National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Adult Cancer Pain

V.1.2008

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Adult Cancer Pain

Table of Contents

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

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus

SUMMARY OF GUIDELINES UPDATES

Summary of changes in the 2008 version of the Adult Cancer Pain guidelines from the 1.2007 version include:

PAIN-1

- Comprehensive pain assessment factors were removed and a link to PAIN-C was added.
- A new pathway for "anticipated painful events and procedures" was added.
- For universal screening, if pain present, "Severe uncontrolled pain is a medical emergency and should be evaluated promptly" was added.
- "Management of uncontrolled pain" was clarified as "management of pain."

PAIN-2

- The title of the page was clarified as, "Management of pain in patients not taking opioids."
- "Severe, moderate and mild" were added as descriptors for "Pain 7-10, Pain 4-6 and Pain 1-3," respectively.
- "Repeat comprehensive reassessment" was replaced by "Reevaluate" for severe and moderate pain categories and "Reevaluate pain at each contact and as needed" for the mild pain category.
- "Consider adding co-analgesics for specific pain syndrome" replaced "Nonopioid analgesics as indicated" for all pain categories.
- "Optimize nonpharmacologic interventions" is a new management option for all pain categories.

PAIN-3

- For intravenous, not taking opioids, the initial dose was changed from "*1*-5 mg" to "*2* to 5 mg".
- For both oral and intravenous bolus, "Pain score unchanged or increased: "Administer double dose" was changed to "Increase dose by 50-100%."

PAIN-4

- "Provide written pain plan" was added as a subsequent treatment for pain.
- For severe and moderate pain, "Reevaluate co-analgesics as indicated" and "Continue co-analgesic titration" were added respectively.
- "Repeat comprehensive reassessment" was replaced by "Reevaluate" for severe and moderate pain categories.

PAIN-5

- The title of the page was changed from "Subsequent follow-up" to "Ongoing care".
- Clinician issues/responsibilities, routine follow-up:
  - "Assess pain during each outpatient contact or at least each day for inpatients" was added.
  - "Written follow-up pain plan" was clarified by adding "including prescribed medication."
- Clinician issues/responsibilities: "Maintain communication and coordinate care with pain specialist and relevant providers" was added.

PAIN-A 1 of 2

- "The Faces Pain Rating Scale" has been updated with a new reference.

PAIN-A 2 of 2

- "Pain assessment in the nonverbal patient" is new to the guidelines.

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Continued on next page

SUMMARY OF GUIDELINES UPDATES (CONTINUED)

PAIN-B
- "Procedure-related pain and anxiety" is new to the guidelines.

PAIN-C 1 of 2
- Comprehensive pain assessment was reorganized and modified.

PAIN-C 2 of 2
- "Impact of pain measurement" scale is new to the guidelines.

PAIN-E 1 of 3
- General principles: Converting from one opioid to another was added.

PAIN-E 2 of 3
- The table was modified to dose equivalences "as compared with morphine" and corresponding footnotes were added.

PAIN-E 3 of 3
- Converting to transdermal fentanyl is new to the guidelines.

PAIN-F 1of 3
- "Principles of management of opioid side effects" were added.
- Constipation, prophylactic medications, for senna with docusate dose: "maximum 8-12 tablets per day" was added for clarification.

PAIN-F 2 of 3
- The management of the opioid side effect, "pruritus" was added.

PAIN-F 3 of 3
- Respiratory depression, a statement regarding reversing agents was added, "If reversing an opioid with a long half life such as methadone, consider naloxone infusion."
- Sedation, "modafinil" was added as an example and "when using CNS stimulants for sedation, limit dosing to morning and early afternoon to avoid insomnia at night" was added.

PAIN-G
- "Co-analgesics for neuropathic pain (antidepressants, anticonvulsants, and topical agents)" is new to the guidelines.

PAIN-K
- "If needed, consider short term use of ketorolac, 15-30 mg IV every 6 hr for maximum of 5 days" is a new bullet.
- Patients at high risk for "cardiac toxicities: history of cardiovascular disease or at high risk for cardiovascular disease" was added.
- For treatment of GI toxicities: "If patient develops gastric upset or nausea" and "If patient develops gastrointestinal peptic ulcer or gastrointestinal hemorrhage, discontinue NSAID" were added.
- For treatment of cardiac toxicities, "discontinue NSAID if hypertension develops or worsens."
- Footnote 1 is new to the page.

PAIN-L
- "Pain Speciality Consultations" is new to the guidelines.

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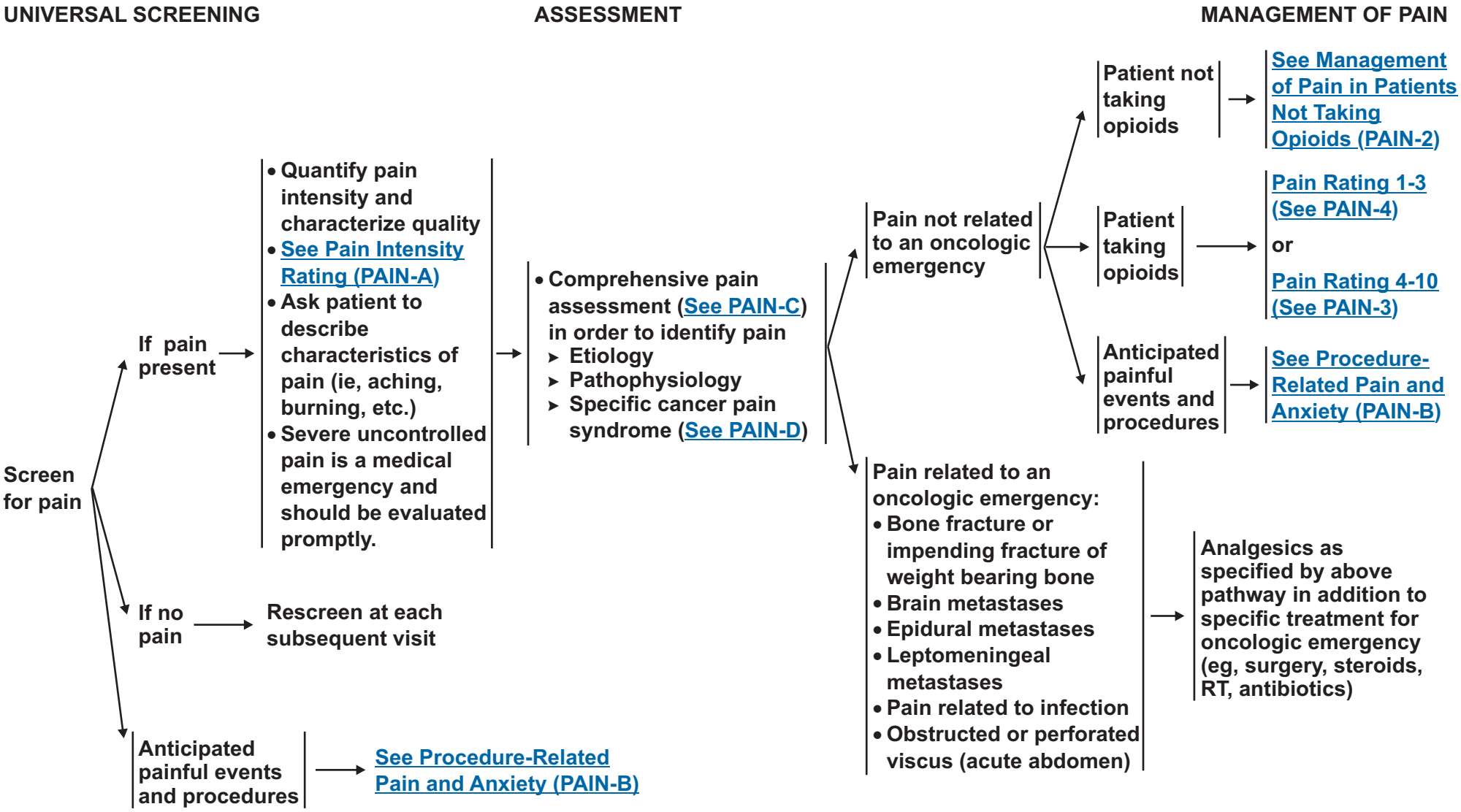
Adult Cancer Pain

