National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Adult Cancer Pain

Version 1.2013

NCCN.org

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

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

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

See NCCN Categories of Evidence and Consensus.

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Updates in Version 1.2013 of the NCCN Guidelines for Adult Cancer Pain from Version 2.2012 include:

PAIN-1

- Principles of Cancer Pain Management
  - 1st bullet was modified as: "There is increasing evidence in oncology that survival is linked to *symptom* ~~pain~~ control *and that pain management contributes to quality-of-life improvement*. To maximize patient outcomes, pain *management* is an essential part of oncologic management."
  - 4th bullet was modified as: "Comprehensive pain assessment must be performed *if pain is present*."
  - 7th bullet was modified as: "Pain intensity must be quantified *and quality must be characterized* by the patient..."
  - Three new bullets were added:
    - Goals of pain management are improved comfort and function.
    - Persistent cancer pain often requires treatment with regularly scheduled analgesics, and supplemental doses of analgesics are often required to manage breakthrough pain.
    - Optimize integrative interventions (See PAIN-J).

PAIN-2

- Assessment, the following bullets were clarified as:
  - Comprehensive pain assessment (See PAIN-C) in order to identify ~~pain~~
    - *Pain* etiology
    - *Pain* pathophysiology
    - Specific cancer pain syndrome (See PAIN-D)
    - ~~Determine~~ Patient goals for comfort and function
- Pain related to an oncologic emergency
  - "Brain metastases" was removed.
- Footnotes
  - Footnote "c" was modified by adding: "...and therefore have not developed significant tolerance. The FDA identifies tolerance as receiving at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer." (Also for PAIN-3 and PAIN-4)
  - Footnote "d" was modified by adding: "The FDA identifies tolerance as receiving at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer." (Also for PAIN-5 and PAIN-6)

PAIN-3

- For all pain levels
  - 7th bullet was added: "Consider nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen (See PAIN-K)." This bullet was removed from "Mild Pain (1-3)."

PAIN-5

- Footnote "f" was added: "Not including transmucosal fentanyl dose."

PAIN-6

- For all pain levels
  - 5th bullet was added: "Optimize integrative interventions (See PAIN-J)."

PAIN-7

- Ongoing care
  - 1st bullet was modified: ...including extended-release *or long-acting agen*t with rescue doses..."
  - 6th bullet, a sub-bullet was added: "Clarify which clinician will be prescribing patient's ongoing analgesics."
  - 8th bullet, a link to PAIN-I for patient and family/caregiver education was added.

PAIN-C 1 of 3

- Pain experience
  - New bullet was added: "Breakthrough pain is episodic pain not controlled with existing pain regimen; see breakthrough pain on PAIN-E 3 of 9."
  - Special issues relating to pain, the 3rd sub-bullet was modified as: "Cultural beliefs toward pain, pain expression, *and treatment*."

PAIN-C 2 of 3

- Pyschosocial
  - Sub-bullet was modified: "Patient, environmental, and social factors *as identified by a detailed patient evaluation and/or screening tools (eg, SOAPP-R or ORT)*." Three supporting references were added.

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Updates in Version 1.2013 of the NCCN Guidelines for Adult Cancer Pain from Version 2.2012 include:

PAIN-D

- Bone pain without oncologic emergency
  - 2nd and 3rd sub-bullets were separated and clarified as:
    - Consider trial of bone-modifying agents (eg, bisphosphonates)
    - *Diffuse bone pain:* Consider hormonal or chemotherapy, corticosteroids, and/or systemic administration of radioisotopes
  - 4th sub-bullet was modified: "...nerve block (eg, rib pain), *or vertebroplasty*"
  - 6th sub-bullet was added: "Consider orthopedic consultation for stabilization, if feasible."
  - 7th sub-bullet was modified: ~~"For resistant pain:~~ Consider referral to a pain specialist *for* ~~and/or the use of~~ interventional ~~strategies~~ *consultation*.

PAIN-E 1 of 10

- General Principles
  - 2nd bullet was modified as: "...decreased renal/hepatic function, ~~COPD,~~ *chronic lung disease*, and upper airway compromise..."
  - 3rd bullet was modified by removing: "...(ie, IV, subcutaneous, rectal, transdermal, transmucosal~~, buccal~~)..."
  - 8th bullet was modified by adding: "If/when pain improves...*and optimize use of nonopioid analgesics*..."
  - Last bullet was modified by adding: "May include patient survey tool (eg, COMM)" with a reference.
  - A new bullet was added: "For breakthrough pain, see PAIN-E 3 of 10."

PAIN-E 2 of 10

- Opioids and Risk Evaluation and Mitigation Strategy (REMS)
  - Last sub-bullet was revised as: "REMS programs are currently in place for all transmucosal fentanyl products, *transdermal fentanyl products*, transdermal buprenorphine (See Approved Risk Evaluation and Mitigation Strategies [REMS]), *and in 2013 the FDA will introduce REMS starting with continuing education for morphine-naltrexone combination product, all extended-release opioids, and long-acting opioids (methadone)* ~~extended-release hydromorphone, extended-release tapentadol, extended-release oxymorphone~~. See FDA Questions and Answers for REMS for Extended-Release and Long-Acting Opioid Analgesics."

PAIN-E 3 of 10

- Principles of Maintenance Opioid Therapy
  - 4th bullet was clarified as: "Breakthrough pain (pain that fails to be controlled or "breaks through" a regimen of regularly scheduled opioid) *may require additional doses of opioid for pain not relieved by regular schedule of long-acting (eg, extended release) opioid*. *Breakthrough pain* may be further ~~categorized as~~ *evaluated into the following categories, which have direct impact on treatment:"*

PAIN-E 4 of 10

- Footnote "7" was modified as: "Hydrocodone is only available commercially combined with acetaminophen (325 to 750 mg/tablet) *or ibuprofen (200 mg/tablet*). *The FDA will be limiting the amount of acetaminophen in all prescription drug products to no more than 325 mg per dosage unit*."

PAIN-E 5 of 10

- Miscellaneous analgesics page is new to this section.

PAIN-E 6 of 10

- Convert or Rotate From One Opioid to Another Opioid
  - A 6th point was added: "Data do not support a specific transmucosal fentanyl dose equianalgesic to other opioids or between different transmucosal formulations. Always initiate transmucosal fentanyl with lowest dose in chosen formulation and titrate to effect. (See specific transmucosal prescribing information for appropriate dosing intervals.)"

PAIN-E 7 of 10

- Table 2
  - Transdermal fentanyl dose of "12 mcg/h" and the morphine equivalents were added.

PAIN-E 9 of 10

- 4th bullet was modified as: "Methadone is commercially available in 5 mg and 10 mg tablets and 1 mg/mL, *2 mg/mL, and 10 mg/mL* oral solution."
- 5th bullet was modified by adding: "If more rapid titration is desired, consult with pain or palliative care specialist."

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Updates in Version 1.2013 of the NCCN Guidelines for Adult Cancer Pain from Version 2.2012 include:

PAIN-F 1 of 3

- **Constipation, Preventative Measures**
  - **A new sub-bullet was added: "Stool softener (docusate) alone may not provide benefit in well-hydrated patients."**
- **If constipation develops**
  - **"Treat other causes" was removed.**
- **If constipation persists**
  - **5th sub-bullet was modified: "...(eg, metoclopramide, 10-~~20~~*15* mg PO 4 times a day; *consider limiting* chronic use *to maximum 3 mo,* due to concern for neurologic complications *[tardive dyskinesia], especially in frail, elderly patients*)."**
  - **7th sub-bullet was modified: "*For intractable chronic constipation,* consider opioid rotation to fentanyl or methadone."**

PAIN-F 2 of 3

- **Nausea**
  - **2nd bullet was modified by removing: "If nausea develops ~~(Drugs listed in alphabetical order)~~."**
    - **2nd sub-bullet was modified: "...or metoclopramide, 10-15 ~~20~~ mg PO ~~every 6 hr~~ *4 times daily* as needed; or haloperidol, 0.5-1 mg PO every 6-8 h. *Chronic use of any of these agents may be associated with development of tardive dyskinesia, especially in frail, elderly patients*."**
    - **A new sub-bullet was added: "Consider olanzapine, 2.5-5 mg, especially with bowel obstruction."**
  - **3rd bullet was modified: "*Opioid-induced nausea may resolve with continued exposure;* if nausea persists for more than 1 wk."**
- **Delirium**
  - **4th bullet was modified: "Consider *initial titration with* 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 per day. *With prolonged administration of these agents, it may be necessary to decrease dose due to long elimination half-life.*"**

PAIN-F 3 of 3

- **Respiratory Depression**
  - **3rd bullet was modified: "If respiratory problems *or opioid-induced sedation occurs,* ~~acute changes in mental status occur~~ consider naloxone administration *but use reversing agents cautiously*."**
  - **4th bullet was modified: "If reversing an opioid with a long half-life such as methadone *or for persistent opioid-induced sedation,* consider naloxone infusion."**
  - **5th bullet was added: "Closely monitor for the recurrence of pain as opioid is metabolized during reversal, which may require a cautious administration of an additional opioid."**
- **Sedation**
  - **1st bullet was modified: "If *significant or unexpected* sedation develops and persists for more than *2-3 d* ~~1 wk~~ after initiating *or a significant upward titration of an* opioid."**
  - **Last bullet was added: "If the patient has had marked sleep deprivation related to poor pain control, adjustments of analgesics to improve pain control may result in "catch up" sleep lasting 2-3 days. Therefore, extreme fatigue can result in somnolence that may be difficult to differentiate from opioid-induced sedation. If related to fatigue, patients generally can be fully aroused, although this may require some effort."**

PAIN-G 2 of 2

- **Antidepressants**
  - **Other examples, "Bupropion- Starting dose 100-150 mg daily, increase to 150-450 mg daily" was deleted.**
- **The note regarding tamoxifen was modified as: "Note: Some SSRI, SNRI antidepressants ~~*such as* duloxetine, *and especially* bupropion, may enhance metabolism of tamoxifen~~ *may inhibit the conversion of tamoxifen to its active metabolite,* thereby *decreasing the effectiveness* of tamoxifen - see Discussion."**

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Updates in Version 1.2013 of the NCCN Guidelines for Adult Cancer Pain from Version 2.2012 include:

PAIN-I 1 of 2

- Patient and Family/Caregiver Education
  - This page was reorganized by separating the messages to be conveyed into: "Messages to be conveyed to patient and family/caregiver regarding management of pain" and "Messages to be conveyed to patient and family/caregiver regarding opioid analgesics."
- Messages to be conveyed to patient and family/caregiver regarding opioid analgesics
  - 2nd sub-bullet was clarified as: "When these medications are used to treat cancer pain, addiction is rarely a problem *unless addiction issues existed before the cancer pain*.
  - 3rd sub-bullet, all bullets related to "safe use" of medications were moved to this sub-bullet titled, "These medications are controlled substances and must be used with caution:..."

PAIN-I 2 of 2

- The following must be reviewed:
  - 1st sub-bullet, a new bullet was added: "Plan for obtaining refilled prescriptions, especially schedule II narcotics that cannot be ordered by telephone."
  - 2nd sub-bullet, a new bullet was added: "List may be provided by clinician and/or pharmacy."

PAIN-K

- Acetaminophen
  - 1st bullet was clarified by adding: "Acetaminophen, 650 mg every 4 h or 1 g every 6 h (daily maximum 4 g/d) *in adult patients with normal liver function*."

PAIN-L

- Pain and palliative care specialty consultation
  - The following sub-bullets were added:
    - Consider oral or IV ketamine for pain resistant to other analgesics
    - Adjustment of drugs and doses beyond the expertise of the primary team/ oncologist
    - Management of complicated psychosocial issues, including aberrant drug behavior
    - Clarity of goals of care, especially regarding pain and medication side effects
- A new bullet was added: "Psychiatric consultation."

Pain Definition

Pain is defined by the International Association for the Study of Pain (IASP) as an unpleasant, multidimensional, sensory, and emotional experience associated with actual or potential tissue damage, or described in relation to such damage.[a]

Principles of Cancer Pain Management

- **There is increasing evidence in oncology that survival is linked to symptom control and that pain management contributes to quality-of-life improvement.[b] To maximize patient outcomes, pain management is an essential part of oncologic management.**
- **All patients must be screened for pain at each contact. (See PAIN-2)**
- **Goals of pain management are improved comfort and function.**
- **Comprehensive pain assessment must be performed if pain is present. (See PAIN-C)**
- **Comprehensive management of pain is needed as most patients have multiple pathophysiologies.**
- **Analgesic therapy is done in conjunction with management of multiple symptoms or symptom clusters and the complex pharmacologic therapies that patients with cancer are generally prescribed.**
- **Pain intensity must be quantified and quality must be characterized by the patient (whenever possible).**
- **Reassessment of pain intensity must be performed at specified intervals to ensure that the analgesic therapy selected is having the maximum benefit with as few adverse effects as possible.**
- **Persistent cancer pain often requires treatment with regularly scheduled analgesics, and supplemental doses of analgesics are often required to manage breakthrough pain.**
- **A multidisciplinary team may be needed.**
- **Psychosocial support must be available. (See PAIN-H)**
- **Specific educational material must be provided to the patient and family/caregiver. (See PAIN-I)**
- **Consider the multidimensional impact of "suffering" on patients and their families and address these concerns in a culturally respectful manner.**
- **Optimize integrative interventions (See PAIN-J).**

See Universal Screening (PAIN-2)

[a] Merskey H, Bugduk N. Classification of Chronic Pain. Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms. 2nd ed. Seattle, WA: IASP Press; 1994.
[b] Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733-742.

