National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Adult Cancer Pain

Version 3.2024 — November 25, 2024

NCCN.org

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

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Discussion

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Continue

φ Anesthesiology
Ÿ Complementary and integrative medicine
^ Emergency medicine
‡ Hematology/Hematology oncology
Þ Internal medicine
∩ Interventional radiology
† Medical oncology
# Nursing
¥ Patient advocacy
Σ Pharmacology
§ Radiotherapy/Radiation oncology
£ Supportive care including palliative, pain management, pastoral care, & oncology social work
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Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

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

See NCCN Categories of Evidence and Consensus.

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Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

Updates in Version 3.2024 of the NCCN Guidelines for Adult Cancer Pain from Version 2.2024 include:

MS-1

• The Discussion section has been updated to reflect the changes in the algorithm.

Updates in Version 2.2024 of the NCCN Guidelines for Adult Cancer Pain from Version 1.2024 include:

PAIN-K

• Management Strategies for Specific Cancer Pain Syndromes
  ▸ Bone pain without oncologic emergency
    ◊ Footnote added to denosumab: An FDA-approved biosimilar is an appropriate substitute.

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Adult Cancer Pain from Version 2.2023 include:

PAIN-1
- Pain Definition
  - Footnote added: The terms cancer pain and cancer-related pain may be used interchangeably.
- General Principles
  - Bullet 4 modified: ...consider early referral to palliative care (See NCCN Guidelines for Palliative Care) *and psychological/social/spiritual services (See NCCN Guidelines for Cancer Distress Management).*
  - Bullet 7 added: Due to the biopsychosocial nature of pain, health inequities and disparities influence pain experience and access to pain evaluation and care.
- Assessment
  - Bullet 5 revised: Evaluate for risk factors for ~~opioid~~ *analgesic* misuse/diversion.
- Management/Intervention
  - Bullet 2 added: Develop treatment plans with regard for medication availability and cost.
  - Bullet 5 modified: ...and breakthrough*/procedural/incidental* pain with supplemental doses of short-acting analgesics.

PAIN-2
- Pain related to an oncologic emergency
  - Bullet 5 added: Thromboembolic emergency

PAIN-3
- Moderate/Severe Pain
  - Text modified: Morphine 5 mg (solution) or immediate release (IR) 7.5 mg (1/2 of a 15 mg tablet)~~, when appropriate~~
  - Sub-bullet added: May consider half tablet for lower dose titration in frail or older patients
  - Text modified: If multiple doses of short-acting opioid are consistently needed per day, consider addition of a long-acting opioid based on the total daily dose *if appropriate based on expected trajectory of pain* (Also for PAIN-4)

PAIN-6
- Heading modified: Ongoing Care *(after pain is reasonably controlled)*
  - Bullet 5, sub-bullet 2 modified: Clarify which clinician will be prescribing patient's ongoing analgesics *and ensure patient is aware of contact information for prescribing clinician*
- Goals of Treatment; Not achieved
  - Bullet 5 modified: ...which may contribute to poorly controlled ~~physical~~ pain

PAIN-A 2 of 2
- Pain Assessment in the Nonverbal Patient
  - Bullet 7 added: Alternative assessment method and rationale should be documented to facilitate appropriate follow up and reassessment.

PAIN-B 1 of 3
- Pain experience (continued)
  - Prior pain therapies
    - ◊ Text modified: Reason for use, *dosing*, length of use, response...
  - Special issues relating to pain
    - ◊ Sub-bullet 8 revised: Assess risk of ~~opioid~~ *analgesic* misuse/diversion *and substance use disorders (SUD)*
    - ◊ Sub-bullet added: Evaluate for factors impacting equitable access to pain therapies

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Adult Cancer Pain from Version 2.2023 include:

PAIN-B 2 of 3
- Psychosocial Support
  - Screening tools: CAGE-AID added
    - References for CAGE-AID added:
      - Keall R, Keall P, Kiani C, et al. A systematic review of assessment approaches to predict opioid misuse in people with cancer. Support Care Cancer 2022;30:5645-5658.
      - Yennurajalingam S, Arthur J, Reddy S, et al. Frequency of and Factors Associated With Nonmedical Opioid Use Behavior Among Patients With Cancer Receiving Opioids for Cancer Pain. JAMA Oncol 2021;7:404-411.
- Medical history
  - Sub-bullet 1 revised: Oncologic treatment including current and prior ~~chemotherapy~~ *systemic anti-tumor therapy,* hormonal therapy, RT, and surgery
  - Sub-bullet 3 modified: Pre-existing chronic pain *and treatment history*

PAIN-E 1 of 2
- Acetaminophen
  - Bullet 5 added: Use acetaminophen with caution in the setting of immunotherapy given possible impacts on the efficacy of immunotherapy.
    - Corresponding reference added: Bessede A, Marabelle A, Guégan JP, et al. Impact of acetaminophen on the efficacy of immunotherapy in cancer patients. Ann Oncol 2022;33:909-915.
  - Bullet 6 added: Note that there may be concerns about the risk of masking fever in immunocompromised patients.

PAIN-E 2 of 2
- Renal Toxicities
  - Bullet 3 modified: All NSAIDs*, including COX-2 inhibitors,* with systemic administration have been associated with renal toxicities.
- GI Toxicities
  - Treatment
    - Sub-bullet 1 modified: If patient develops gastric upset or nausea, consider discontinuing NSAID, *adding proton pump inhibitors*, or changing to selective COX-2 inhibitor.

PAIN-F 1 of 2
- Principles of Adjuvant Analgesic Use
  - Bullet 10 added: Expectations for onset of effect of adjuvant analgesics should also be discussed with patients.

PAIN-F 2 of 2
- The order of agents on this page have been reorganized.