Guidelines Index
Cancer Pain TOC
MS, References



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Adult Cancer Pain

To quantify pain intensity, See Pain Intensity Rating (PAIN-A)

MANAGEMENT OF PAIN IN PATIENTS NOT TAKING OPIOIDS

Severe Pain 7-10 →

- Rapidly titrate short-acting opioid (See PAIN-E)
  - ▸ Begin bowel regimen (See PAIN-F)
- Recognize and treat opioid side effects (See PAIN-F)
- Consider adding co-analgesics (See PAIN-G) for specific pain syndrome (See PAIN-D)
- Provide psychosocial support (See PAIN-H)
- Provide patient and family education (See PAIN-I)
- Optimize nonpharmacologic interventions (See PAIN-J)

→ See Response to Severe, Moderate or Increased Pain with Short-Acting Opioids (PAIN-3) → Reevaluate within 24 h to meet patient goals for comfort and function

Moderate Pain 4-6 →

- Titrate short-acting opioid (See PAIN-E)
  - ▸ Begin bowel regimen (See PAIN-F)
- Recognize and treat opioid side effects (See PAIN-F)
- Consider adding co-analgesics (See PAIN-G) for specific pain syndrome (See PAIN-D)
- Provide psychosocial support (See PAIN-H)
- Provide patient and family education (See PAIN-I)
- Optimize nonpharmacologic interventions (See PAIN-J)

→ See Response to Severe, Moderate or Increased Pain with Short-Acting Opioids (PAIN-3) → Reevaluate within 24-48 h to meet patient goals for comfort and function

→ See Subsequent Treatment for Pain (PAIN-4)

Mild Pain 1-3 →

- Consider NSAID or acetaminophen without opioid if patient is not on analgesics (See PAIN-K)
  or
- Consider titrating short-acting opioid (See PAIN-E)
  - ▸ Begin bowel regimen (See PAIN-F)
- Recognize and treat side effects (See PAIN-F)
- Consider adding co-analgesics (See PAIN-G) for specific pain syndrome (See PAIN-D)
- Provide psychosocial support (See PAIN-H)
- Provide patient and family education (See PAIN-I)
- Optimize nonpharmacologic interventions (See PAIN-J)

→ Reevaluate pain at each contact and as needed to meet patient goals for comfort and function → See Ongoing Care (PAIN-5)

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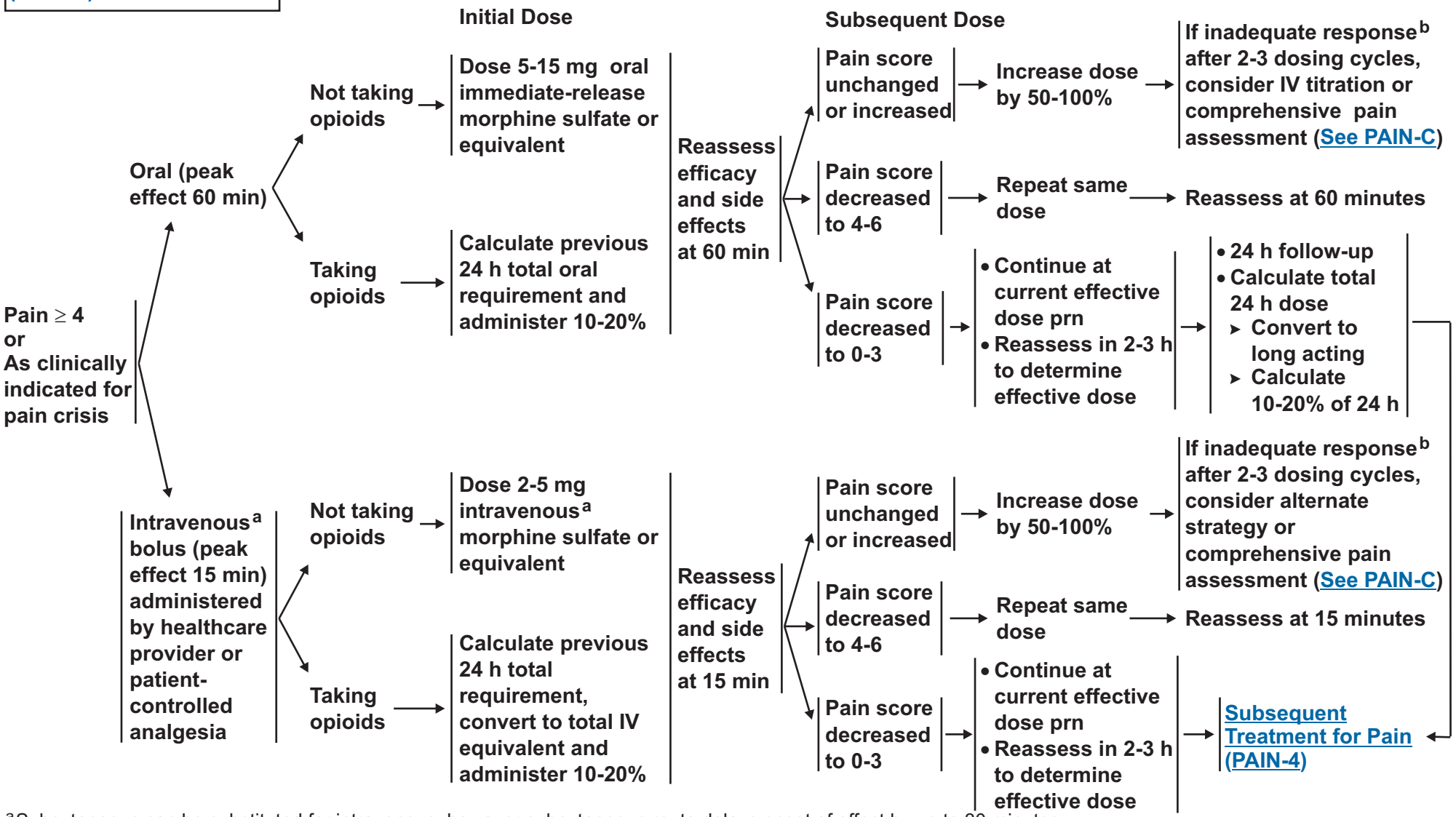
Adult Cancer Pain

