National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Adult Cancer Pain

V.1.2010

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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

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Summary of the Guidelines Updates

Summary of changes in the 2010 version of the Adult Cancer Pain guidelines from the 1.2009 version include:

PAIN-1

- If pain present, last bullet was modified, "Severe uncontrolled pain is a medical emergency and should be *responded to promptly*."
- Assessment, new bullet, "Determine patient goals for comfort, function" was added.
- For "Pain not related to an oncologic emergency," the algorithm has been separated into "opioid naïve patients" and "opioid tolerant patients." The titles of the corresponding pages were modified to reflect this change.
- Footnote a "Opioid naïve includes patients who are not chronically receiving opioid analgesic on a daily basis" was added.
- Footnote b, "Opioid tolerant includes patients who are chronically receiving opioid analgesic on a daily basis" was added.

PAIN-2

- "Management of pain in opioid naïve patients," the management recommendations which are "For ALL levels of pain" were separated in order to clarify the page.
- For Pain 7-10 and Pain 4-6, links to both PAIN-3 for initiating short-acting opioids and PAIN-E for additional details of opioid principles, prescribing, titration, and maintenance were added.

PAIN-3

- Initiating short-acting opioids in opioid naïve patients
  - For both oral and IV dose with pain score decreased to 0-3, the subsequent dose was modified as, "Continue at current effective dose as needed *over initial 24 h*" with a link to "See Subsequent Pain Management and Treatment in Opioid Tolerant Patients-Mild Pain 0-3 (PAIN-5)." Also for management of pain in opioid tolerant patients on PAIN-4.
  - For oral dose, pain score unchanged or increased and pain score decreased to 4-6, "After 2-3 cycles, consider IV titration and/or see PAIN-5 for subsequent management and treatment" was added as a subsequent management strategy. Also for management of pain in opioid tolerant patients on PAIN-4.
  - For IV dose, pain score unchanged or increased and pain score decreased to 4-6, "After 2-3 cycles, see PAIN-5 for subsequent management and treatment" was added for as a subsequent management strategy. Also for management of pain in opioid tolerant patients on PAIN-4.

PAIN-5

- The "subsequent pain management and treatment in opioid tolerant patients" page was reorganized and the following bullets were added:
  - For ALL levels of pain
    - Provide psychosocial support
    - Provide patient and family education
  - For mild pain 0-3
    - Reassess and modify regimen to minimize side effects
    - Co-analgesics as needed
  - Goals of treatment
    - Reevaluate patient's goals of comfort and function at each contact" and options if goals are "achieved" or "not achieved".

PAIN-6

- The first bullet, "Convert to oral medications (if feasible) including extended-release agent with rescue doses (Conversion details, see PAIN-E)" was added.
- The fourth bullet, "Ensure adequate access to prescribed medications" was modified by adding "*especially during transition between sites of care*".

PAIN-A 1 of 2

- The statement regarding the use of the pain intensity ratings scale was modified as, "At minimum, patients should be asked about *"current" pain*, as well as "worst" pain and "usual" pain in the past 24 hours".

PAIN-A 2 of 2

- A bullet regarding the importance of cultural and linguistic assessment was added to the page.

PAIN -B

- "Wound care" was added as an example of a therapeutic procedure.

PAIN-C 1 of 2

- Comprehensive pain assessment, statement "If the patient is unable to speak normally..." was changed to "If the patient is unable to *verbally report pain*...".
- Special issues relating to pain, the following bullets were modified:
  - Meaning *and consequences* of pain for patient and family
  - Cultural beliefs toward pain *and pain expression*
  - Spiritual, religious considerations, *and existential suffering*

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Summary of the Guidelines Updates (continued)

Summary of changes in the 2010 version of the Adult Cancer Pain guidelines from the 1.2009 version include:

PAIN-D

- The title of the page was clarified by adding, "*additional interventions for* cancer pain syndromes".
- A statement, "In general, cancer pain is treated with opioids as indicated on PAIN-2, these interventions are meant to complement management" was added.
- Examples of interventions for "bowel obstruction" were added.

PAIN-E 1 of 7

- General principles:
  - A new principle, "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 PAIN-M" was added.
  - Bullet 4 was modified by adding, "*According to FDA guidelines*, switch from preparations..."
- Principles of opioid maintenance:
  - Second bullet was added, "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".
  - Third bullet,
    - First subbullet was modified as, "When possible, use same opioid for short-acting and extended release forms."
    - Second subbullet, "Ongoing need for repeated rescue doses may indicate a need for adjustment of regularly-scheduled opioid dose" was added.
    - Third subbullet was modified, "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.)*

PAIN-E 2 of 7

- "Partial agonists (buprenorphine)" was removed from the "not recommended" list and from the corresponding footnote 10.
- Footnote 1, "Dosage must be monitored for safe limits as it maybe available in combination with acetylsalicylic acid (ASA) or acetaminophen. Dose listed refers only to opioid portion" is new to the page.
- Footnote 2, "Avoid using codeine or morphine in patients with renal failure due to accumulation of renally-cleared metabolites" is new to the page.
- Footnote 3, "The equianalgesic dose listed only applies to IV fentanyl compared to other IV opioids. For transdermal fentanyl conversion, see PAIN-E 4 of 7" is new to the page.
- Footnote 6 was modified by adding a link, "See Converting from Oral Morphine to Oral Methadone PAIN-E 6 of 7".
- Footnote 8 was changed from "Not recommended for long term or high dose use..." to "Not recommended *for cancer pain management*..."

