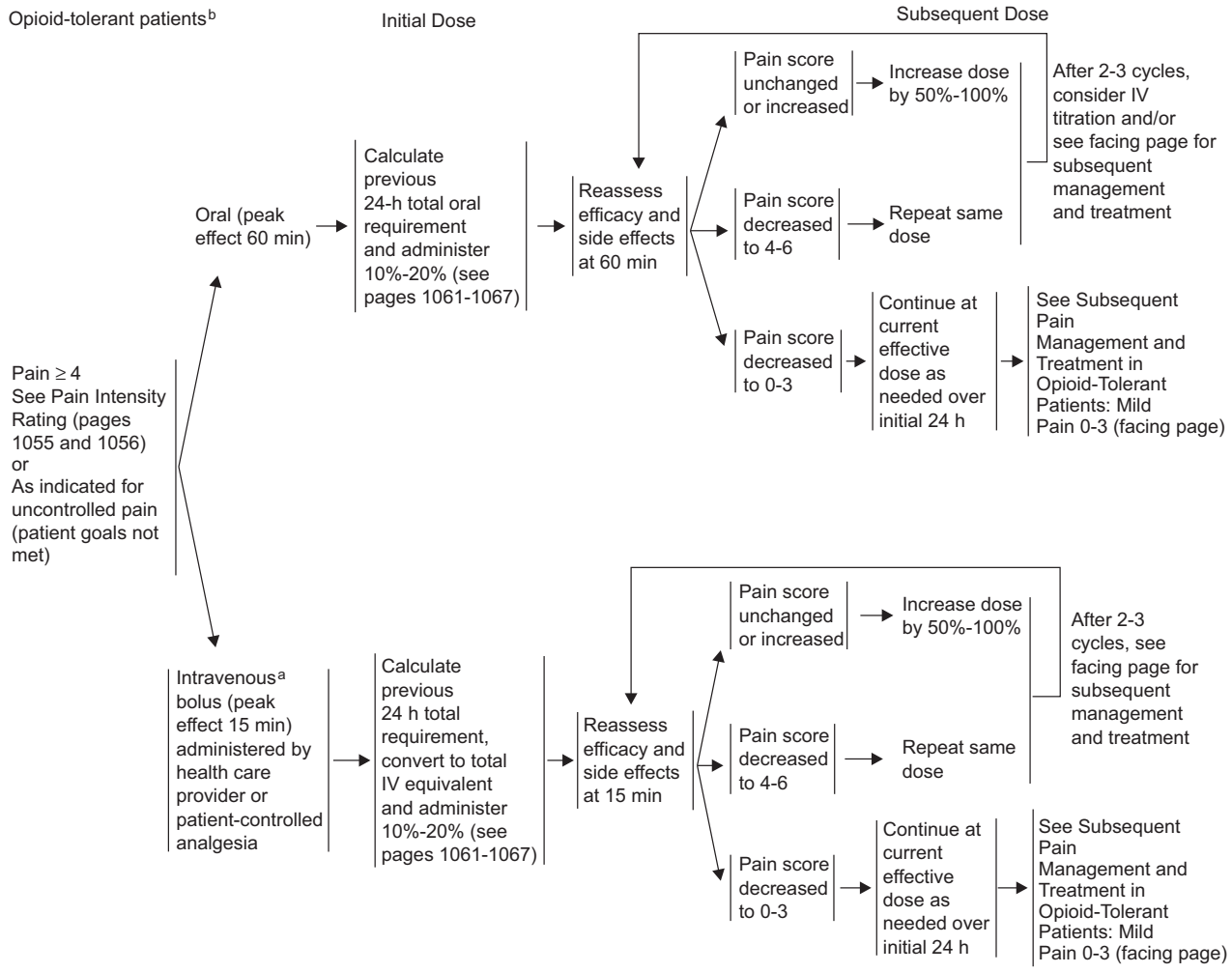
Monitor for acute and chronic adverse effects. (See Management of Opioid Side Effects on pages 1068 and 1069.)



[a]Opioid-naïve patients include those who are not chronically receiving opioid analgesics on a daily basis.
[c]Subcutaneous can be substituted for intravenous; however, subcutaneous route delays onset of effect by up to 30 min.

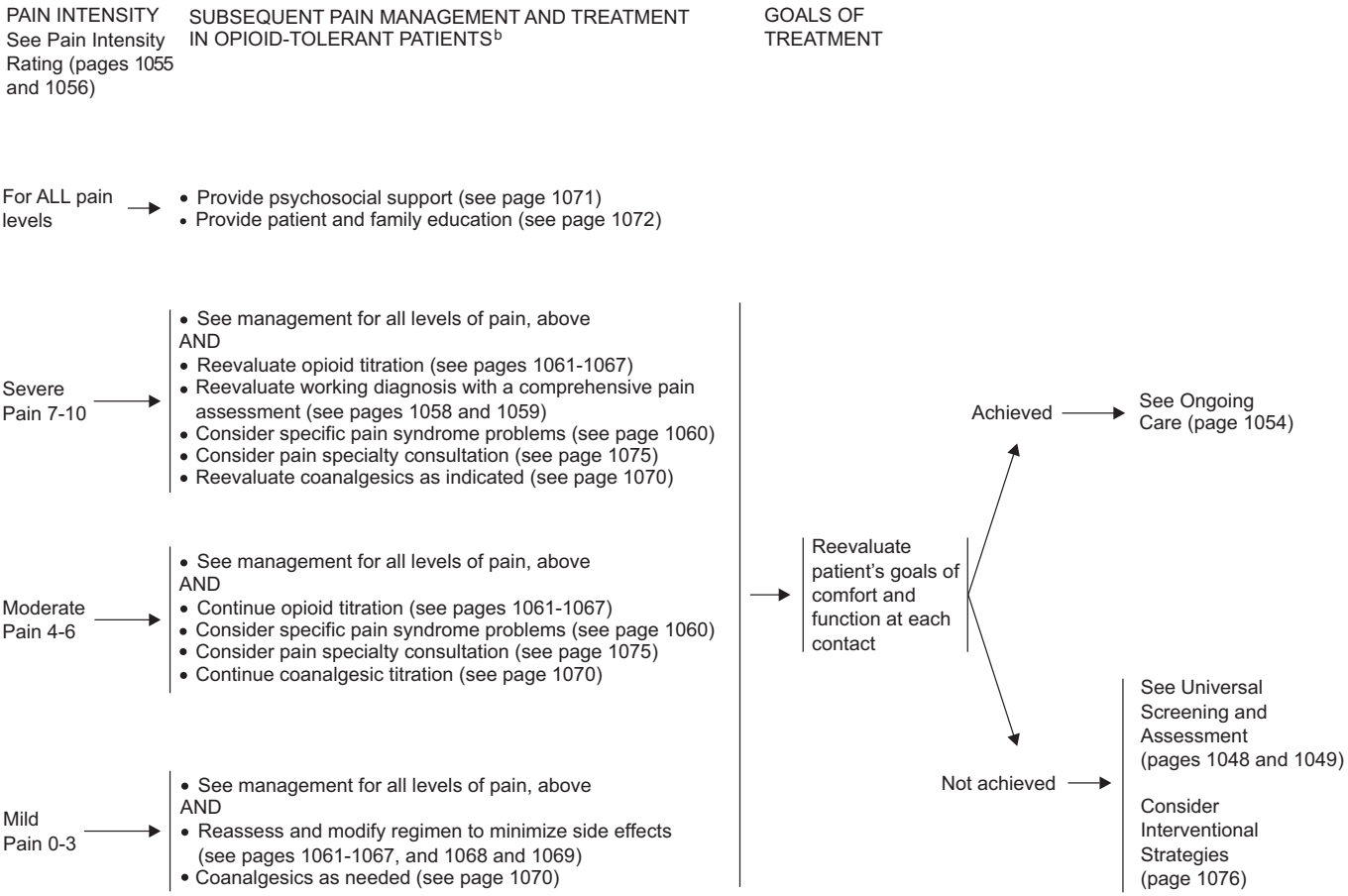
MANAGEMENT OF PAIN IN OPIOID-TOLERANT PATIENTS[b]

Monitor for acute and chronic adverse effects. (See Management of Opioid Side Effects on pages 1068 and 1069.)



[b]Opioid-tolerant patients include those who are chronically receiving opioid analgesics on a daily basis.
[c]Subcutaneous can be substituted for intravenous; however, subcutaneous route delays onset of effect by up to 30 min.

Adult Cancer Pain Version 1:2010



[b] Opioid-tolerant patients include those who are chronically receiving opioid analgesics on a daily basis.

ONGOING CARE

Clinician responsibilities

- Convert to oral medications (if feasible) including extended-release agent with rescue doses (Conversion details, see pages 1061-1067)
- Routine follow-up
  - Assess pain during each outpatient contact or at least each day for inpatients or more frequently based on:
    - Patient's condition
    - Institutional standards
    - Regulatory requirements
- Provide written follow-up pain plan, including prescribed medications (see page 1072)
- Ensure adequate access to prescribed medications, especially during transition between sites of care
- Instruct the patient on the importance of the following:
  - Follow documented pain plan (see page 1072)
  - Maintain clinic appointments
  - Contact clinician if pain worsens or side effects inadequately controlled
- Process realistic goals, revise, and review
- Address system barriers
  - Obtain assistance from social services
- Maintain communication and coordinate care with pain specialist and relevant providers
- On-call/as-needed availability

GOALS OF TREATMENT

Reevaluate patient's goals of comfort and function at each contact

Achieved → Continue routine follow-up

Not achieved → See Universal Screening and Assessment (pages 1048 and 1049)

Consider Interventional Strategies (page 1076)

PAIN INTENSITY RATING (1 of 2)

Pain intensity rating scales can be used as part of universal screening and comprehensive pain assessment. At minimum, patients should be asked about “current” pain, and “worst" and "usual" pain in the past 24 hours. For comprehensive assessment, also include "worst pain in past week", "pain at rest", and "pain with movement". See Comprehensive Pain Assessment (pages 1058 and 1059) for more details

Table 1: Numerical Rating Scale

Numerical rating scale:

- Verbal: “What number describes your worst pain in the past 24 hours from 0 (no pain) to 10 (worst pain you can imagine)?”
- Written: “Circle the number that describes your worst pain in the past 24 hours.”

0 1 2 3 4 5 6 7 8 9 10
No pain Worst pain you can imagine

Categorical scale:

“What is the worst pain you have had in the past 24 hours?”

None (0), Mild (1–3), Moderate (4–6), or Severe (7–10)

Table 2: The Faces Pain Rating Scale[1]

Instructions: “These faces show how much something can hurt. This face (point to the left-most face) shows no pain. Each face shows more and more pain (point to each face from left to right) up to this one (point to the right-most face), which shows very much pain. Point to the face that shows how much you hurt (right now).”

Continued on page 1056

[1] Ware LJ, Epps CD, Herr K, Packard A. Evaluation of the Revised Faces Pain Scale, Verbal Descriptor Scale, Numeric Rating Scale, and Iowa Pain Thermometer in older minority adults. Pain Manag Nurs 2006;7:117-125.

PAIN INTENSITY RATING (2 of 2)

Pain Assessment in the Nonverbal Patient[1]

- The inability of patients to verbally communicate pain intensity because of cognitive or physiologic issues is a major barrier relating to pain assessment and management. Therefore, the American Society for Pain Management Nursing (www.aspmn.org) has developed a position statement and clinical practice recommendations that clinicians may find useful in caring for these patients.
- In the absence of self-report, observation of behavior is a valid approach to pain assessment with the understanding that behaviors may also indicate another source of distress, such as emotional distress. Potential causes and the context of the behavior must be considered when making pain treatment decisions.
- A multifaceted approach is recommended that combines direct observation, family/caregiver input, and evaluation of response to pain medicines or nonpharmacologic interventions.
- For patients with advanced dementia, a comprehensive review of currently published tools is available at http://prc.coh.org/pain_assessment.asp. These tools are in varying stages of development and validation, and include:
  - The Assessment of Discomfort in Dementia Protocol (ADD)[2]
  - Checklist of Nonverbal Pain Indicators (CNPI)[3]
  - The Pain Assessment in Advanced Dementia Scale (PAINAD)[4]
- For patients who are intubated and/or are unconscious, pain assessment tools have been tested in specific situations, and include:
  - Behavioral Pain Scale (BPS);[5] tested in adults and intensive care
  - Critical-Care Pain Observation Tool (CPOT);[6] tested in adults and intensive care
- Clinicians are encouraged to monitor current research regarding new developments in strategies and tools for assessing pain in patients who have difficulty with self-report.