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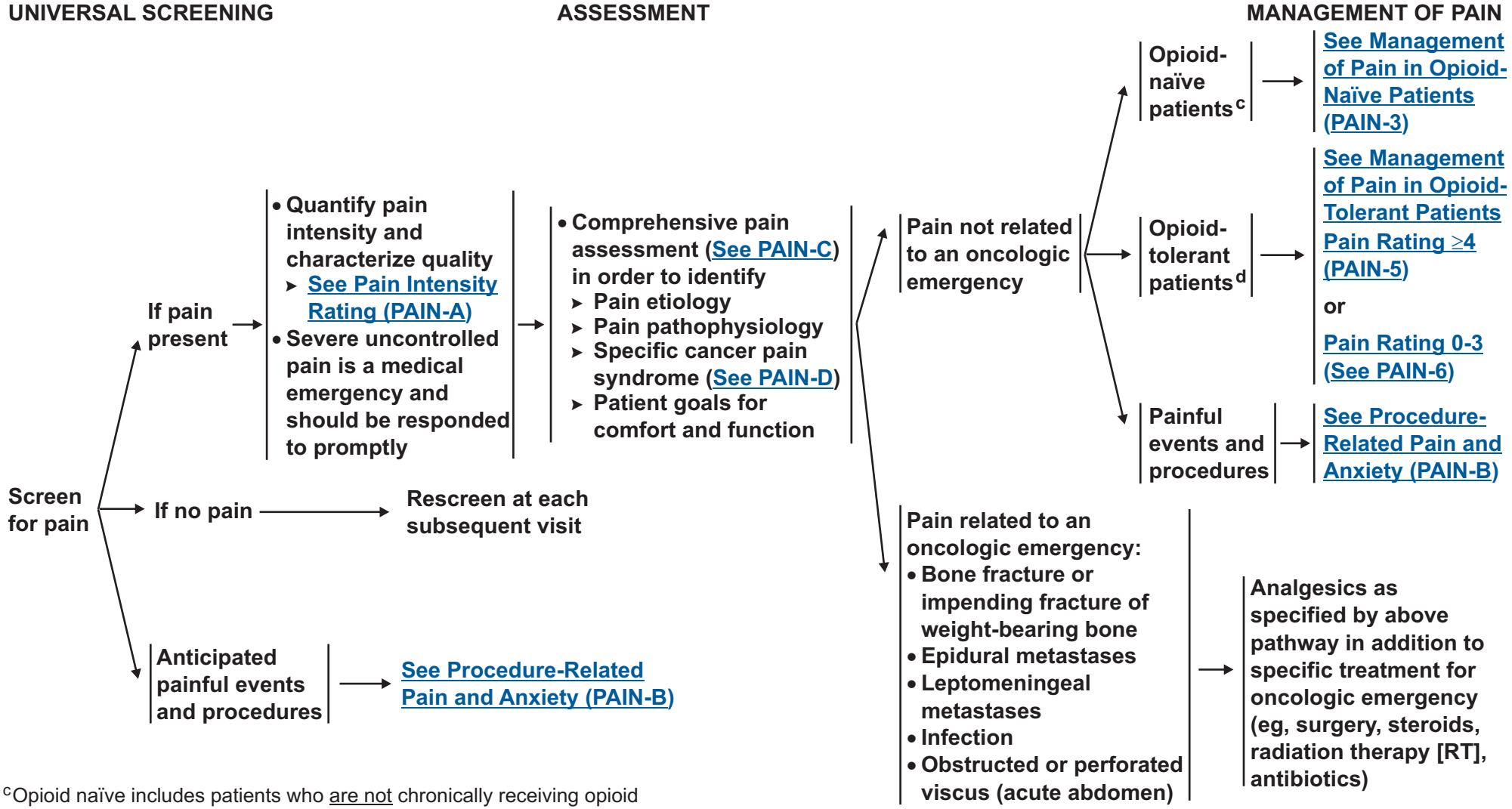

[c] Opioid naïve includes patients who are not chronically receiving opioid analgesic on a daily basis and therefore have not developed significant tolerance. The FDA identifies tolerance as receiving at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

[d] Opioid tolerant includes patients who are chronically receiving opioid analgesic on a daily basis. The FDA identifies tolerance as receiving at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

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PAIN INTENSITY
See Pain Intensity Rating (PAIN-A)

MANAGEMENT OF PAIN IN OPIOID-NAÏVE PATIENTS[c]

For *ALL* levels of pain →
- For opioid principles, prescribing, titration, and maintenance, see PAIN-E
- Anticipate and treat analgesic adverse effects (See PAIN-F)
- Consider adding adjuvant analgesics (See PAIN-G) for specific pain syndrome (See PAIN-D)
- Provide psychosocial support (See PAIN-H)
- Provide patient and family/caregiver education (See PAIN-I)
- Optimize integrative interventions (See PAIN-J)
- Consider nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen (See PAIN-K)

→ Reevaluate pain at each contact and as needed to meet patient goals for comfort and function → See Ongoing Care (PAIN-7)

Severe Pain 7-10 →
- See management for *all* levels of pain above AND
- Rapidly titrate short-acting opioid, see PAIN-4 for initiating short-acting opioids
  - ➤ 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-4 for initiating short-acting opioids
  - ➤ Begin bowel regimen (See PAIN-F)

Mild Pain 1-3 →
- See management for *all* levels of pain above AND
- 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-7)

[c]Opioid naïve includes patients who are not chronically receiving opioid analgesic on a daily basis and therefore have not developed significant tolerance. The FDA identifies tolerance as receiving at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

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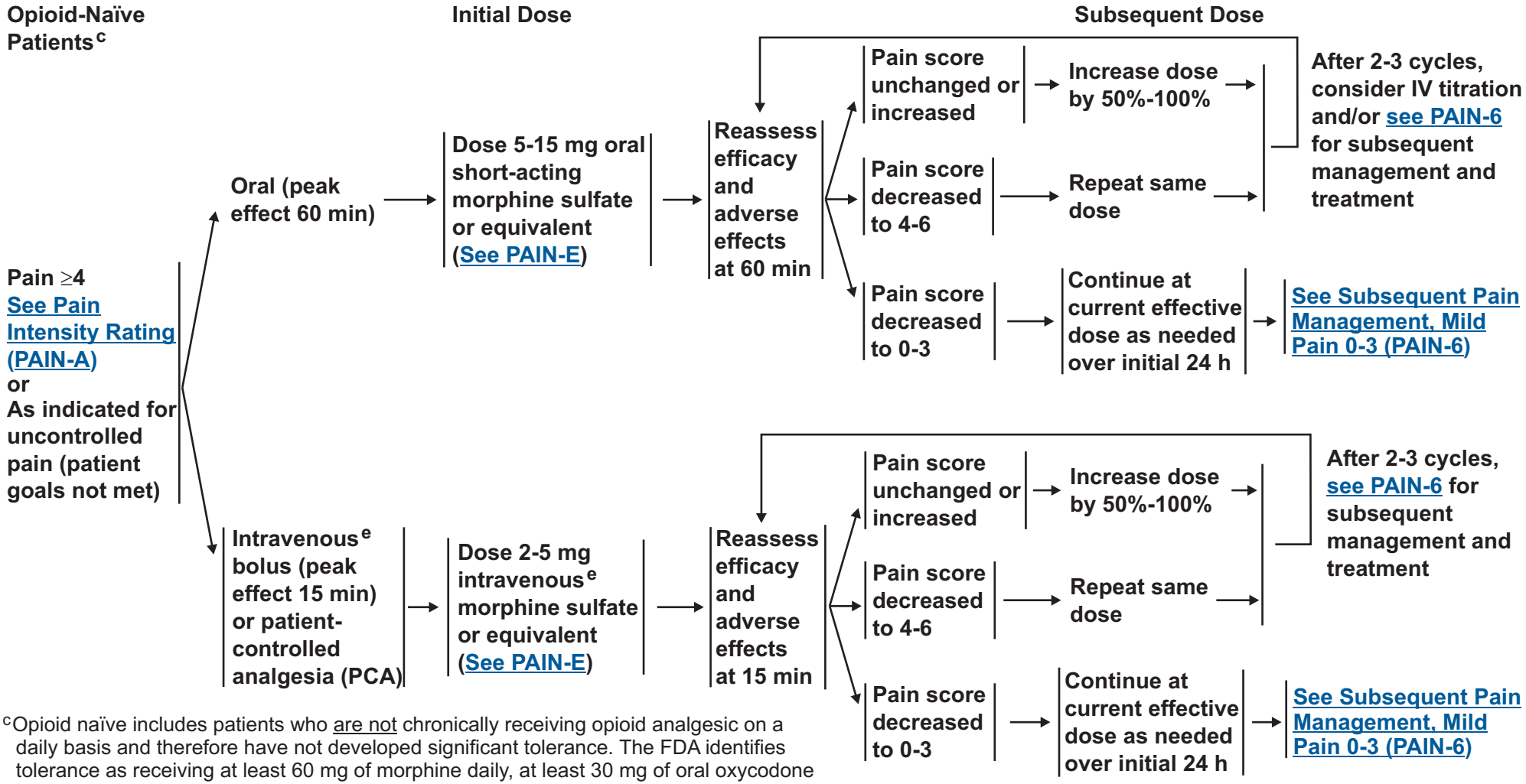
INITIATING SHORT-ACTING OPIOIDS IN OPIOID-NAÏVE PATIENTS[c]

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



[c]Opioid naïve includes patients who are not chronically receiving opioid analgesic on a daily basis and therefore have not developed significant tolerance. The FDA identifies tolerance as receiving at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

[e]Subcutaneous can be substituted for intravenous; however, peak effect subcutaneously is usually 30 min.

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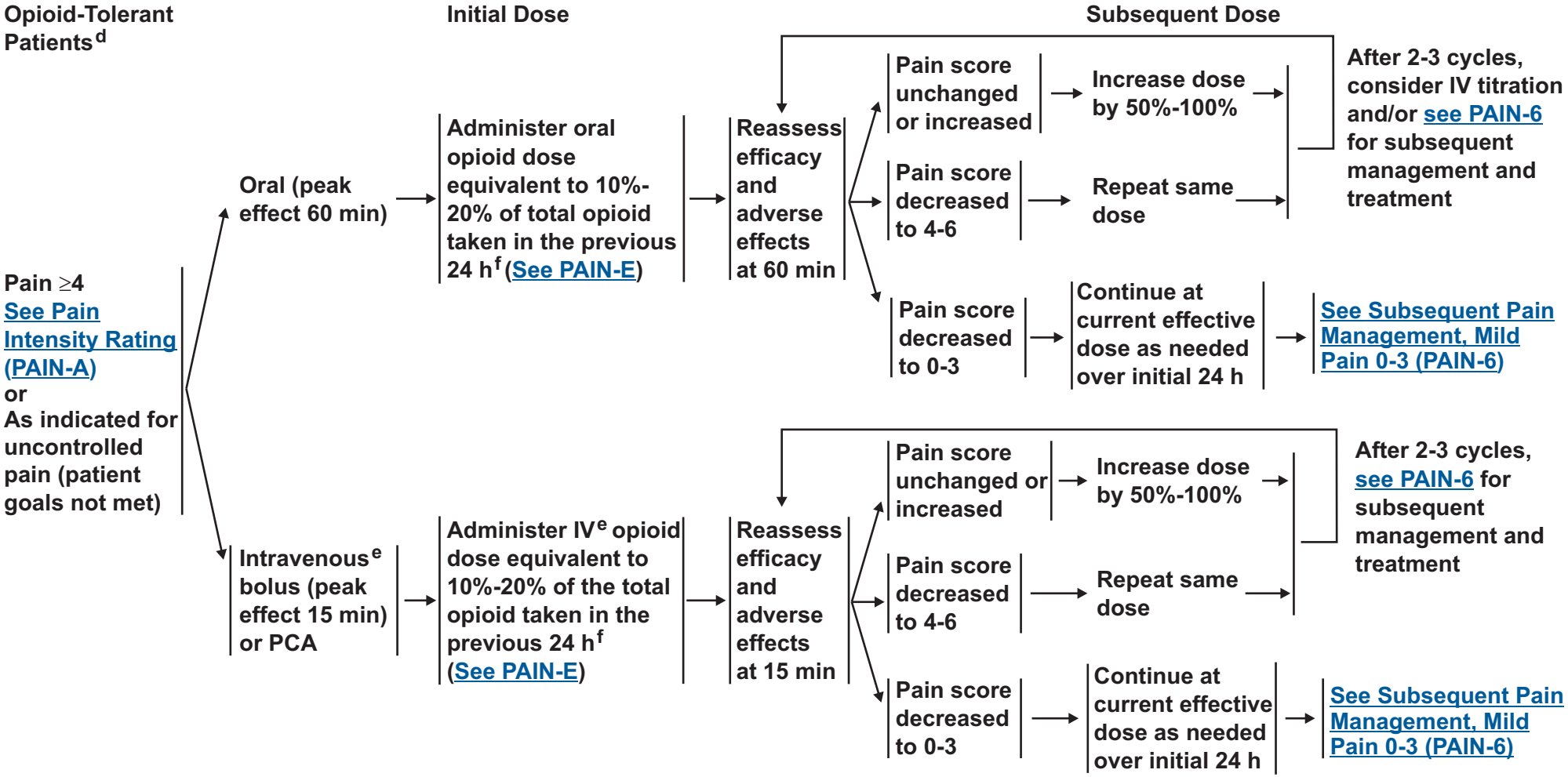
MANAGEMENT OF PAIN IN OPIOID-TOLERANT PATIENTS[d]

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



[d] Opioid tolerant includes patients who are chronically receiving opioid analgesic on a daily basis. The FDA identifies tolerance as receiving at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

[e] Subcutaneous can be substituted for intravenous; however, peak effect subcutaneously is usually 30 min.