PAIN-G 1 of 21
- General Principles
  - Bullet 3 added: UDT should be strongly considered at baseline (prior to opioid therapy initiation) and during treatment (at least annually) for all patients receiving opioid analgesics for subacute or chronic pain (PAIN-G 7 of 21).
  - Bullet 6 modified: Generally, oral route is most common; however, other routes (i.e., IV, subcutaneous, rectal, transdermal, transmucosal) can be considered as indicated to maximize patient comfort *(especially in context of unreliable GI absorption).*

PAIN-G 2 of 21
- Principles of Maintenance Opioid Therapy
  - Bullet 3 modified: When using methadone as a long-acting opioid, a short-acting opioid should also be provided for breakthrough pain *as needed.*
  - Bullet 6 added: Recommend using a single short-acting agent for breakthrough pain.
  - Bullet 8 modified: ...(transmucosal fentanyl requires REMS certification *for both prescriber and pharmacist*...
  - Bullet 9 modified: Continue to monitor patients for opioid adverse effects and patients/*caregiver*/family...
  - Bullet 11 added: Renal insufficiency has the least impact on pharmacology of transdermal fentanyl, methadone, and buprenorphine. These medications should be considered in this setting.

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Adult Cancer Pain from Version 2.2023 include:

PAIN-G 3 of 21
- Principles of Opioid Dose Reduction
  - Bullet 4 added: Opioid dose reduction must be individualized to meet patient goals of care and minimize symptoms of withdrawal. If patient experiences withdrawal, slower taper may be needed.

PAIN-G 4 of 21
- Opioids and Risk Evaluation and Mitigation Strategy (REMS)
  - Bullet 4 revised: It is important for prescribers to be aware of the range of opioid use patterns to detect ~~any~~ potential aberrant behaviors.
  - Bullet 4, sub-bullet 1 revised: Potential risk factors for ~~misuse of prescribed analgesics include~~ *non-medical use of analgesics (as established in the treatment plan) and/or increased risk of opioid use disorder (OUD) include*
  - Bullet 6 added: As of June 27, 2023 as part of the Consolidated Appropriations Act of 2023, the DEA requires all prescribers applying for a new or renewed DEA registration will have to attest to completed a total of at least 8 hours of training on the treatment and management of patients with OUD or other SUD.

PAIN-G 6 of 21
- Opioid Risk Mitigation Strategies During Chronic Opioid Use
  - CAGE-AID link added
- Risk Mitigation for All Patients Receiving Opioid Analgesics
  - Bullet 2 modified: Discuss the role of naloxone for administration by caregivers in the event of respiratory depression and sedation and make available as indicated *or as required by local and/or state regulations.*
  - Sub-bullet added: After patient stabilization, reevaluation in-person is recommended. In the interim, if additional analgesics are required, consider reduced dose and frequency, as well as evaluation of other contributing respiratory depressants.

PAIN-G 7 of 21 through PAIN-G 9 of 21
- NEW pages added for Urine Drug Testing with principles, tables, and references.

PAIN-G 10 of 21
- Table header added: Drug conversions below are estimates; institutional variations should be considered

PAIN-G 11 of 21
- Convert or Rotate From One Opioid to Another Opioid
  - Sentence #5 revised: ...if using long-acting opioid~~:~~ , ~~2 doses for extended-release morphine every 12 hours~~ *dose and frequency would depend on formulation used). Monitor closely for end-of-dose failure between doses of long-acting opioid.*
  - Footnote added: Opioid-naïve patients are those not chronically receiving opioid analgesic on a daily basis and therefore have not developed significant tolerance. Opioid tolerant includes patients who are chronically receiving opioid analgesic on a daily basis. The FDA identifies tolerance as receiving at least 25 mcg/h fentanyl patch, at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, or an equianalgesic dose of another opioid for a week or longer. (Also for PAIN-G 12 of 21)

PAIN-G 12 of 21
- General Comments Regarding Transdermal Fentanyl
  - Bullet 2 modified: Fever, topical application of heat *(or external heat sources)*, or ~~extreme~~ strenuous exertion may accelerate transdermal fentanyl absorption...

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Adult Cancer Pain from Version 2.2023 include:

PAIN-G 14 of 21
- Buprenorphine for (OUD)
  - Bullet added: Buprenorphine may be considered as a first-line opioid for cancer pain management in patients with OUD.

PAIN-G 15 of 21
- Regulatory requirements for use of buprenorphine (Note: revised with DEA regulation changes early 2023)
  - Bullet removed: DEA will enact new training requirements for all prescribers effective 6/21/2023.

PAIN-G 19 of 21
- Mixed-Mechanism Drugs
  - Sub-bullet added: *Tramadol should be used with caution due to marked variability with drug metabolism* (See PAIN-N for pharmacogenetic considerations).

PAIN-G 20 of 21
- References have been updated.

PAIN-H 1 of 3
- Management of Opioid Adverse Effects
  - Constipation
    - ◊ Bullet 1, sub-bullet 7 modified: Docusate*, which is a stool softener, may have limited benefit for constipation* ~~does not provide benefit~~.
    - ◊ Bullet 3, sub-bullet 7 modified: For intractable chronic constipation, consider opioid rotation to transdermal fentanyl, *buprenorphine,* or methadone. *These medications may have less risk of constipation.*

PAIN-H 2 of 3
- Nausea
  - Bullet added: Consider side effect profile when selecting an antiemetic, as some side effects may be of benefit to other symptoms (eg, metoclopramide for constipation, olanzapine for insomnia).
- Pruritus
  - Bullet 1, sub-bullet 2 modified: Consider antihistamines such as cetirizine, 5–10 mg PO once daily *or 10 mg IV daily*;...
- Delirium
  - Bullet 1 revised: Assess for other ~~causes of~~ *contributing factors for delirium* (eg, infection, hypercalcemia, CNS, metastases, other psychoactive medications*, uncontrolled pain*).

PAIN-I 1 of 2
- To assess for patient and family/caregiver educational needs regarding pain treatment, the health care team should:
  - Bullet 5 modified: Assess for meaning and understanding of the use and risks of ~~opioid~~ analgesics*, including opioids*.
- Messages to be conveyed to patient and family/caregiver regarding opioid analgesics:
  - Bullet 2, sub-bullet 2 modified: Patients*/caregivers/family* with a history of prescription, illicit drug, or SUD are at increased risk.