PAIN-E 3 of 7

- A case example of converting or rotating from one opioid to another opioid was added.

PAIN-E 4 of 7

- The steps to convert or rotate from another opioid to transdermal fentanyl were clarified as:
  1. Determine the 24-h analgesic requirement of current opioid. Table 2 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 per hour 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.
- Special Notes Regarding Transdermal Fentanyl:
  - First bullet, "Use fentanyl patch only in patients tolerant to opioid therapy" was added.
  - Third bullet, was modified by adding, "When converting from *continuous* parenteral *infusion* fentanyl..." and the statement "In some patients, additional dose titration of the fentanyl patch may be necessary" was added.

PAIN-E 5 of 7

- Two case examples of converting or rotating from another opioid to transdermal fentanyl were added.

PAIN-E 6 of 7

- Steps for converting from oral morphine to oral methadone was added with a case example on PAIN-E 7 of 7.

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Summary of the Guidelines Updates (continued)

Summary of changes in the 2010 version of the Adult Cancer Pain guidelines from the 1.2009 version include:

PAIN-F 1 of 3

- Principles of management of opioid side effects:
  - First bullet, "tolerance generally develops" was replaced with "*Opioid side effects generally improve over time...*"
  - Third bullet was modified by adding, "*and side effects may be from other treatments or cancer itself.*"
- If constipation persists, 6th subbullet was modified from, "For patients with advanced illness receiving palliative care, consider methylnaltrexone..." to "*When response to laxative therapy has not been sufficient for opioid-induced constipation in* patients with advanced illness, consider methylnaltrexone..."

PAIN-G 2 of 2

- "Extrapolated from non cancer neuropathic pain management" was added below the title indicating from where the information is derived.
- Trial of anticonvulsants:
  - For both gabapentin and pregabalin, the two statements, "Slower titration for the elderly *or* medically frail. *Dose adjustment required for* those with renal insufficiency" were clarified.
  - For pregabalin, a statement "May increase further to a maximum dose of 600 mg in divided doses two to three times a day" was added and the statement, "Titration to the analgesic dose requires just 2 or 3 steps, rather than the multiple steps frequently required with gabapentin" was removed.

PAIN-H

- A new bullet under support was added, "Assess impact upon family and significant others and provide education and support as indicated."

PAIN-I

- A new bullet, "Assess patient and family for literacy to ensure understanding of education" was added.
- The subbullet, "Morphine and morphine-like medications are often used to relieve pain" was modified by adding, "*For patients with a history of substance abuse, see PAIN-L.*"

PAIN-J

- Physical modalities, "energy conservation, pacing of activities" were added as examples.

PAIN-K

- NSAID, first bullet, "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" was added.
- NSAID and toxicities, the following changes were made:
  - Patients at high risk for GI toxicities, a subbullet, "Discontinue NSAID if liver function studies increase 1.5 times the upper limit of normal" was added.
  - Patients at high risk for cardiac toxicities: "NSAIDs taken with prescribed anticoagulants, such as warfarin or heparin, may significantly increase the risk of bleeding complications" was added.
  - Monitoring for NSAID toxicities, "liver function studies [alkaline phosphatase, LDH, SGOT, SGPT]" was added.
- Acetaminophen, "The FDA is currently evaluating daily maximum dosing. Due to 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 website for latest information on acetaminophen side effects and dosing" was added.
- A bullet, "For further prescribing and safety information, see FDA website www.fda.gov." was added.

PAIN-L

- Title of page was change from "Pain speciality consultation" to "*Speciality consultations for improved pain management*".
- For pain and palliative care specialty consultation, a new subbullet "Consider palliative sedation for intractable pain" was added.