[f] Not including transmucosal fentanyl dose.

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PAIN INTENSITY See Pain Intensity Rating (PAIN-A)

SUBSEQUENT PAIN MANAGEMENT[d]

GOALS OF TREATMENT

For *ALL* pain levels →
- For persistent pain, initiate regular schedule of opioid with rescue dose as needed
- Continue management of constipation (See PAIN-F)
- Provide psychosocial support (See PAIN-H)
- Provide patient and family/caregiver education (See PAIN-I)
- Optimize integrative interventions (See PAIN-J)

Severe Pain 7-10 →
- See management for *all* pain levels 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 adjuvant analgesics as indicated (See PAIN-G)

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

AND
- Continue opioid titration (See PAIN-E)
- Consider specific pain syndrome problems (See PAIN-D)
- Consider pain specialty consultation (See PAIN-L)
- Continue adjuvant analgesic titration (See PAIN-G)

Mild Pain 0-3 →
- See management for *all* pain levels above

AND
- Reassess and modify regimen to minimize adverse effects (See PAIN-E and See PAIN-F)
- Adjuvant analgesics as needed (See PAIN-G)

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

Achieved → See Ongoing Care (PAIN-7)

Not achieved →
- See Universal Screening and Assessment (PAIN-2)
- Consider pain management specialty consultation for interventional strategies (PAIN-M) or other treatments
- Consider palliative care consultation (See NCCN Palliative Care Guidelines)

[d] Opioid tolerant includes patients who are chronically receiving opioid analgesic on a daily basis. The FDA identifies tolerance as receiving at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

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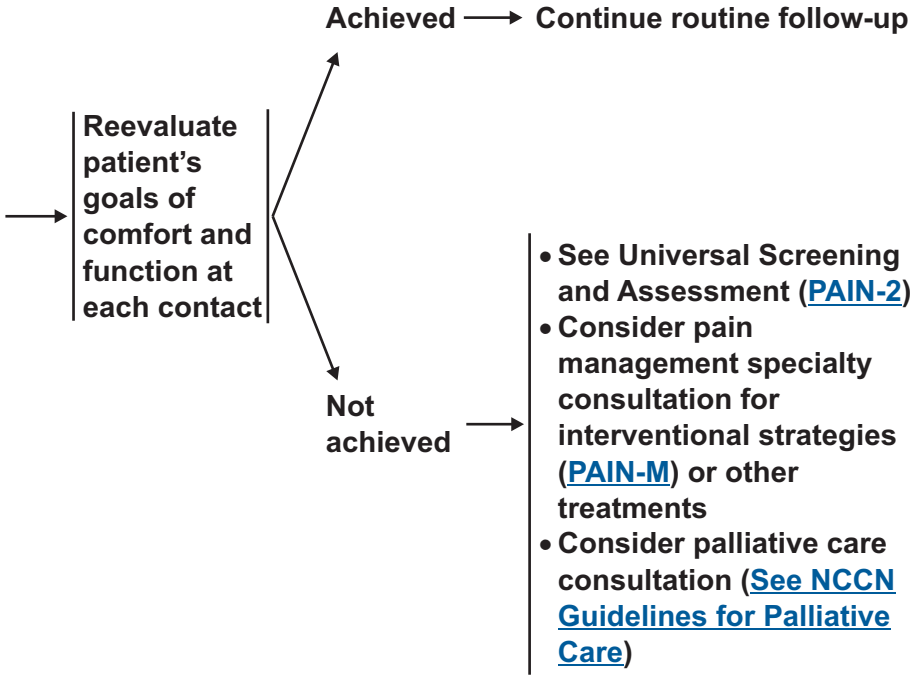
ONGOING CARE

- Convert to oral medications (if feasible) including extended-release or long-acting agent with rescue doses (Conversion details, see PAIN-E)
  - Simplify analgesic regimen for improved patient compliance, if feasible.
- 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
- Monitor for the use of analgesics as prescribed, especially in patients with risk factors for or history of abuse
- Provide written follow-up pain plan, including prescribed medications (See PAIN-I)
- Collaborate with patient's pharmacist
- Ensure adequate access to prescribed medications, especially during transition between sites of care
  - Clarify which clinician will be prescribing patient's ongoing analgesics
- Address system barriers
  - Analgesic cost/pharmacy benefit coverage
  - Availability of analgesics
  - Local laws/regulations
  - Obtain assistance from social services
- Instruct the patient on the importance of the following: (See PAIN-I)
  - Following documented pain plan
  - Scheduling and keep outpatient appointments
  - Contacting clinician if pain worsens or adverse effects are inadequately controlled, including availability of after hours assistance
  - Safely handling and disposing-of analgesics
- Process realistic goals, revise, and review
- Maintain communication and coordinate care with pain specialist and relevant providers, especially during transition between sites of care

GOALS OF TREATMENT



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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, "usual" pain, and "least" pain in the past 24 hours. For each pain intensity rating, use one of the scales below.**
- **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 pain from 0 (no pain) to 10 (worst pain you can imagine)?"**
- **Written: "Circle the number that describes your pain."**

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

Categorical scale:

"What word best describes your pain?"
None (0), Mild (1–3), Moderate (4–6), or Severe (7–10)

Table 2: The Faces Pain Rating Scale - Revised[1,2]

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]Hicks CL, von Baeyer CL, Spafford P, et al. The Faces Pain Scale - Revised: Toward a common metric in pediatric pain measurement. Pain 2001;93:173-183.
[2]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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Continued on next page
PAIN-A 2 of 2

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 other sources of distress, such as emotional stress or delirium, which may complicate assessment (See NCCN Guidelines for Distress Management). 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, including those available at http://prc.coh.org/pain_assessment.asp, is recommended. These tools are in varying stages of development and validation and include, but are not limited to:**
  - **The Assessment of Discomfort in Dementia (ADD) protocol[2]**
  - **Checklist of Nonverbal Pain Indicators (CNPI)[3]**
  - **The Pain Assessment in Advanced Dementia (PAINAD) scale[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]

- **Health care providers should be aware of impact of cultural and linguistic diversity during universal screening and comprehensive pain assessment and respond with trained interpreters and culturally and linguistically appropriate educational materials.**

[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 Manag Nurs 2000;1:13-21.
[4] Lane P, Kuntupis M, MacDonald S, et al. A pain assessment tool for people with advanced Alzheimer's and other progressive dementias. Home Healthc Nurse 2003;21:32-37.
[5] Payen JF, Bru O, Bosson JL, et al. Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med 2001;29:2258-2263.
[6] Gélinas C, Johnston C, et al. Pain assessment in the critically ill ventilated adult: validation of the Critical-Care Pain Observation Tool and physiologic indicators. Clin J Pain 2007;23:497-505.
[7] Al-Atiyyat 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

- **Anticipate and offer analgesic and anxiolytic therapy for procedures that are frequently accompanied by pain and/or 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, radiation procedure), as well as transportation/change in position for patient's with incident pain, merit pretreatment with an analgesic intervention.**

- **Providing information regarding all of the analgesic techniques described below prior to the procedure is ideal as it allows the patient and family/caregiver the time they may need to assimilate all of the information, ask questions, and master the techniques while reducing anticipatory anxiety.**
- **Intervention may be multimodal and potentially include one or more of the following as appropriate.**
  - **Analgesics**
    - **Supplemental doses of analgesics should be given in anticipation of procedure-related pain.**
    - **If procedure or transportation precludes continuation of IV PCA, give the prescribed IV bolus dose immediately before procedure/transport and administer a subcutaneous dose equivalent to 2-h basal infusion rate.**
    - **Additional analgesics and/or local anesthetics should be available immediately for further titration as needed.**
  - **Anxiolytics**
    - **Anxiolytics should be given preemptively when feasible.**
  - **Local anesthetics such as:**
    - **Topical local anesthetics creams (containing lidocaine, prilocaine, or tetracaine) applied to intact skin with sufficient time for effectiveness as per package insert.**
    - **Subcutaneous administration of lidocaine with a 27 gauge needle.**
  - **Administration of sedatives/analgesics/general anesthesia by trained personnel.**
  - **Integrative interventions for relief of pain and/or anxiety (See PAIN-J).**

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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).**
- **The goal of the comprehensive pain assessment is to find the cause of the pain and identify optimal therapies. Individualized treatment of the pain is based on the characteristics, cause of pain, the patient's clinical condition, and patient-centered goals of care.**
- **The etiology and pathophysiology of the pain should be investigated, including medical history (including psychosocial factors), physical exam, laboratory tests, and imaging studies.**
  - **Etiology factors may include direct involvement of cancer itself, cancer therapy (chemotherapy, RT, surgery) or procedures, and coincidental or noncancer pain (eg, arthritis).**
  - **Pathophysiology factors may include nociceptive, neuropathic, visceral, effective, behavioral, and cognitive components.**

- **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 3 of 3)
    - **General activity, mood, walking ability, work ability, relationship with others, sleep, appetite, and enjoyment of life**
  - **Timing: onset, duration, course, persistent, or intermittent**
  - **Description or quality**
    - **Aching, stabbing, throbbing, or pressure often associated with somatic pain in skin, muscle, and bone**
    - **Gnawing, cramping, aching, or sharp pain often associated with visceral pain in organs or viscera**
    - **Burning, tingling, shooting, or electric/shocking pain often associated with neuropathic pain caused by nerve damage**
  - **Aggravating and alleviating factors**
  - **Other current symptoms; symptom clusters**
  - **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?**

Pain experience continued

- **Response to current therapy**
  - **Pain relief**
  - **Patient adherence to medication plan**
  - **Medication adverse effects such as constipation, sedation, cognitive slowing, nausea, and others**
- **Breakthrough pain is episodic pain not controlled with existing pain regimen; see breakthrough pain on PAIN-E 3 of 10.**
- **Prior pain therapies**
  - **Reason for use, length of use, response, reasons for discontinuing, and adverse effects encountered**
- **Special issues relating to pain**
  - **Meaning and consequences of pain for patient and family/caregiver**
  - **Patient and family/caregiver knowledge and beliefs surrounding pain and pain medications**
  - **Cultural beliefs toward pain, pain expression, and treatment**
  - **Spiritual, religious considerations, and existential suffering**
  - **Patient goals and expectations regarding pain management**
  - **Assess for use of alternative or complementary therapies and screen for potential adverse interactions or effects**

Continued on PAIN-C 2 of 3

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Return to Universal Screening (PAIN-2)

COMPREHENSIVE PAIN ASSESSMENT

- **Psychosocial (See PAIN-H)**
  - **Patient distress (See NCCN Guidelines for Distress Management)**
  - **Family and other support; assess impact and burden on caregiver and recommend resources as appropriate**
  - **Psychiatric history including current or prior patient, family/caregiver, or household history of substance abuse**
  - **Risk factors for aberrant use or diversion of pain medication**
    - **Patient, environmental, and social factors as identified by a detailed patient evaluation[1] and/or screening tools (eg, SOAPP-R[2], ORT[3])**
  - **Risk factors for undertreatment of pain**
    - **Being a pediatric, geriatric, minority, or female patient; 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**
- **Laboratory and imaging studies to evaluate for disease progression**

[1]Moore,TM, Jones T, Browder JH, Daffron S, Passik S D. A comparison of common screening methods for predicting aberrant drug-related behavior among patients receiving opioids for chronic pain management. Pain Medicine 2009; 10;1426-1433.
[2]Butler SF, Fernandez K, Benoit C et al. Validation of the revised Screener and Opioid Assessment for Patients with Pain (SOAPP-R). J Pain 2008;9:360-372.
[3]Webster LR and Webster RM. Predicting aberrant behaviors in opioid-treated patients: Preliminary validation of the opioid risk tool. Pain Med 2005;6:432-442.