PAIN-K
- Management Strategies for Specific Cancer Pain Syndromes
  - Bullets have been reorganized and reordered
  - Pain from oral mucositis
    - ◊ Sub-bullet modified: For more information~~, including for GI mucositis~~ *on the prevention and treatment of mucositis*, see...
  - Nerve pain
    - ◊ Sub-bullet added: Optimize local disease control as appropriate; consider RT or other treatments

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Updates in Version 1.2024 of the NCCN Guidelines for Adult Cancer Pain from Version 2.2023 include:

PAIN-L

- Specialty Consultations for Improved Pain Management
  - Pain and/or Palliative Care Specialty Consultation
    - ◊ Bullet 9 revised: Management of complicated psychosocial issues~~, including aberrant drug behavior~~
  - SUD Specialist Consultation
    - ◊ Header revised: SUD Specialist *(Addiction Medicine)* Consultation
  - Mental Health Consultation
    - ◊ Bullet 4, sub-bullet 1 modified: Integrative medicine practitioners, *psychologists, and other mental health professionals* can be used to...

PAIN-M

- Interventional Strategies
  - Bullet 1, sub-bullet 1 modified: 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~~ *chest with intercostal nerve block*)
  - Footnote added: Most of these procedures can be performed in a non-neurodestructive manner as well (eg, a nerve block).

PRINCIPLES OF CANCER PAIN MANAGEMENT

Pain Definition

- Pain is defined by the International Association for the Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.[a] IASP defines chronic cancer-related pain as chronic pain caused by the primary cancer itself, or metastases (chronic cancer pain) or its treatment (chronic post-cancer treatment pain).[b,c]

General Principles

- Optimal use of disease-specific therapies is essential to managing tumor-related pain.
- Survival is linked to symptom control and pain management, which contribute to broad quality-of-life improvement. Pain management is an essential part of oncologic management and contributes to overall function and quality of life.
- Analgesic therapy is done in conjunction with management of multiple symptoms or symptom clusters. Consider the interaction of complex pharmacologic therapies and the risk for analgesic misuse.
- A multidisciplinary team is optimal (PAIN-L); consider early referral to palliative care (NCCN Guidelines for Palliative Care) and psychological/social/spiritual services (NCCN Guidelines for Distress Management).
- Provide/refer for psychosocial support, including emotional and informational support and coping skills training (PAIN-C).
- Provide accessible educational material to improve pain assessment, pain management, and the safe use of analgesics based on the patient's identified needs[b] (PAIN-I).
  - Involve patients in developing treatment plans and setting meaningful, realistic expectations and measurable goals to include patient values and preferences.
- Due to the biopsychosocial nature of pain, health inequities and disparities influence pain experience and access to pain evaluation and care.
- Address the multidimensional impact of suffering on patients and caregivers in a culturally respectful manner.

Assessment

- Screen all patients for pain at each contact (PAIN-2).
- Routinely quantify and document pain intensity and quality as characterized by the patient (whenever possible). Include patient reporting of breakthrough pain, treatments used and their impact on pain, satisfaction with pain relief, pain interference, provider assessment of impact on function, and any special issues for the patient relevant to pain treatment and access to care.
- If necessary, get additional information from caregiver regarding pain and impact on function.
- Perform comprehensive pain assessment if new or worsening pain is present and regularly for persisting pain (PAIN-B).
- Evaluate for risk factors for analgesic misuse/diversion.

Management/Intervention

- Goals of pain management are highlighted by the "5 A's" of outcomes:[d]
  1. Analgesia (optimize analgesia)
  2. Activities (optimize activities of daily living)
  3. Adverse effects (minimize adverse effects) (PAIN-H)
  4. Aberrant behavior (monitor for aberrant drug-use behavior) (PAIN-G)
  5. Affect (relationship between pain and mood)
- Develop treatment plans with regard for medication availability and cost.
- Prevention of analgesic side effects, especially constipation, is of paramount importance.
- For acute, severe pain or pain crisis, consider hospital or inpatient hospice admission.
- Treat persistent cancer pain with regularly scheduled analgesics or long-acting analgesics, and breakthrough/procedural/incidental pain with supplemental doses of short-acting analgesics.
- For chronic pain in cancer survivors, see NCCN Guidelines for Survivorship.