Cultural and Linguistic Assessment[7,8]

- Health care providers should be aware of the impact that cultural and linguistic diversity may have during universal screening and comprehensive pain assessment.

[1] Herr K, Coyne P, Key T, et al. Pain assessment in the nonverbal patient: position statement with clinical practice recommendations. Pain Manag Nurs 2006;7:44-52.
[2] Kovach CR, Noonan PE, Griffie J, et al. The assessment of discomfort in dementia protocol. Pain Manag Nurs 2002;3:16-27.
[3] Feldt KS. Checklist of nonverbal pain indicators. Pain Manag Nurs 2000;1:13-21.
[4] Lane P, Kuntupis M, MacDonald S, et al. A pain assessment tool for people with advanced Alzheimer's and other progressive dementias. Home Healthc Nurse 2003;21:32-37.
[5] Payen JF, Bru O, Bosson JL, et al. Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med 2001;29:2258-2263.
[6] Gélinas C, Johnston C, et al. Pain assessment in the critically ill ventilated adult: validation of the Critical-Care Pain Observation Tool and physiologic indicators. Clin J Pain 2007;23:497-505.
[7] Al-Atiyyat HN, Mohammed N. Cultural diversity and cancer pain. J Hosp Palliat Nurs 2009;11:154-164.
[8] Ezenwa MO, Ameringer S, Ward SE, Serlin RC. Racial and ethnic disparities in pain management in the United States. J Nurs Scholarsh 2006;38:225-233.

PROCEDURE-RELATED PAIN and ANXIETY

Events that are expected to cause discomfort to the patient, such as diagnostic and therapeutic procedures (e.g., wound care, IV, arterial line, central line, injection, manipulation, bone marrow aspiration, lumbar puncture, skin biopsy, bone marrow biopsy), and transportation/change in position for patients with a fracture, should merit pretreatment with an analgesic intervention. Additional analgesics and/or local anesthetics should be available immediately for further titration by the caregiver as needed.

Consistent adequate analgesia for all pain-related procedures and anxiety is critical. Intervention may be multimodal and include one or more of the following techniques as appropriate.

- Local anesthetics such as:
  - Topical local anesthetics creams (containing lidocaine, prilocaine, tetracaine) applied to intact skin with sufficient time for effectiveness as per package insert
  - Physical approaches (ultrasound, cutaneous warming, laser or jet injection) may accelerate the onset of cutaneous anesthesia
  - Ionophoretic devices to provide lidocaine delivery through the skin without needles in 10-15 min
  - Subcutaneous administration of lidocaine with a 27-gauge needle
- Administration of sedatives/analgesics/general anesthesia by trained personnel
- Additional nonpharmacologic interventions (see page 1073)

Providing information regarding all of these analgesic techniques before the procedure is ideal because it allows patients and their families the time they may need to assimilate all of the information, ask questions, and master the techniques while reducing anticipatory anxiety.

COMPREHENSIVE PAIN ASSESSMENT

Patient's self-report of pain is the standard of care. If the patient is unable to verbally report pain, an alternative method to obtain pain rating and response should be utilized (see page 1056).

- Pain Experience
  - Location, referral pattern, radiation of pains
  - Intensity (see Pain Intensity Rating, on pages 1055 and 1056)
    - Past 24 hours and current pain
    - At rest and with movement
  - Interference with activities
    See Impact of Pain Measurement (page 1059)
    - General activity, mood, relationship with others, sleep, appetite
  - Timing: onset, duration, course, persistent, or intermittent
  - Description or quality
    - Aching, stabbing, throbbing, pressure, often associated with somatic pain in skin, muscle, bone
    - Gnawing, cramping, aching, sharp, often associated with visceral pain in organs or viscera
    - Sharp, tingling, ringing, shooting, often associated with neuropathic pain caused by nerve damage
  - Aggravating and alleviating factors
  - Other current symptoms
  - Current pain management plan, both pharmacologic and non-pharmacologic. If medications are used, determine:
    - What medications, prescription, and/or over the counter?
    - How much?
    - How often?
    - Current prescriber?
  - Response to current therapy
    - Pain relief
    - Patient adherence to medication plan
    - Medication side effects such as constipation, sedation, cognitive slowing, nausea, others
  - Prior pain therapies
    - Reason for use, length of use, response, reasons for discontinuing
  - Special issues relating to pain
    - Meaning and consequences of pain for patient and family
    - Patient and family knowledge and beliefs surrounding pain and pain medications
    - Cultural beliefs toward pain and pain expression
    - Spiritual, religious considerations, and existential suffering
    - Patient goals and expectations regarding pain management
- Psychosocial (see page 1071)
  - Patient distress (see NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] on Distress Management*)
  - Family and other support
  - Psychiatric history including current or prior history of substance abuse
  - Risk factors for aberrant use or diversion of pain medication
    - Patient, environmental, and social factors
  - Risk factors for undertreatment of pain
    - Pediatric, geriatric, minorities, female, communication barriers, history of substance abuse, neuropathic pain, and cultural factors
- Medical history
  - Oncologic treatment including current and prior chemotherapy, radiation therapy, and surgery
  - Other significant illnesses, conditions
  - Preexisting chronic pain
- Physical examination
- Relevant laboratory and imaging studies to evaluate for disease progression
- The end point of the assessment is to establish the "pain diagnosis" and individualized pain treatment plan based on mutually developed goals. The "pain diagnosis" includes the etiology and pathophysiology of pain:
  - Etiology
    - Cancer
    - Cancer therapy (RT, chemotherapy, surgery) or procedures
    - Coincidental or noncancer
  - Pathophysiology
    - Nociceptive
    - Neuropathic

Return to Initial Screening
(pages 1048 and 1049)

*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

IMPACT OF PAIN MEASUREMENT[1-3]

Mark the number that describes how much, in the past [week/24 hours] pain has interfered with your:

1. General activity	0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes
2. Mood	0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes
3. Walking ability	0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes
4. Normal work (includes both work outside the home and housework)	0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes
5. Relations with other people	0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes
6. Sleep	0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes
7. Enjoyment of life	0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

[1] Cleeland CS, Nakamura Y, Mendoza TR, et al. Dimensions of the impact of cancer pain in a four country sample: new information from multidimensional scaling. Pain 1996;67:267-273.
[2] Serlin RC, Mendoza TR, Nakamura Y, et al. When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. Pain 1995;61:277-284.
[3] To view the complete Brief Pain Inventory assessment tool, visit mdanderson.org/bpi.

ADDITIONAL INTERVENTIONS FOR CANCER PAIN SYNDROMES

In general, cancer pain is treated with opioids as indicated on page 1050; these interventions are meant to complement management.

- Pain associated with inflammation:
  - Trial of NSAIDs or glucocorticoids

- Nerve compression or inflammation:
  - Trial of glucocorticoids

- Bone pain without oncologic emergency:
  - NSAIDs and titrate analgesic to effect; see Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and Acetaminophen Prescribing (page 1074)
  - Local bone pain: consider local radiation therapy or nerve block (e.g., rib pain)
  - Diffuse bone pain: consider trial of bisphosphonates, hormonal therapy or chemotherapy, glucocorticoids, and/or systemic administration of radioisotopes
  - Consider physical medicine evaluation; see Pain Specialty Consultations for Improved Pain Management (page 1075)
  - For resistant pain: consider referral to a pain specialist and/or the use of interventional strategies (see Interventional Strategies, on page 1076)

- Bowel obstruction
  - Bowel rest, nasogastric suction, glucocorticoids, octreotide

- Neuropathic pain:
  - Trial of antidepressant: start with low dose and increase every 3-5 d if tolerated or lengthen interval up to 14 d (e.g., nortriptyline, 10-150 mg/d; doxepin, 10-150 mg/d; desipramine, 10-150 mg/d; venlafaxine, 37.5-225 mg/d divided in 2-3 doses; duloxetine, 30-60 mg/d)

    and/or
  - Trial of anticonvulsant: start with low dose and increase every 3-5 d if tolerated or lengthen interval up to 14 d (e.g., gabapentin,100-1200 mg 3 times a day; carbamazepine, 100-400 mg 2 times a day; pregabalin 100-600 mg/d divided in 2-3 doses, or other anticonvulsants)

    and/or
  - Consider topical agents, such as local anesthetics including lidocaine patch
  - For resistant pain, consider referral to a pain specialist and/or the use of interventional strategies (see Interventional Strategies, on page 1076)

- Painful lesions that are likely to respond to antineoplastic therapies:
  - Consider trial of radiation, hormones, or chemotherapy

- For severe refractory pain in the imminently dying:
  - See NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) on Palliative Care*

*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

OPIOID PRINCIPLES, PRESCRIBING, TITRATION, AND MAINTENANCE (1 of 7)

GENERAL PRINCIPLES

- The appropriate dose is the dose that relieves the patient's pain throughout the dosing interval without causing unmanageable side effects.
- Generally, oral route is most common; however, other routes (IV, subcutaneous, rectal, transdermal, transmucosal, buccal) can be considered as indicated to maximize patient comfort. For intrathecal route administration, see page 1076.
- Calculate dosage increase based on total opioid dose (around the clock/scheduled and as needed) taken in the previous 24 h.
- Increase both around-the-clock and as needed doses. The rapidity of dose escalation should be related to the severity of the symptoms. See Management of Pain in Opioid-Tolerant Patients (page 1052).
- According to FDA guidelines, switch from preparations of opioid combined with other medications (such as aspirin or acetaminophen) to pure opioid preparation if opioid dose required would result in excessive (or inadequate) dosing of the non-opioid component of combination (see page 1074).
- Steady state is achieved in about 5 half-lives.
- If patient is experiencing unmanageable side effects and pain is < 4, consider downward dose titration by approximately 25% and reevaluate. Patient would require close follow-up to make sure pain did not escalate.
- Consider opioid rotation if pain inadequately controlled or persistent side effects from current therapy.

PRINCIPLES OF MAINTENANCE OPIOID THERAPY

- For continuous pain, it is appropriate to give pain medication on a regular schedule with supplemental doses for breakthrough pain.
- Add extended release or long-acting formulation to provide background analgesia for control of chronic persistent pain controlled on stable doses of short-acting opioids.
- Provide rescue doses of short-acting opioids for pain not relieved by extended-release opioids including breakthrough pain or acute exacerbations of pain, activity or position related pain, or pain at the end of dosing interval:
  - When possible, use the same opioid for short-acting and extended release forms.
  - Allow rescue doses of short-acting opioids of 10%–20% of 24-h oral dose (mg) every 1 h as needed. Ongoing need for repeated rescue doses may indicate a need for adjustment of regularly scheduled opioid dose.
  - Consider transmucosal fentanyl (lozenge, tablets, film) only in opioid tolerant patients for brief episodes of acute exacerbation of pain not attributed to inadequate dosing of around the clock opioid. Data do not support a specific transmucosal fentanyl dose equianalgesic to other opioids. Initiate transmucosal fentanyl with lowest dose (200-mcg lozenge or 100-mcg buccal tablet or 200-mcg buccal soluble film) and titrate to effect. (See specific transmucosal prescribing information for appropriate dosing intervals.)
- Increase dose of extended-release opioid if patient persistently needs doses of as-needed opioids or when dose of around the clock opioid fails to relieve pain at peak effect or at end of dose.

Continued on page 1062

OPIOID PRINCIPLES, PRESCRIBING, TITRATION, AND MAINTENANCE (2 of 7)

Table 1: Oral and Parenteral Opioid Equivalences and Relative Potency of Drugs Compared with Morphine Based on Single-Dose Studies

Opioid Agonists	Parenteral Dose	Oral Dose	Factor (IV to PO)	Duration of Action[9]
Codeine[1,2]	130 mg	200 mg	1.5	3-4 h
Fentanyl[3]	100 mcg	--	--	1-3 h
Hydrocodone[4]	--	30-45 mg	--	3-5 h
Hydromorphone	1.5 mg	7.5 mg	5	2-3 h
Levorphanol[5]	2 mg	4 mg	2	3-6 h
Methadone[5,6]	--	--	--	--
Morphine[2,7]	10 mg	30 mg	3	3-4 h
Oxycodone[1]	--	15-20 mg	--	3-5 h
Oxymorphone	1 mg	10 mg	10	3-6 h
Tramadol[8]	--	50-100 mg	--	3-7 h

NOT RECOMMENDED

Meperidine[10]

Propoxyphene[10]

Mixed agonist-antagonists (pentazocine, nalbuphine, butorphanol, dezocine)

Special Note: Mixed agonists-antagonists have limited usefulness in cancer pain. They should NOT be used in combination with opioid agonist drugs. Converting from an agonist to an agonist-antagonist could precipitate a withdrawal crisis in opioid-dependent patients.