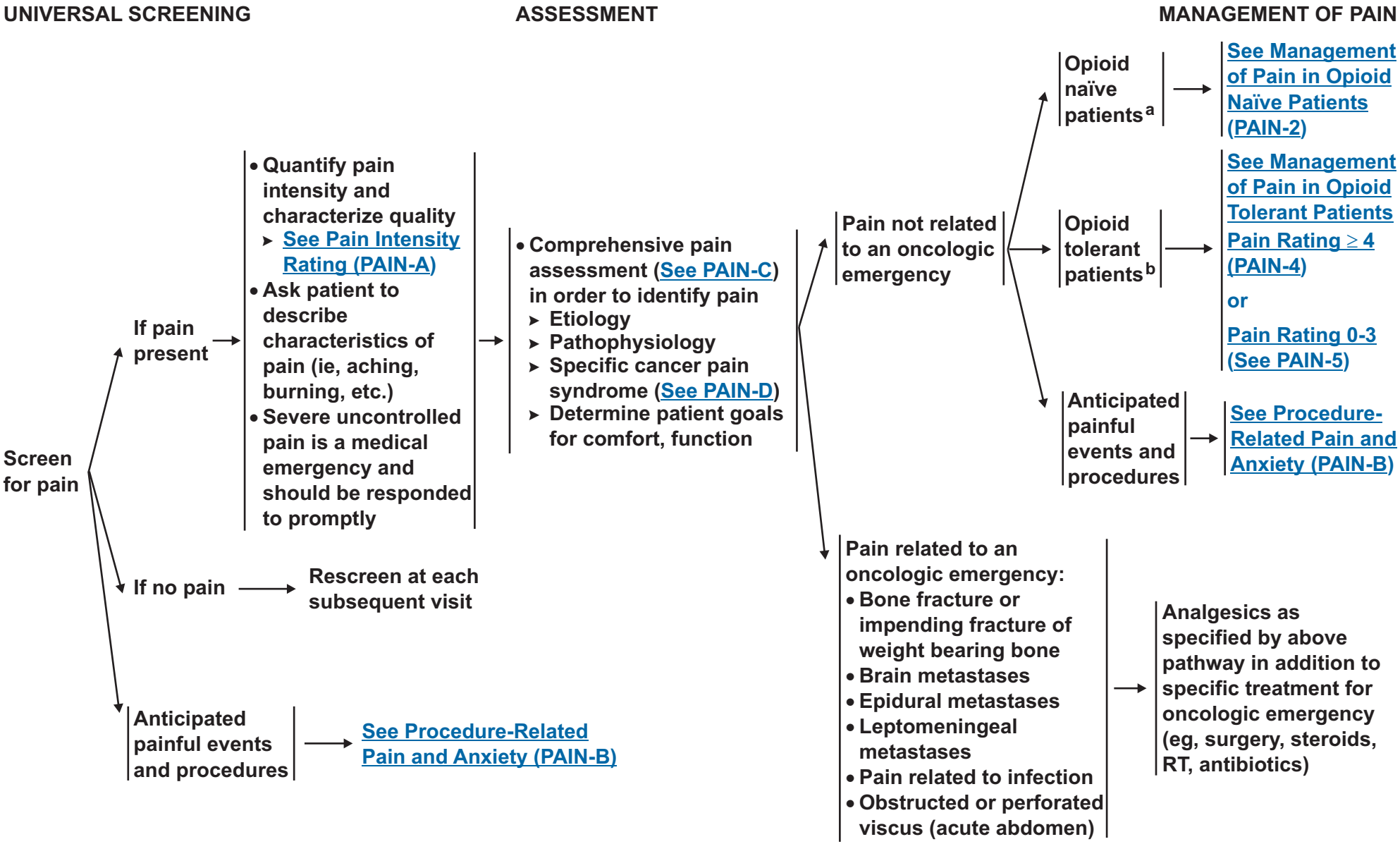
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[a]Opioid naïve includes patients who are not chronically receiving opioid analgesic on a daily basis.
[b]Opioid tolerant includes patients who are chronically receiving opioid analgesic on a daily basis.

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PAIN INTENSITY
See Pain Intensity Rating (PAIN-A)

MANAGEMENT OF PAIN IN OPIOID NAÏVE PATIENTS[a]

For *ALL* levels of pain →
- Recognize and treat analgesic 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)

Severe Pain 7-10 →
- See management for *all* levels of pain above

AND
- Rapidly titrate short-acting opioid, see PAIN-3 for initiating short-acting opioids and see PAIN-E for additional details of opioid principles, prescribing, titration, and maintenance
  - ➤ Begin bowel regimen (See PAIN-F)

Moderate Pain 4-6 →
- See management for *all* levels of pain above

AND
- Titrate short-acting opioid, see PAIN-3 for initiating short-acting opioids and see PAIN-E for additional details of opioid principles, prescribing, titration, and maintenance
  - ➤ Begin bowel regimen (See PAIN-F)

Mild Pain 1-3 →
- See management for *all* levels of pain above

AND
- Consider nonsteroidal anti-inflammatory drugs (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)

→ Reevaluate pain at each contact and as needed to meet patient goals for comfort and function → See Ongoing Care (PAIN-6)

[a]Opioid naïve includes patients who are not chronically receiving opioid analgesic on a daily basis.

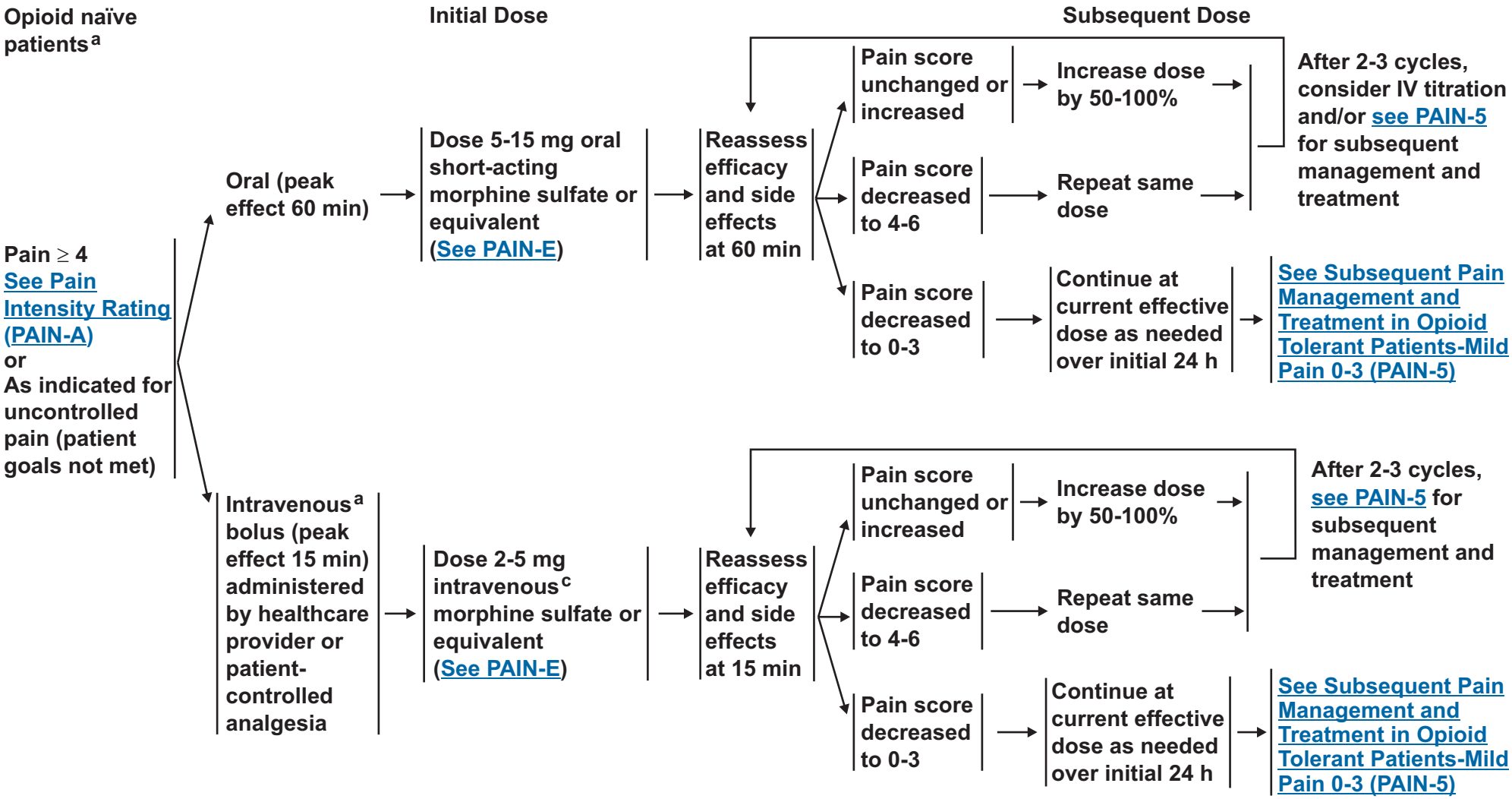
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INITIATING SHORT-ACTING OPIOIDS IN OPIOID NAÏVE PATIENTS[a]