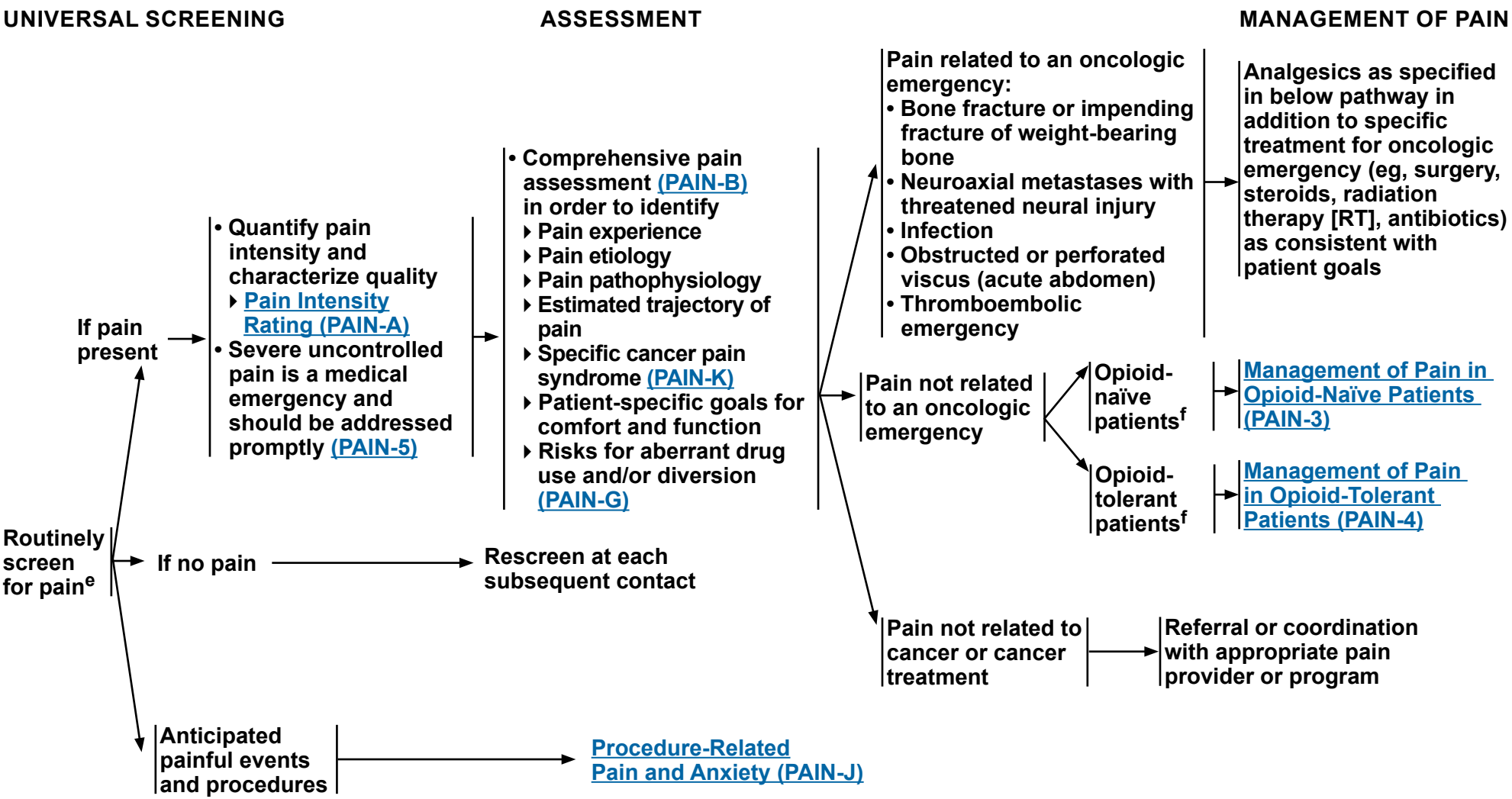
Reassessment

- Perform pain reassessment at specified intervals to ensure that analgesic therapy is providing maximum benefit with minimal adverse effects, and that the treatment plan is followed.
- Encourage patients to report ongoing pain assessments in between visits, as needed.

[a] Raja SN, et al. Pain 2020;161:1976-1982.
[b] Bennett MI, et al. Pain 2019;160:38-44.
[c] The terms cancer pain and cancer-related pain may be used interchangeably.
[d] The Joint Commission. New and Revised Pain Assessment and Management Standards. 2018. https://www.jointcommission.org/resources/patient-safety-topics/pain-management-standards-for-accredited-organizations/.

Note: All recommendations are category 2A unless otherwise indicated.

Universal Screening (PAIN-2)



[e] For chronic pain in cancer survivors, see the NCCN Guidelines for Survivorship.
[f] Opioid-naïve patients are those not chronically receiving opioid analgesic on a daily basis and therefore have not developed significant tolerance. Opioid tolerant includes patients who are chronically receiving opioid analgesic on a daily basis. The FDA identifies tolerance as receiving at least 25 mcg/h fentanyl patch, at least 60 mg of morphine daily, at least 30 mg of PO oxycodone daily, at least 8 mg of PO hydromorphone daily, or an equianalgesic dose of another opioid for a week or longer.

Note: All recommendations are category 2A unless otherwise indicated.

PAIN INTENSITY

Pain Intensity Rating (PAIN-A)

MANAGEMENT OF PAIN IN OPIOID-NAÏVE PATIENTS[f]

General Principles — Principles of Cancer Pain Management (PAIN-1)

- Optimize pain management therapies to improve function and meet patient's goals of care
- Select the most appropriate analgesic regimen based on the pain diagnosis (PAIN-K), comorbid conditions, safety, potential drug interactions, estimated trajectory of pain, medication availability, and expense/financial toxicity
- Analgesic regimen may include an opioid (PAIN-G), acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs) (PAIN-E), and/or adjuvant analgesics (PAIN-F)
  - If pain is continuous, consider regularly scheduled analgesics
- Anticipate and treat analgesic adverse effects, including opioid-induced constipation (PAIN-H)
- Provide psychosocial support (PAIN-C)
- Provide patient and family/caregiver education (PAIN-I)
- Optimize integrative interventions (PAIN-D) and multidisciplinary care (PAIN-L)

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

Mild Pain →

- See General Principles above
  AND
- First consider non-opioids and adjuvant therapies, unless these are contraindicated due to adverse effects, potential drug interactions, or comorbid conditions (PAIN-G)

Moderate/ Severe Pain →

- See General Principles above
  AND
- Non-opioids and adjuvant therapies as appropriate with short-acting opioids as needed (PAIN-G)
- Start and titrate short-acting opioid, every 3–4 hours as needed[g,h] (PAIN-G, 10 of 21)
  - Morphine 5 mg (solution) or immediate release (IR) 7.5 mg (1/2 of a 15 mg tablet)
  - Hydromorphone 2 mg orally (PO)
  - Oxycodone IR 2.5–5 mg with or without acetaminophen 325 mg[i]
  - Hydrocodone 5 mg with acetaminophen 325 mg[i]
  - May consider half tablet for lower dose titration in patients who are frail or older
- If multiple doses of short-acting opioid are consistently needed per day, consider addition of a long-acting opioid based on the total daily dose if appropriate based on expected trajectory of pain

→
- Titrate further as needed
- If pain is stable, see Ongoing Care (PAIN-6)
- If pain is inadequately controlled, reevaluate working diagnosis with a comprehensive pain assessment (PAIN-B)
- Consider pain specialty and/or palliative care consultation (PAIN-L)
- Consider opioid rotation if dose-limiting adverse effects are noted

Severe Pain/ Pain Crisis → For acute, severe pain or pain crisis, consider hospital or inpatient hospice admission to achieve patient-specific goals for comfort and function (PAIN-5)

Footnotes on PAIN-3A

Note: All recommendations are category 2A unless otherwise indicated.