[1] Dosage must be monitored for safe limits as it may be available in combination with acetylsalicylic acid (ASA) or acetaminophen. Dose listed refers only to opioid portion.

[2] Avoid using codeine or morphine in patients with renal failure from accumulation of renally cleared metabolites.

[3] The equianalgesic dose listed only applies to IV fentanyl compared with other IV opioids. For transdermal fentanyl conversions, see page 1064.

[4] Equivalence data not substantiated. Clinical experience suggests use as a mild, initial use opioid but effective dose may vary. Usually combined with ASA or acetaminophen in doses from 325 to 750 mg. Dosage must be monitored for safe limits of ASA or acetaminophen. Dose listed refers only to opioid portion.

[5] Long half-life, observe for drug accumulation and side effects after 2-5 d. May need to be dosed every 4 h initially then changed to every 6-8 h after steady state achieved (1-2 wk).

[6] The oral conversion ratio of methadone varies. PRACTITIONERS ARE ADVISED TO CONSULT WITH A PAIN OR PALLIATIVE CARE SPECIALIST IF THEY ARE UNFAMILIAR WITH METHADONE PRESCRIBING. (See Converting from Oral Morphine to Oral Methadone, page 1066).

[7] Conversion factor listed for chronic dosing.

[8] Weak opioid receptor agonist with some antidepressant activity. For mild to moderate pain. Recommended dose of 100 mg 4 times a day (maximum daily dose, 400 mg) to avoid CNS toxicity. Even at maximum dose of 100 mg 4 times a day, tramadol is less potent than other opioid analgesics, such as morphine.

[9] Shorter time generally refers to parenterally administered opioids (except for controlled-release products, which have some variability); longer time generally applies to oral dosing.

[10] Not recommended for cancer pain management because of CNS toxic metabolites (normeperidine, norpropoxyphene).

OPIOID PRINCIPLES, PRESCRIBING, TITRATION, AND MAINTENANCE (3 of 7)

CONVERT OR ROTATE FROM ONE OPIOID TO ANOTHER OPIOID

- To convert or rotate from one opioid to another opioid:
  1. Determine the amount of current opioid(s) taken in a 24-h period that effectively controls pain.
  2. Calculate the equianalgesic dose of the new opioid. See Table 1 (previous page).
  3. If pain was effectively controlled, reduce the dose by 25%-50% to allow for incomplete cross-tolerance between different opioids. During the first 24 h, titrate liberally and rapidly to analgesic effect. If previous dose was ineffective, may begin with 100% of equianalgesic dose or increase that by 25%.
  4. Lastly, for oral opioids divide the total daily dose of new opioid needed by the number of doses per day to determine the individual dose (e.g., 6 doses for regular PO morphine every 4 h; 2 doses for extended-release morphine every 12 h).

Case example of converting IV morphine to IV hydromorphone

A patient is taking IV morphine at 8 mg/h and must be converted to IV hydromorphone.

1. Determine the total amount of current IV morphine in a 24-h period for this patient
   (8 mg/h x 24 h =192 mg/d)
   (total amount of IV morphine this patient is taking is 192 mg/d)

2. From Table 1 on previous page, calculate the equianalgesic dose of IV hydromorphone
   (10 mg IV morphine = 1.5 mg IV hydromorphone therefore,
   192 mg/d IV morphine = 28.8 mg/d IV hydromorphone = 1.2 mg/h IV hydromorphone)

3. If patient was effectively controlled with IV morphine (192 mg/d) reduce the dose of hydromorphone by 25%-50%
   (28.8 mg/d reduced by 25% = 21.6 mg/d IV hydromorphone = 0.9 mg/h IV hydromorphone)
   (28.8 mg/d reduced by 50% = 14.4 mg/d IV hydromorphone= 0.6 mg/h IV hydromorphone)
   If dose of IV morphine was ineffective in controlling pain, may begin with 100% of equianalgesic hydromorphone dose
   (28.8 mg/d IV hydromorphone = 1.2 mg/h IV hydromorphone)
   or increase that by 25%
   (36 mg/d IV hydromorphone = 1.5 mg/h IV hydromorphone)

Continued on page 1064

OPIOID PRINCIPLES, PRESCRIBING, TITRATION, AND MAINTENANCE (4 of 7)

CONVERT OR ROTATE FROM ANOTHER OPIOID TO TRANSDERMAL FENTANYL

- To convert or rotate from another opioid to transdermal fentanyl:
  1. Determine the 24-h analgesic requirement of current opioid. Table 2 (below) can be used directly for patients on oxycodone, hydromorphone, and codeine. If not one of these opioids, convert to equianalgesic dose of morphine requirement.
  2. From Table 2, select the mcg/h dose of transdermal fentanyl based on the 24-h dose of morphine, oxycodone, hydromorphone, or codeine as listed. For fentanyl dosage requirements > 100 mcg/h, multiple patches are used.

  Note: An as-needed (prn) dose of morphine or other short-acting opioid should be prescribed and will be needed particularly during the first 8 to 24 h. Once the levels have reached steady state after at least 2-3 d, increase the patch dosage based on the average amount of stable daily prn opioid required. Continue breakthrough medication once the patch dose is stabilized.

Table 2: Recommended Dose Conversion From Other Opioids to Transdermal Fentanyl[1]

See facing page for case examples

Transdermal Fentanyl	Morphine[2]		Oxycodone	Hydromorphone		Codeine	
	IV/SubQ*	Oral	Oral	IV/SubQ*	Oral	IV/SubQ*	Oral
25 mcg/h	20 mg/d	60 mg/d	30 mg/d	1.5 mg/d	7.5 mg/d	130 mg/d	200 mg/d
50 mcg/h	40 mg/d	120 mg/d	60 mg/d	3.0 mg/d	15.0 mg/d	260 mg/d	400 mg/d
75 mcg/h	60 mg/d	180 mg/d	90 mg/d	4.5 mg/d	22.5 mg/d	390 mg/d	600 mg/d
100 mcg/h	80 mg/d	240 mg/d	120 mg/d	6.0 mg/d	30.0 mg/d	520 mg/d	800 mg/d

*Parenteral dosing such as IV (intravenous) or SubQ (subcutaneous)

NOTE: Because of patient variability, the doses suggested in this guide are approximate and clinical judgement must be used to titrate to the desired response.

Special Notes Regarding Transdermal Fentanyl:

- Pain should be relatively well controlled on a short-acting opioid before initiating the fentanyl patch. Patches are NOT recommended for unstable pain requiring frequent dose changes. Use fentanyl patch only in patients tolerant to opioid therapy.
- Fever or topical application of heat (e.g., heat from heat lamps, electric blankets) may accelerate transdermal fentanyl absorption and are contraindications to transdermal fentanyl.
- When converting from continuous parenteral infusion fentanyl to transdermal fentanyl, a straight 1:1 ratio[3] is appropriate (i.e., the mcg/h of parenteral fentanyl should be approximately equal to the mcg/h of transdermal fentanyl). In some patients, additional dose titration of the fentanyl patch may be necessary.
- The fentanyl patch analgesic duration is usually 72 h, but some patients require fentanyl patch replacement every 48 h.

[1] Breitbart W, Chandler S, Eagel B, et al. An alternative algorithm for dosing transdermal fentanyl for cancer-related pain. Oncology 2000;14:695-702.
[2] Equianalgesic doses to morphine adapted from Foley K. The treatment of cancer pain. N Engl J Med 1985;313:84-95.
[3] Kornick CA, Santiago-Palma J, Khojainova N, et al. A safe and effective method for converting patients from intravenous to transdermal fentanyl. Cancer 2001;92:3056-3061.

OPIOID PRINCIPLES, PRESCRIBING, TITRATION, AND MAINTENANCE (5 of 7)

CONVERT OR ROTATE FROM ANOTHER OPIOID TO TRANSDERMAL FENTANYL (continued)

Example of opioid using Table 2 directly:

Case example of converting oral oxycodone to transdermal fentanyl patch
A patient is taking 30 mg of sustained-release oral oxycodone every 12 h and must be converted to transdermal fentanyl patch.

1. Calculate the total amount of current oral oxycodone in a 24-h period
   (oral oxycodone 30 mg x 2 = 60 mg/d oral oxycodone)

2. Using Table 2, select the the mcg/h dose of transdermal fentanyl
   (60 mg/d oral oxycodone is approximately 50 mcg/h transdermal fentanyl patch)

Example of opioid not listed on Table 2:
Case example of converting oral oxymorphone to transdermal fentanyl patch
A patient is taking 10 mg of sustained-release oral oxymorphone every 12 h and needs to be converted to transdermal fentanyl patch.

1. Calculate the total amount of current oral oxymorphone in a 24-h period
   (oral oxymorphone 10 mg x 2 = 20 mg/d oral oxymorphone)

2. From Table 1 on page 1062, convert the equianalgesic dose of oral morphine
   (Based on Table 1, 10 mg oral oxymorphone = 30 mg oral morphine, therefore
   20 mg/d oral oxymorphone x 3 = total daily dose oral morphine of 60 mg/d)

3. Using Table 2 on page 1064, select the mcg/h dose of transdermal fentanyl
   (60 mg/d oral morphine is approximately 25 mcg/h transdermal fentanyl patch)

Continued on page 1066

OPIOID PRINCIPLES, PRESCRIBING, TITRATION, AND MAINTENANCE (6 of 7)

CONVERT FROM ORAL MORPHINE TO ORAL METHADONE[1]

- To convert from oral morphine to oral methadone:

1. Calculate the total daily oral morphine dose (or morphine-equivalent dose) the patient is using
2. Based on the oral morphine dose, use Table 3 (below) to determine the appropriate dose conversion ratio and calculate the oral methadone dose
3. Reduce the calculated equianalgesic dose of oral methadone by 25%-50% to account for incomplete cross-tolerance, dosing ratio variability, and patient variability
4. Divide the total daily oral methadone dose into 3 or 4 daily doses

Table 3: Dose Conversion Ratios for Oral Morphine to Oral Methadone

ORAL MORPHINE	DOSE CONVERSION RATIO (oral morphine:oral methadone)
30-90 mg	4:1
91-300 mg	8:1
> 300 mg	12:1

Note: If the total daily dose equivalent of morphine is > 800 mg, a higher dose ratio is necessary and cross-titration is recommended. A pain or palliative care specialist should be consulted.

Special Notes Regarding Oral Methadone:

- The conversion ratio varies with the amount of morphine (or other opioid) a patient is using chronically. The higher the dose of morphine, the more potent the methadone.
- To a significantly greater extent than with other opioids, methadone has been associated with several drug-drug interactions. The potential for such interactions must be investigated in each patient before initiating methadone.
- Methadone is widely available in 5- and 10-mg tablets.
- Methadone may be titrated up every 5-7 d, usually by 5 mg per dose.
- Because methadone is associated with QTc prolongation, a baseline and follow-up ECG is recommended for methadone doses > 100 mg/d and for patients with cardiac disease, or when methadone is used in patients taking other medications also known to prolong QTc (including tricyclic antidepressants), if consistent with patient's goals of care.
- These conversion ratios should NOT be used in converting methadone to other opioids. After methadone is discontinued, it will take several days for it to be cleared, because of a long elimination half-life; therefore, the amount of other opioids needed for an equivalent effect will seem to change as the residual methadone is cleared. On the first day of conversion (while there is still significant methadone present), a conservative conversion ratio for oral methadone to oral morphine of 1:1 may be used, and supplemented with additional short-acting opioid, as needed. As methadone is cleared, morphine (or other opioid) doses will likely require frequent adjustment (every day or two) toward the higher conversion ratios listed for morphine-to-methadone conversion.

[1] Manfredi PL, Houde RW. Prescribing methadone, a unique analgesic. J Support Oncol 2003;1:216-220.