To quantify pain intensity, See Pain Intensity Rating (PAIN-A)

RESPONSE TO SEVERE, MODERATE, OR INCREASED PAIN WITH SHORT-ACTING OPIOIDS

Monitor for acute and chronic adverse effects. (See Management of Opioid Side Effects PAIN-F)



[a] Subcutaneous can be substituted for intravenous, however subcutaneous route delays onset of effect by up to 30 minutes.

[b] Inadequate response includes insufficient pain relief as well as the presence of adverse effects due to analgesics.

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To quantify pain intensity, See Pain Intensity Rating (PAIN-A)

SUBSEQUENT TREATMENT FOR PAIN

- Consider conversion to sustained-release agent with rescue medications as appropriate (See PAIN-E)
- Reassess and modify regimen to minimize side effects (See PAIN-F)
- Co-analgesics as indicated (See PAIN-G)
- Provide psychosocial support (See PAIN-H)
- Provide patient and family education (See PAIN-I)
- Provide written pain plan (See PAIN-I)

Severe Pain 7-10 →
- Reevaluate opioid titration (See PAIN-E)
- Reevaluate working diagnosis (See PAIN-C)
- Consider specific pain syndrome problems (See PAIN-D)
- Consider pain specialty consultation (See PAIN-L)
- Reevaluate co-analgesics as indicated (PAIN-G)

Moderate Pain 4-6 →
- Continue opioid titration (See PAIN-E)
- Consider specific pain syndrome problems (See PAIN-D)
- Consider pain specialty consultation (See PAIN-L)
- Continue co-analgesic titration (PAIN-G)

Mild Pain 1-3 → Reevaluate pain at each contact and as needed to meet patient goals for comfort and function → See Ongoing Care (PAIN-5)

→ See Response to Severe, Moderate or Increased Pain with Short-Acting Opioids (PAIN-3)

See Universal Screening and Assessment (PAIN-1)

See Nonpharmacologic Interventions (PAIN-J) and Interventional Strategies (PAIN-M)

→ Reevaluate within 24 h

→ Reevaluate within 24-48 h

Patient goals/ expectations NOT achieved:
- Comfort
- Function

Patient goals/ expectations ACHIEVED:
- Comfort
- Function

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ONGOING CARE

Clinician issues/responsibilities

- Routine follow-up
  - Assess pain during each outpatient contact or at least each day for inpatients
    - Patient condition
    - Institutional standards
    - Regulatory requirements
- Provide written follow-up pain plan, including prescribed medications (See PAIN-I)
- Ensure adequate access to prescribed medications
- Instruct the patient on the importance of the following:
  - Adherence to medication plan
  - Maintain clinic appointments
  - Contact clinician if pain worsens or side effects inadequately controlled
  - Follow documented plan (See PAIN-I)
- Process realistic goals, revise and review
- Address system barriers
  - Social services
- Maintain communication and coordinate care with pain specialist and relevant providers
- On-call/prn availability

Goals of treatment ACHIEVED:
- Comfort
- Function

→ Continue routine follow-up

Goals of treatment NOT achieved:
- Comfort
- Function

→ See Universal Assessment and Screening (PAIN-1)

Consider Interventional Strategies (PAIN-M)

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PAIN INTENSITY RATING (1 of 2)

Table 1: Numerical Rating Scale

Numerical rating scale:

- **Verbal: "How much pain are you having?" from 0 (no pain) to 10 (worst imaginable pain)**
- **Written: "Circle the number that describes how much pain you are having."**

0 1 2 3 4 5 6 7 8 9 10
No pain — Worst imaginable pain

Categorical scale:

"How much pain are you having?"

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. The faces show more and more pain (point to each face from left to right) up to this one (point to the right-most face)- it shows very much pain. Point to the face that show how much you hurt (right now)."

See Pain Assessment in the Nonverbal Patient on PAIN-A 2 of 2

[1]Hicks CL, von Baeyer CL, Spafford P, et al. The Faces Pain Scale - Revised: toward a common metric in pediatric pain measurement. Pain 2001;93:173-183.

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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 clinicians may find useful in caring for such 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 multi-faceted 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://www.cityofhope.org/prc/pain_assessment.asp. These tools are in varying stages of development and validation and include but are not limited to:**
  - **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 but are not limited to:**
  - **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.**

[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 Management Nursing 2002;3:16-27.
[3]Feldt KS. Checklist of nonverbal pain indicators. Pain Management Nursing 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.

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PROCEDURE-RELATED PAIN and ANXIETY

Events that are expected to cause discomfort to the patient such as diagnostic and therapeutic procedures (eg, IV, arterial line, central line, injection, manipulation, bone marrow aspiration, lumbar puncture, skin biopsy, bone marrow biopsy) as well as transportation/change in position for a patient with a fracture, should merit pre-treatment 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 multi-modal 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.**
  - **Recently developed 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 minutes.**
  - **Subcutaneous administration of lidocaine with a 27 guage needle.**
- **Administration of sedatives/analgesics/general anesthesia by trained personnel.**
- **Additional nonpharmacologic interventions (See PAIN-I)**

Providing all these techniques prior to the procedure is ideal as it allows the patient and their family the time they may need to assimilate all of the information, ask questions, and master the techniques while reducing anticipatory anxiety.

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Adult Cancer Pain

COMPREHENSIVE PAIN ASSESSMENT

Patient's self report of pain is the standard of care. If the patient is unable to speak normally, an alternative method to obtain pain rating and response should be utilized (See PAIN-A 2 of 2).