FOOTNOTES

[f] Opioid-naïve patients are those not chronically receiving opioid analgesic on a daily basis and therefore have not developed significant tolerance. Opioid tolerant includes patients who are chronically receiving opioid analgesic on a daily basis. The FDA identifies tolerance as receiving at least 25 mcg/h fentanyl patch, at least 60 mg of morphine daily, at least 30 mg of PO oxycodone daily, at least 8 mg of PO hydromorphone daily, or an equianalgesic dose of another opioid for a week or longer.

[g] Select, extended-release opioids may also be indicated for opioid-naïve patients in rare circumstances.

[h] More frequent dosing may be indicated in select situations.

[i] Non-Opioid Analgesic (Nonsteroidal Anti-Inflammatory Drugs [NSAIDS] and Acetaminophen) Prescribing (PAIN-E).

Note: All recommendations are category 2A unless otherwise indicated.

PAIN INTENSITY | **MANAGEMENT OF PAIN IN OPIOID-TOLERANT PATIENTS[f]**

Pain Intensity Rating (PAIN-A)

General Principles Principles of Cancer Pain Management (PAIN-1) →

- Optimize pain management therapies to improve function and meet patient's goals of care
- Select the most appropriate analgesic regimen based on the pain diagnosis (PAIN-K), comorbid conditions, safety, potential drug interactions, estimated trajectory of pain, medication availability, and expense/financial toxicity
- Analgesic regimen may include an opioid (PAIN-G), acetaminophen, NSAIDs (PAIN-E), and/or adjuvant analgesics (PAIN-F)
  - If pain is continuous, consider regularly scheduled analgesics
- Anticipate and treat analgesic adverse effects, including opioid-induced constipation (PAIN-H)
- Provide psychosocial support (PAIN-C)
- Provide patient and family/caregiver education (PAIN-I)
- Optimize integrative interventions (PAIN-D) and multidisciplinary care (PAIN-L)

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

Mild Pain →

- See General Principles above

AND

- Non-opioids and adjuvant therapies, unless these are contraindicated due to adverse effects or potential drug interactions (PAIN-G)
- Re-evaluate need for opioids and reduce if appropriate (PAIN-G, 3 of 21)

Moderate/ Severe Pain →

- See General Principles above

AND

- Non-opioids and adjuvant therapies as appropriate with short-acting opioids as needed (PAIN-G)
- Titrate short-acting opioid (may require dose increase of 30%–100%) (PAIN-5)
- If multiple doses of short-acting opioid are consistently needed per day, consider addition or increase in dose of a long-acting opioid based on the total daily dose if appropriate based on expected trajectory of pain

Severe Pain/ Pain Crisis →

For acute, severe pain or pain crisis, consider hospital or inpatient hospice admission to rapidly titrate analgesic and quickly achieve patient-specific goals for comfort and function (PAIN-5)

→

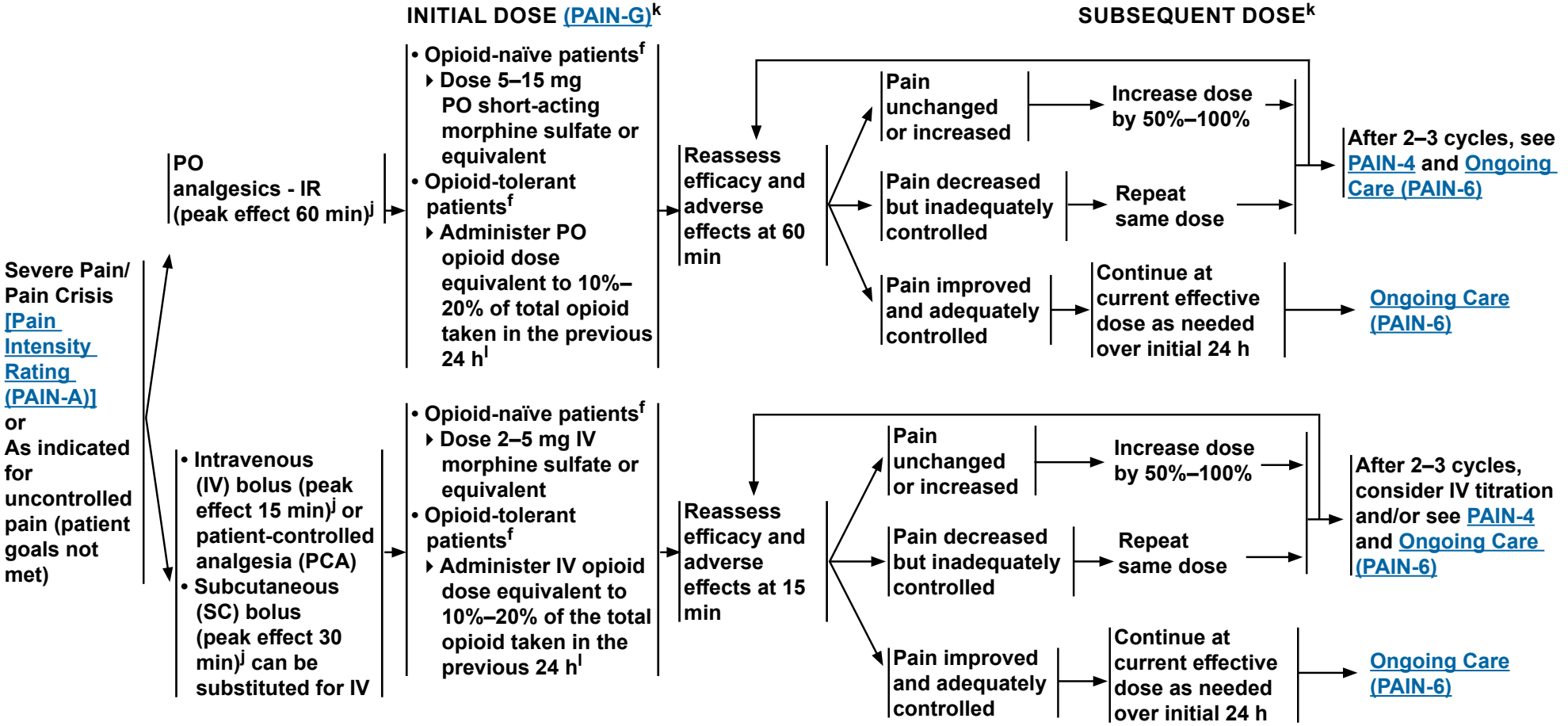
- Titrate further as needed
- If pain is stable, see Ongoing Care (PAIN-6)
- If pain is inadequately controlled, reevaluate working diagnosis with a comprehensive pain assessment (PAIN-B)
- Consider pain specialty and/or palliative care consultation (PAIN-L)
- Consider opioid rotation if dose-limiting adverse effects are noted