OPIOID PRINCIPLES, PRESCRIBING, TITRATION, AND MAINTENANCE (7 of 7)

CONVERT FROM ORAL MORPHINE TO ORAL METHADONE (continued)

Case example of converting oral morphine to oral methadone
A patient is taking oral morphine at 30 mg every 4 hours and must be converted to oral methadone

1. Calculate the total amount of current oral morphine in a 24-h period for this patient
   (30 mg x 6 = 180 mg/d)
   (Total amount of oral morphine this patient is taking is 180 mg/d)

2. From Table 3 (Dose Conversion Ratios for Oral Morphine to Oral Methadone, previous page), calculate equianalgesic dose of oral methadone
   (for 180 mg/d of oral morphine:oral methadone, the dose conversion ratio is 8:1, therefore 180 mg/d morphine = 22.5 mg/d methadone)

3. Reduce the calculated equianalgesic dose of oral methadone by 25%-50% to account for incomplete cross-tolerance, dosing ratio variability, and patient variability
   (e.g., 22.5 mg/d oral methadone reduced by 25% = 16.875 mg/d oral methadone equal to approximately 15 mg/d oral methadone)

4. Divide the total daily oral methadone dose into 3 daily doses
   (e.g., reduced dose of 15 mg/d oral methadone divided by 3 daily doses = 5 mg oral methadone every 8 h)

MANAGEMENT OF OPIOID SIDE EFFECTS

Principles of Management of Opioid Side Effects

- Opioid side effects generally improve over time, except with constipation. Maximize nonopioid and nonpharmacologic interventions to limit opioid dose and treat side effects. If side effects persist, consider opioid rotation.
- Multisystem assessment is necessary.
- Recognize that pain is rarely treated in isolation in cancer and side effects may be from other treatments or cancer itself.

Constipation

- Preventive measures
  - Prophylactic medications
    - Stimulant laxative ± stool softener (e.g., senna ± docusate, 2 tablets every morning; maximum 8-12 tablets per day).
    - Increase dose of laxative when increasing dose of opioids
  - Maintain adequate fluid intake
  - Maintain adequate dietary fiber intake; compounds such as Metamucil are unlikely to control opioid induced constipation and are not recommended
  - Exercise, if feasible
- If constipation develops
  - Assess for cause and severity of constipation
  - Rule out obstruction
  - Treat other causes
  - Titrate stool softner/laxatives as needed with goal of one nonforced bowel movement every 1-2 d
  - Consider coanalgesic to allow reduction of the opioid dose
- If constipation persists
  - Reassess for the cause and severity of constipation, rule out bowel obstruction
  - Check for impaction
  - Consider adding another agent, such as magnesium hydroxide, 30-60 mL daily; bisacodyl, 2-3 tablets PO daily, or 1 rectal suppository daily; lactulose, 30-60 mL daily; sorbitol, 30 mL every 2 h x 3, then as needed, or magnesium citrate, 8 oz PO daily, polyethelene glycol (1 capful/8 oz water PO 2 times a day)
  - Fleet, saline, or tap water enema
  - Consider use of a prokinetic agent (e.g., metoclopramide, 10-20 mg PO 4 times a day)
  - When response to laxative therapy has not been sufficient for opioid-induced constipation in patients with advanced illness, consider methylnaltrexone, 0.15 mg/kg subcutaneously, maximum 1 dose per day
  - Consider neuraxial analgesics or neuroablative techniques to potentially reduce opioid dose

Nausea

- Preventive measures
  - For patients with a prior history of opioid induced nausea, prophylactic treatment with antiemetic agents (see below) are highly recommended.
- If nausea develops
  - Assess for other causes of nausea (e.g., constipation, central nervous system pathology, chemotherapy, radiation therapy, hypercalcemia)
  - Consider prochlorperazine, 10 mg PO every 6 h as needed; or thiethylperazine, 10 mg PO every 6 h as needed; or haloperidol, 0.5-1 mg PO every 6-8 h; or metoclopramide, 10-20 mg PO every 6 h as needed
  - If nausea persists despite as needed regimen, administer antiemetics around the clock for 1 wk, then change to as needed
  - Consider adding a serotonin antagonist (e.g., granisetron, 2 mg PO daily; or ondansetron, 8 mg PO 3 times a day; or dolasetron, 100-200 mg PO; or palonosetron, 300 mcg/kg IV); use with caution as constipation is a side effect
  - Dexamethasone can be considered
- If nausea persists for more than 1 wk
  - Reassess cause and severity of nausea
  - Consider opioid rotation
- If nausea persists after a trial of several opioids and above measures
  - Reassess cause and severity of nausea
  - Consider neuraxial analgesics or neuroablative techniques to potentially reduce opioid dose

MANAGEMENT OF OPIOID SIDE EFFECTS

Pruritus

- If pruritus develops
  - Assess for other causes (other medications, etc.)
  - Consider antihistamines such as diphenhydramine, 25-50 mg IV or PO every 6 h; or promethazine, 12.5-25 mg PO every 6 h
- If pruritus persists
  - Consider changing to another opioid if symptomatic management has failed.
  - Consider adding to analgesic regimen: small doses of mixed agonist-antagonist, nalbuphine, 0.5-1 mg IV every 6 h as needed
- Consider continuous infusion of naloxone, 0.25 mcg/kg/h and titrate up to 1 mcg/kg/h for relief of pruritus without decreasing effectiveness of the analgesic.

Delirium

- Assess for other causes of delirium (e.g., hypercalcemia, CNS, metastases, other psychoactive medications)
- If one cannot determine other possible causes of delirium, consider changing the opioid
- Consider nonopioid analgesic to allow reduction of the opioid dose
- Consider haloperidol, 0.5-2 mg PO or IV every 4-6 h; or olanzapine, 2.5-5 mg PO or sublingual every 6-8 h; or risperidone, 0.25-0.5 mg 1-2 times day
- For further information about delirium, see NCCN Guidelines on Palliative Care*

Motor and Cognitive Impairment

- Studies have shown that stable doses of opioids (> 2 wk) are not likely to interfere with psychomotor and cognitive function, but these functions should be monitored during analgesic administration and titration.

Respiratory depression

- Use reversing agents cautiously. If reversing an opioid with a long half-life, such as methadone, consider naloxone infusion.
- If respiratory problems or acute changes in mental status occur, consider naloxone administration. Dilute one ampule of naloxone (0.4 mg/1 mL) into 9 mL of normal saline for a total volume of 10 mL. Give 1-2 mL (0.04-0.08 mg) every 30-60 seconds until improvement in symptoms is noted. Be prepared to repeat this process (the half-life of opioids is generally longer than that of the naloxone). If the patient is not responsive within 10 min and total naloxone dose of 1 mg, consider another reason for the change in neurological status.

Sedation

- If sedation develops and persists for more than 1 wk after initiating opioids
  - Assess for other causes of sedation (e.g., CNS pathology, other sedating medications, hypercalcemia, dehydration, sepsis, hypoxia)
  - Decrease the dose of opioid if pain control can be maintained at a lower dose
  - Consider changing the opioid
  - Consider nonopioid analgesic to allow reduction of the opioid dose
  - Consider a lower dose of opioid given more frequently to decrease peak concentrations
  - Consider the addition of caffeine, 100-200 mg PO every 6 h; or methylphenidate, 5-10 mg 1-3 times per day; or dextroamphetamine, 5-10 mg PO 1-3 times per day; or modafinil, 100-200 mg per day. When using CNS stimulants for sedation, limit dosing to morning and early afternoon to avoid insomnia at night
- If sedation persists despite several changes of opioids and the above measures
  - Reassess cause and severity of sedation
  - Consider neuraxial analgesics or neuroablative techniques to potentially reduce opioid dose

*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

COANALGESICS FOR NEUROPATHIC PAIN (ANTIDEPRESSANTS, ANTICONVULSANTS, AND TOPICAL AGENTS)

PRINCIPLES OF COANALGESIC USE

- Antidepressant and anticonvulsants are first-line coanalgesics for the treatment of cancer-related neuropathic pain.
- These drugs can be helpful for patients whose pain is only partially responsive to opioids.
- The use of coanalgesics in the cancer population is still often guided solely by anecdotal experience or guidelines derived from data in nonmalignant pain populations.
- Effective use is predicated on an assessment that clarifies the nature of the pain.
- As with opioids, it is likely that response to different coanalgesics may vary among types of neuropathic pain and individual patients.
- Drug selection may be influenced by the presence of certain nonpain symptoms and comorbidities. For example, a sedating drug may be useful in a patient in whom insomnia is a problem.
- Patient education should emphasize the trial and error nature of the treatment so that patients do not get discouraged.
- Doses should be increased until the analgesic effect is achieved, side effects become unmanageable, or the conventional maximal dose is reached.

EXAMPLES OF COANALGESIC USE

(Extrapolated from noncancer neuropathic pain management)

- Trial of antidepressant: Analgesic effectiveness is not dependent on its antidepressant activity. Effective analgesic dose is often lower than that required to treat depression. The onset of analgesic action is usually earlier. Frequently used as a coanalgesic in combination with an opioid for the neuropathic component of the pain.
  - Tricyclic antidepressants (e.g., amitriptyline, imipramine, nortriptyline, desipramine)
    - Start with low dose and increase every 3-5 days if tolerated. (e.g., nortriptyline and desipramine starting dose 10-25 mg nightly increase to 50-150 mg nightly. The tertiary amines [amitriptyline, imipramine] may be more efficacious but secondary amines [nortriptyline, desipramine] are better tolerated. Anticholinergic adverse effects such as sedation, dryness of mouth, urinary hesitancy are more likely to occur with amitriptyline and imipramine.)
  - Other examples:
    - Duloxetine: Starting dose 30-60 mg daily, increase to 60-120 mg daily
    - Venlafaxine: Starting dose 50-75 mg daily, increase to 75-225 mg daily
    - Bupropion: Starting dose 100-150 mg daily, increase to 150-450 mg daily

- Trial of anticonvulsants: Frequently used as a coanalgesic in combination with an opioid for the neuropathic component of the pain.
  - Anticonvulsant examples:
    - Gabapentin: Starting dose 100-300 mg nightly, increase to 900-3600 mg daily in divided doses 2 to 3 times a day. Dose increments of 50%-100% every 3 days. Slower titration for the elderly or medically frail. Dose adjustment required for those with renal insufficiency.
    - Pregabalin: Starting dose 50 mg 3 times a day, increase to 100 mg 3 times a day. Slower titration for the elderly or medically frail. Dose adjustment required for those with renal insufficiency. Pregabalin more efficiently absorbed through the GI tract than gabapentin. May increase further to a maximum dose of 600 mg in divided doses 2 to 3 times a day.
    - Consider other anticonvulsant agents, many of which have been shown to have efficacy in non cancer neuropathic pain.

- Trial of topical agents: Act locally and may be used as a coanalgesic in combination with an opioid, antidepressant, and/or an anticonvulsant.
  - Topical agent examples:
    - Lidocaine patch, 5%: Apply daily to the painful site. Minimal systemic absorption.
    - Consider NSAID: diclofenac gel, 1%, 4 times daily; or diclofenac patch, 180 mg, one patch daily or one patch twice daily

- Trial of corticosteroids: Long half-life of these drugs allows for once daily dosing. Useful in the acute management of a pain crisis when neural structures or bones are involved. Long-term adverse effects significant.

PSYCHOSOCIAL SUPPORT

Support

- Inform patient and family that emotional reactions to pain are normal and are evaluated and treated as part of pain treatment.
- Provide emotional support to patients and families that acknowledges the pain is a problem to be addressed.
- Assist in accessing treatment as needed.
- State that you will work together with the patient and family as part of the team to address the pain problem.
- Describe the plan of action to be taken and when results can be expected.
- Express your commitment to staying available until the pain is better managed.
- Verbally repeat your concern and the plan of action to be taken.
- Inform patient and family that there is ALWAYS something else that can be done to try to adequately manage pain and other noxious symptoms.
- Assess impact upon family and significant others and provide education and support as indicated.

Skills Training

- Teach coping skills to provide pain relief, enhance a sense of personal control, and refocus energy on optimizing quality of life.
- Coping skills for acute pain include Lamaze-type breathing exercises, distraction techniques, and cognitive coping statements to encourage assertiveness and to maximize comfort.
- Coping skills for chronic pain (not pain emergency) include all of the above plus relaxation techniques, guided imagery, graded task assignments, and hypnosis to maximize function.
- Educate patient and family that pain management is a team effort. Members of the team may include: oncologist, nurse, pain specialist, palliative care clinician, physiatry, neurologist, psychologist, social worker, psychiatrist, physical therapist, and spiritual counselor. See Patient and Family Education (page 1072).