- **Pain Experience**
  - **Location, referral pattern, radiation of pain(s)**
  - **Intensity See Pain Intensity Rating (PAIN-A)**
    - **At rest**
    - **With movement**
  - **Interference with activities See Impact of Pain Measurement (PAIN-C 2 of 2)**
    - **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**
  - **Associated symptoms**
  - **Current pain management plan, both pharmacologic and non-pharmacologic. If medications are used, determine**
    - **What medication(s), 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 of pain for patient and family**
    - **Patient and family knowledge and beliefs surrounding pain and pain medications**
    - **Cultural beliefs toward pain**
    - **Spiritual or religious considerations**
    - **Patient goals and expectations regarding pain management**
- **Psychosocial**
  - **Patient distress See NCCN Distress Management Guidelines**
  - **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 factors, 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**
  - **Pre-existing chronic pain**
- **Physical examination**
- **Relevant laboratory and imaging studies**
- **The endpoint 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 or procedures**
    - **Coincidental or noncancer**
  - **Pathophysiology**
    - **Nociceptive**
    - **Neuropathic**

Return to Initial Screening (PAIN-1)

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IMPACT OF PAIN MEASUREMENT[1,2,3]

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

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

[1] Cleeland CS, Nakamura Y, Mendoza 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] For the complete Brief Pain Inventory assessment tool, see http://www.mdanderson.org/departments/PRG/

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CANCER PAIN SYNDROMES

Pain associated with inflammation - Trial of NSAIDs or glucocorticoids

Bone pain without oncologic emergency:

- NSAIDs and titrate analgesic to effect See Nonsteroidal Anti-inflammatory Drugs (NSAID) and Acetaminophen Prescribing (PAIN-K)
- Local bone pain: consider local radiation therapy or nerve block (eg, rib pain)
- Diffuse bone pain: consider trial of bisphosphonates, hormonal or chemotherapy for responsive tumors, glucocorticoids and/or systemic administration of radioisotopes in selected patients
- Consider physical medicine evaluation See Pain Specialty Consultations (PAIN-L)
- For resistant pain, consider additional treatment modality including anesthetic procedure (nerve blocks, spinal opioids and anesthetics), radiation therapy, orthopedic, or neurosurgical approaches

Nerve compression or inflammation - Trial of glucocorticoids

Neuropathic pain:

- Trial of anticonvulsant: start with low dose and increase every 3-5 days if tolerated or lengthen interval up to 14 days (eg, gabapentin, 100-1,200 mg tid; carbamazepine, 100-400 mg bid; pregabalin 100-600 mg/d divided in 2-3 doses, or other anticonvulsants and/or
- Trial of antidepressant: start with low dose and increase every 3-5 days if tolerated or lengthen interval up to 14 days (eg, 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
- Consider topical agents (eg, capsaicin and local anesthetics including lidocaine patch)
- If results are not optimal after a 2-3 week trial at a reasonable dose, consider referral to a pain service or pain expert, or to an anesthesiologist/neurosurgeon for an appropriate procedure See Interventional Strategies (PAIN-M)

Painful lesions that are likely to respond to antineoplastic therapies:

- Consider trial of radiation, hormones, or chemotherapy

For severe refractory pain or imminently dying See NCCN Palliative Care Guideline

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OPIOID PRINCIPLES, PRESCRIBING, TITRATION, AND MAINTENANCE (1 of 3)

I. GENERAL PRINCIPLES

- The appropriate dose is the dose that relieves the patient's pain throughout the dosing interval without causing unmanageable side effects.
- Calculate dosage increase based upon 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 Response to Severe, Moderate or Increased Pain with Short-Acting Opioids (PAIN-3).
- Switch from fixed-combination opioids to single-entity opioids when nonopioid maximum dose is reached, eg, acetaminophen dose > 4000 mg/d.
- 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.
- Equilibrium is achieved in about 5 half lives.
- To convert from one opioid to another:
  1. Total the amount of current opioid(s) taken in a 24-hour period that effectively controls pain.
  2. Calculate the equianalgesic dose of the new opioid. See Oral And Parenteral Opioid Equivalences and Relative Potency of Drugs as Compared with Morphine Based on Single Dose Studies (PAIN-E 2 of 3).
  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 hours, 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, divide the total daily dose of new opioid needed by the number of doses per day to determine the individual dose (eg, 6 doses for regular PO morphine every 4 hrs; 2 doses for controlled release morphine every 12 hours).

II. 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.
- Consider converting from short-acting opioids to extended release opioids for control of chronic persistent pain when 24 h opioid requirement is stable.
- Provide rescue doses of short-acting opioids for pain not relieved by sustained release opioids including breakthrough pain or acute exacerbations of pain, activity, or position related pain or pain at the end of dosing interval:
  - Use short-acting form of sustained release opioid whenever possible
  - Allow immediate-release rescue doses of 10% to 20% of 24-h oral dose (mg) every 1 h prn
  - Consider transmucosal lozenge or buccal tablet fentanyl 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. Initiate with lowest dose and titrate to effect.
- Increase dose of sustained 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.

OPIOID PRINCIPLES, PRESCRIBING AND TITRATION, AND MAINTENANCE continued on next page

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OPIOID PRINCIPLES, PRESCRIBING, TITRATION, AND MAINTENANCE (2 of 3)

III. ORAL AND PARENTERAL OPIOID EQUIVALENCES AND RELATIVE POTENCY OF DRUGS AS COMPARED WITH MORPHINE BASED ON SINGLE DOSE STUDIES

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

Not Recommended

Meperidine[8]

Propoxyphene[8]

Partial agonists (buprenorphine)[9]

Mixed agonist-antagonist (pentazacine, nalbuphine, butorphanol, dezocine)[9]

Special Note: Partial agonists and 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 the narcotic dependent patient.

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

[2] Available in transdermal system for sustained dosing (see instructions on PAIN-E 3 of 3) and oral transmucosal or buccal systems for breakthrough pain.

[3] 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.

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

[5] With higher doses of morphine, the oral conversion ratio of morphine to methadone may be closer to 10 to 1 rather that 3 to 2. PRACTITIONERS ARE ADVISED TO CONSULT WITH A PAIN SPECIALIST IF THEY ARE UNFAMILIAR WITH METHADONE PRESCRIBING.

[6] Conversion factor listed for chronic dosing. Avoid using morphine in renal failure due to accumulation of morphine-6-glucuronide metabolite.

[7] 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 100 mg four times a day, tramadol is less potent than other opioid analgesics such as morphine.

[8] Not recommended for long term or high dose use because of CNS toxic metabolites (normeperidine, norpropoxyphene).

[9] Partial agonists and mixed agonist-antagonists may produce withdrawal in opioid-dependent patients.

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OPIOID PRINCIPLES, PRESCRIBING AND TITRATION continued on next page

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

IV. CONVERT TO TRANSDERMAL FENTANYL

1. Pain should be relatively well-controlled on a short acting opioid prior to initiating the patch. Patches are NOT recommended for unstable pain requiring frequent dose changes.
2. Determine 24 hour parenteral morphine equivalent requirement using the table Oral And Parenteral Opioid Equivalences and Relative Potency of Drugs as Compared with Morphine Based on Single Dose Studies (PAIN-E 2 of 3).
3. Select the mg per hour dose according to the ranges listed below. For dosage requirements > 100 mg/hr multiple patches can be used.
4. The patch duration is usually 72 hours. Duration in some may be only 48 hours; fever and heat from heat lamps, electric blankets, etc. may accelerate drug release and should be avoided.
5. An as needed (prn) dose of morphine or other short-acting opioid should be prescribed and may be needed particularly during the first 8-24 hours. Increase the patch dosage based on the average amount of additional opioid required over the 72 hour period. Continue breakthrough medication once the patch dose is stabilized.