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Return to Universal Screening (PAIN-2)

IMPACT OF PAIN MEASUREMENT[4,5,6]

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

[4] 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.

[5] 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.

[6] 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-3; these interventions are meant to complement management.

- **Pain associated with inflammation:**
  - **Trial of NSAIDs or corticosteroids**

- **Bone pain without oncologic emergency:**
  - **NSAIDs and titrate analgesic to effect**
    See Non-Opioid Analgesic (Nonsteroidal Anti-Inflammatory Drugs [NSAIDs] and Acetaminophen) Prescribing (PAIN-K)
  - **Consider trial of bone-modifying agents (eg, bisphosphonates)**
  - **Diffuse bone pain: Consider hormonal therapy or chemotherapy, corticosteroids, and/or systemic administration of radioisotopes**
  - **Local bone pain: Consider local radiation therapy, nerve block (eg, rib pain), or vertebroplasty**
  - **Consider physical medicine evaluation**
    See Pain Specialty Consultation (PAIN-L)
  - **Consider orthopedic consultation for stabilization, if feasible**
  - **Consider referral to a pain specialist for interventional consultation. See Interventional Strategies (PAIN-M)**

- **Bowel obstruction**
  - **Evaluate etiology of bowel obstruction. If resulting from cancer, consider palliative surgery, radiation, and/or chemotherapy for symptomatic bowel obstruction.**
  - **Palliative management of bowel obstruction could include bowel rest, nasogastric suction (or percutaneous gastrostomy drainage), corticosteroids, and/or octreotide.**

- **Nerve pain**
  - **Nerve compression or inflammation:**
    - **Trial of corticosteroids**
  - **Neuropathic pain:**
    - **Trial of antidepressant, see PAIN-G**
      and/or
    - **Trial of anticonvulsant, see PAIN-G**
      and/or
    - **Consider trial of topical agent, see PAIN-G**
    - **For refractory pain,**
      - **Trial of opioid**
      - **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 Guidelines for Palliative Care.**

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OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY (1 of 10)

GENERAL PRINCIPLES

- The appropriate dose is the dose that relieves the patient's pain throughout the dosing interval without causing unmanageable adverse effects.
- Titrate with caution in patients with risk factors such as decreased renal/hepatic function, chronic lung disease, upper airway compromise, sleep apnea, and poor performance status.
- Generally, oral route is most common; however, other routes (ie, IV, subcutaneous, rectal, transdermal, transmucosal) 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-5).
- According to FDA guidelines, when higher doses of analgesic are needed, switch from preparations of opioid combined with other medications [such as aspirin or acetaminophen] to a pure opioid preparation to provide adequate analgesic to relieve pain while avoiding the toxicities of the non-opioid component of the combination (See PAIN-K).
- Steady state is achieved in about 5 half lives.
- If/when pain improves, it is important to look for opportunities to reduce opioid dose and optimize use of nonopioid analgesics as possible without compromising pain control. Where appropriate, opioid dose could be reduced by 10%-25% with subsequent reevaluation and further dose adjustment.
- If patient is experiencing unmanageable adverse effects and pain is <4, consider downward dose titration by approximately 25% and reevaluate. Close follow-up is required to make sure that the pain does not escalate, and that the patient does not develop symptoms of withdrawal.
- Consider opioid rotation if pain is inadequately controlled or there are persistent adverse effects from current therapy. Other indications for switching to a different opioid include: out-of-pocket costs, limitations based upon insurance formularies, etc.
- For breakthrough pain, see PAIN-E 3 of 10.
- Monitor for aberrant drug-taking behaviors. May include patient survey tool (eg, COMM[1]).

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[1]Butler SF, Budman SH, Fernandez KC, Houle B, et al. Development and validation of the Current Opioid Misuse Measure. Pain 2007;142:144-156.

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OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY (2 of 10)

OPIOIDS AND RISK EVALUATION AND MITIGATION STRATEGY (REMS)

- **Opioids are the principle analgesics for moderate to severe pain, yet opioids pose risks to patients and society. In the United States, poisoning is now the leading cause of death from injuries and 89% of poisonings are related to drugs. In 2008, of the 36,500 drug poisoning deaths, 14,800 (40%) involved opioid analgesics, compared to 5,100 cocaine-related deaths and 3,000 heroin-related deaths. See National Center for Health Statistics Data Brief, Drug Poisoning Deaths in the United States, 1980–2008.**
  - **Responding to the "public health crisis of addiction, misuse, abuse, overdose, and death" the FDA is in the process of establishing REMS programs for all potent opioid products. See Opioid Drugs and Risk Evaluation and Mitigation Strategies (REMS). Provider and patient education are the principle recommendations of proposed opioid REMS programs. Highlights include:**
    - **Prescriber should establish opioid analgesic goals of therapy for each patient and regularly evaluate therapeutic opioid response to guide further therapy.**
    - **Prescriber should evaluate each patient for risk factors associated with opioid misuse or abuse**
    - **Prescriber should educate each patient on safe use, storage, and disposal of opioid (See PAIN-I)**
    - **Prescriber should routinely monitor patients for opioid misuse or abuse.**
  - **REMS programs are currently in place for all transmucosal fentanyl products, transdermal fentanyl products, and transdermal buprenorphine (See Approved Risk Evaluation and Mitigation Strategies [REMS]), and in 2013 the FDA will introduce REMS starting with continuing education for morphine-naltrexone combination product, all extended-release opioids, and long-acting opioids (methadone). See FDA questions and answers for REMS for extended-release and long-acting opioid analgesics.**

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OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY (3 of 10)

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.
  - Initial range for converting to long-acting opioid would be 50% of the daily requirement.
- When possible, use the same opioid for short-acting and extended-release forms.
- Breakthrough pain (pain that fails to be controlled or "breaks through" a regimen of regularly-scheduled opioid) may require additional doses of opioid for pain not relieved by regular schedule of long-acting (eg, extended-release) opioid. Breakthrough pain may be further evaluated into the following categories, which have direct impact on treatment:
  - Incident pain: pain associated with or incident to specific activities or events, potentially managed with short-acting opioid given in anticipation of those events
  - End-of-dose failure pain: pain recurring towards the end of dosing interval for regularly scheduled opioid, potentially managed by increasing the dose or frequency of regularly scheduled opioid
  - Uncontrolled persistent pain: pain routinely uncontrolled by existing regularly scheduled opioid, potentially managed by adjusting dose of regularly scheduled opioid
  - 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.
- 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 rapidly acting transmucosal fentanyl (various formulations and delivery systems are available) in opioid-tolerant patients for brief episodes of incident pain not attributed to inadequate dosing of around-the-clock opioid.
  - Data do not support a specific transmucosal fentanyl dose equianalgesic to other opioids or between different transmucosal formulations. Always initiate transmucosal fentanyl with lowest dose in chosen formulation and titrate to effect. (See specific transmucosal prescribing information for appropriate dosing intervals.)

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OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY (4 of 10)

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]
Morphine[2,3]	10 mg	30 mg	3	3-4 h
Hydromorphone[2]	1.5 mg	7.5 mg	5	2-3 h
Fentanyl[4]	–	–	–	–
Levorphanol[5]	2 mg	4 mg	2	3-6 h
Methadone[5,6]	–	–	–	–
Oxycodone	–	15-20 mg	–	3-5 h
Hydrocodone[7]	–	30-45 mg	–	3-5 h
Oxymorphone	1 mg	10 mg	10	3-6 h
Codeine[2,8]	–	200 mg	–	3-4 h

NOT RECOMMENDED

Meperidine[10]

Mixed agonist-antagonists[11] (pentazocine, nalbuphine, butorphanol)

See Miscellaneous Analgesics (PAIN-E 5 of 10)

[2] Codeine, morphine, or hydromorphone should be used with caution in patients with fluctuating renal function due to potential accumulation of renally cleared metabolites - monitor for neurologic adverse effects.

[3] Conversion factor listed for chronic dosing.

[4] In single-dose administration, 10 mg IV morphine is equivalent to approximately 100 mcg IV fentanyl but with chronic fentanyl administration, the ratio of 10 mg IV morphine is equivalent to approximately 250 mcg IV fentanyl. For transdermal fentanyl conversions, see PAIN-E 7 of 10.

[5] Long half-life, observe for drug accumulation and adverse 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 Special Notes Regarding Oral Methadone PAIN-E 9 of 10).

[7] Equivalence data not substantiated. Clinical experience suggests use as a mild, initial use opioid but effective dose may vary. Hydrocodone is only available commercially combined with acetaminophen (325 to 750 mg/tablet) or ibuprofen (200 mg/tablet). The FDA will be limiting the amount of acetaminophen in all prescription drug products to no more than 325 mg per dosage unit. Dosage must be monitored for safe limits of ASA or acetaminophen.

[8] Codeine has no analgesic effect unless it is metabolized into morphine, morphine-6-glucuronide; therefore, in the 10%-30% of individuals in whom metabolism is ineffective, codeine would have no analgesic effect and should be avoided. 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.

[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 metabolite - normeperidine.

[11] 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.

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OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY (5 of 10)

MISCELLANEOUS ANALGESICS

Mixed-mechanism drugs:

- **Tramadol is a weak mu-opioid agonist with some norepinephrine and serotonin reuptake inhibition used for mild to moderate pain. A maximum daily dose of 400 mg (100 mg four times daily) is recommended for adults with normal hepatic and renal function, and lower daily doses are recommended for older adults (75 y and greater) and those with hepatic and/or renal dysfunction, to reduce the risk of seizures. Even at a maximum dose of 100 mg four times a day, tramadol is less potent than other opioid analgesics such as morphine.**
- **Tapentadol[12] is a mu-opioid analgesic with norepinephrine reuptake inhibition for treatment of moderate to severe pain. Typical doses would start at 50-100 mg PO every 4 hours PRN, with a maximal daily dose of 500 mg per day (if using the extended release) or 600 mg per day (if using the immediate release only) due to lack of published data regarding higher doses. Some comparative data suggest tapentadol may have a lower incidence of gastrointestinal (GI) adverse effects than oxycodone.**

Partial agonists:

- **Transdermal buprenorphine,[13] a partial mu-agonist, has been approved for chronic pain. Although experience with this drug in the management of cancer pain is limited, anecdotal reports, a few small prospective uncontrolled studies, and at least one randomized trial support its use in cancer-related pain. Because buprenorphine is a partial mu-receptor agonist, it exhibits a ceiling to analgesic efficacy and may precipitate withdrawal symptoms if administered to individuals currently taking a high-dose opioid. FDA guidelines recommend limiting dose to 20 mcg per hour due to concern for QT prolongation.**

Non-opioid analgesic:

- **Ketamine[14] is a noncompetitive NMDA receptor antagonist that blocks glutamate. Low (subanesthetic) doses produce analgesia and modulate central sensitization, hyperalgesia, and opioid tolerance. There are only limited data regarding the use of ketamine as an adjuvant to opioids for management of cancer pain.**

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[12] Hartrick CT, Rodriguez Hernandez JR: Tapentadol for pain: a treatment evaluation. Expert Opin Pharmacother 2012;13: 283-286.
[13] Pergolizzi JV Jr, Mercadante S, Echaburu AV, et al, Euromed Communications meeting. The role of transdermal buprenorphine in the treatment of cancer pain: an expert panel consensus. Curr Med Res Opin 2009;25:1517-1528.
[14] Bell RF, Eccleston C, Kalso EA. Ketamine as an adjuvant to opioids for cancer pain. Cochrane Database of Systematic Reviews 2012, Issue 11. Art. No.: CD003351. DOI: 10.1002/14651858.CD003351.pub2.

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OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY (6 of 10)

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 4 of 10).**
  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.**
  4. **If previous dose was ineffective, may begin with 100% or 125% of equianalgesic dose.**
  5. **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).**
  6. **Data do not support a specific transmucosal fentanyl dose equianalgesic to other opioids or between different transmucosal formulations. Always initiate transmucosal fentanyl with lowest dose in chosen formulation and titrate to effect. (See specific transmucosal prescribing information for appropriate dosing intervals.)**

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 4 of 10, 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, MAINTENANCE, AND SAFETY (7 of 10)

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 morphine.**
  2. **From Table 2, select the mcg-per-hour dose of transdermal fentanyl based on the 24-h dose of morphine as listed. For fentanyl dosage requirements >100 mcg/h, multiple patches are used. See Table 1 (PAIN-E 4 of 10) for converting other opioids to morphine equivalent with subsequent conversion to transdermal fentanyl.**

Table 2 Recommended Dose Conversion from Morphine to Transdermal Fentanyl[15]

See next page for case examples

Transdermal Fentanyl	Morphine	
	IV/SubQ *	Oral
12 mcg/h	10 mg/d	30 mg/d
25 mcg/h	20 mg/d	60 mg/d
50 mcg/h	40 mg/d	120 mg/d
75 mcg/h	60 mg/d	180 mg/d
100 mcg/h	80 mg/d	240 mg/d

See Table 1 (PAIN-E 4 of 10) for converting other opioids to morphine equivalent with subsequent conversion to transdermal fentanyl.