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



[a]Opioid naïve includes patients who are not chronically receiving opioid analgesic on a daily basis.
[c]Subcutaneous can be substituted for intravenous, however subcutaneous route delays onset of effect by up to 30 minutes.

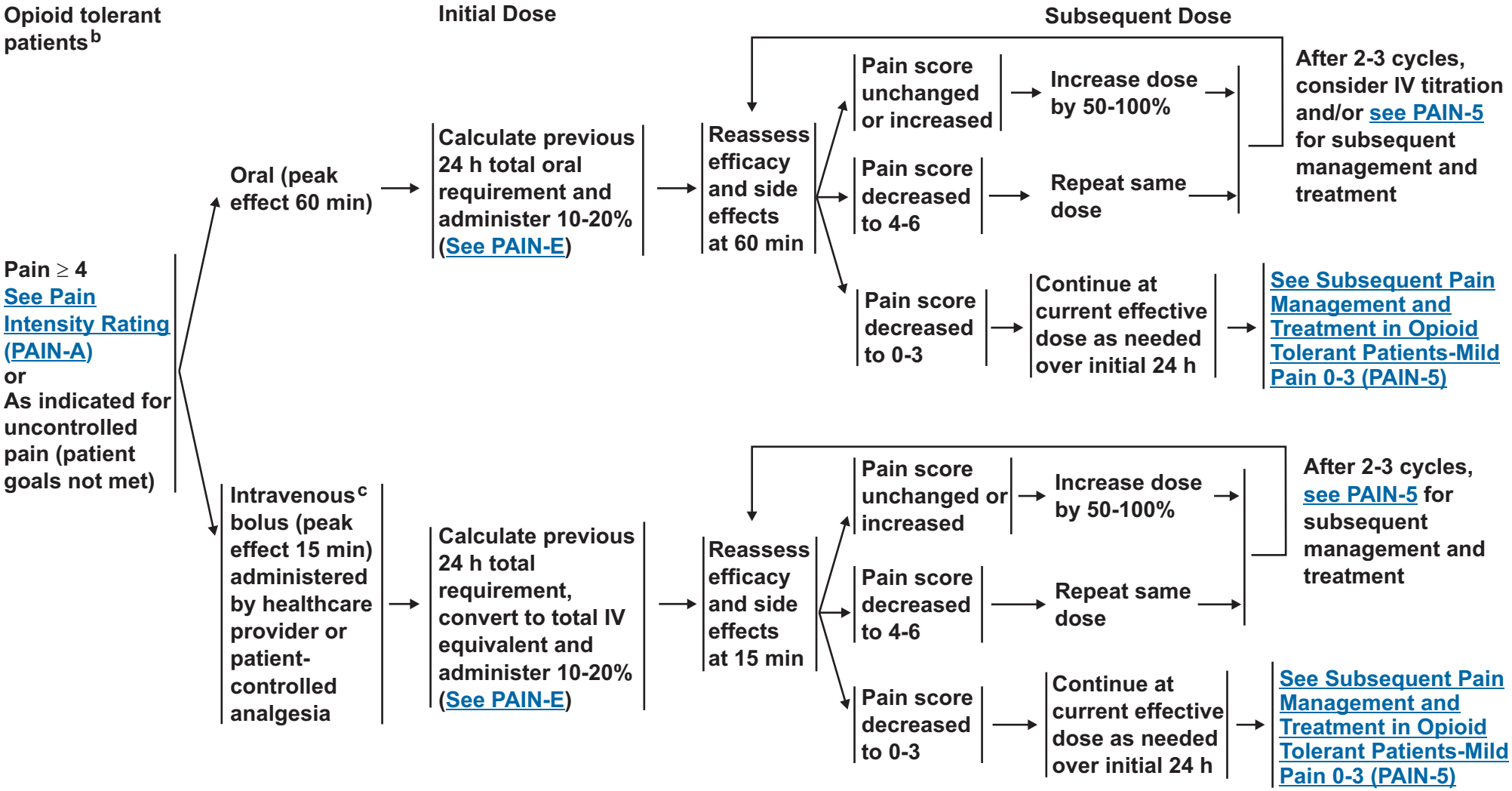
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MANAGEMENT OF PAIN IN OPIOID TOLERANT PATIENTS[b]

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



[b] Opioid tolerant includes patients who are chronically receiving opioid analgesic on a daily basis.