Oral Morphine (mg/24 hrs)	Parenteral Morphine (mg/24 hrs)	Transdermal Fentanyl Equivelant (mcg/hr)
25-65	8-22	25
65-115	23-37	50
116-150	38-52	75
151-200	53-67	100
201-225	68-82	125
226-300	83-100	150

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

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MANAGEMENT OF OPIOID SIDE EFFECTS (1 of 3)

Principles of Management of Opioid Side Effects

- Tolerance generally develops, except with constipation. Maximize non-opioid 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. Symptoms need to be evaluated as contributing factors.

Constipation

- Preventive measures
  - Prophylactic medications
    - Stimulant laxative + stool softener (eg, senna with docusate, 2 tablets every morning; maximum 8-12 tablets per day).
    - Increase dose of laxative when increasing dose of opioids
  - Increase fluids
  - Increase dietary fiber
  - Exercise, if feasible
- If constipation develops
  - Assess for cause and severity of constipation
  - Rule out obstruction
  - Treat other causes
  - Titrate as needed with goal of one non-forced bowel movement every 1-2 d.
  - Consider co-analgesic to allow reduction of the opioid dose
- If constipation persists
  - Reassess for cause and severity of constipation
  - 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 prn, or magnesium citrate, 8 oz PO daily, polyethelene glycol (1 capful/8 oz water PO bid)
  - Fleet, saline, or tap water enema
  - Consider use of a prokinetic agent (eg, metoclopramide, 10-20 mg PO qid)
  - Consider neuraxial analgesics or neuroablative techniques to potentially reduce opioid dose

MANAGEMENT OF OPIOID SIDE EFFECTS continued on next page

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MANAGEMENT OF OPIOID SIDE EFFECTS (2 of 3)

Nausea

- Preventive measures
  - Make antiemetics available with opioid prescription
- If nausea develops
  - Assess for other causes of nausea (eg, constipation, central nervous system pathology, chemotherapy, radiation therapy, hypercalcemia)
  - Consider prochlorperazine, 10 mg PO every 6 h prn; thiethylperazine, 10 mg PO every 6 h prn; haloperidol, 0.5-1.0 mg PO every 6-8 h; or metoclopramide, 10-20 mg PO every 6 h prn
  - If nausea persists despite prn regimen, administer antiemetics around the clock for 1 wk, then change to prn
  - Consider adding a serotonin antagonist (eg, granisetron, 2 mg PO daily, or ondansetron, 8 mg PO tid, or dolasetron 100-200 mg PO, or palonosetron 300 mcg/kg IV). Use with caution as constipation is a side effect.
- 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

Pruritus

- Assess for other causes (other medications, etc.)
- Consider antihistamines such as diphenhydramine, 25-50 mg/kg/dose IV or PO every 6 h, or promethazine, 12.5-25 mg/kg/dose IV or PO every 6 h, or nalbuphine, 0.5-1.0 mg/kg/dose IV every 6-8 h prn
- Consider changing to another opioid if symptomatic management has failed.
- 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.

MANAGEMENT OF OPIOID SIDE EFFECTS continued on next page

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MANAGEMENT OF OPIOID SIDE EFFECTS (3 of 3)

Delirium

- Assess for other causes of delirium (eg, hypercalcemia, CNS, metastases, other psychoactive medications, etc.)
- Consider changing the opioid
- Consider nonopioid analgesic to allow reduction of the opioid dose

Consider haloperidol, 0.5-2 mg PO every 4-6 h or alternative neuroleptic agents

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 minutes 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 (eg, 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; methylphenidate, 5-10 mg 1-3 times per day; 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

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CO-ANALGESICS FOR NEUROPATHIC PAIN (ANTIDEPRESSANTS, ANTICONVULSANTS, AND TOPICAL AGENTS)

PRINCIPLES OF CO-ANALGESIC USE

- Antidepressant and anticonvulsants are first-line co-analgesics 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 the co-analgesics in the cancer population is still often guided solely by anecdotal experience or guidelines derived from data in non-malignant 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 co-analgesics may vary among types of neuropathic pain and individual patients.
- Drug selection may be influenced by the presence of certain non-pain symptoms and co-morbidities. 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 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.

See Examples of Co-Analgesics Use for Neuropathic Pain (PAIN-G 2 of 2)

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CO-ANALGESICS FOR NEUROPATHIC PAIN (ANTIDEPRESSANTS, ANTICONVULSANTS, AND TOPICAL AGENTS)

EXAMPLES OF CO-ANALGESIC USE

- Trial of antidepressant: Analgesic effectiveness not dependent on their 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 co-analgesic in combination with an opioid for the neuropathic component of the pain.
  - Tricyclic antidepressants (eg, amitriptyline, imipramine, nortriptyline, desipramine)
    - Start with low dose and increase every 3- 5 days if tolerated. (eg, nortriptyline and desipramine starting dose 10- 25 mg nightly increase to 50- 150 mg nightly. Watch for anticholinergic adverse effects such as sedation, dryness of mouth, urinary hesitancy.)
  - Others examples:
    - Venlafaxine- Starting dose 50- 75 mg daily, increase to 75- 225 mg daily
    - Bupropion-Starting dose 100- 150 mg daily increase to 140-450 mg daily
    - Duloxetine 60 mg daily.

- Trial of anticonvulsants: Frequently used as a co-analgesic in combination with an opioid for the neuropathic component of the pain.
  - Anticonvulsants examples:
    - Gabapentin- Starting dose 100- 300 mg nightly, increase to 900- 3,600 mg daily in divided doses BID- TID. Dose increments of 50-100% every 3 days. Slower titration for the elderly, medically frail or those with renal insufficiency.
    - Pregabalin- Starting dose 50 mg TID, increase to 100 mg TID. Lower doses in elderly and those with renal insufficiency. Pregabalin more efficiently absorbed through the GI tract than gabapentin. Titration to the analgesic dose requires just 2 or 3 steps, rather than the multiple steps frequently required with gabapentin.
    - Lamotrigine- Starting dose 25- 50 mg daily, increase to 200- 400 mg daily in divided doses BID.

- Trial of topical agents: Act locally and may be used as a co-analgesic 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.
    - Capsaicin- Extract from chili peppers and poorly tolerated because of the burning sensation. Must be used 3-4 times a day and may take several weeks to show effect.

- 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.

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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.