*** 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, topical application of heat (such as heat from heat lamps, electric blankets, etc.), or extreme exertion may accelerate transdermal fentanyl absorption and are contraindications for transdermal fentanyl.**
- **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 hours.**
- **Once the levels have reached a steady state after at least 2-3 days, increase the patch dosage based on the average amount of stable daily as-needed (prn) opioid required. Continue breakthrough medication once the patch dose is stabilized.**
- **When converting from continuous parenteral infusion fentanyl to transdermal fentanyl, a straight 1:1 ratio[16] 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.**

[15] Breitbart W, Chandler S, Eagel B, et al. An alternative algorithm for dosing transdermal fentanyl for cancer-related pain. Oncology 2000;14:695-702.

[16] 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, MAINTENANCE, AND SAFETY (8 of 10)

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

Example of opioid using Table 2 directly:
Case example of converting oral morphine to transdermal fentanyl patch
A patient is taking 30 mg of sustained-release oral morphine every 12 h and needs to be converted to transdermal fentanyl patch.

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

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

Example of opioid not listed in 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 4 of 10, convert to 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 7 of 10, 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, MAINTENANCE, AND SAFETY (9 of 10)

Special Notes Regarding Oral Methadone:

- **Due to the unique nature of methadone with a long and variable half-life, caution should be used and frequent and careful evaluation should be performed.**
- **The conversion ratio varies with the amount of morphine (or other opioid) a patient has been using chronically. The higher the dose of morphine, the more potent methadone is. PRACTITIONERS ARE ADVISED TO CONSULT WITH A PAIN OR PALLIATIVE CARE SPECIALIST IF THEY ARE UNFAMILIAR WITH METHADONE PRESCRIBING or if individual patient considerations necessitate very rapid switching to or from methadone.**
- **To a significantly greater extent than with other opioids, methadone has been associated with many drug-drug interactions. The potential for such interactions must be investigated in each patient before initiating methadone.**
- **Methadone is commercially available in 5 mg, and 10 mg tablets and 1 mg/mL, 2 mg/mL, and 10 mg/mL oral solution.**
- **Methadone may be titrated up every 5-7 days, usually by 5 mg/dose. If more rapid titration is desired, consult with pain or palliative care specialist.**
- **Methadone is typically given at a regular schedule with additional doses of a short-acting opioid given as needed.**
- **Because methadone is associated with QTc prolongation, a baseline and follow-up electrocardiogram (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. QTc $\geq$ 450 may indicate need to reduce or discontinue methadone dose.**
- **These conversion ratios should NOT be used in converting from 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.**
- **It may be necessary to educate patients and families about analgesic utility of methadone. Some may only be familiar with methadone use for maintenance of addiction and be unaware of its utility as a potent opioid analgesic.**

See Convert from Oral Morphine to Oral Methadone (PAIN-E 10 of 10)

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OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY (10 of 10)

CONVERT FROM ORAL MORPHINE TO ORAL METHADONE[17]

See Special Notes Regarding Oral Methadone (PAIN-E 9 of 10)

- **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 dose titration is recommended. A pain or palliative care specialist should be consulted.

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 above, 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)

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

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MANAGEMENT OF OPIOID ADVERSE EFFECTS (1 of 3)

Principles of Management of Opioid Adverse Effects

- Adverse effects to opioids are common, should be anticipated, and should be managed aggressively.
- Patient and family/caregiver education is essential for successful anticipation and management of pain and opioid adverse effects.
- Recognize that pain is rarely treated in isolation in cancer and adverse effects may be from other treatments or cancer itself.
- Opioid adverse effects generally improve over time, except with constipation. Maximize non-opioid and nonpharmacologic interventions to limit opioid dose and treat adverse effects. If adverse effects persist, consider opioid rotation.
- Multisystem assessment is necessary.
- Information from patient and family/caregiver about adverse effects is essential for appropriate opioid dose adjustment and treatment of adverse effects.

Constipation

- Preventive measures
  - Prophylactic medications
    - Stimulant laxative ± stool softener (eg, senna ± docusate, 2 tablets every morning; maximum 8-12 tablets per day).
    - Polyethylene glycol (1 capful/8 oz water PO two times a day)
    - Increase dose of laxative when increasing dose of opioids
  - Maintain adequate fluid intake
  - While maintaining adequate dietary fiber intake is recommended, supplemental medicinal fiber such as psyllium (eg, Metamucil) is unlikely to control opioid-induced constipation and is not recommended.
  - Stool softener (docusate) alone may not provide benefit in well-hydrated patients
  - Exercise, if feasible
- If constipation develops
  - Assess for cause and severity of constipation
  - Rule out obstruction
  - Titrate stool softener/laxatives as needed with goal of one non-forced bowel movement every 1-2 d
  - Consider adjuvant 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; 1 rectal suppository daily; lactulose, 30-60 mL daily; sorbitol, 30 mL every 2 h x 3, then as needed;
    magnesium citrate, 8 oz PO daily; or 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, 10-15 mg PO 4 times a day; consider limiting chronic use to maximum 3 mo, due to concern for neurologic complications [tardive dyskinesia], especially in frail, elderly patients)
  - 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
  - For intractable chronic constipation, consider opioid rotation to fentanyl or methadone
  - Consider neuraxial analgesics, neuroablative techniques, or other interventions to decrease pain, alleviate constipation, and/or reduce opioid dose

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MANAGEMENT OF OPIOID ADVERSE EFFECTS (2 of 3)

Nausea

- Preventive measures
  - Ensure that patient is having bowel movements consistently.
  - For patients with a prior history of opioid-induced nausea, prophylactic treatment with antiemetic agents (see below) is highly recommended.
- If nausea develops
  - Assess for other causes of nausea (eg, central nervous system pathology, chemotherapy, radiation therapy, hypercalcemia).
  - Consider prochlorperazine, 10 mg PO every 6 h as needed; or metoclopramide, 10-15 mg PO 4 times daily as needed; or haloperidol, 0.5-1 mg PO every 6-8 h. Chronic use of any of these agents may be associated with development of tardive dyskinesia, especially in frail, elderly patients.
  - If nausea persists despite as-needed regimen, administer antiemetics around the clock for 1 wk, then change as needed.
  - Consider adding a serotonin antagonist (eg, ondansetron, 8 mg PO 3 times a day; granisetron, 2 mg PO daily). Use with caution as constipation is an adverse effect.
  - Dexamethasone can be considered.
  - Consider olanzapine, 2.5-5 mg, especially with bowel obstruction.
- Opioid-induced nausea may resolve with continued exposure; 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, neuroablative techniques, and other interventions to potentially reduce opioid dose.

Pruritus

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

Delirium

- Assess for other causes of delirium (eg, hypercalcemia, CNS, metastases, other psychoactive medications)
- If other possible causes of delirium are excluded, consider changing the opioid
- Consider nonopioid analgesic to allow reduction of the opioid dose
- Consider initial titration with 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 per day. With prolonged administration of these agents, it may be necessary to decrease dose due to long elimination half-life.
- For further information about delirium, see NCCN Guidelines for Palliative Care.

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MANAGEMENT OF OPIOID ADVERSE EFFECTS (3 of 3)

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

- Patients with limited cardiopulmonary reserve are more susceptible.
- Hypercarbia occurs before hypoxia.
- If respiratory problems or opioid-induced sedation occurs, consider naloxone administration but use reversing agents cautiously.
  - 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 [plasma half-life is 30-80 minutes]).
  - If the patient is not responsive within 10 minutes and total naloxone dose of 1 mg, consider another reason for the change in neurologic status.
- If reversing an opioid with a long half-life such as methadone or for persistent opioid-induced sedation, consider naloxone infusion.
- Closely monitor for the recurrence of pain as opioid is metabolized during reversal, which may require a cautious administration of an additional opioid.

Sedation

- If significant or unexpected sedation develops and persists for more than 2-3 d after initiating or a significant upward titration of an opioid
  - Assess for other causes of sedation (eg, CNS pathology, other sedating medications, hypercalcemia, dehydration, sepsis, hypoxia)
  - Consider a lower dose of opioid given more frequently to decrease peak concentrations
  - Decrease the dose of opioid if pain control can be maintained at a lower dose
  - Consider opioid rotation
  - Consider nonopioid analgesic to allow reduction of the opioid dose
  - 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, neuroablative techniques, and other interventions to potentially reduce opioid dose
- If the patient has had marked sleep deprivation related to poor pain control, adjustments of analgesics to improve pain control may result in "catch up" sleep lasting 2-3 days. Therefore, extreme fatigue can result in somnolence that may be difficult to differentiate from opioid-induced sedation. If related to fatigue, patients generally can be fully aroused, although this may require some effort.

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ADJUVANT ANALGESICS FOR NEUROPATHIC PAIN (1 of 2) (ANTIDEPRESSANTS, ANTICONVULSANTS, AND TOPICAL AGENTS)

Principles of Adjuvant Analgesic Use

- Antidepressants and anticonvulsants are first-line adjuvant 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 adjuvant analgesics in the cancer population is often based on guidelines or experience derived from data for the treatment of pain not caused by cancer (non-malignant pain).
- Effective use is predicated on an assessment that clarifies the nature of the pain as most adjuvant analgesics are more likely to be effective in management of neuropathic pain.
- As with opioids, response to adjuvant analgesics may vary according to the type/cause of neuropathic pain and the individual patient.
- Drug selection may be influenced by other symptoms and comorbidities. For example, a sedating drug may be useful in a patient in whom insomnia is a problem.
- Patient education should emphasize the trial and error nature of the treatment so patients do not get discouraged.
- Doses should be increased until the analgesic effect is achieved, adverse effects become unmanageable, or the conventional maximal dose is reached.

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

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ADJUVANT ANALGESICS FOR NEUROPATHIC PAIN (2 of 2) (ANTIDEPRESSANTS, ANTICONVULSANTS, TOPICAL AGENTS, AND CORTICOSTEROIDS)

Examples of Adjuvant Analgesics Use

- Extrapolated from non-cancer neuropathic pain management
- Both antidepressants and anticonvulsants are frequently used as an adjuvant analgesic in combination with an opioid to treat neuropathic components of pain.

- Antidepressants: Analgesic effectiveness is not dependent on its antidepressant activity. Effective analgesic dose 1) may be lower than that required to treat depression, and 2) the onset of analgesic relief may occur earlier than anti-depressive effects.
- Frequently used as an adjuvant 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, and 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

Note: Some SSRI, SNRI antidepressants may inhibit the conversion of tamoxifen to its active metabolite, thereby decreasing the effectiveness of tamoxifen - see Discussion.

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

- Topical agents: Act locally and may be used as an adjuvant 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

- 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

- **Due to the complexity of cancer-related pain and associated symptoms, health care providers should anticipate patients' and families' need for support and education in management strategies.**
- **Assessing each patients' need for psychosocial support is an essential component of a comprehensive pain assessment (See PAIN-C).**

Support

- **Inform patient and family/caregiver that emotional reactions to pain are normal and are evaluated and treated as part of pain treatment.**
- **Provide emotional support to patient and family/caregiver that acknowledges that 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/caregiver 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 being available to help with pain management.**
- **Inform patient and family/caregiver 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; provide education and support as indicated.**
- **Verbally repeat your concern and the plan of action to be taken.**

Skills training

- **Teach coping skills (to be used in conjunction with and not in lieu of appropriate analgesia) 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**
  - **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**
  - **Training to encourage assertiveness to maximize comfort**
- **Educate patient and family/caregiver that in pain management a team effort is necessary to comprehensively assess and treat the impact of pain. Members of the team may include: oncologist, nurse, pain specialist, palliative care clinician, physiatrist, neurologist, psychologist, social worker, psychiatrist, physical therapist, and spiritual counselor.**
  See Patient and Family/Caregiver Education (PAIN-I)

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PATIENT AND FAMILY/CAREGIVER EDUCATION (1 of 2)

- **To assess for patient and family/caregiver educational needs regarding pain treatment, the health care team should:**
  - **Assess for meaning and consequences of pain for patient and family/caregiver.**
  - **Assess for literacy to ensure understanding of education.**
  - **Assess existing knowledge of pain and pain treatment to aid in developing appropriate patient and family/caregiver education plan.[1,2]**

- **Messages to be conveyed to patient and family/caregiver regarding management of pain**
  - **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 an analgesic on a regular schedule will improve pain control.**
  - **Patients with pain often have other symptoms (eg, constipation, nausea, fatigue, insomnia, depression) that need to be controlled; management of these other symptoms may facilitate control of pain.**

- **Messages to be conveyed to patient and family/caregiver regarding opioid analgesics**
  - **Morphine and morphine-like medications are principle medications used to relieve severe pain.**
    - **If you take these medications now, they will still work later.**
    - **If these medications do not work, many other options are available.**
  - **When these medications are used to treat cancer pain, addiction is rarely a problem unless addiction issues existed before the cancer pain.**
    - **Patients with a history of prescription, illicit drug, or alcohol dependence/substance abuse may be at increased risk for prescribed medication misuse/abuse (see PAIN-L).**
    - **Patients with history of opioid use/abuse may also have increased tolerance, which may require higher doses for optimal pain control (see PAIN-L).**
  - **These medications are controlled substances and must be used with caution:**
    - **These medications should not be mixed with alcohol or illicit substances.**
    - **Potent analgesics should be taken only as prescribed and by the person for whom the medication is prescribed; advise patients not to self-adjust dosage or frequency unless discussed with health care provider; and advise patients to contact healthcare provider if the pain management regimen is not controlling their pain.**
    - **Analgesics must be in a secured location, preferably a locked box and not in a medicine cabinet.**
    - **Unused or unneeded medications (especially opioid analgesics) must be properly disposal of:**
      - **In general, advise not to flush down sink or toilet.**
      - **Check with local pharmacy or law enforcement about proper medication disposal.**
      - **Read the product-specific disposal information included with the extended release/long-acting opioid product.**
    - **Provide information pertaining to local regulations regarding the operation of machinery or motor vehicles while taking potentially sedating medication and advise patient and family/caregiver accordingly and provide appropriate medical counseling.**

[1] Stewart M, Brown JB, Donner A, McWhinney I, et al. The impact of patient centered care on outcomes. The Journal of Family Practice 2000;49:797-804.
[2] Syrjala KL, Abrams JR, Polissar NL, et al. Patient training in cancer pain management using integrated print and video materials: a multisite randomized controlled trial. Pain 2008,135:175-186.