PATIENT AND FAMILY EDUCATION

- Assess patient and family for literacy to ensure understanding of education.
- Messages to be conveyed to patient and family:
  - Relief of pain is medically important and there is no medical benefit to suffering with pain.
  - Pain can usually be well controlled with pain medications. For persistent pain, taking analgesic on a regular schedule will improve pain control.
  - If these medications do not work, many other options are available.
  - Potent analgesics should be taken only as prescribed and by the person for whom the medication is prescribed; do not self adjust dosage or frequency unless discussed with your health care provider.
  - Morphine and morphine-like medications are often used to relieve pain. For patients with a history of substance abuse, see page 1075.
    - When these drugs are used to treat cancer pain, addiction is rarely a problem.
    - If you take these medications now, they will still work later.
    - These are controlled substances that need to be properly safeguarded in the home.
    - These medications must be used with caution, and should not be mixed with alcohol or illicit substances.
  - Communication with the health care provider is critical.
    - Health care providers cannot tell how much pain you have unless you tell them.
    - Health care providers want to know about any problems that you think the pain medications may be causing, as there are probably ways to make these better.
    - Tell your health care providers if you are having any difficulty getting your medication or concerns about taking them. They have dealt with such issues before and will help you.
    - Expect optimal management for pain and side effects. Inform patient of right to expect pain management as part of overall care.
- The following must be reviewed with each patient and family and provided in written form, which is dated:
  - A list of each medication prescribed, a description of what each medication is for, and instructions as to how and when to take each one
  - A list of potential side effects of these medications and what to do if they occur
  - A list of all medications to be discontinued
  - A list of telephone numbers to reach an appropriate healthcare provider and specific instructions to call regarding:
    - Any problems in getting the prescriptions or taking the medication
    - New pain, change in pain, or pain not relieved with medication
    - Nausea and vomiting that prevents eating for 1 day
    - No bowel movements for 3 days
    - Difficulty arousing the patient from sleep easily during the daytime
    - Confusion
  - A plan for follow-up visits and/or phone calls
- The health care team should be familiar with local regulations pertaining to the operation of machinery or motor vehicles while taking potentially sedating medication and advise patient and family accordingly.

NONPHARMACOLOGIC INTERVENTIONS

Consider nonpharmacologic interventions for:

Pain likely to be relieved or function improved with physical, cognitive, or interventional modalities

- Physical modalities
  - Bed, bath, and walking supports
  - Positioning instruction
  - Physical therapy
  - Energy conservation, pacing of activities
  - Massage
  - Heat and/or ice
  - Transcutaneous electrical nerve stimulation (TENS)
  - Acupuncture or acupressure
  - Ultrasonic stimulation
- Cognitive modalities
  - Imagery/hypnosis
  - Distraction training
  - Relaxation training
  - Active coping training
  - Graded task assignments, setting goals, pacing and prioritizing
  - Cognitive behavioral training
  - Depression/distress consultation (see NCCN Guidelines on Distress Management*)
  - Consider pain and palliative care specialty consultation (see NCCN Guidelines on Palliative Care*)
    - Complex management
    - Diagnosis and treatment of underlying condition
  - Spiritual care

See Interventional Strategies (page 1076)

*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) AND ACETAMINOPHEN PRESCRIBING

NSAID

- Use NSAIDs with caution in patients at high risk for renal, GI, cardiac toxicities, thrombocytopenia, or bleeding disorder. Note that the potential side effects of chemotherapy, such as hematologic, renal, hepatic, and cardiovascular toxicities, can be increased by the concomitant prescription of NSAIDS. Opioid analgesics are a safe and effective alternative analgesic to NSAIDs.
- Use any NSAID that the patient has found effective and tolerated well in the past, otherwise consider ibuprofen to the maximal dose.
  - Ibuprofen, 400 mg, 4 times a day (daily maximum = 3200 mg)
  - If needed, consider short-term use of ketorolac, 15-30 mg IV, every 6 h for maximum of 5 days
  - Compounds that do not inhibit platelet aggregation:
    - Nonacetylated salicylate
    - Choline + magnesium salicylate combinations, 1.5-4.5 g/d, in 3 divided doses
    - Salsalate, 2-3 g/d, in 2 or 3 divided doses
    - Selective COX-2 inhibitor
- NSAIDs and toxicities
  - Patients at high risk for renal toxicities: age > 60 y, compromised fluid status, interstitial nephritis, papillary necrosis, and concomitant administration of other nephrotoxic drugs (including cyclosporin, cisplatin) and renally excreted chemotherapy
    - Treatment of renal toxicities: discontinue NSAIDs if BUN or creatinine doubles or if hypertension develops or worsens
  - Patients at high risk for GI toxicities: age > 60 y, history of peptic ulcer disease or significant alcohol use (≥ 3 alcoholic beverages per day), major organ dysfunction including hepatic dysfunction, high-dose NSAIDs given for long periods
    - Treatment of GI toxicities: if patient develops gastric upset or nausea, consider discontinuing NSAIDs or changing to selective COX-2 inhibitor. COX-2 inhibitors are associated with lower incidence of GI side effects and do not inhibit platelet aggregation; however, they have not been shown to have reduced renal side effects.
    - Consider adding antacids, H2 receptor antagonists, misoprostol, omeprazole. If patient develops gastrointestinal peptic ulcer or gastrointestinal hemorrhage, discontinue NSAIDs.
    - Discontinue NSAIDs if liver function studies increase 1.5 times the upper limit of normal.
  - Patients at high risk for *cardiac toxicities*: history of cardiovascular disease, or at risk for cardiovascular disease or complications. NSAIDs taken with prescribed anticoagulants, such as warfarin or heparin, may significantly increase the risk of bleeding complications.
    - Treatment of cardiac toxicities: discontinue NSAIDs if hypertension develops or worsens
  - Monitoring for NSAID toxicities:
    - Baseline blood pressure, BUN, creatinine, liver function studies (alkaline phosphatase, LDH, SGOT, SGPT), CBC, and fecal occult blood
    - Repeat every 3 mo to ensure lack of toxicity
- Further NSAID considerations:
  - If 2 NSAIDs are tried in succession without efficacy, use another approach to analgesia
  - If NSAIDs are effective but treatment is limited by toxicities that are not deemed serious, consider trial of another NSAID
  - When systemic administration is not feasible, consider topical NSAID preparations
  - Toxicity of anticancer treatment may increase the risk profile of anti-inflammatory treatment

Acetaminophen

- Acetaminophen, 650 mg every 4 h, or 1 g every 6 h (daily maximum 4 g/d). The FDA is currently evaluating daily maximum dosing. Becuase of concerns with liver toxicity, acetaminophen should be used with caution or not used at all with combination opioid-acetaminophen products to prevent excess acetaminophen dosing. See FDA Web site for latest information on acetaminophen side effects and dosing.
- For further prescribing and safety information, see FDA Web site (www.fda.gov).

[1] Antman EM, Bennett JS, Daugherty A, et al. Use of nonsteroidal antiinflammatory drugs: an update for clinicians. A scientific statement from the American Heart Association. Circulation 2007;115:1634-1642.

SPECIALITY CONSULTATIONS FOR IMPROVED PAIN MANAGEMENT

- Major indication for referral is:
  - Pain likely to be relieved or function improved with physical, cognitive, or interventional modalities delivered by a specialty service provider. Note the specific provider of these services may vary in different treatment settings.
- Pain and palliative care specialty consultation
  See NCCN Guidelines on Palliative Care*
  - Consider interventional strategies (see page 1076)
  - Management of symptoms refractory to initial treatment
  - Diagnosis and treatment of underlying condition
  - Consider palliative sedation for intractable pain
- Substance abuse and diversion consultation if questions/concerns about medication misuse or diversion
  - Evaluation for substance use disorder
  - Assist with establishing treatment agreements, limit setting, single provider/ pharmacy as needed
  - Communicate regarding need to accomplish pain relief, but avoid misuse/diversion
- Depression/Distress consultation (see NCCN Guidelines on Distress Management*)
- Spiritual care
  - Determine importance to patient/family and current availability of support
- Psychological supportive services
  - Cognitive modalities
    - Imagery/hypnosis
    - Distraction training
    - Relaxation training
    - Active coping training
    - Graded task assignments, setting goals, pacing, and prioritizing
    - Cognitive behavioral training
- Physical/occupational therapy, rehabilitation/mobility specialists
  - Physical modalities
    - Bed, bath, and walking supports
    - Positioning instruction
    - Physical therapy
    - Massage
    - Heat and/or ice
    - TENS
    - Acupuncture or acupressure
    - Ultrasonic stimulation

*To view most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org

INTERVENTIONAL STRATEGIES

Interventional Consultation

- Major indications for referral:
  - Pain likely to be relieved with nerve block (e.g., pancreas/upper abdomen with celiac plexus block, lower abdomen with superior hypogastric plexus block, intercostal nerve, or peripheral nerve)
  - Failure to achieve adequate analgesia without intolerable side effects (may be handled with intraspinal agents, blocks, spinal cord stimulation, or destructive neurosurgical procedures)

- Commonly used interventional procedures:
  - Regional infusions (requires infusion pump)
    - Epidural: easy to place; requires large volumes and an externalized catheter; for infusions of opioids, local anesthetics, clonidine; useful for acute postoperative pain
    - Intrathecal: easy to internalize to implanted pump; for infusions of opioids, local anesthetics, clonidine, and ziconotide
    - Regional plexus: for infusions of local anesthetics; used to anesthetize single extremity
  - Percutaneous vertebroplasty/kyphoplasty
  - Neurodestructive procedures for well-localized pain syndromes (spinal analgesics are used more frequently)
    - Head and neck: peripheral nerve block
    - Upper extremity: brachial plexus neurolysis
    - Thoracic wall: epidural neurolysis, intercostal neurolysis
    - Upper abdominal pain (visceral): celiac plexus block, thoracic splanchnicectomy
    - Midline pelvic pain: superior hypogastric plexus block
    - Rectal pain: intrathecal neurolysis, midline myelotomy or superior hypogastric plexus block
    - Unilateral pain syndromes: cordotomy
    - Consider intrathecal L/S phenol block
  - Neurostimulation procedures for cancer-related symptoms (i.e., peripheral neuropathy)
  - Radiofrequency ablation for bone lesions

- If interventional approaches are appropriate,
  - Evaluate which pain site can be relieved
  - Verify interventional technique will provide suffiecient benefit

- If interventional approaches are not appropriate[1]
  - Reassess therapeutic plan

[1] Infection, coagulopathy, very short or lengthy life expectancy, distorted anatomy, patient unwillingness, medications that increase risk for bleeding (e.g., antiangiogenesis agents such as bevacizumab) or technical expertise is not available.

Text continued from p. 1047

Second, the guidelines acknowledge the range of complex decisions faced in caring for these patients. As a result, they provide dosing guidelines for NSAIDs, opioids, and coanalgesics. They also provide specific suggestions for titrating and rotating opioids, escalation of opioid dosage, management of opioid adverse effects, and when and how to proceed to other techniques/interventions for the management of cancer pain.

Pathophysiologic Classification

Different types of pain occur in cancer patients. Several attempts have been made to classify pain according to different criteria. Pain classification includes differentiating between pain associated with tumor, pain associated with treatment, and pain unrelated to either. Acute and chronic pain should also be distinguished when deciding what therapy to use. Therapeutic strategy depends on the pain pathophysiology, which is determined through patient examination and evaluation. Pain has 2 predominant mechanisms of pathophysiology: nociceptive and neuropathic.[10,11]

Nociceptive pain is the result of injury to somatic and visceral structures and the resulting activation of nociceptors. Nociceptors are present in skin, viscera, muscles, and connective tissues. Nociceptive pain can be further divided into somatic pain and visceral pain.[12] Pain described as sharp, well-localized, throbbing, and pressure-like is probably somatic nociceptive pain, and often occurs after surgical procedures or from bone metastasis. Visceral nociceptive pain is frequently described as more diffuse, aching, and cramping. It is secondary to compression, infiltration, or distension of abdominal thoracic viscera.

Neuropathic pain results from injury to the peripheral or central nervous system. This type of pain might be described as burning, sharp, or shooting. Examples of neuropathic pain include pain from spinal stenosis or diabetic neuropathy, or as an adverse effect of chemotherapy (e.g., vincristine) or radiation therapy.

Comprehensive Pain Assessment

A comprehensive evaluation is essential to ensure proper pain management. Failure to adequately assess pain frequently leads to poor pain control. These guidelines begin with the premise that all patients with cancer should be screened for pain (page 1048) during the initial evaluation, at regular follow-up intervals, and whenever new therapy is initiated.