[f] Opioid-naïve patients are those not chronically receiving opioid analgesic on a daily basis and therefore have not developed significant tolerance. Opioid tolerant includes patients who are chronically receiving opioid analgesic on a daily basis. The FDA identifies tolerance as receiving at least 25 mcg/h fentanyl patch, at least 60 mg of morphine daily, at least 30 mg of PO oxycodone daily, at least 8 mg of PO hydromorphone daily, or an equianalgesic dose of another opioid for a week or longer.

Note: All recommendations are category 2A unless otherwise indicated.

MANAGEMENT OF PAIN CRISIS

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



[f] Opioid-naïve patients are those not chronically receiving opioid analgesic on a daily basis and therefore have not developed significant tolerance. Opioid tolerant includes patients who are chronically receiving opioid analgesic on a daily basis. The FDA identifies tolerance as receiving at least 25 mcg/h fentanyl patch, at least 60 mg of morphine daily, at least 30 mg of PO oxycodone daily, at least 8 mg of PO hydromorphone daily, or an equianalgesic dose of another opioid for a week or longer.

[j] Preference of PO or IV/SC route of delivery may differ based on the location of care.

[k] Dose and 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.

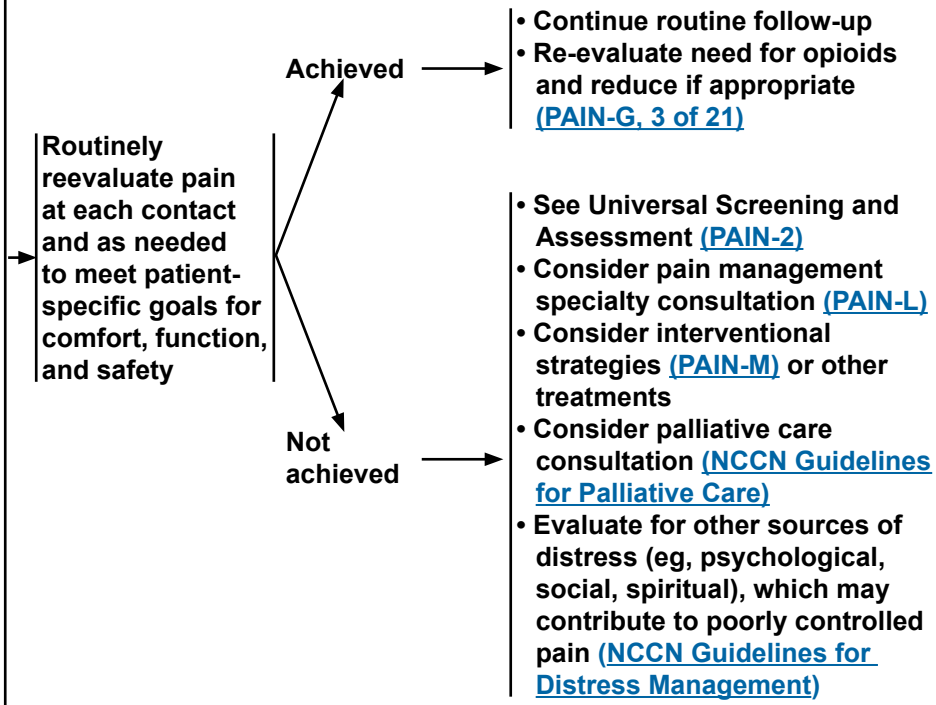
[l] Not including transmucosal fentanyl dose.

Note: All recommendations are category 2A unless otherwise indicated.

ONGOING CARE (AFTER PAIN IS REASONABLY CONTROLLED)

- If applicable, convert from parenteral to PO/transdermal opioids (if feasible) including extended-release or long-acting agent with rescue doses (see conversion details on PAIN-G)
  - Simplify analgesic regimen for improved patient adherence, if feasible.
- Have regular follow-up schedule to monitor pain therapy outcomes
  - Assess pain during each outpatient contact or at least each day for inpatients or more frequently based on:
    - ◊ Patient's condition, including analgesic therapy adverse effects
    - ◊ Institutional standards
    - ◊ Regulatory requirements
- Monitor for the use of analgesics as prescribed, especially in patients with risk factors for or history of substance misuse/diversion or cognitive dysfunction
- Provide written follow-up pain plan, including prescribed medications (PAIN-I)
- Ensure continuity of care during transition between sites of care
  - Collaborate with patient's pharmacist and insurance company if needed
  - Clarify which clinician will be prescribing patient's ongoing analgesics and ensure patient is aware of contact information for prescribing clinician
  - Ensure adequate access and supply of analgesics
- Address system barriers, and recruit assistance from social services as needed
  - Analgesic cost/pharmacy benefit coverage
  - Availability of analgesics
  - Local laws/regulations
- Instruct the patient on the importance of: (PAIN-I)
  - Following documented pain plan
  - Scheduling and keeping outpatient appointments
  - Contacting clinician if pain worsens or adverse effects are inadequately controlled, including availability of after-hours assistance to facilitate titration of analgesic
  - Safe handling, storage, and disposal of analgesics
  - Considering use of a pain diary to facilitate communication between patient and provider
- Reevaluate patient-centered goals of care in the context of current disease and available therapies
- Maintain communication and consider referral to pain/palliative care specialist and relevant providers, especially during transition between sites of care (NCCN Guidelines for Palliative Care)

GOALS OF TREATMENT



Note: All recommendations are category 2A unless otherwise indicated.