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 (PAIN-I)

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Adult Cancer Pain

PATIENT AND FAMILY EDUCATION

- **Messages to be conveyed to patient and family**
  - **Relief of pain is important and there is no benefit to suffering with pain.**
  - **Pain can usually be well controlled with medications taken by mouth.**
  - **If these medications do not work, many other options are available.**
  - **Morphine and morphine-like medications are often used to relieve pain.**
    - **When these drugs are used to treat cancer pain, addiction is rarely a problem.**
    - **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.**
    - **If you take these medications now, they will still work later.**
  - **Communication with the doctors and nurses is critical.**
    - **Doctors and nurses cannot tell how much pain you have unless you tell them.**
    - **Doctors and nurses 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 doctor or nurse 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 treatment for pain and side effects. Inform patient of right to expect pain treatment 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 professional 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.**

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NONPHARMACOLOGIC INTERVENTIONS

Major indication for referral is:

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**
  - **Massage**
  - **Heat and/or ice**
  - **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 Distress Management Guidelines**
  - **Consider pain and palliative care specialty consultation** **See NCCN Palliative Care Guidelines**
    - **Complex management**
    - **Diagnosis and treatment of underlying condition**
  - **Spiritual care**

See Interventional Strategies (PAIN-M)

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NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAID) AND ACETAMINOPHEN PRESCRIBING

- **Use NSAIDs with caution in patients at high risk for renal, GI, or cardiac toxicities.**
- **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 qid (daily maximum = 3,200 mg)**
  - **If needed, consider short term use of ketorolac, 15-30 mg IV every 6 hr 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 three divided doses**
    - **Salsalate, 2-3 g/d in two or three divided doses**
    - **Selective COX-2 inhibitor**
  - **Other nonopioid analgesics**
    - **Acetaminophen, 650 mg every 4 h or 1 gm every 6 h (daily maximum 4 g/d) (use caution with combination opioid-acetaminophen products to prevent excess acetaminophen ingestion)**
  - **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**
    - **GI toxicities: age > 60 y, history of peptic ulcer disease or excess alcohol use, major organ dysfunction, high-dose NSAIDs given for long periods**
    - **Cardiac toxicities: history of cardiovascular disease or at risk for cardiovascular disease[1]**
  - **Monitoring for toxicities**
    - **Baseline blood pressure, BUN, creatinine, CBC, and fecal occult blood**
    - **Repeat every 3 mo to ensure stability**
  - **Treatment of toxicities:**
    - **Renal toxicities: discontinue NSAID if BUN or creatinine doubles or if hypertension develops or worsens**
    - **GI toxicities: if patient develops gastric upset or nausea, consider discontinuing NSAID or changing to selective COX-2 inhibitor. Consider adding antacids, H_2 receptor antagonists, misoprostol, omeprazole. If patient develops gastrointestinal peptic ulcer or gastrointestinal hemorrhage, discontinue NSAID.**
    - **Cardiac toxicities: discontinue NSAID if hypertension develops or worsens**
- **Further NSAID decisions:**
  - **If two 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**
  - **COX-2 inhibitors are associated with lower incidence of GI side effects and do not inhibit platelet aggregation, however, they have not been demonstrated to have reduced renal side effects.**
  - **Toxicity of anti-cancer treatment may increase the risk profile of anti-inflammatory treatment**

[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(12):1634-42.

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PAIN SPECIALITY CONSULTATION

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.

- 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

- Psychological supportive services, psychologists, counselors
  - Cognitive modalities
    - Imagery/hypnosis
    - Distraction training
    - Relaxation training
    - Active coping training
    - Graded task assignments, setting goals, pacing and prioritizing
    - Cognitive behavioral training
  - Other modalities
    - Acupuncture/acupressure
    - Therapeutic Touch/Reiki

- Substance abuse and diversion consultation if questions/concerns about medication misuse or diversion
  - Assist with contracting, limit setting, single provider/ pharmacy
  - Communicate regarding need to accomplish pain relief, but avoid misuse/diversion

- Depression/Distress consultation See NCCN Distress Management Guidelines

- Consider pain and palliative care specialty consultation See NCCN Palliative Care Guidelines
  - Consider interventional strategies (See PAIN-M)
  - Complex management
  - Diagnosis and treatment of underlying condition

- Spiritual care- determine importance to patient/family and current availability of support

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Adult Cancer Pain

Guidelines Index
Cancer Pain TOC
MS, References

INTERVENTIONAL STRATEGIES

Interventional consultation

- **Major indications for referral:**
  - **Pain likely to be relieved with nerve block (eg, 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)**

Interventional approaches are appropriate

- **Commonly used 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 post-operative pain**
    - **Intrathecal: easy to internalize to implanted pump; for infusions of opioids, local anesthetics, clonidine, and ziconotide**
    - **Regional plexus: for infusions of local anesthetics, 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 (ie, peripheral neuropathy)**

Interventional approaches are appropriate
- **Nerve blocks**
- **Neuroaxial analgesia**
- **Percutaneous vertebroplasty/ kyphoplasty**
- **Neuroablative**
- **Neurostimulation**

→ **Evaluate which pain site can be relieved; Will interventional technique provide tangible benefit?**

- **Yes →** **Assess results of interventional technique**
- **No →** **Reassess therapeutic plan interventional approaches not indicated at this time**

Interventional approaches are not appropriate[1] → **Reassess therapeutic plan interventional approaches not indicated at this time**

[1] Advise interventionalist regarding risk factors such as lack of technical expertise, infection, coagulopathy, limited or lengthy life expectancy, distorted anatomy, patient unwillingness, medications that increase risk for bleeding (eg, bevacizumab).

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Manuscript

NCCN Categories of Evidence and Consensus

Category 1: Based on high-level evidence and uniform consensus.

Category 2A: Based on lower-level evidence including clinical experience and uniform consensus.

Category 2B: Based on lower-level evidence including clinical experience and nonuniform consensus (but no major disagreement).

Category 3: Based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

Pain is one of the most common symptoms associated with cancer. Pain is defined as "a sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[1] Cancer pain or cancer-related pain distinguishes pain experienced by cancer patients from that 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] In addition, this is one of the symptoms patients fear most. Unrelieved pain denies them comfort and greatly affects their activities, motivation, interactions with family and friends, and overall quality of life.

The importance of relieving pain and the availability 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 World Health Organization (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, the patient should be escalated to a "weak opioid," such as codeine, and subsequently 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 three-tiered "cancer pain ladder" suggests.

This clinical practice guideline, developed by the National Comprehensive Cancer Network (NCCN) Adult Cancer Pain panel, is unique in several important ways. First, it contains several required components:

- Pain intensity must be quantified, as 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; and
- Specific educational material must be provided to the patient.

Second, the guidelines acknowledge the range of complex decisions faced in caring for these patients. As a result, they provide dosing guidelines for nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and co-analgesics. They also provide specific suggestions for the escalation of opioid dosage, management of opioid adverse effects,

and when and how to proceed to other techniques for the management of cancer pain.