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PATIENT AND FAMILY/CAREGIVER EDUCATION (2 of 2)

- **Communication with the health care provider is critical for the patient and family/caregiver to assist in meeting goals of care.**
  - **Explain that health care providers cannot discern the patient's pain level, and that describing pain is not viewed as "complaining," but rather is an essential source of information to enable the health care provider to adjust treatment.**
  - **Explain that health care providers want to know about any problems the patient believes the pain medications may be causing, as there are probably ways to alleviate these issues.**
  - **Tell the patient to let the health care providers know about difficulty obtaining medication or concerns about taking medication. Explain that providers have dealt with such issues before and that they can help.**
  - **Expect optimal management for pain and adverse effects. Inform the patient of the right to expect pain management as part of overall care.**

- **The following must be reviewed with each patient and family/caregiver 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**
    - **Plan for obtaining refilled prescriptions, especially schedule II narcotics that cannot be ordered by telephone**
  - **A list of potential adverse effects of these medications and what to do if they occur**
    - **List may be provided by clinician and/or pharmacy**
  - **A list of all medications to be discontinued**
  - **A list of telephone numbers to reach an appropriate health care 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**
    - **Problems with bowel movements, including 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, including availability of after hours assistance**
  - **A plan for proper storage and disposal (see PAIN-I 1 of 2)**

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.

INTEGRATIVE INTERVENTIONS

Consider integrative interventions in conjunction with pharmacologic interventions as needed. Integrative interventions may be especially important in vulnerable populations (eg, frail, elderly, pediatric) in whom standard pharmacologic interventions may be less tolerated or based on patient preference. The utility of integrative interventions underscores the necessity for pain management to be carried out with a team approach that contains a wide range of treatment options.

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**
- **Spiritual care (See NCCN Guidelines for Distress Management)**
- **See Interventional Strategies (PAIN-M)**

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NON-OPIOID ANALGESIC (NONSTEROIDAL ANTI-INFLAMMATORY DRUGS [NSAIDS] AND ACETAMINOPHEN) PRESCRIBING (1 of 2)

Acetaminophen

- Acetaminophen, 650 mg every 4 h or 1 g every 6 h (daily maximum 4 g/d) in adult patients with normal liver function. The FDA is currently evaluating daily maximum dosing and has considered the daily maximum dose for chronic use be limited to 3 g/d or less.
- 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 the FDA website (www.fda.gov) for the latest information on acetaminophen adverse effects and dosing.

NSAIDs

- Use NSAIDs with caution in patients at high risk for renal, GI (upper GI surgery, RT), or cardiac toxicities; thrombocytopenia; or bleeding disorder.
- Note that the potential adverse effects of chemotherapy (especially angiogenesis inhibitors), such as hematologic (thrombocytopenia, coagulopathy), renal, hepatic, and cardiovascular toxicities, can be increased by the concomitant prescription of NSAIDs.
- For some patients opioid analgesics may be a safe and effective alternative analgesic to NSAIDs.
- Use any NSAID that the patient has found to be effective and well tolerated in the past; otherwise, consider ibuprofen to the maximal dose.
  - Ibuprofen, 400 mg four times a day (daily maximum = 3200 mg)
  - If needed, consider short-term use of ketorolac, 15-30 mg IV every 6 h for a 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

Continued on next page

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NON-OPIOID ANALGESIC (NONSTEROIDAL ANTI-INFLAMMATORY DRUGS [NSAIDS] AND ACETAMINOPHEN) PRESCRIBING (2 of 2)

- **NSAIDs and toxicities**
  - **Patients at high risk for *renal toxicities*: age >60 y, compromised fluid status, multiple myeloma, diabetes, interstitial nephritis, papillary necrosis, and concomitant administration of other nephrotoxic drugs (including cyclosporin, cisplatin) and renally excreted chemotherapy**
    - **Treatment of *renal toxicities*: reevaluate NSAID use if renal function deteriorates 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, concomitant steroid use**
    - **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 adverse effects and do not inhibit platelet aggregation; however, they have not been demonstrated to have reduced renal adverse effects.**
    - **Consider adding antacids, H2 receptor antagonists, misoprostol, or omeprazole. If patient develops GI peptic ulcer or GI 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.[1] 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 congestive heart failure or hypertension develops or worsens. Naproxen and ibuprofen are preferred NSAIDs for individuals at high risk for cardiac toxicities.**
  - **Monitoring for NSAID toxicities:**
    - **Baseline blood pressure, BUN, creatinine, liver function studies [alkaline phosphatase, LDH, SGOT, SGPT], CBC, and fecal occult blood**
    - **Repeat every 3 mo to ensure lack of toxicity**
- **Further NSAID considerations:**
  - **If 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 in place of oral NSAIDs.**
  - **Toxicity of anti-cancer treatment may increase the risk profile of anti-inflammatory treatment.**

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

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SPECIALTY CONSULTATIONS FOR IMPROVED PAIN MANAGEMENT

- **Major indication for referral is:**
  - Pain likely to be relieved or function improved through consultation delivered by a specialty service provider as suggested below. Note that the specific provider of these services may vary in different treatment settings.

- **Pain and palliative care specialty consultation**
  See NCCN Guidelines for Palliative Care
  - Consider interventional strategies (See PAIN-M)
  - Management of symptoms refractory to initial treatment
  - Management of sleep disturbances
  - Diagnosis and treatment of underlying condition
  - Consider oral or IV ketamine for pain resistant to other analgesics
  - Consider palliative sedation for intractable pain
  - Adjustment of drugs and doses beyond the expertise of the primary team/oncologist
  - Management of complicated psychosocial issues, including aberrant drug behavior
  - Clarity of goals of care, especially regarding pain and medication side effects

- **Psychiatric consultation**
  - Pharmacologic management and psychotherapy

- **Depression/distress consultation**
  See NCCN Guidelines for Distress Management

- **Psychology consultation**
  - Cognitive modalities
    - Imagery/hypnosis
    - Distraction training
    - Relaxation training
    - Active coping training
    - Graded task assignments, setting goals, pacing, and prioritizing
    - Cognitive behavioral training

- **Social work consultation**
  - Caregiver burden and support needs
  - Recommend use of community care resources

- **Substance abuse consultation if questions/concerns about medication misuse or diversion**
  - Evaluate 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

- **Spiritual care consultation**
  - Determine importance to patient and family/caregiver and current availability of support
  - Manage spiritual, existential concerns

- **Physical/occupational therapy, rehabilitation/mobility specialty consultation**
  - Physical modalities
    - Bed, bath, and walking supports
    - Positioning instruction
    - Energy conservation, pacing of activities
    - Massage
    - Heat and/or ice
    - TENS
    - Acupuncture or acupressure
    - Ultrasonic stimulation
  - Lymphedema management

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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, peripheral/plexus nerve)**
  - **Failure to achieve adequate analgesia and/or the presence of intolerable adverse 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, and clonidine, useful for acute postoperative pain**
    - **Intrathecal: easy to internalize to implanted pump; for infusions of opioids, local anesthetics, clonidine, and ziconotide**
    - **Regional plexus: for infusions of local anesthetics, 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 or intrathecal, intercostal, or dorsal root ganglion neurolysis**
    - **Upper abdominal pain (visceral): celiac plexus block, thoracic splanchnicectomy**
    - **Midline pelvic pain: superior hypogastric plexus block**
    - **Rectal pain: intrathecal neurolysis, midline myelotomy, superior hypogastric plexus block, or ganglion impar block**
    - **Unilateral pain syndromes: cordotomy**
    - **Consider intrathecal L/S phenol block**
  - **Neurostimulation procedures for cancer-related symptoms (ie, peripheral neuropathy, neuralgias, complex regional pain syndrome)**
  - **Radiofrequency ablation for bone lesions**

- **If interventional approaches are appropriate**
  - **Evaluate which pain site can be relieved**
  - **Verify that interventional technique will provide sufficient 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

This discussion is being updated to correspond with the newly updated algorithm. Last updated 09/26/12

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

Pain is one of the most common symptoms associated with cancer. Pain is defined by the International Association for the Study of Pain (IASP) as an unpleasant multidimensional, sensory and emotional experience associated with actual or potential tissue damage, or described in relation to 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. There is mounting evidence in oncology that survival is linked to pain control.[5]

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.[6-8] 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).[9, 10] 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 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Adult Cancer Pain is unique in several important ways. First, it lists the principles of pain management:

- All patients must be screened for pain at each contact and a comprehensive pain assessment must be performed.
- Comprehensive management of pain is needed as most patients have multiple pathophysiologies.
- Analgesic therapy must be administered in conjunction with the management of multiple symptoms or symptom clusters and the complex pharmacologic therapies that patients with cancer are generally prescribed.

- Pain intensity must be quantified by the patient (whenever possible), the NCCN Guidelines bases therapeutic decisions on a numerical value assigned to the severity of the pain.
- Reassessment of pain intensity must be performed at specified intervals to ensure that the therapy selected is having the maximum benefit with as few adverse effects as possible.
- A multidisciplinary team may be needed for comprehensive pain management.
- Psychosocial support must be made available.
- Specific educational material must be provided to the patient and family.
- The experience of pain has been associated with suffering. The multi-dimensional impact of “suffering” on patients and their families must be considered and these concerns must be addressed in a culturally respectful manner.

Second, the NCCN Guidelines acknowledge the range of complex decisions faced in the management of these patients. As a result, they provide dosing guidelines for opioids, non-opioid analgesics, and adjuvant 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.[11, 12]

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.[13] 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 (CNS). 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. It is therefore important to find the cause of the pain and identify optimal therapies. This algorithm begins with the premise that all patients with cancer should be screened for pain 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).[14-17] 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. 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. The comprehensive pain assessment should focus on the type and quality of pain, pain history (such as onset, duration, course, etc.), pain intensity (i.e., pain experienced at rest; with movement; interference with activities); location, referral pattern, radiation of pain; the associated factors that exacerbate or relieve the pain, current pain management plan; patient's response to current therapy; prior pain therapies; important psychosocial factors (such as patient distress, family and other support, psychiatric history, risk factors for aberrant use of pain medication, risk factors for undertreatment of pain, etc); other special issues relating to pain (such as meaning of pain for patient and family, cultural beliefs toward pain and pain expression, spiritual or religious considerations and existential suffering).[18, 19] Finally, the patient's goals and expectations of pain management should be discussed, including level of comfort and function.

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 Adult Cancer Pain

For management of cancer related pain in adults, the algorithm distinguishes three levels of pain intensity, based on a 0-10 numerical value obtained using numerical or the pictorial rating scale (with 0 being no pain to 10 being the worst pain). The three levels of pain intensity listed in the algorithm are mild pain (1-3); moderate pain (4-6); and severe pain (7-10).

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 (opioid naïve) from patients 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 (FDA), "patients considered opioid tolerant are those who are taking at least: 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer." Therefore, patients who do not meet 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

For all patients experiencing pain, care providers should 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. The patient and the family must be educated regarding pain management and related issues.[20, 21] Patients should be reevaluated at each contact and as needed to meet their goals for comfort and function.

Although pharmacologic analgesics, including non-opioids, opioids, and adjuvant analgesics are the cornerstone of cancer pain management, they are not always adequate and are associated with many adverse effects thus often necessitating the implementation of additional therapies or treatments. Optimal use of nonpharmacological integrative interventions (physical, cognitive modalities and spiritual) may serve as valuable additions to pharmacologic interventions.

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 section below on Opioid Principles, Prescribing, Titration, and Maintenance). Short-acting formulations have the advantage of rapid 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.