PAIN INTENSITY RATING

- **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, "average" 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-B) for more details.**

Table 1: 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."**

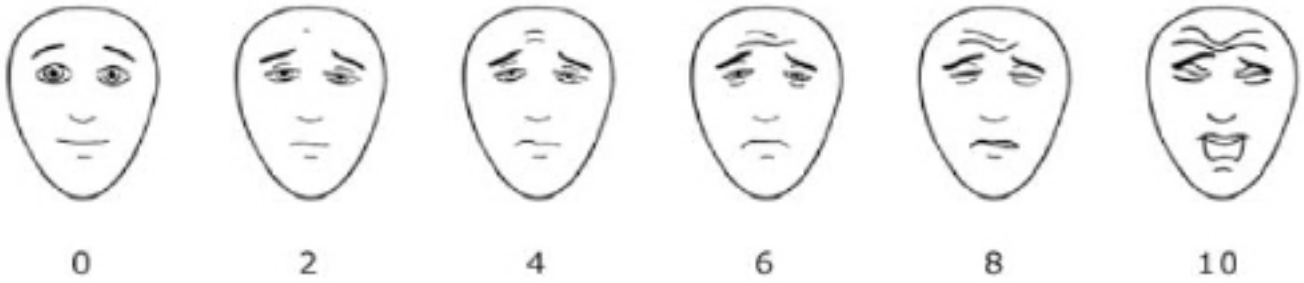
0 1 2 3 4 5 6 7 8 9 10

No pain — **Worst pain you can imagine**

Categorical scale: "What word best describes your pain?"

None (0) Mild (1–3) Moderate (4–6) 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. FPS-R © 2001, International Association for the Study of Pain. All rights reserved.
[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.

Note: All recommendations are category 2A unless otherwise indicated.

PAIN INTENSITY RATING

Pain Assessment in the Nonverbal Patient[3]

- **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 (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 https://prc.coh.org/pain_assessment_new.asp, is recommended.**
- **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) tested in adults in intensive care: http://www.ncbi.nlm.nih.gov/pubmed/11801819**[4]
  - **Critical-Care Pain Observation Tool (CPOT) tested in adults in intensive care: http://www.ncbi.nlm.nih.gov/pubmed/17575489**[5]
- **Clinicians are encouraged to monitor current research regarding new developments in strategies and tools for assessing pain in patients who have difficulty with self-reporting.**
- **Alternative assessment method and rationale should be documented to facilitate appropriate follow-up and reassessment.**

Cultural and Linguistic Assessment[6,7]

- **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.**

[3] 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.
[4] 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.
[5] Gélinas C, Johnston C. 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.
[6] Al-Atiyyat HNM. Cultural diversity and cancer pain. J Hosp Palliat Nurs 2009;11:154-164.
[7] 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.

Note: All recommendations are category 2A unless otherwise indicated.

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 (PAIN-A, 2 of 2).**
- **The goal of comprehensive pain assessment is to find the cause of the pain and identify optimal therapies. Individualized pain treatment is based on the etiology and characteristics of pain, pain trajectory, 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 the cancer itself, cancer therapy (ie, chemotherapy, RT, surgery) or procedures, and coincidental or acute or chronic noncancer pain (eg, arthritis).**
  - **Pathophysiology factors may include nociceptive, neuropathic, visceral, affective, behavioral, and cognitive components.**

- **Pain experience**
  - **Location, referral pattern, and radiation of pain(s)**
  - **Intensity [Pain Intensity Rating (PAIN-A)]**
    - **Last 24 hours: worst and least pain and pain now**
    - **At rest and with movement**
  - **Interference with activities [Impact of Pain Measurement (PAIN-B, 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 (OTC)?**
    - **Dose, route of administration, and frequency?**
    - **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-G, 2 of 21.**
  - **Prior pain therapies**
    - **Reason for use, dosing, 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 including patient experience of medical or other trauma**
    - **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 integrative therapies (PAIN-D)**
    - **Screen for potential adverse interactions or effects**
    - **Assess risk of analgesic misuse/diversion and substance use disorders (SUD)**
    - **Evaluate for factors impacting equitable access to pain therapies**

- **List of potential risk factors for misuse (PAIN-G, 4 of 21)**

Return to Universal Screening (PAIN-2)

Note: All recommendations are category 2A unless otherwise indicated.

COMPREHENSIVE PAIN ASSESSMENT

- **Psychosocial Support (PAIN-H) (NCCN Guidelines for Palliative Care)**
  - **Patient distress (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 SUD**
  - **Risk factors for aberrant use or diversion of pain medication (PAIN-G, 4 of 21)**
    - ◊ **Patient, environmental, and social factors as identified by a detailed patient evaluation[1] and/or screening tools at initiation of care (eg, SOAPP-R,[2] ORT,[3] CAGE-AID[4,5]) and monitoring of ongoing analgesic use (eg, COMM)[6] (Specific screening tools have not been validated in the setting of cancer care)[7] (PAIN-G, 6 of 21)**
  - **Risk factors for undertreatment of pain**
    - ◊ **People who are older, female,* or historically marginalized; communication barriers; history of SUD; neuropathic pain; and cultural factors**
- **Medical history**
  - **Oncologic treatment including current and prior systemic anti-tumor therapy, hormonal therapy, RT, and surgery**
  - **Other significant illnesses or conditions**
  - **Pre-existing chronic pain and treatment history**
- **Clinical assessment, physical examination, and laboratory and imaging studies to evaluate for disease progression**

***On this page, the term "female" refers to sex assigned at birth based on the availability of data in this population. However, it is important to note that transgender individuals may also be at risk of undertreatment of pain.**

[1] Moore TM, Jones T, Browder JH, Daffron S, Passik SD. 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.
[4] Keall R, Keall P, Kiani C, et al. A systematic review of assessment approaches to predict opioid misuse in people with cancer. Support Care Cancer 2022;30:5645-5658.
[5] Yennurajalingam S, Arthur J, Reddy S, et al. Frequency of and factors associated with nonmedical opioid use behavior among patients with cancer receiving opioids for cancer pain. JAMA Oncol 2021;7:404-411.
[6] Meltzer EC, Rybin D, Saitz R, et al. Identifying prescription opioid use disorder in primary care: diagnostic characteristics of the current opioid misuse measure (COMM). Pain 2011;152:397-402.
[7] Anghelescu DL, Ehrentraut JH, Faughnan LG, et al. Opioid misuse and abuse: risk assessment and management in patients with cancer pain. J Natl Compr Canc Netw 2013;11:1023-1031.