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

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PAIN INTENSITY (See Pain Intensity Rating (PAIN-A))

SUBSEQUENT PAIN MANAGEMENT AND TREATMENT IN OPIOID TOLERANT PATIENTS[b]

GOALS OF TREATMENT

For ALL pain levels →
- Provide psychosocial support (See PAIN-H)
- Provide patient and family education (See PAIN-I)

Severe Pain 7-10 →
- See management for *all* levels of pain above
AND
- Reevaluate opioid titration (See PAIN-E)
- Reevaluate working diagnosis with a comprehensive pain assessment (See PAIN-C)
- Consider specific pain syndrome problems (See PAIN-D)
- Consider pain specialty consultation (See PAIN-L)
- Reevaluate co-analgesics as indicated (See PAIN-G)

Moderate Pain 4-6 →
- See management for *all* levels of pain above
AND
- 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 (See PAIN-G)

Mild Pain 0-3 →
- See management for *all* levels of pain above
AND
- Reassess and modify regimen to minimize side effects (See PAIN-E and See PAIN-F)
- Co-analgesics as needed (See PAIN-G)

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

- **Achieved →** See Ongoing Care (PAIN-6)
- **Not achieved →** See Universal Screening and Assessment (PAIN-1)
  Consider Interventional Strategies (PAIN-M)

[b] Opioid tolerant includes patients who are chronically receiving opioid analgesic on a daily basis.

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ONGOING CARE

Clinician responsibilities

- Convert to oral medications (if feasible) including extended-release agent with rescue doses (Conversion details, see PAIN-E)
- 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 PAIN-I)
- 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 PAIN-I)
  - 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 (PAIN-1)

  Consider Interventional Strategies (PAIN-M)

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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, as well as "worst" pain 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 (PAIN-C) 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)- it shows very much pain. Point to the face that shows how much you hurt (right now)."

[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.

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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://prc.coh.org/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.**

Cultural and linguistic assessment[7,8]

- **Healthcare providers should be aware of impact of cultural and linguistic diversity 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, Muchka S, Weissman DE. The assessment of discomfort in dementia protocol. Pain Manag Nurs. 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.
[7]Al-Atiyyat HNM. Cultural diversity and cancer pain. Journal of Hospice & Palliative Nursing 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.

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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, wound care, 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.**
  - **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 gauge needle.**
- **Administration of sedatives/analgesics/general anesthesia by trained personnel.**
- **Additional nonpharmacologic interventions (See PAIN-J)**

Providing information regarding all of these analgesic 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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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 PAIN-A 2 of 2).

- Pain Experience
  - Location, referral pattern, radiation of pain(s)
  - Intensity See Pain Intensity Rating (PAIN-A)
    - Last 24 hours and current pain
    - At rest and 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
  - Other current 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 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 PAIN-H)
  - 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, 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
  - Pre-existing chronic pain
- Physical examination
- Relevant laboratory and imaging studies to evaluate for disease progression
- 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 (RT, chemotherapy, surgery) 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 mdanderson.org/bpi

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ADDITIONAL INTERVENTIONS FOR CANCER PAIN SYNDROMES

In general, cancer pain is treated with opioids as indicated on PAIN-2, 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 (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, glucocorticoids and/or systemic administration of radioisotopes**
  - **Consider physical medicine evaluation**
    See Pain Specialty Consultation (PAIN-L)
  - **For resistant pain: consider referral to a pain specialist and/or the use of interventional strategies.**
    See Interventional Strategies (PAIN-M)
- **Bowel obstruction**
  - **Bowel rest, nasogastric suction, glucocorticoids, octreotide**
- **Neuropathic pain:**
  - **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
  - **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 three times a day; carbamazepine, 100-400 mg two 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 (PAIN-M)
- **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 Palliative Care Guideline.**

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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 PAIN-M.
- 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 Management of Pain in Opioid Tolerant Patients (PAIN-4).
- 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 PAIN-K)
- 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% to 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.

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

Table 1 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[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 the opioid dependent patient.

[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 due to accumulation of renally-cleared metabolites.

[3] The equianalgesic dose listed only applies to IV fentanyl compared to other IV opioids. For transdermal fentanyl conversions, see PAIN-E 4 of 7.

[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 days. May need to be dosed every 4 h initially then changed to every 6-8 h after steady state achieved (1-2 wks).

[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 PAIN-E 6 of 7).

[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 four 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.

[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).

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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 (PAIN-E 2 of 7).**
  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 (eg, 6 doses for regular PO morphine every 4 hrs; 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 needs to 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 hr =192 mg/day)
   (Total amount of IV morphine this patient is taking is 192 mg/day.)