If pain is present on a screening evaluation, the pain intensity must be quantified by the patient whenever possible. Because pain is inherently subjective, patient's self-report of pain is the current standard of care for assessment. Intensity of pain should be quantified using a 0 to 10 numeric rating scale, a categorical scale, or a pictorial scale (e.g., the Faces Pain Rating Scale; see page 1055).[13–15] The Faces Pain Rating Scale may be successful for patients who have difficulty with other scales, such as children, elderly patients, and patients with language or cultural differences or other communication barriers. If the patient is unable to verbally report pain, an alternative method must be used to assess and rate the pain (see page 1056).

In addition to pain intensity, the patient should be asked to describe the characteristics of their pain (e.g., aching, burning). If the patient has no pain, rescreening should be performed at each subsequent visit or as requested. Identifying the presence of pain through repeated screening is essential to allow implementation of effective pain management.

If the Pain Rating Scale score is greater than 0, a comprehensive pain assessment is initiated (see pages 1058 and 1059). The comprehensive pain assessment should focus on the type and quality of pain, pain history (e.g., onset, duration, course), pain intensity (e.g., pain experienced at rest or with movement, or that interferes with activities), location, referral pattern, radiation of pain, associated factors that exacerbate or relieve the pain, current pain management plan, patient's response to current therapy, prior pain therapies, important psychosocial factors (e.g., patient distress, family and other support, psychiatric history, risk factors for aberrant use of pain medication, risk factors for undertreatment of pain), and other special issues relating to pain (e.g., meaning of pain for patient and family, cultural beliefs toward pain and pain expression, spiritual or religious considerations and existential suffering).[16,17] Finally, the patient's goals and expectations of pain management should be discussed, including level of comfort and function (see pages 1058 and 1059).

In addition, a thorough physical examination and review of appropriate laboratory and imaging

studies are essential for a comprehensive pain assessment. This evaluation should enable caregivers to determine if the pain is related to an underlying cause that requires specific therapy. For example, providing only opioids to a patient experiencing pain from impending spinal cord compression is inappropriate. Without glucocorticoids and local radiation therapy, the pain is unlikely to be well controlled and the patient will remain at high risk for spinal cord injury.

The end point of comprehensive pain assessment is to diagnose the origin and pathophysiology (somatic, visceral, or neuropathic) of the pain. Treatment must be individualized based on clinical circumstances and patient wishes, with the goal of maximizing function and quality of life.

Management of Pain

For management of cancer-related pain in adults, the algorithm distinguishes 3 levels of pain intensity, based on a 0 to 10 numeric rating scale (with 10 being the worst pain): severe pain (7–10); moderate pain (4–6); and mild pain (1–3).[12,14]

Pain related to an oncologic emergency is important to separate from pain not related to an oncologic emergency (e.g., from bone fracture or impending fracture of weight-bearing bone; brain, epidural, or leptomeningeal metastases; infection; obstructed or perforated viscus). Pain associated with oncologic emergency should be directly treated while proceeding with treatment of the underlying condition.

The algorithm also distinguishes pain that is unrelated to oncologic emergencies in patients not chronically taking opioids (opioid-naïve) from the pain experienced by those who have previously or are chronically taking opioids for cancer pain (opioid-tolerant), and also from anticipated procedure-related pain and anxiety.

According to the FDA, "patients considered opioid tolerant are those who are taking at least: 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer." Therefore, patients who do not meet these criteria for opioid-tolerant, and who have not had opioid doses at least as much as those stated for a week or more, are considered to be opioid-naïve.

Management of Pain Not Related to an Oncologic Emergency in Opioid-Naïve Patients

Opioid-naïve patients (those who are not chronically receiving opioids on a daily basis) experiencing severe pain (i.e., pain intensity rating 7–10) should receive rapid titration of short-acting opioids (see page 1050, and Opioid Principles, Prescribing, Titration, and Maintenance, facing page). Short-acting formulations have the advantage of rapid onset of analgesic effect. The route of opioid administration (oral vs. intravenous) is decided based on what is best suited to the patient's ongoing analgesic needs.

Treatment with opioids must be accompanied by a bowel regimen, and nonopioid analgesics as indicated. Details of prophylactic bowel regimens and antiemetics are provided on pages 1068 and 1069; management of these common opioid adverse effects should be started simultaneously with initiation of opioid therapy. Opioid-induced bowel dysfunction should be anticipated and treated prophylactically with a stimulating laxative to increase bowel motility, with or without stool softeners as indicated.[18]

The pathways are similar for opioid-naïve patients who have a pain intensity rating between 4 and 6 at presentation and those who have a pain intensity rating of 7 to 10. The main differences include treatment beginning with slower titration of short-acting opioids.

Opioid-naïve patients experiencing mild pain intensity (1–3) should undergo treatment with NSAIDs or acetaminophen, or treatment with consideration of slower titration of short-acting opioids.

Addition of coanalgesics for specific pain syndromes should be considered for all groups of patients (see Additional Therapies, page 1082, and page 1070). Coanalgesics are drugs used to enhance the effects of opioids or NSAIDs.[19]

For all patients experiencing pain, health care providers should also provide psychosocial support and begin educational activities. Psychosocial support is needed to ensure that appropriate aid is provided to patients encountering common barriers to appropriate pain control (e.g., fear of addiction or side effects, inability to purchase opioids) or needing assistance in managing additional problems (e.g., depression, rapidly declining functional status; page 1071). Patients and families must be educated regarding pain management and related issues.

Although pharmacologic analgesics are the cor-

nerstone of cancer pain management, they are not always adequate and are associated with many side effects, thus often necessitating the implementation of additional therapies or treatments. Optimal use of nonpharmacologic interventions may serve as valuable additions to pharmacologic interventions. A list of nonpharmacologic interventions that include physical and cognitive modalities are outlined on page 1073 and interventional strategies are discussed in the next section and on page 1076.

Opioid Principles, Prescribing, Titration, and Maintenance

Selecting an Appropriate Opioid: While starting therapy, attempts should be made to determine the underlying pain mechanism and diagnose the pain syndrome. Optimal analgesic selection will depend on the patient's pain intensity, any current analgesic therapy, and concomitant medical illnesses. Morphine, hydromorphone, fentanyl, and oxycodone are the opioids commonly used in the United States. An individual approach should be used to determine opioid starting dose, frequency, and titration to achieve a balance between pain relief and medication adverse effects.

In patients not previously exposed to opioids, morphine is generally considered the standard preferred starting drug.[20,21] An initial oral dose of 5 to 15 mg of morphine sulfate or equivalent or 2 to 5 mg of intravenous morphine sulfate or equivalent is recommended for opioid-naïve patients.

Pure agonists (e.g., codeine, oxycodone, oxymorphone, fentanyl) are the most commonly used medications in the management of cancer pain. The opioid agonists with a short half-life (morphine, hydromorphone, fentanyl, and oxycodone) are preferred because they can be more easily titrated than the analgesics with a long half-life (methadone and levorphanol).[22] Transdermal fentanyl is not indicated for rapid opioid titration and only should be recommended after pain is controlled by other opioids.[23] Conversion from intravenous fentanyl to transdermal fentanyl can be accomplished effectively using a 1:1 conversion ratio[24] (see pages 1061–1067).

Morphine should be avoided in patients with renal disease and hepatic insufficiency. Morphine-6-glucoronide, an active metabolite of morphine, contributes to analgesia and may worsen adverse effects as it accumulates in patients with renal insufficiency.[25,26]

Individual variations in methadone pharmacokinetics (long half-life ranging from 8 to > 120 hours) make its use very difficult in patients with cancer.[27] Because of its long half-life, high potency, and interindividual variations in pharmacokinetics, methadone should be started at lower-than-anticipated doses and slowly titrated upwards with provision of adequate short-acting breakthrough pain medications during the titration period. Consultation with a pain management specialist should be considered before its application.

Agents such as mixed agonist–antagonists (e.g., butorphanol, pentazocine), propoxyphene and meperidine, and placebos are not recommended for cancer patients. For treatment of severe pain, mixed agonist–antagonist drugs have limited efficacy and may precipitate opioid withdrawal if used in patients receiving pure opioid agonist analgesics. Meperidine and propoxyphene are contraindicated for chronic pain, especially in patients with impaired renal function or dehydration, because accumulation of renally cleared metabolites may result in neurotoxicity or cardiac arrhythmias.[28] Use of placebo in the treatment of pain is unethical.

Propoxyphene is an inhibitor of the hepatic enzyme, CYP2D6.[29,30] Because data suggest that CYP2D6-inhibiting antidepressants increase risk of recurrence in patients with breast cancer treated with tamoxifen[31,32] (see Additional Therapies, page 1082), it is reasonable to assume that propoxyphene may have the same effect. Therefore, propoxyphene should be avoided in patients treated with tamoxifen. In general, propoxyphene should be avoided in cancer pain management because its risks far outweigh any benefits.

Selecting a Route of Administration: The least invasive, easiest, and safest route of opioid administration should be provided to ensure adequate analgesia.

Oral is the preferred route of administration for chronic opioid therapy.[28,33,34] The oral route should be considered first in patients who can take oral medications unless a rapid onset of analgesia is required or the patient experiences side-effects associated with the oral administration. Continuous parenteral infusion, intravenous or subcutaneous, is recommended for patients who cannot swallow or absorb opioids enterally. Opioids, given parenterally, may produce fast and effective plasma concentrations compared with oral or transdermal opioids. Intravenous route is considered for faster analgesia

because of the short lag-time between injection and effect (peak, 15 minutes) compared with oral dosing (peak, 60 minutes).[35]

The following methods of ongoing analgesic administration are widely used in clinical practice: around-the-clock, as-needed, and patient-controlled. Around-the-clock dosing is provided for continuous pain relief in patients with chronic pain, and a rescue dose of short-acting opioids should be provided as a subsequent treatment for pain that is not relieved (see pages 1061–1067). Opioids administered on an as-needed basis are for patients who have intermittent pain with pain-free intervals. The as-needed method is also used when rapid dose titration is required. The patient-controlled analgesia technique allows patients to control a device that delivers a bolus of analgesic on demand (according to, and limited by, parameters set by a physician).

Opioid Adverse Effects

Constipation, nausea and vomiting, pruritus, delirium, respiratory depression, motor and cognitive impairment, and sedation are fairly common, especially when multiple agents are used.[36–41] Each adverse effect requires a careful assessment and treatment strategy. Proper management is necessary to prevent and reduce analgesic adverse effects (see pages 1068 and 1069).[36,42–50] Constipation can almost always be anticipated with opioid treatment; administration of prophylactic bowel regimen is recommended. However, evidence is limited on which to base the selection of the most appropriate bowel regimen. One study shows that adding a stool softener, docusate, to the laxative, sennosides, was less effective than the laxative alone.[51] Therefore, the panel recommends a stimulant laxative with or without a stool softener. Details of prophylactic bowel regimens and other measures to prevent constipation, and antiemetics are provided on page 1068.

Opioid Rotation

No single opioid is optimal for all patients.[52] If opioid adverse effects are significant, an improved balance between analgesia and adverse effects might be achieved by changing to an equivalent dose of an alternative opioid. This approach is known as opioid rotation.[36] Relative effectiveness is important to consider when switching between oral and parenteral routes to avoid subsequent over- or underdosing. Equianalgesic dose ratios, opioid titration and maintenance, and clinical examples of converting from one opioid to another are listed on pages 1061–1067.

Initiating Short-Acting Opioids in Opioid-Naïve Patients

The route of administration of opioid (oral or intravenous) must be selected based on the needs of the patient.

For opioid-naïve patients experiencing a pain intensity of 4 or higher, or a pain intensity less than 4 whose goals of pain control and function are not met, an initial dose of 5 to 15 mg of oral morphine sulfate or 1 to 5 mg of intravenous morphine sulfate or equivalent is recommended (see page 1051). Assessment of efficacy and side effects should be performed every 60 minutes for orally administered opioids, and every 15 minutes for intravenous opioids, to determine a subsequent dose (see page 1051). If assessment shows that the pain score is unchanged or is increased, the panel recommends increasing the dose by 50% to 100% to achieve adequate analgesia. If the pain score decreases to 4 to 6, the same dose of opioid is repeated and reassessment is performed at 60 minutes for orally administered opioids and every 15 minutes for intravenously administered opioids. If inadequate response is seen in patients with moderate to severe pain on reassessment after 2 to 3 cycles of the opioid, changing the route of administration from oral to intravenous or subsequent management strategies (outlined on page 1053) can be considered. If the pain score decreases to 0 to 3, the current effective dose of opioid is administered as needed over an initial 24 hours before proceeding to subsequent management strategies (see page 1051).