A number of adverse effects are potentially associated with the use of opioid analgesics. The management of these common opioid induced 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.[22] Addition of adjuvant analgesic for specific pain syndromes should be considered for all groups of patients. Adjuvant analgesics are drugs used to enhance the effects of opioids or NSAIDs.[23]

For opioid naïve patients, whose pain intensity is moderate with rating 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 (rating between 1-3) should receive treatment with nonopioid analgesics such as

NSAIDs or acetaminophen or treatment with consideration of slower titration of short-acting opioids.

Patients with chronic persistent pain controlled by stable doses of short-acting opioids should be provided with round-the-clock extended release or long-acting formulation opioids with provision of a 'rescue dose' to manage break-through or transient exacerbations of pain. The rescue dose is usually equivalent to 10%–20% of the total daily dose given every hour as needed. Opioids with a rapid onset and short duration are preferred as rescue doses. The repeated need for rescue doses per day may indicate the necessity to adjust the baseline treatment.

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). 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.[24, 25] Oral administration is the preferred route. An initial oral dose of 5-15 mg of oral short-acting morphine sulfate or equivalent is recommended for opioid naïve patients. Patients presenting with severe pain needing urgent relief should be treated with parenteral opioids, usually administered by the intravenous (IV) route or the subcutaneous (SC) route. If given parenterally, the equivalent dose is one-third of the oral dose.[26] An initial dose of or 2-5 mg of IV 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 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).[27]

Fentanyl is a highly lipid soluble opioid that can be administered by the parenteral, spinal, transdermal, transmucosal, buccal, and intranasal routes. Transdermal fentanyl is not indicated for rapid opioid titration and only should be recommended after pain is controlled by other opioids in opioid tolerant patients.[28] It is usually the treatment of choice for patients who are unable to swallow, patients with poor tolerance to morphine and patients with poor compliance. Conversion from intravenous fentanyl to transdermal fentanyl can be accomplished effectively using a 1:1 conversion ratio.[29] Transmucosal fentanyl may be considered in opioid tolerant patients for brief episodes of incident pain not attributed to inadequate dosing of around the clock opioid. Data do not support a specific transmucosal fentanyl dose equianalgesic to other opioids or between different transmucosal formulations. There is increasing data showing that buccal fentanyl is effective in treatment of breakthrough pain in patients with cancer. [30-32]

Hydrocodone is approximately equipotent with oral morphine however its equivalence data is not substantiated. Clinical experience suggests use as a mild, initial use opioid but effective dose may vary. It is available only in combination with oral agents such as acetaminophen. or ibuprofen.

Codeine is a prodrug that is metabolized to codeine-6-glucuronide, norcodeine, morphine, morphine-3-glucuronide, morphine-6-glucuronide, and normorphine.[33] This process is largely through the action of the cytochrome P450 enzyme, CYP2D6. It is important to note that CYP2D6 exhibits polymorphism between various ethnic groups, and between individuals. A significant portion individuals who are poor metabolizers would obtain reduced or no analgesic effects.[34]

Hydromorphone has properties similar to morphine and is available in oral tablets, liquids, suppositories, and parenteral formulations.[35] There is some evidence suggesting that the metabolite of hydromorphone may lead to opioid neurotoxicity, including myoclonus, hyperalgesia, and seizures.[36] This metabolite may be more neurotoxic than the morphine metabolite.[37]

Morphine is available in a wide range of formulations and routes, including oral, parenteral, and rectal delivery.[38] Morphine-6-glucoronide, an active metabolite of morphine, contributes to analgesia and may worsen adverse effects as it accumulates in patients with renal insufficiency.[39, 40]

Morphine, hydromorphone, or codeine should be used with caution in patients with fluctuating renal function due to potential accumulation of renally cleared metabolites that may cause neurologic toxicity.

Oxycodone and oxymorphone are available as immediate- and extended- release formulations.[41-45] Oxycodone is also available in combination with acetaminophen; therefore the dosage must be monitored for safe limits.

Methadone is commercially available in multiple strength oral tablets or oral solution. Individual variations in methadone pharmacokinetics (long half-life ranging from 8 to more than 120 hours) make its usage very difficult in cancer patients.[46] Due of its long half-life, high potency, and inter-individual variations in pharmacokinetics, methadone should be started at doses lower than anticipated and slowly titrated upwards with provision of adequate short-acting breakthrough pain medications during the titration period. The dosing ratio between methadone and morphine or other opioids, as well as conversion from another opioid to methadone, is not known.[47, 48] Studies show that outpatient initiation and rotation to methadone can be successfully done in cancer patients without serious adverse effects,[49] The NCCN Panel caution and advise the practitioners to consult pain management specialist if they are unfamiliar with methadone prescribing or if individual patient considerations necessitate very rapid switching to or from methadone.

There is evidence suggesting that high doses of methadone (300 mg and above) may lead to QTc prolongation and torsades de pointes which if uncorrected, may lead to sudden cardiac death.[50-52] Oral methadone is commonly used for the treatment of cancer pain, and the average dosing appears to be much lower than is used to treat opioid dependency and chronic nonmalignant pain. A recent study conducted in cancer patients suggests that QT interval changes exist commonly at baseline and are not changed with the addition of methadone.[53] However, physicians initiating methadone to be aware of the drug interactions. The NCCN panel recommends a baseline and follow-up ECG for patients treated with 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). QTc ≥ 450 may indicate need to reduce or discontinue methadone dose.

Methadone use should be initiated by physicians with experience and expertise in its use. Patients and their families may need to be educated about analgesic utility of methadone. Some may only be

familiar with methadone use for maintenance of addiction and be unaware of its utility as a potent opioid analgesic.

Tramadol is a weak opioid receptor agonist with some norepinephrine and serotonin reuptake inhibition used for mild to moderate pain. Tramadol should be avoided in patients receiving selective serotonin reuptake inhibitors (SSRI) or tricyclic antidepressants. Tramadol is thought to be approximately one tenth as potent as morphine in cancer patients.[54] In a double-blind study of cancer patients, tramadol produced more adverse effects, including vomiting, dizziness, and weakness, when compared with hydrocodone and codeine.[55] The NCCN Panel recommends a dose of 50-100 mg four times a day (maximum daily dose 400 mg) to avoid CNS toxicity.

Tapentadol is a new opioid that binds to the mu opioid receptor activation and inhibits norepinephrine reuptake.[56] To date, *no* studies have been published for its role in managing cancer pain.

The following agents are not recommended for cancer patients: 1) mixed agonist-antagonists (e.g. butorphanol, pentazocine), 2) meperidine, and 3) placebos.. Mixed agonist-antagonist should not be used in combination with opioid agonist drugs for cancer pain mamangement. Converting from an agonist to an agonist-antagonist could precipitate the abstinence syndrome (a withdrawal crisis) if given to a patient who is physically dependent on a pure opioid agonist. Meperidine is contraindicated for chronic pain especially in patients with impaired renal function or dehydration, because accumulation of metabolites that are cleared renally may result in neurotoxicity (seizures) or cardiac arrhythmias.[57] Use of placebo in the treatment of pain is unethical.

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.[57-59] 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 adverse effects associated with the oral administration. Continuous parenteral infusion, IV or 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).[60] The SC route has a slower onset and lower peak (30 minutes) effect when compared with IV route.

Principles of opioid prescription, titration, and maintenance

The appropriate dose of opioid is based on the patient's pain intensity and their goals without causing undesirable and unmanageable adverse drug effects.

The physicians should be aware of potential drug-drug and drug-disease interactions while determining the treatment plan. The patient's goals and quality of life should also be considered when modifying the treatment plan.

The following methods of ongoing analgesic administration are widely used in clinical practice: "around the clock", "as needed", and "patient-controlled analgesia". For most patients, dosing should be used for continuous pain relief. Additional doses of opioid may be required for pain not relieved by regular schedule of long-acting (eg, extended release) opioid.

The NCCN panel recommends considering opioid rotation if pain inadequately controlled or persistent adverse effects from current therapy. Other indications for switching to a different opioid include: out-of-pocket costs, limitations based upon insurance formularies, etc.

For patients who have intermittent pain with pain-free intervals, opioids are administered on an “as needed” basis. 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).

Breakthrough pain is defined as pain that fails to be controlled or “breaks through” a regimen of regularly-scheduled opioid and may be further categorized as: incident pain that is associated with specific activities or events, potentially managed with “rescue doses” of short-acting opioid given in anticipation of those events; end-of-dose failure pain that recurs towards the end of dosing interval for regularly scheduled opioid, potentially managed by increasing the dose or frequency of regularly scheduled opioid; and uncontrolled persistent pain that is routinely uncontrolled by existing regularly-scheduled opioid, potentially managed by adjusting dose of regularly-scheduled opioid.

The NCCN Guidelines for adult cancer pain management provide guidance for initiating short-acting opioids in opioid-naïve and opioid-tolerant patients.

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 2-5 mg of intravenous morphine sulfate or equivalent is recommended. Assessment of efficacy and adverse effects should be performed every 60 minutes for orally administered opioids and every 15 minutes for intravenous opioids to determine a subsequent dose. 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 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.

Opioid Adverse Effects
A number of adverse effects are associated with the use of opioid analgesics. Constipation, nausea and vomiting, pruritus, delirium, respiratory depression, motor and cognitive impairment, and sedation are fairly common, especially when multiple agents are used.[61-66] Each adverse effect requires a careful assessment and treatment strategy. Management of opioid-induced adverse effects is integral to opioid pain management.[61, 67-75]

Constipation can almost always be anticipated with opioid treatment and patients do not develop tolerance to constipation, therefore administration of prophylactic bowel regimen is recommended.

However, there is not much evidence on which to base the selection of the most appropriate prophylactic bowel regimen. There is one study showing that addition of a stool softener, such as docusate to the laxative, sennosides was less effective than administering laxative, sennosides alone.[76] Therefore for prophylaxis, the NCCN Adult Cancer Pain Guidelines Panel members recommend a stimulant laxative with or without a stool softener or a capful of polyethylene glycol (PEG) with 8 oz of water two times a day along with maintaining adequate fluid intake. While maintaining adequate dietary fiber intake is recommended, supplemental medicinal fiber, such as psyllium, are ineffective and unlikely to reduce opioid induced constipation.

Once constipation develops, the cause and severity of constipation must be assessed to rule out obstruction. Stool softeners or laxatives may be titrated as needed with goal of achieving one non-forced bowel movement every 1-2 days. Adjuvant analgesic may be considered to allow reduction of the opioid dose.

If constipation persists, the cause and severity of constipation must be assessed again to rule out bowel obstruction or impaction. Adding stimulant laxatives, such as magnesium-based products, bisacodyl (available in tablets or suppositories), or osmotic laxatives (such as sorbitol, lactulose, and PEG) may be helpful. Opioid rotation to fentanyl or methadone may be considered. Prokinetic agents such as metoclopramide enhance gastric antral contractility and may be useful in managing persistent constipation. However chronic use of metoclopramide may be limited due to concern for neurologic complications, including tardive dyskinesia. Enema with fleet, saline, or tap water may be helpful as it dilates the bowel, stimulates peristalsis, and lubricates the stool to encourage a bowel movement. When response to laxative therapy has not been sufficient in patients with advanced illness, methylnaltrexone, an opioid antagonist that works on receptors in the gastrointestinal system and is given subcutaneously, can be used as a rescue when constipation is clearly related to opioid therapy.[77-81] Neuraxial analgesics, neuroablative techniques or other interventions to decrease pain, alleviate constipation, and/or reduction opioid dose may also be considered to reduce its adverse effects.

For patients with a prior history of opioid induced nausea, prophylactic treatment with antiemetic agents is highly recommended. If nausea develops, other causes of nausea (eg, constipation, central nervous system pathology, chemotherapy, radiation therapy, hypercalcemia) must be assessed for. Effective agents that may be considered include benzodiazepines such as prochlorperazine or thiethylperazine or dopamine receptor antagonists such as metoclopramide or haloperidol. If nausea persists despite an as needed regimen, administer antiemetics around the clock for 1 week, then change dosing as needed. When managing opioid-induced persistent nausea, instead of replacing one antiemetic with another, adding therapies that target different mechanisms of action, resulting in a synergistic effect may be helpful. Adding serotonin receptor antagonists such as granisetron or ondansetron, may be helpful. Corticosteroids can also be quite beneficial for reducing opioid-induced nausea and vomiting, and in particular have been found to be effective in combination with metoclopramide and ondansetron.[82] If nausea persists for longer than a week. The cause of nausea needs to be reassessed and opioid rotation must be considered.

Pruritus or itchiness is a particularly common and distressing complaint. Pruritus occurs in 10-50% of patients receiving opioids. Even in the presence of attentive skin care, opioids can produce recalcitrant pruritus. If pruritus develops, other causes of pruritus such as use of any other medication must be first assessed. Pruritus is more likely to occur early in the course of treatment. Antihistamines such as

diphenhydramine or promethazine may be beneficial. If pruritus persists, consider changing to another opioid if symptomatic management has failed. Opioid antagonists have also proven useful in the management of patients whose pruritus is not relieved by antihistamines.[83] Mixed agonist/antagonists (eg. nalbuphine) can be used to treat opioid-induced pruritus. Mu-receptor antagonists, naloxone is also used to reverse the effects of opioid-induced adverse effects[84] and careful dose titration can produce relief without reversing analgesic efficacy.