2. **From Table 1 on PAIN-E 2 of 7, calculate the equianalgesic dose of IV hydromorphone**
   (10 mg IV morphine = 1.5 mg IV hydromorphone therefore,
   192 mg/day IV morphine = 28.8 mg/day IV hydromorphone = 1.2 mg/h IV hydromorphone)

3. **If patient was effectively controlled with IV morphine (192 mg/day) reduce the dose of hydromorphone by 25-50%.**
   (28.8 mg/day reduced by 25% = 21.6 mg/day IV hydromorphone = 0.9 mg/h IV hydromorphone)
   (28.8 mg/day reduced by 50% = 14.4 mg/day 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/day IV hydromorphone = 1.2 mg/h IV hydromorphone)
   or increase that by 25%
   (36 mg/day IV hydromorphone = 1.5 mg/h IV hydromorphone)

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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 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 per hour 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 days, increase the patch dosage based on the average amount of stable daily as need (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 next 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: Due to 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 prior to 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 (such as heat from heat lamps, electric blankets, etc.) may accelerate transdermal fentanyl absorption and are contraindications for transdermal fentanyl.
- When converting from continuous parenteral infusion fentanyl to transdermal fentanyl, a straight 1:1 ratio[3] is appropriate, ie, the number of mcg of parenteral fentanyl per hour should be approximately equal to the number of mcg of transdermal fentanyl per hour. In some patients, additional dose titration of the fentanyl patch may be necessary.
- The fentanyl patch analgesic duration is usually 72 hours but some patients require fentanyl patch replacement every 48 hours.

[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.

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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 needs to 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/day oral oxycodone)

2. Using Table 2, select the the mcg per hour dose of transdermal fentanyl
(60 mg/day 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/day oral oxymorphone)

2. From Table 1 on PAIN-E 2 of 7, convert the equianalgesic dose of oral morphine
(Based on Table 1, 10 mg oral oxymorphone = 30 mg oral morphine, therefore 20 mg/day oral oxymorphone x 3 = total daily dose oral morphine of 60 mg/day)

3. Using Table 2 on PAIN-E 4 of 7, select the mcg per hour dose of transdermal fentanyl
(60 mg/day oral morphine is approximately 25 mcg/h transdermal fentanyl patch)

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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 greater than 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 methadone is.
- 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 mg and 10 mg tablets.
- Methadone may be titrated up every 5 - 7 days, usually by 5 mg/dose.
- Because methadone is associated with QTc prolongation, a baseline and follow-up ECG is recommended for methadone doses > 100 mg/day and for patients with cardiac disease, or when methadone is used in patients taking other medications also known to prolong QTc (including tricyclic anti-depressants), 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, due to a long elimination half-life; therefore, the amount of other opioid needed for an equivalent effect will appear 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) towards 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.

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See next page for case example

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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-h and needs to 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/day)
   (Total amount of oral morphine this patient is taking is 180 mg/day)

2. **From Table 3 (Dose Conversion Ratios for Oral Morphine to Oral Methadone- PAIN-E-6 of 7), calculate equianalgesic dose of oral methadone**
   (For 180 mg/day of oral morphine : oral methadone, the dose conversion ratio is 8:1 therefore 180 mg/day morphine = 22.5 mg/day 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**
   (for example, 22.5 mg/day oral methadone reduced by 25% = 16.875 mg/day oral methadone equal to approximately 15 mg/day oral methadone)

4. **Divide the total daily oral methadone dose into 3 daily doses**
   (for example, reduced dose of 15 mg/day oral methadone divided by 3 daily doses = 5 mg oral methadone every 8 h)

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MANAGEMENT OF OPIOID SIDE EFFECTS (1 of 3)

Principles of Management of Opioid Side Effects

- Opioid side effects generally improve over time, 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 and side effects may be from other treatments or cancer itself.

Constipation

- Preventive measures
  - Prophylactic medications
    - Stimulant laxative ± stool softener (eg, 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 non-forced bowel movement every 1-2 d
  - Consider co-analgesic 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 two times a day)
  - Fleet, saline, or tap water enema
  - Consider use of a prokinetic agent (eg, metoclopramide, 10-20 mg PO four 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 one dose per day
  - 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
  - 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 (eg, 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 (eg, granisetron, 2 mg PO daily; or ondansetron, 8 mg PO three 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

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.

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.)
- 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 Palliative Care Guidelines

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; 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

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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 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

(Extrapolated from non cancer 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 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. 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 co-analgesic in combination with an opioid for the neuropathic component of the pain.**
  - **Anticonvulsant examples:**
    - **Gabapentin- Starting dose 100- 300 mg nightly, increase to 900- 3,600 mg daily in divided doses two times to three 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 three times a day, increase to 100 mg three 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 two to three 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 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.**
    - **Consider NSAID- diclofenac gel 1%, four 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.**

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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.
- 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 (PAIN-I)

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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 healthcare provider.
  - Morphine and morphine-like medications are often used to relieve pain. For patients with a history of substance abuse, see PAIN-L.
    - 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 healthcare provider is critical.
    - Healthcare providers cannot tell how much pain you have unless you tell them.
    - Healthcare 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 healthcare 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 healthcare 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.

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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 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

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 four times a day (daily maximum = 3,200 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 three divided doses**
    - **Salsalate, 2-3 g/d in two or three divided doses**
    - **Selective COX-2 inhibitor**
- **NSAID 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 NSAID 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 or more alcoholic beverages/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 NSAID 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 demonstrated to have reduced renal side effects.**
    - **Consider adding antacids, H2 receptor antagonists, misoprostol, omeprazole. If patient develops gastrointestinal peptic ulcer or gastrointestinal hemorrhage, discontinue NSAID.**
    - **Discontinue NSAID 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 NSAID 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**

Continued on next page

[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):1634-1642.