Management of Pain Not Related to an Oncologic Emergency in Opioid-Tolerant Patients

Opioid-tolerant patients take opioids chronically for pain relief. According to the FDA, opioid tolerant patients "are those who are taking at least: 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer."

In opioid-tolerant patients experiencing breakthrough pain intensity of 4 or greater, or less than 4 whose goals of pain control and function are not met, the previous 24-hour total oral or intravenous opioid requirement must be calculated and the new

rescue dose increased by 10% to 20% to achieve adequate analgesia[33,53] (see page 1052). Efficacy and side effects should be assessed every 60 minutes for orally administered opioids and every 15 minutes for intravenous opioids to determine a subsequent dose (see page 1052). On assessment, if the pain score is unchanged or increased, administration of 50% to 100% of the previous rescue dose of opioid is recommended. If the pain score decreases to 4 to 6, the same dose of opioid is repeated and reassessment is performed at 60 minutes for orally administered opioids and every 15 minutes for intravenously administered opioids. If the pain score remains unchanged on reassessment after 2 to 3 cycles of the opioid in patients with moderate to severe pain, changing the route of administration from oral to intravenous or alternate management strategies (outlined on page 1053) can be considered. If the pain score decreases to 0 to 3, the current effective dose of either oral or intravenous opioid is administered as needed over an initial 24 hours before proceeding to subsequent management strategies.

Subsequent Management of Pain in Opioid-Tolerant Patients

Subsequent treatment is based on the patient's continued pain rating score (see page 1053). Approaches for all pain intensity levels must be coupled with psychosocial support and education for patients and their families.

If the pain at this time is severe, unchanged, or increased, the working diagnosis must be reevaluated and comprehensive pain assessment performed. For patients unable to tolerate dose escalation of their current opioid because of adverse effects, an alternate opioid must be considered (see pages 1061–1067). Addition of coanalgesics (see page 1070) should be reevaluated to either enhance the analgesic effect of the opioids or, in some cases, counter the adverse effects associated with the opioids.[18] Given the multifaceted nature of cancer pain, additional interventions (see page 1060) for specific cancer pain syndromes and specialty consultation (see page 1075) must be considered to provide adequate analgesia.

If the patient is experiencing moderate pain intensity of 4 to 6 and adequate analgesic relief on their current opioid, the current titration of the opioid may be continued or increased. In addition, similar to patients experiencing severe pain, addition of coanalgesics (see page 1070), additional interventions for specific cancer pain syndromes (see page 1060), and specialty consultation must be considered (see page 1075).

For opioid-tolerant patients with mild pain who are experiencing adequate analgesia but intolerable or unmanageable side effects, the analgesic dose may be reduced by 25% of the current opioid dose (see page 1075). Addition of coanalgesics may be considered.

Ongoing Care

Although pain intensity ratings will be obtained frequently to evaluate opioid dose increases, a formal reevaluation to determine patient goals of comfort and function is mandated at each contact.

If an acceptable level of comfort and function has been achieved for the patients and 24-hour opioid requirement is stable, the panel recommends converting to an extended-release oral medication (if feasible) or other extended-release formulation (e.g., transdermal fentanyl) or long-acting agent (e.g., methadone; see page 1054). Subsequent treatment is based on the patient's continued pain rating score. Rescue doses of the short-acting formulation of the same long-acting drug may be provided during maintenance therapy for the management of pain in cancer patients not experiencing relief with extended-release opioids.

Routine follow-up of inpatients should be performed during each outpatient contact, or at least each day, depending on patient conditions and institutional standards.

Patients should be provided with a written follow-up plan and instructed on the importance of adhering to the medication plan, maintaining clinic appointments, and following up with clinicians (see page 1072).

If an acceptable level of comfort and function has not been achieved, universal screening and assessment must be performed and additional strategies for pain relief considered.

Management of Procedure-Related Pain and Anxiety

Procedure-related pain represents an acute short-lived experience that may be accompanied by a great deal of anxiety (see page 1057). Procedures reported as painful include bone marrow aspirations; wound care; lumbar puncture; skin and bone marrow biopsies; intravenous, arterial, and central lines; and injections. Many of the data available on procedure-related pain are from studies on pediatric patients

with cancer, which are then extrapolated to adults. Interventions to manage procedure-related pain should take into account the type of procedure, the anticipated level of pain, and other individual characteristics of the patients, such as age and physical condition. The interventions may be multimodal and may include pharmacologic and/or nonpharmacologic approaches.

Local anesthetics can be used to manage procedure-related pain with sufficient time for effectiveness as per package insert. Examples of local anesthetics include lidocaine, prilocaine, and tetracaine. Physical approaches such as cutaneous warming, laser or jet injection, and ultrasound may accelerate the onset of cutaneous anesthesia. Sedatives may also be used. However, deep sedation and general anesthesia must be performed only by trained professionals. In addition, use of nonpharmacologic interventions listed on page 1073 may be valuable in managing procedure-related pain and anxiety. The major goal of nonpharmacologic interventions that include physical and cognitive modalities is to promote a sense of control, thereby increasing hope and reducing helplessness experienced by many patients with pain from cancer.

Patients usually tolerate procedures better when they know what to expect. Therefore, patients and family members should receive written instructions for managing the pain. Preprocedure patient education on procedure details and pain management strategies is essential. Patients and family members should receive written information regarding pain management options.

Interventional Strategies

Some patients experience inadequate pain control despite pharmacologic therapy, or may not tolerate an opioid titration program because of side effects. Some patients may prefer procedural options over a chronic medication regimen. The major indications for referral for interventional strategies include pain that is likely to be relieved with nerve block (e.g., pancreas/upper abdomen with celiac plexus block, lower abdomen with superior hypogastric plexus block, intercostal nerve, or peripheral nerve) and/or patients failing to achieve adequate analgesia without intolerable side effects. For example, a patient with pancreatic cancer who was unable to tolerate opioids or experience adequate analgesia could be offered a celiac plexus block.

Several interventional strategies (see page 1076) are available for patients who do not experience adequate analgesia. Regional infusion of analgesics (epidural, intrathecal, and regional plexus) is one approach. This approach minimizes the distribution of drugs to receptors in the brain, potentially avoiding side effects of systemic administration. The intrathecal route of opioid administration should be considered in patients with intolerable sedation, confusion, and/or inadequate pain control with systemic opioid administration. This approach is a valuable tool to improve analgesia in patients experiencing pain in various anatomic locations (e.g., head and neck, upper and lower extremities, trunk).[54] Neuroablative procedures used for well-localized pain syndromes (e.g., back pain from facet or sacroiliac joint arthropathy; visceral pain from abdominal or pelvic malignancy), such as percutaneous vertebroplasty/kyphoplasty, neurostimulation procedures (i.e., for peripheral neuropathy), and radiofrequency ablation for bone lesions, have proven successful in managing pain (see page 1076), especially in patients unable to experience adequate analgesia without intolerable effects. In some cases, these techniques have been successfully used to eliminate or significantly reduce the level of pain, and/or may allow a significant decrease in systemic analgesics.

These interventional strategies are not appropriate in unwilling patients or those with infections, coagulopathy, or very short life expectancy. Furthermore, the experts performing the interventions must be made aware of any medications the patients are taking that might increase risk for bleeding (e.g., anticoagulants [warfarin, heparin], antiplatelet agents [clopidogrel, dipyridamole], antiangiogenesis agents [bevacizumab]). In these cases, the patient may have to be off the medication for an appropriate amount of time before the pain intervention is initiated and may need to continue to stay off the medication for a specified amount of time after the procedure. Interventions are not appropriate if technical expertise is not available.

Additional Therapies

Additional strategies specific to the pain situation can be considered. Specific recommendations for inflammatory pain, bone pain, nerve compression or

inflammation, neuropathic pain, pain cause by bowel obstruction, and pain likely to respond to antineoplastic therapies are provided in the algorithm (see page 1060). Overall, neuropathic pain is less responsive to opioids than pain caused by other pathophysiologies.

Other therapies, including specific nontraditional analgesic drugs, are usually indicated for neuropathic pain syndrome.[55] For example, a patient with neuropathic pain who failed to gain sufficient relief from opioids would be given a coanalgesic.

Clinically, coanalgesics consist of a diverse range of drug classes, including anticonvulsants[56] (e.g., gabapentin, pregabalin), antidepressants (e.g., tricyclic antidepressants), corticosteroids, and local anesthetics (e.g., topical lidocaine patch).

Several antidepressants are known inhibitors of hepatic drug metabolism through inhibition of cytochrome P450 enzymes, especially CYP2D6. Tamoxifen is an estrogen receptor blocker commonly used in patients with hormone receptor–positive breast cancer. Tamoxifen undergoes extensive hepatic metabolism, and inhibition of CYP2D6 decreases production of tamoxifen-active metabolites, potentially limiting tamoxifen efficacy. Clinical studies indicate increased risk of breast cancer recurrence in patients with breast cancer treated with tamoxifen and selective serotonin reuptake inhibitor (SSRI) antidepressants compared with those receiving tamoxifen alone.[31,32] If concomitant use of an SSRI is required in patient receiving tamoxifen, use of a mild CYP2D6 inhibitor (sertraline, citalopram, venlafaxine, escitalopram) may be preferred over a moderate-to-potent inhibitor (paroxetine, fluoxetine, fluvoxamine, bupropion, duloxetine).[57]

Coanalgesics are commonly used to help manage bone pain, neuropathic pain, and visceral pain, and to reduce systemic opioid requirement. They are particularly important in treating neuropathic pain that is resistant to opioids.[58]

Acetaminophen[59]; NSAIDs including selective COX-2 inhibitors; tricyclic antidepressants; anticonvulsant drugs; bisphosphonates; and hormonal therapy are among the most commonly used medications. The NSAID and acetaminophen prescribing guidelines are presented on page 1074. History of peptic ulcer disease, advanced age (> 60 years), male gender, and concurrent corticosteroid therapy should be considered before NSAID administration to prevent upper gastrointestinal tract bleeding and perforation. Well-tolerated proton pump inhibitors are recommended to reduce gastrointestinal side effects induced by NSAIDs. To prevent renal toxicities, NSAIDs should be prescribed with caution in patients who are older than 60 years or have compromised fluid status or renal insufficiency, or when given with concomitant administration of other nephrotoxic drugs and renally excreted chemotherapy.

Nonpharmacologic specialty consultations for physical (e.g., massage, physical therapy) and cognitive modalities (e.g., hypnosis, relaxation) may provide extremely beneficial adjuncts to pharmacologic interventions (see page 1073).

Attention should also be focused on psychosocial support (see page 1071), providing education to patients and families (see page 1072), and reducing side effects of the opioid analgesics.

Continued pain ratings should be obtained and documented in patients' medical records to ensure that the pain remains under good control and goals of treatment are achieved. Specialty consultations can be helpful in providing interventions to assist with difficult cancer pain problems (see page 1075). The major indication for referral to a specialty service provider is whether the pain is likely to be relieved or will help patients become functional in their daily activities. These modalities are delivered by a specialty service provider, and pain management is accomplished through establishing individualized goals and providing specific treatment and education for patients. The specialties include physical/occupational therapy and psychosocial supportive services, and other fields with expertise in interventional modalities.

Summary

In most patients, cancer pain can be successfully controlled with appropriate techniques and safe drugs. The overall approach to pain management encompassed in these guidelines is comprehensive. It is based on routine pain assessments, utilizes both pharmacologic and nonpharmacologic interventions, and requires ongoing reevaluation of the patient. The NCCN Adult Cancer Pain Guidelines panel advises that cancer pain can be well controlled in the vast majority of patients if the algorithms presented are systematically applied, carefully monitored, and tailored to the needs of the individual patient.