Sedation may hinder the achievement of dose titration of opioids to levels that provide adequate analgesia.[22] If opioid-induced sedation develops and persists for over a week, it may be managed by administration of a psychostimulants such as or methylphenidate, dextroamphetamine, or modafinil or by adding caffeine. When using CNS stimulants for sedation, the dosing should be limited to morning and early afternoon to avoid insomnia at night.

Delirium is a pathophysiological condition characterized by altered consciousness and inattention, cognitive dysfunction, and disturbed psychomotor behavior. Delirium may be treated with various interventions, for example adding a neuroleptic drug such as haloperidol, olanzapine, or risperidone or switching to another opioid.[85]

Studies have shown that stable doses of opioids (> 2 weeks) are not likely to interfere with psychomotor and cognitive function but these functions should be monitored during analgesic administration and titration.[86]

Respiratory depression is another adverse effect that is feared both by physicians and patients. The physicians should be aware patients with limited cardiopulmonary reserve are more susceptible and hypercarbia occurs before hypoxia. Naloxone remains a useful antidote for the reversal of opioid-induced respiratory and central nervous system depression.

The details of prophylactic regimens and other measures to prevent opioid-induced adverse effects are provided in the algorithms on the page titled “Management of Opioid Adverse Effects”

Opioid Rotation

No single opioid is optimal for all patients.[87] 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.[61, 88] 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 the algorithms on the page titled “Opioid principles, prescribing, titration, and maintenance”.

Opioids and Risk Evaluation and Mitigation Strategy (REMS)

While opioids are the principle analgesics for management of moderate to severe pain, they pose risks to patients and society. The abuse of opioids is also an increasing concern. In the US, poisoning is now the leading cause of death from injuries and 89% of poisonings are related to drugs. In the year 2008, of the 36,500 drug poisoning deaths, 14,800 (40%) involved opioid analgesics, compared to 5,100 cocaine-related deaths and 3,000 heroin-related deaths.[89] While it is important to ensure that opioids continue to be prescribed for patients for whom it is appropriate, it is also essential to ensure that these drugs are prescribed carefully. To reduce addiction, misuse, abuse, overdose, and death the FDA is establishing REMS programs for all potent opioid

products.[90] The principle recommendations of opioid REMS programs are educating the provider and patient/family. The highlights of provider responsibilities included in the REMS are:

- Establishing goals of opioid analgesic therapy for each patient and regularly evaluating therapeutic opioid response to guide further therapy.
- Evaluating each patient for risk factors associated with opioid misuse or abuse.
- Educating each patient on safe use, storage, and disposal of opioid.
- Routinely monitoring patients for opioid misuse or abuse.

The REMS programs are currently in place for all transmucosal fentanyl products; all extended release opioids; transdermal buprenorphine; and morphine-naltrexone combination product.[91, 92] The complete list of currently approved REMS is available on the FDA website.[91]

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

In opioid tolerant patients who are 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 an opioid dose equivalent to 10-20% of total opioid taken in the previous 24 hours.[58, 93]

Efficacy and adverse effects should be assessed every 60 minutes for orally administered opioids and every 15 minutes for intravenous opioids to determine a subsequent dose. 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 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

The subsequent treatment is based upon the patient's continued pain rating score. All approaches for all pain intensity levels must be administering regular doses of opioids with rescue doses as needed, management of constipation 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. Addition of adjuvant analgesics 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.[22] Given the multifaceted nature of cancer pain, additional interventions for specific cancer pain syndromes and specialty consultation 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 adjuvant analgesics; additional interventions for specific cancer pain syndromes; and specialty consultation must be considered.

For patients experiencing mild pain, if they have adequate analgesia but intolerable or unmanageable adverse effects, the analgesic dose may be reduced by 25% of the current opioid dose. Addition of adjuvant analgesics may be considered.

Ongoing Care

Although pain intensity ratings will be obtained frequently to evaluate opioid dose increases, a formal re-evaluation to assess 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 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). The subsequent treatment is based upon the patient's continued pain rating score. Rescue doses of the short-acting formulation of the same long-acting drug may be provided during maintenance therapy for the management of pain in cancer patients not 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.

System-related barriers exist that include cost of analgesics and a lack of access to/availability of analgesics, particularly in minority neighborhoods or for those who are poor. Studies have documented the inequalities that persist since those with financial burdens or minorities have less access to pain treatment.[19, 94] The NCCN panel recommends addressing such system barriers.[95-98]

The patients must be provided written follow-up pain plan, including prescribed medications. It is important to ensure that the patient has adequate access to prescribed medications, maintain communication and coordination of care with pain specialist and relevant providers especially during transition between sites of care. Equally important is monitoring for the use of analgesics as prescribed, especially in patients with risk factors for or history of abuse.

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.

Specialty Consultations

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. 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, pain and palliative care services, substance abuse consultation if there are questions/concerns about medication misuse or diversion, depression/distress consultation, spiritual care consultation, or social work services.

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. Procedures reported as painful include bone marrow aspirations; wound care; lumbar puncture; skin and bone marrow biopsies; intravenous line, arterial line, central line; injections and manipulations. 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. Supplemental doses of analgesics should be given in anticipation of procedure-related pain. Anxiolytics are drugs used for the treatment of anxiety, and its related psychological and physical symptoms. Anxiolytics should be given preemptively for control of procedure-related anxiety when feasible.

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 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.

Additional therapies

Opioids alone may not provide the optimal therapy, but when used in conjunction with nonopioid analgesics (such as an NSAID) or adjuvant analgesics (antidepressants, anticonvulsants, topical agents, and corticosteroids) along with psychologic and physical approaches, they can help to improve patient outcomes.[22]

Adjuvant Analgesics for Neuropathic Pain

The term adjuvant refers to medications that are coadministered to manage an adverse effect of an opioid or to adjuvant analgesics that are added to enhance analgesia. These drugs can be helpful for patients whose pain is only partially responsive to opioids.

Clinically, adjuvant analgesics consist of a diverse range of drug classes, including anticonvulsants[99] (e.g., gabapentin, pregabalin),

antidepressants (e.g., tricyclic antidepressants), corticosteroids, and local anesthetics/topical agents (e.g., topical lidocaine patch).

Adjuvant 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.[100]

Extrapolating from studies conducted in neuropathic pain conditions, in noncancer conditions, tricyclic antidepressants are believed to provide relief from neuropathic pain.[101-103] 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 SSRI antidepressants versus those receiving tamoxifen alone.[104, 105] 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).[106]

The most commonly employed anticonvulsant drugs for the treatment of cancer pain are gabapentin and pregabalin.[107] They have been studied primarily in noncancer neuropathy syndromes.[108] Gabapentin has been reported to reduce mucositis pain in patients receiving concomitant radiotherapy and chemotherapy.[109]

A review of cancer trials found that adjuvant analgesics (antidepressants and antiepileptics) added to opioids provide additional neuropathic pain relief.[110]

Local anesthetics/topical agents are useful in preventing procedural pain and in relieving neuropathic pain. They act locally and may be used as an analgesic in combination with an opioid, antidepressant, and/or an anticonvulsant. Topical agents include lidocaine or diclofenac patch. Both the gel and patch forms of lidocaine have been shown to reduce the pain of postherpetic neuropathy and cancer-related pain.[111,112]

Corticosteroids have long been used to relieve neuropathic pain syndromes. Corticosteroids have also been effective for treating bone pain due to their anti-inflammatory effects as well as relieving malignant intestinal obstruction.[23, 113]

Nonopioid Analgesics

The non-opioid analgesics include NSAIDs and acetaminophen.

Acetaminophen is analgesic and antipyretic but not anti-inflammatory.[114] Recently, attention has been drawn towards the relative limited efficacy and significant adverse effects of acetaminophen, particularly hepatic and renal toxicity.[115, 116] This concern is compounded by the inclusion of acetaminophen in a variety of prescription opioid preparations (eg, hydrocodone or codeine) as well as in a wide selection of over-the-counter products. Due to concerns with liver toxicity, the NCCN Panel members advise that acetaminophen should be used with caution or not used at all with combination opioid-acetaminophen products to prevent excess acetaminophen dosing.

The FDA believes that limiting the amount of acetaminophen per tablet, capsule, or other dosage unit in prescription products will reduce the risk of severe liver injury from acetaminophen overdosing, an adverse event that can lead to liver failure, liver transplant, and death. In order to reduce the risk of severe liver injury from acetaminophen overdosing, the FDA recently announced that it is asking "manufacturers of prescription acetaminophen combination products to limit the maximum amount of acetaminophen in these products to 325 mg per tablet, capsule, or other dosage unit." The drug companies will have three years from the date of publication of the Federal Register Notice (January 14, 2011) to limit the amount of acetaminophen in their prescription drug products to 325 mg per dosage unit. The FDA is requiring a new boxed warning to communicate the risk of severe liver injury associated with acetaminophen to healthcare professionals. In addition, the companies are required to add a new warning about the risk of allergic reactions, including anaphylaxis, to the label of all prescription acetaminophen-containing products.

NSAIDs produce analgesia by blocking the biosynthesis of prostaglandins, inflammatory mediators that initiate, cause, intensify, or maintain pain. 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 adverse 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. The addition of NSAIDs to opioids has the potential benefit of reducing the opioid dose when sedation, cognitive function, or other central nervous system effects of opioid analgesic therapy become burdensome.

In patients at high risk for cardiac toxicities such as those with 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. NSAIDs should be discontinued if congestive heart failure or hypertension develops or worsens. Naproxen and ibuprofen are preferred NSAIDS for individuals at high risk for cardiac toxicities.

The NSAID and acetaminophen prescribing guidelines are listed in the algorithms on page "Non-Opioid Analgesic (NSAID and Acetaminophen) Prescribing".

Integrative Interventions

Since pain encompasses physical, psychosocial, and spiritual dimensions, the treatment of cancer pain inherently requires integration of therapies inclusive of cognitive-behavioral interventions.

Use of nonpharmacological integrative interventions (physical, cognitive and spiritual) may serve as valuable additions to pharmacologic interventions. Physical measures include massage, use of heat or cold, acupuncture, acupressure etc. Cognitive interventions are aimed at enhancing a sense of control over the pain or underlying disease. Breathing exercises, relaxation, imagery/hypnosis, and other behavioral therapies can be very useful.[117-123] Attention should also be focused on psychosocial support and providing education to patients and families.[124] All of these can greatly enhance patients' sense of control as well as greatly reduce the family caregivers' feeling of helplessness.[122]

The integration of physical, psychosocial, and spiritual modalities should also be based on assessment of cultural considerations. In cancer care, there is growing interest in attention to spiritual needs and the existential concerns often associated with pain. Many patients hold cultural beliefs about such treatments, and home remedies, rituals, prayer, and other spiritual practices may be most helpful in relieving or coping with pain. Involvement of chaplains and other spiritual care providers is essential.[125] Spiritual needs should be routinely assessed and spiritual care should be incorporated as a component of comprehensive pain management.

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 interventional therapies instead of a chronic medication regimen. Interventional 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 therapies, including nerve blocks, vertebroplasty, kyphoplasty, and other techniques, can be useful in the relief of cancer pain.[22, 126-130] The major indications for referral for interventional therapies include a 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/plexus nerve, etc) and/or in patients failing to achieve adequate analgesia and/or the presence of intolerable side effects. For example, a patient with pancreatic cancer who was not tolerating opioids or not receiving adequate analgesia could be offered a neurolytic celiac plexus block. Neurolytic celiac plexus block may offer some improvement in pain control over systemic analgesics, but is generally associated with reduction in adverse effects. [131, 132]

Several interventional strategies are available if a patient does not achieve adequate analgesia. Regional infusion of analgesics (epidural, intrathecal, and regional plexus) is one of the approaches. This approach minimizes the distribution of drugs to receptors in the brain, potentially avoiding adverse 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).[133]

Percutaneous kyphoplasty and vertebroplasty might be useful for the treatment of lytic osteoclastic spinal metastases or in cases of vertebral compression fractures or spinal instability for which surgery is not feasible or indicated. Vertebroplasty/kyphoplasty helps restore mechanical stability while reducing pain and neurological symptoms.[134-139]

Neurodestructive procedures may be 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).

Neurostimulation procedures has been suggested to be useful for painful chemotherapy-induced peripheral neuropathies neuralgias, complex regional pain syndrome, etc.[140]

Radiofrequency ablation for bone lesions has proven successful in pain management especially those failing to achieve adequate analgesia without intolerable effects.[141, 142]

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 off 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.

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 multimodal and comprehensive. It is based on routine pain assessments, utilizes both pharmacologic and nonpharmacologic interventions, and requires ongoing reevaluation of the patient. The NCCN Adult Cancer Pain Guidelines Panel advises that cancer pain can be well controlled in the vast majority of patients if the algorithms presented are systematically applied, carefully monitored, and tailored to the needs of the individual patient.

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