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NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAID) AND ACETAMINOPHEN PRESCRIBING

- **Further NSAID considerations:**
  - **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**
  - **When systemic administration is not feasible, consider topical NSAID preparations.**
  - **Toxicity of anti-cancer 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. Due to 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 website for latest information on acetaminophen side effects and dosing.**

- **For further prescribing and safety information, see FDA website www.fda.gov.**

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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 Palliative Care Guidelines
  - Consider interventional strategies (See PAIN-M)
  - 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 Distress Management Guidelines

- 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

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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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)**

- **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 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)**
  - **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 (eg, anti-angiogenesis agents such as bevacizumab) or technical expertise is not available.

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Discussion

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.

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 by the patient (whenever possible), 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.

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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 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. 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 likely to be 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, by the patient (whenever possible). 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 unable to verbally report pain, an alternative method to obtain pain rating and pain assessment must be utilized (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

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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 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 (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. 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 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).[12,14]

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). Pain associated with oncologic emergency should be directly treated while proceeding with treatment of the underlying condition.

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

According to the U.S Food and Drug Administration, "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 the above definition of opioid tolerant, and who have not had opioid doses at least as much as those listed above 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 PAIN-2 and the section below on Opioid Principles, Prescribing, Titration, and Maintenance). Short-acting formulations have the advantage of rapid

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onset of analgesic effect. The route of administration of opioid is decided (oral versus intravenous) based on what is best suited to the patient's ongoing analgesic needs.

Treatment with opioids must be accompanied with a bowel regimen, and non-opioid analgesics as indicated. 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.[18]

For opioid naïve patients, whose pain intensity rating is between 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.

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

Addition of co-analgesic for specific pain syndromes should be considered for all groups of patients (see section below on Additional Therapies and PAIN- G). Co-analgesics are drugs used to enhance the effects of opioids or NSAIDs.[19]

For all patients experiencing pain, 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 related issues.

Although pharmacologic analgesics are the cornerstone 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 nonpharmacological interventions may serve as valuable additions to pharmacologic interventions. A list of nonpharmacologic interventions that include physical and cognitive modalities are outlined in PAIN-J and interventional strategies are discussed in the section below and in PAIN-M.

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 illness(es). Morphine, hydromorphone, fentanyl, oxycodone are the opioids commonly used in the United States. 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.

In a patient who has not been exposed to opioids in the past, morphine is generally considered the standard starting drug of choice.[20,21] An initial oral dose of 5-15 mg of morphine sulfate or equivalent or 2-5 mg of intravenous morphine sulfate or equivalent is recommended for opioid naïve patients.

Pure agonists (such as codeine, oxycodone, oxymorphone and fentanyl) are the most commonly used medications in the management

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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] 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 PAIN-E).

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 pharmocokinetics (long half-life ranging from 8 to more than 120 hours) make its usage very difficult in cancer patients.[27] 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.

The following agents namely 1) mixed agonist-antagonists (e.g. butorphanol, pentazocine), 2) propoxyphene and meperidine, and 3) 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] Since data suggests that CYP2D6-inhibiting anti-depressants increase risk of recurrence in breast cancer patients treated with tamoxifen,[31,32] (see section on Additional Therapies below) 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 as 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 (IV) or subcutaneous (SC), is recommended for patients who cannot swallow or absorb opioids enterally. Opioids, given parenterally, may produce fast and effective plasma concentrations in comparison 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) in comparison 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 analgesia”. “Around the clock” dosing is provided to chronic pain patients for continuous pain relief. A “rescue dose” should also be provided as a subsequent treatment for patients receiving ”around-the-clock” doses. Rescue doses of short-acting opioids should be provided for pain that is not relieved by regularly scheduled, “around-the-clock” doses (PAIN-E). Opioids administered on an “as needed” basis are for patients who have intermittent pain with pain-free

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intervals. The "as needed" method is also used when rapid dose titration is required. The patient-controlled analgesia 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).

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 (PAIN-F).[36,42-50] Constipation can almost always be anticipated with opioid treatment, administration of prophylactic bowel regimen is recommended. However there is not much evidence on which to base the selection of the most appropriate bowel regimen. There is one study showing that addition of a stool softener, docusate to the laxative, sennosides was less effective than administering laxative , sennosides alone.[51] Therefore, the NCCN Adult Cancer Pain panel recommends a stimulant laxative with or without a stool softener. The details of prophylactic bowel regimens and other measures to prevent constipation, and antiemetics are provided on page PAIN-F, 1 of 3.

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] It is important to consider relative effectiveness when switching between oral and parenteral routes to avoid subsequent overdosing or under-dosing. Equianalgesic dose ratios, opioid titration and maintenance and clinical examples of converting from one opioid to another are listed in PAIN-E.

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 pain intensity of greater than or equal to 4 or a pain intensity less than 4 but whose goals of pain control and function are not met, an initial dose of 5-15 mg of oral morphine sulfate or 1-5 mg of intravenous morphine sulfate or equivalent is recommended (PAIN-3). 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 (PAIN-3). Upon assessment, if the pain score remains unchanged or is increased, to achieve adequate analgesia, it is recommended that the dose be increased by 50%-100% of the previous dose of opioid. If the pain score decreases to 4-6, 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, upon reassessment after 2-3 cycles of the opioid, changing the route of administration from oral to intravenous or subsequent management strategies (outlined on PAIN-5) can be considered. If the pain score decreases to 0-3, the current effective dose of opioid is administered "as needed" over initial 24 hours before proceeding to subsequent management strategies (PAIN-3).