Pathophysiologic Classification

Different types of pain occur in cancer patients. A number of 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 from each other when deciding what therapy to use. Therapeutic strategy depends on the pain pathophysiology, which is determined by patient examination and evaluation. There are two predominant mechanisms of pain 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 further be divided into somatic pain and visceral pain.[12] Pain described as sharp, well localized, throbbing, and pressure-like is somatic nociceptive pain. It occurs often after surgical procedures or from bone metastasis. Visceral nociceptive pain is often 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 due to spinal stenosis or diabetic neuropathy, or as an adverse effect of chemotherapy (eg, 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. This algorithm begins with the premise that all patients with cancer should be screened for pain (PAIN-1) 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. Since pain is inherently subjective, patient's self-report to pain is the current standard of care for assessment. Intensity of pain should be quantified using a 0-10 numerical rating scale, a categorical scale, or a pictorial scale (e.g., The Faces Pain Rating Scale) (PAIN-A 1 of 2).[13-15] The Faces Pain Rating Scale may be successful with patients who have difficulty with other scales, for example, children, the elderly, and patients with language or cultural differences or other communication barriers. If the patient is non-verbal an alternative method to obtain pain rating and pain assessment is used (PAIN-A, 2 of 2).

In addition to pain intensity, the patient should be asked to describe the characteristics of their pain (i.e., aching, burning etc.). If the patient has no pain, re-screening 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 above 0, a comprehensive pain assessment is initiated (PAIN-C). The comprehensive pain assessment should focus on the type and quality of pain, pain history (such as onset, duration, course, etc.), pain intensity (i.e., pain experienced at rest; with movement; interference with activities); location, referral pattern, radiation of pain; the associated factors that exacerbate or relieve the pain, current pain management plan; patient's response to current therapy; prior pain therapies; important psychosocial factors (such as patient distress, family and other support, psychiatric history, risk factors for aberrant use of pain medication, risk factors for

undertreatment of pain, etc); other special issues relating to pain (such as meaning of pain for patient and family, cultural beliefs toward pain, spiritual or religious considerations). Finally, the patient's goals and expectations of pain management should be discussed, including level of comfort and function (PAIN-C).

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, it is inappropriate to provide only opioids to a patient suffering pain from impending spinal cord compression. 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 endpoint of comprehensive pain assessment is to diagnose the etiology and pathophysiology (somatic, visceral, or neuropathic) of the pain and individualize pain treatment plan based on mutually developed goals.

Management of Pain

For management of cancer related pain in adults (PAIN-2), the algorithm distinguishes three levels of pain intensity, based on a 0-10 numerical rating scale (with 10 being the worst pain): severe pain (7-10); moderate pain (4-6); and mild pain (1-3).[12,13]

It is important to separate pain related to an oncologic emergency from pain not related to an oncologic emergency (such as pain due bone fracture or impending fracture of weight bearing bone; brain, epidural, or leptomeningeal metastases; pain related to infection; obstructed or perforated viscus).

In addition, the algorithm distinguishes pain not related to oncologic emergencies in patients not taking opioids from patients who have previously or are currently taking opioids for cancer pain, and also anticipated procedure related pain and anxiety.

Management of pain not related to an oncologic emergency in patients not taking opioids

Patients not taking opioids experiencing severe (i.e. pain intensity rating 7-10) should receive rapid titration of short-acting opioids, along with a bowel regimen, and nonopioid analgesics as indicated. Care providers should also provide psychosocial support and begin educational activities. Psychosocial support is needed to ensure that 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) receive appropriate aid (PAIN-H). The patient and the family must be educated regarding pain management and issues related to it. An individual approach should be used to determine opioid starting dose, frequency, and titration in order to achieve a balance between pain relief and medication adverse effects. Details of prophylactic bowel regimens and antiemetics are provided on page PAIN-F; 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.[16] Although pain intensity ratings will be obtained frequently to judge opioid dose increases, a formal re-evaluation is mandated within 24 hours for severe pain. If the pain at this time is unchanged or increased, the working diagnosis must be re-evaluated. In addition, the adequacy of opioid titration must be re-evaluated by calculating and comparing the total parenteral morphine equivalents administered each day.

For patients not taking opioids, whose pain intensity rating is less than 7 (i.e. 4-6) at presentation, the pathways are quite similar to those for pain intensity 7-10 (above). The main differences include treatment beginning with slower titration of short-acting opioids and the option to perform the formal pain intensity re-evaluation less frequently (within 24-48 hours)

Patients not taking opioids and experiencing mild pain intensity (1-3) should receive treatment with NSAID or acetaminophen or treatment with slower titration of short-acting opioids. Re-evaluation of pain should be performed at each visit or as needed (PAIN-2).

Addition of co-analgesic for specific pain syndromes should be considered for all groups of patients (PAIN- G). Co-analgesics are drugs used to enhance the effects of opioids or NSAIDs.[17] Also, optimize nonpharmacologic interventions (PAIN-J). Co-analgesics belong to diverse classes of drugs and are commonly used to help manage bone pain, neuropathic pain, visceral pain and to reduce systemic opioid requirement. Acetaminophen,[18] NSAIDs including selective COX-2 inhibitors, tricyclic anti-depressants (TCA), anti-convulsant drugs, bisphosphonates, and hormonal therapy are among the most commonly used medications. The NSAID and acetaminophen prescribing guidelines are presented on page PAIN-K. History of peptic ulcer disease, advanced age (>60 years old), male gender, and concurrent corticosteroid therapy should be considered before NSAIDs administration to prevent upper gastrointestinal tract bleeding and perforation. Well-tolerated proton pump inhibitors are recommended to prevent gastrointestinal side-effects induced by NSAIDs. NSAIDs should be prescribed with caution in patients older than 60 years of age or in those having compromised fluid status, renal insufficiency, concomitant administration of other nephrotoxic drugs, and renally excreted chemotherapy in order to prevent renal toxicities.

Selecting an Appropriate Opioid and Route of Administration

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 illness(es). Morphine, hydromorphone, fentanyl, oxycodone are the opioids commonly used in the United States. 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, known as opioid rotation, is now a widely accepted technique used to address poorly responsive pain.[19] Relative effectiveness is important to consider when switching between oral and parenteral routes to avoid subsequent overdosing or underdosing. Equianalgesic dose ratios, opioid titration and maintenance are shown in the algorithm (PAIN-E). For example, the morphine/hydromorphone ratio is about 6 for parenteral dose administration (10 mg of morphine equal to 1.5 mg of hydromorphone), which should be considered during opioid rotation.

Individual variations in methadone pharmocokinetics (long half-life ranging from 8 to more than 120 hours) make its usage very difficult in cancer patients.[20] Because of its long half-life, high potency, and inter-individual 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.

Propoxyphene, meperidine, mixed agonist-antagonists, partial agonists, and placebos are not recommended for cancer patients. Meperidine and propoxyphene are especially contraindicated in patients with impaired renal function or dehydration, because accumulation of renally-cleared metabolites may result in neurotoxicity or cardiac

arrhythmias.[21] Pure agonists (such as codeine, oxycodone, oxymorphone and fentanyl) are the most commonly used medications in the management of cancer pain. The short half-life opioid agonists (morphine, hydromorphone, fentanyl, and oxycodone) are preferred, because they can be more easily titrated than the long half-life analgesics (methadone and levorphanol).[22]

The following methods of ongoing analgesic administration are widely used in clinical practice: “around the clock”, “as needed”, and “patient-controlled analgesia”. “Around the clock” dosing is provided to chronic pain patients for continuous pain relief. A “rescue dose” should be provided as a subsequent treatment for patients receiving these controlled-release medications. Rescue doses of short-acting opioids should be provided for pain that is not relieved by sustained/controlled release opioids (PAIN-E, 3 of 3). 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 escalation is required. The patient-controlled analgesia (PCA) technique allows a patient to control a device that delivers a bolus of analgesic “on demand” (according to and limited by parameters set by a physician).