References

1. Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. Prepared by the International Association for the Study of Pain, Subcommittee on Taxonomy. Pain Suppl 1986;3(Supp 1):226.
2. Cohen MZ, Easley MK, Ellis C, et al. Cancer pain management and the JCAHO's pain standards: an institutional challenge. J Pain Symptom Manage 2003;25:519–527.
3. Goudas LC, Bloch R, Gialeli-Goudas M, et al. The epidemiology of cancer pain. Cancer Invest 2005;23:182–190.
4. Svendsen KB, Andersen S, Arnason S, et al. Breakthrough pain in malignant and non-malignant diseases: a review of prevalence, characteristics and mechanisms. Eur J Pain 2005;9:195–206.
5. Cleeland CS, Gonin R, Hatfield AK, et al. Pain and its treatment in outpatients with metastatic cancer. N Engl J Med 1994;330:592–596.
6. Martin LA, Hagen NA. Neuropathic pain in cancer patients: mechanisms, syndromes, and clinical controversies. J Pain Symptom Manage 1997;14:99–117.
7. Mercadante S. Malignant bone pain: pathophysiology and treatment. Pain 1997;69:1–18.
8. Stjernsward J. WHO cancer pain relief programme. Cancer Surv 1988;7:195–208.
9. Stjernsward J, Colleau SM, Ventafridda V. The World Health Organization Cancer Pain and Palliative Care Program. Past, present, and future. J Pain Symptom Manage 1996;12:65–72.
10. Caraceni A, Weinstein SM. Classification of cancer pain syndromes. Oncology (Williston Park) 2001;15:1627–1640.
11. Hewitt DJ. The management of pain in the oncology patient. Obstet Gynecol Clin North Am 2001;28:819–846.
12. Portenoy RK. Cancer pain. Epidemiology and syndromes. Cancer 1989;63:2298–2307.
13. Hicks CL, von Baeyer CL, Spafford PA, et al. The Faces Pain Scale-Revised: toward a common metric in pediatric pain measurement. Pain 2001;93:173–183.
14. Serlin RC, Mendoza TR, Nakamura Y, et al. When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. Pain 1995;61:277–284.
15. Soetenga D, Frank J, Pellino TA. Assessment of the validity and reliability of the University of Wisconsin Children's Hospital Pain scale for Preverbal and Nonverbal Children. Pediatr Nurs 1999;25:670–676.
16. Al-Atiyyat HN. Cultural diversity and cancer pain. J Hosp Palliat Nurs 2009;11:154–164.
17. Ezenwa MO, Ameringer S, Ward SE, Serlin RC. Racial and ethnic disparities in pain management in the United States. J Nurs Scholarsh 2006;38:225–233.
18. American Pain Society. Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain, 5th ed. Glenview, IL: American Pain Society; 2003.
19. Mercadante SL, Berchovich M, Casuccio A, et al. A prospective randomized study of corticosteroids as adjuvant drugs to opioids in advanced cancer patients. Am J Hosp Palliat Care 2007;24:13–19.
20. Klepstad P, Kaasa S, Borchgrevink PC. Start of oral morphine to cancer patients: effective serum morphine concentrations and contribution from morphine-6-glucuronide to the analgesia produced by morphine. Eur J Clin Pharmacol 2000;55:713–719.
21. Klepstad P, Kaasa S, Skauge M, Borchgrevink PC. Pain intensity and side effects during titration of morphine to cancer patients using a fixed schedule dose escalation. Acta Anaesthesiol Scand 2000;44:656–664.
22. Cherny NI. The pharmacologic management of cancer pain. Oncology (Williston Park) 2004;18:1499–1515.
23. Hanks GW, Conno F, Cherny N, et al. Morphine and alternative opioids in cancer pain: the EAPC recommendations. Br J Cancer 2001;84:587–593.
24. Kornick CA, Santiago-Palma J, Khojainova N, et alL. A safe and effective method for converting cancer patients from intravenous to transdermal fentanyl. Cancer 2001;92:3056–3061.
25. Tiseo PJ, Thaler HT, Lapin J, et al. Morphine-6-glucuronide concentrations and opioid-related side effects: a survey in cancer patients. Pain 1995;61:47–54.
26. Portenoy RK, Foley KM, Stulman J, et al. Plasma morphine and morphine-6-glucuronide during chronic morphine therapy for cancer pain: plasma profiles, steady-state concentrations and the consequences of renal failure. Pain 1991;47:13–19.
27. Davis MP, Homsi J. The importance of cytochrome P450 monooxygenase CYP2D6 in palliative medicine. Support Care Cancer 2001;9:442–451.
28. Bruera E, Kim HN. Cancer pain. JAMA 2003;290:2476–2479.
29. Barkin RL, Barkin SJ, Barkin DS. Propoxyphene (dextropropoxyphene): a critical review of a weak opioid analgesic that should remain in antiquity. Am J Ther 2006;13:534–542.
30. Goldstein DJ, Turk DC. Dextropropoxyphene: safety and efficacy in older patients. Drugs Aging 2005;22:419–432.
31. Aubert R, Stanek, EJ, Yao J, et al. Risk of breast cancer recurrence in women initiating tamoxifen with CYP2D6 inhibitors [abstract]. J Clin Oncol 2009;27(Suppl 1):Abstract CRA508.
32. Dezentje V, Van Blijderveen NJ, Gelderblom H, et al. Concomitant CYP2D6 inhibitor use and tamoxifen adherence in early-stage breast cancer: a pharmacoepidemiologic study [abstract]. J Clin Oncol 2009;27(Suppl 1):Abstract CRA509.
33. Portenoy RK, Lesage P. Management of cancer pain. Lancet 1999;353:1695–1700.
34. Stevens RA, Ghazi SM. Routes of opioid analgesic therapy in the management of cancer pain. Cancer Control 2000;7:132–141.
35. Harris JT, Suresh Kumar K, Rajagopal MR. Intravenous morphine for rapid control of severe cancer pain. Palliat Med 2003;17:248–256.
36. McNicol E, Horowicz-Mehler N, Fisk RA, et al. Management of opioid side effects in cancer-related and chronic noncancer pain: a systematic review. J Pain 2003;4:231–256.
37. Mercadante S. Comments on Wang et al., PAIN, 67 (1996) 407-416. Pain 1998;74:106–107.
38. Mercadante S. Pathophysiology and treatment of opioid-related myoclonus in cancer patients. Pain 1998;74:5–9.
39. Wilson RK, Weissman DE. Neuroexcitatory effects of opioids: patient assessment #57. J Palliat Med 2004;7:579.
40. Moryl N, Carver, A, Foley KM. Pain and palliation. In: Holland JF, Frei E, eds. Cancer Medicine. Vol. I7. Hamilton, ON: BC Decker Inc; 2006:1113–1124.
41. Moryl N, Obbens EA, Ozigbo OH, Kris MG. Analgesic effect of gefitinib in the treatment of non-small cell lung cancer. J Support Oncol 2006;4:111.
42. Boettger S, Breitbart W. Atypical antipsychotics in the management of delirium: a review of the empirical literature. Palliat Support Care 2005;3:227–237.
43. Breitbart W, Marotta R, Platt MM, et al. A double-blind trial of

haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. Am J Psychiatry 1996;153:231–237.

44. Bruera E, Belzile M, Neumann C, et al. A double-blind, crossover study of controlled-release metoclopramide and placebo for the chronic nausea and dyspepsia of advanced cancer. J Pain Symptom Manage 2000;19:427–435.
45. Challoner KR, McCarron MM, Newton EJ. Pentazocine (Talwin) intoxication: report of 57 cases. J Emerg Med 1990;8:67–74.
46. Katcher J, Walsh D. Opioid-induced itching: morphine sulfate and hydromorphone hydrochloride. J Pain Symptom Manage 1999;17:70–72.
47. Marinella MA. Acute colonic pseudo-obstruction complicated by cecal perforation in a patient with Parkinson's disease. South Med J 1997;90:1023–1026.
48. Reissig JE, Rybarczyk AM. Pharmacologic treatment of opioid-induced sedation in chronic pain. Ann Pharmacother 2005;39:727–731.
49. Tarcatu D, Tamasdan C, Moryl N, Obbens E. Are we still scratching the surface? A case of intractable pruritus following systemic opioid analgesia. J Opioid Manag 2007;3:167–170.
50. Prommer E. Modafinil: is it ready for prime time? J Opioid Manag 2006;2:130–136.
51. Hawley PH, Byeon JJ. A comparison of sennosides-based bowel protocols with and without docusate in hospitalized patients with cancer. J Palliat Med 2008;11:575–581.
52. Slatkin NE. Opioid switching and rotation in primary care: implementation and clinical utility. Curr Med Res Opin 2009;25:2133–2150.
53. Mercadante S, Arcuri E, Ferrera P, et al. Alternative treatments of breakthrough pain in patients receiving spinal analgesics for cancer pain. J Pain Symptom Manage 2005;30:485–491.
54. Greenberg HS, Taren J, Ensminger WD, Doan K. Benefit from and tolerance to continuous intrathecal infusion of morphine for intractable cancer pain. J Neurosurg 1982;57:360–364.
55. Chen H, Lamer TJ, Rho RH, et al. Contemporary management of neuropathic pain for the primary care physician. Mayo Clin Proc 2004;79:1533–1545.
56. Lussier D, Huskey AG, Portenoy RK. Adjuvant analgesics in cancer pain management. Oncologist 2004;9:571–591.
57. Jin Y, Desta Z, Stearns V, et al. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. J Natl Cancer Inst 2005;97:30–39.
58. Manfredi PL, Gonzales GR, Sady R, et al. Neuropathic pain in patients with cancer. J Palliat Care 2003;19:115–118.
59. Stockler M, Vardy J, Pillai A, Warr D. Acetaminophen (paracetamol) improves pain and well-being in people with advanced cancer already receiving a strong opioid regimen: a randomized, double-blind, placebo-controlled cross-over trial. J Clin Oncol 2004;22:3389–3394.

Recommended Readings

Levy MH, Chwistek M, Mehta RS. Management of chronic pain in cancer survivors. Cancer J 2008;14:401–409.

Levy MH, Samuel TA. Management of cancer pain. Semin Oncol 2005;32:179–193.

Kochhar R, Legrand SB, Walsh D, et al. Opioids in cancer pain: common dosing errors. Oncology (Williston Park) 2003;17:571–575; discussion 575–576, 579.

Ripamonti C, Zecca E, Bruera E. An update on the clinical use of methadone for cancer pain. Pain 1997;70:109–115.

Individual Disclosures of the NCCN Adult Cancer Pain Panel

Panel Member	Clinical Research Support	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
Amy Pickar Abernethy, MD	DARA Pharmaceuticals; and Wyeth Pharmaceuticals	Pfizer Inc.	None	None	10/28/09
Doralina L. Anghelescu, MD	None	None	None	None	10/28/09
Costantino Benedetti, MD	None	None	None	None	1/6/10
Craig D. Blinderman, MD, MA	None	Cephalon, Inc.	None	None	7/6/09
Barry Boston, MD	BEST	Bayer HealthCare; Onyx Pharmaceuticals, Inc.; Pfizer Inc.; and sanofi-aventis U.S.	None	None	10/28/09
Charles Cleeland, PhD	None	None	None	None	8/16/10
Nessa Coyle, PhD, NP	None	None	None	None	10/28/09
Oscar A. deLeon-Casasola, MD	None	Forrester Pharma; King Pharma; Pfizer Inc.; Vertex Pharmaceuticals Incorporated; and Wyeth Pharmaceuticals	None	None	4/6/10
June G. Eilers, PhD, APRN	None	Novartis Pharmaceuticals Corporation; and EUSA Pharmaceuticals	None	None	12/21/09
Betty Ferrell, RN, PhD	None	None	None	None	1/18/10
Nora A Janjan, MD, MPSA, MBA	Accuray Incorporated; and ICON Contract Research Organization	Accuray Incorporated; and ICON Contract Research Organization	None	Accuray Incorporated; and ICON Contract Research Organization	12/21/09
Sloan Beth Karver, MD	None	Eli Lilly and Company; and Wyeth Pharmaceuticals	None	None	10/28/09
Michael H. Levy, MD, PhD	Cephalon, Inc.; Johnson & Johnson; and Wyeth Pharmaceuticals	None	None	None	10/28/09
Maureen Lynch, MS, APRN	None	None	None	None	10/28/09
Natalie Moryl, MD					Pending*
Barbara A. Murphy, MD	None	None	None	None	10/28/09
Suzanne A. Nesbit, PharmD, BCPS	Medtronic, Inc.	None	None	None	10/28/09
Linda Oakes, RN, MSN	None	None	None	None	12/21/09
Eugenie A. Obbens, MD, PhD	None	None	None	None	7/9/09
Judith A. Paice, PhD, RN	None	None	None	None	10/28/09
Michael W. Rabow, MD	None	None	None	None	9/30/09
Robert Swarm, MD	None	None	None	None	10/28/09
Karen L. Syrjala, PhD	None	None	None	None	10/28/09
Susan Urba, MD	Eisai Inc.	Merck & Co., Inc.; and Wyeth Pharmaceuticals	None	None	10/28/09
Sharon M. Weinstein, MD	None	None	None	None	10/28/09

The NCCN Guidelines staff have no conflicts to disclose.
*Information not available at press. Please go to www.NCCN.org for updates.