Management of pain that is not related to an oncologic emergency in opioid tolerant patients

Opioid tolerant patients are those chronically taking opioids for pain relief. According to the U.S Food and Drug administration 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

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oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer."

In opioid tolerant patients, experiencing breakthrough pain of intensity greater than or equal to 4, a pain intensity less than 4 but whose goals of pain control and function are not met, in order to achieve adequate analgesia the previous 24 hour total oral or IV opioid requirement must be calculated and the new "rescue" dose must be increased by 10-20%[33,53] (PAIN-4). 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 (PAIN-4). Upon assessment, if the pain score remains unchanged or is increased, administration of 50%-100% of the previous rescue dose of opioid is recommended. If the pain score decreases to 4-6, 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 pain score remains unchanged upon reassessment after 2-3 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 PAIN-5) can be considered. If the pain score decreases to 0-3, the current effective dose of either oral or intravenous opioid is administered "as needed" over initial 24 hours before proceeding to subsequent management strategies.

Subsequent Management of Pain in Opioid Tolerant Patients

The subsequent treatment is based upon the patient's continued pain rating score (PAIN-5). All 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 re-evaluated and comprehensive pain assessment must be carried out. For patients unable to tolerate dose escalation of their current opioid due to adverse effects, an alternate opioid must be considered (opioid rotation, see PAIN-E). Addition of co-analgesics (see PAIN-G) should be re-evaluated to either enhance the analgesic effect of the opioids or in some cases to counter the adverse effects associated with the opioids.[18] Given the multifaceted nature of cancer pain, additional interventions (PAIN-D) for specific cancer pain syndromes and specialty consultation (PAIN-L) must be considered to provide adequate analgesia.

If the patient is experiencing moderate pain of intensity 4-6 and if they have adequate analgesic relief on their current opioid, the current titration of the opioid may be continued or increased. In addition, as with patients experiencing severe pain, addition of co-analgesics (see PAIN-G); additional interventions for specific cancer pain syndromes (see PAIN-D); and specialty consultation must be considered (see PAIN-L).

For opioid tolerant patients experiencing mild pain, if they have adequate analgesia but intolerable or unmanageable side-effects the analgesic dose may be reduced by 25% of the current opioid dose (see PAIN-E). Addition of co-analgesics may be considered.

Ongoing Care

Although pain intensity ratings will be obtained frequently to evaluate opioid dose increases, a formal re-evaluation to evaluate patient's 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 NCCN Adult Cancer Pain panel recommends converting to an extended-release oral medication (if feasible) or other extended-release formulation (i.e. transdermal fentanyl), or other long-acting agent (e.g. methadone) (PAIN-6). The subsequent treatment is based upon the patient's continued pain rating score. Rescue doses of the short-acting

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formulation of the same long-acting drug may be provided during maintenance therapy for the management of pain in cancer patients not relieved by extended-release opioids.

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).

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

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; wound care; lumbar puncture; skin and bone marrow biopsies; intravenous line, arterial line, central line; and 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. In addition, use of nonpharmacological interventions listed on PAIN-J may be valuable in managing procedure-related pain and anxiety. The major goal of nonpharmacological interventions that include physical and cognitive modalities is to promote a sense of control increasing hope and reducing helplessness that many patients with pain from cancer experience.

Patients usually tolerate procedures better when they know what to expect. Therefore, patients and family members should receive written instructions for managing the pain. Pre-procedure patient education, regarding 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 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. The major indications for referral include patient suffering from pain that is 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) and/or in patients failing to achieve adequate analgesia without intolerable side effects. For example, a patient with pancreatic cancer who was not tolerating opioids or not receiving adequate analgesia could be offered a celiac plexus block.

Several interventional strategies (PAIN-M) are available if a patient does not achieve adequate analgesia. Regional infusion of analgesics (epidural, intrathecal, and regional plexus) is one of the approaches.

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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 for patients who have pain from a variety of anatomical locations (e.g., head and neck, upper and lower extremities, trunk).[54] Neuroablative procedures used 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), percutaneous vertebroplasty/kyphoplasty, neurostimulation procedures (i.e., for peripheral neuropathy), and radiofrequency ablation for bone lesions have proven successful in pain management (PAIN-M) especially those failing to achieve adequate analgesia without intolerable effects. 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.

Interventional strategies listed above are not appropriate if patients are unwilling or in patients with Infections, coagulopathy, or very short life expectancy. Also, the experts performing the interventions must be made aware of any medications that the patient are taking that might increase risk for bleeding (i.e. anticoagulants (warfarin, heparin), antiplatelet agents (clopidogrel, dipyridamole), or anti-angiogenesis agents (bevacizumab). In such case, the patient may have to be of the medication for an appropriate amount of time prior to the pain intervention 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 situations can be considered. Specific recommendations for inflammatory pain, bone pain, nerve compression or inflammation, neuropathic pain, pain due to bowel obstruction, and pain likely to respond to antineoplastic therapies are provided (PAIN-D). 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.[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 via 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 tamoxifen-treated breast cancer patients also treated with selective serotonin reuptake inhibitor (SSRI) antidepressants versus those receiving tamoxifen alone.[31,32] If concomitant use of 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]

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

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Acetaminophen,[59] 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 reduce 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.

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.

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. Specialty consultations can be helpful in providing interventions to assist with difficult cancer pain problems (see PAIN-L). 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.

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