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.[22-24] 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 (IV) or subcutaneous (SC), is recommended for patients who cannot swallow or absorb opioids enterally.

Initial oral dosage of opioids for patients with pain rating greater than or equal to 4 or for pain crisis depends on prior administration of opioids. An initial oral dose of 5-15 mg of morphine sulfate or equivalent is recommended for patients not already taking opioids. For patients currently on opioid therapy, the previous 24-hour dose and breakthrough dose (10%-20% of 24-hour dose) should be calculated and administered. Reassessment of efficacy and side-effects should be performed every 60 minutes to determine subsequent dose (PAIN-3). Upon reassessment, if the pain score remains unchanged or is increased, opioid dose is increased by 50%-100%. If inadequate response is seen after 2-3 cycles of 50%-100% increased opioid dose, intravenous (IV) titration can be considered or a comprehensive pain assessment is carried out. If the pain score decreases to 4-6, the same dose of opioid is repeated and reassessment is performed at 60 minutes. If the pain score decreases to 0-3, the current effective dose of opioid is administered as per need and subsequent reassessment is performed in 2-3 hours to determine effective dose (PAIN-3).

Initial intravenous loading dose of opioids for patients with pain rating greater than or equal to 4 or for pain crisis also depends on prior administration of opioids. The dose of 2-5 mg of intravenous morphine sulfate or equivalent is recommended for patients not taking opioids (PAIN-5). For patients currently taking opioids, a dose increase of 10% of daily intravenous morphine equivalent is recommended. Reassessment of efficacy and side-effects should be performed every 15 minutes to calculate the subsequent dose of opioids. The subsequent dose of opioids for intravenous administration depends on the pain score after 15-minute reassessment. Upon reassessment if the pain score remains unchanged or is increased, the opioid dose is increased by 50%-100%. If inadequate response is seen after 2-3 cycles, alternate strategies can be considered or comprehensive pain assessment is carried out. If the pain score decreases to 4-6, the same dose of opioid is repeated and reassessment is performed at 15 minutes. If the pain score decreases to 0-3, the current effective dose

of opioid is administered as per need and subsequent reassessment is performed in 2-3 hours to determine effective dose (PAIN-3).

After the initial response and treatment of uncontrolled pain, the patient should have a comprehensive reassessment. If an acceptable level of comfort and function has not been achieved for the patient, the NCCN Adult Cancer Pain panel recommends possible conversion to sustained-release medication with breakthrough dosing, nonopioid analgesics, management of side-effects, interventional procedures, and psychosocial and educational interventions (PAIN-3). The subsequent treatment is based upon the patient's continued pain rating score.

Subsequent follow-up is recommended if the patient goals/expectations are achieved or for patients with mild (1-3) pain after comprehensive reassessment of the initial pharmacologic management (PAIN-4). Routine follow-up should be done during each outpatient contact or at least each day for inpatients 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 (PAIN-I).

Management of Procedure-Related Pain and Anxiety

Procedure-related pain represents an acute short-lived experience which may be accompanied by a great deal of anxiety (PAIN-B). Procedures reported as painful include bone marrow aspirations; lumbar puncture; skin and bone marrow biopsies; intravenous, arterial line, and central line injections. Much of the data available on procedure-related pain come 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, other individual characteristics of the patients such as age, and physical condition. The interventions may be multi-modal and may include pharmacological and/or nonpharmacological 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 carried out only by trained professionals.

Patients usually tolerate procedures better when they know what to expect. Therefore, patients and family members should receive written instructions for managing the pain.

Interventional Strategies

Some patients experience inadequate pain control despite pharmacological therapy or may not tolerate an opioid titration program because of side effects. Some patients may prefer procedural options instead of a chronic medication regimen. Several interventional strategies are available if a patient does not achieve adequate analgesia. Regional infusion of analgesics (epidural, intrathecal, and regional plexus), neuroablative procedures for well-localized pain syndromes (e.g., back pain due to facet or sacro-iliac joint arthropathy; visceral pain due to abdominal or pelvic malignancy), and neurostimulation procedures (i.e., for peripheral neuropathy) have proven successful in pain management (PAIN-M). These techniques have been demonstrated in some cases, to eliminate or significantly reduce the level of pain, and/or may allow a significant decrease in systemic analgesics. 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 for patients who have pain from a variety of anatomical locations (e.g., head and neck, upper and lower extremities, trunk).[25]

Additional Therapies

Additional strategies specific to the pain situations can be considered. Specific recommendations for inflammatory pain, bone pain, nerve compression or inflammation, neuropathic pain, and pain likely to respond to antineoplastic therapies are provided (PAIN-G). Overall, neuropathic pain is less responsive to opioids than pain caused by other pathophysiologies.

Other therapies, including specific non-traditional analgesic drugs, are usually indicated for neuropathic pain syndrome.[26] For example, a patient with neuropathic pain who failed to gain sufficient relief from opioids would be given a trial of an anticonvulsant or tricyclic antidepressant, whereas a patient with pancreatic cancer who was not tolerating opioids or not receiving adequate analgesia would be offered a celiac plexus block.

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

Attention should also be focused on psychosocial support (PAIN-H), providing education to patients and families (PAIN-I), and reducing the side effects of the opioid analgesics. Adverse effects such as constipation; nausea; sedation; Pruritus; myoclonus, and motor and cognitive impairment in cancer patients are fairly common, especially when multiple agents are used.[27-29] Each adverse side effect requires a careful assessment and treatment Proper management is necessary to prevent and reduce analgesic adverse effects (PAIN-F, 3 of 3).[30-35] In addition, continued pain ratings should be obtained and documented in the medical record to ensure that the patient's pain remains under good control and goals of treatment are achieved. In addition, specialty consultations can be helpful in providing interventions to assist with difficult cancer pain problems. The major indication for referral to a specialty service provider is if 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 by establishing individualized goals, then providing specific treatment and education for patients. The specialties include physical/occupational therapy, psychosocial supportive services, or 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 Practice 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.

Disclosures for the NCCN Adult Pain Guidelines Panel

At the beginning of each panel meeting to develop NCCN guidelines, panel members disclosed financial support they have received in the form of research support, advisory committee membership, or speakers' bureau participation. Members of the panel indicated that they have received support from the following: Cephalon, Endo Pharmaceuticals, GlaxoSmithKline, Pfizer, and Wyeth. Some panel members do not accept any support from industry. The panel did not regard any potential conflicts of interest as sufficient reason to disallow participation in panel deliberations by any member.

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