Return to Universal Screening (PAIN-2)

Note: All recommendations are category 2A unless otherwise indicated.

IMPACT OF PAIN MEASUREMENT[8,9]

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**

[8] Used with permission from Cleeland CS, Nakamura Y, Mendoza TR, et al. Dimensions of the impact of cancer pain in a four country sample: New information from multidimensional scaling. Pain 1996;67:267-273.
[9] For the complete Brief Pain Inventory assessment tool, see mdanderson.org/bpi.

Note: All recommendations are category 2A unless otherwise indicated.

PSYCHOSOCIAL SUPPORT

General

- 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 (PAIN-I).
- Assessing each patient's need for psychosocial support is an essential component of a comprehensive pain assessment (PAIN-B).

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 mutually agreed upon plan of care 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 of continued partnership to manage pain and other 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.
- Consider referral to spiritual care provider (NCCN Guidelines for Distress Management).

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.
  - Consider referral to a licensed mental health professional who is trained in any of the following domains: cognitive behavioral therapy (CBT), hypnosis, biofeedback, and mindfulness-based stress reduction (MBSR).
  - Coping skills for acute pain include breathing exercises and distraction techniques.
  - Coping skills for chronic pain (not pain emergency) include all of the above, plus relaxation techniques, guided imagery, graded task assignments, hypnosis to maximize function, cognitive restructuring, and behavioral activation.
  - Provide training on how 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, palliative care clinician, integrative medicine clinician, physiatrist, neurologist, psychologist, social worker, psychiatrist, physical therapist, and spiritual counselor. See Patient and Family/Caregiver Education (PAIN-I).

Note: All recommendations are category 2A unless otherwise indicated.

INTEGRATIVE INTERVENTIONS

Consider integrative interventions in conjunction with pharmacologic interventions as needed. Integrative interventions may be especially important in vulnerable populations (eg, frail, older) 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-L).

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

- **Cognitive Modalities**
  - Cognitive behavioral therapy (CBT), cognitive restructuring
  - Mindfulness-based stress reduction (MBSR)
  - Imagery
  - Hypnosis
  - Biofeedback
  - Acceptance-based training
  - Distraction training
  - Relaxation training
  - Active coping training
  - Graded task assignments, setting goals, pacing, and prioritizing
  - Behavioral activation

- **Spiritual Care** (NCCN Guidelines for Distress Management)

- **Physical Modalities**
  - Bed, bath, and walking supports
  - Positioning instruction
  - Instruction in therapeutic and conditioning exercise
  - Energy conservation, pacing of activities
  - Massage
  - Heat and/or ice
  - Transcutaneous electrical nerve stimulation (TENS)
  - Acupuncture, electro-acupuncture, or acupressure
  - Ultrasonic stimulation

- **Nutritional Modalities**
  - Nutrition consult
  - Dietary recommendations
  - Assess and educate on herbal, botanical, and dietary supplements

- See Interventional Strategies (PAIN-M)

Note: All recommendations are category 2A unless otherwise indicated.

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

Acetaminophen

- Acetaminophen, 650 mg every 4 hours or 1 g every 6 hours (daily maximum 4 g/day) in adult patients with normal liver function. For chronic administration or use in older adults, consider limiting the maximum daily dose to 3 g/day or less due to concerns for hepatic toxicity.
- 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.
- Consider OTC medications as additional sources of acetaminophen.
- Use acetaminophen with caution in the setting of immunotherapy given possible impacts on the efficacy of immunotherapy.[1]
- Note that there may be concerns about the risk of masking fever in immunocompromised patients.

NSAIDs

- Use NSAIDs with caution, especially for chronic use, as many patients with cancer may be at high risk for renal, gastrointestinal (GI) (ie, upper GI surgery, RT), or cardiac toxicities; thrombocytopenia; or bleeding disorder (PAIN-E 2 of 2).
  - If an NSAID is determined to be of analgesic benefit, use should be coordinated with other oncologic therapies to avoid unintended risk of adverse effects.
  - The FDA warns that NSAID use increases the risk of heart attack or stroke (http://www.fda.gov/Drugs/DrugSafety/ucm451800.htm).
- Note that the potential adverse effects of chemotherapy (especially angiogenesis inhibitors), such as hematologic (ie, 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. Shortest duration, lowest effective dose of NSAIDs should be used while a safer, long-term pain management strategy is being developed.
  - Ibuprofen, 400–800 mg 4 times daily (daily maximum = 3200 mg); or naproxen 220–500 mg 2–3 times daily (daily maximum of 1500 mg). If needed, consider short-term use of ketorolac, 15–30 mg IV every 6 hours for a maximum of 5 days.
  - Compounds that do not inhibit platelet aggregation:
    - ◊ Nonacetylated salicylate (eg, salsalate), 2–3 g/day in two or three divided doses; magnesium salicylate, OTC
    - ◊ Celecoxib (selective COX-2 inhibitor) up to 200 mg/twice daily
- Consider topical NSAID for peripheral joint pain due to reduced systemic absorption - diclofenac gel 1% 4 times/day; or diclofenac patch 1.3% 1–2 patches/day

NSAIDs and Toxicities (PAIN-E, 2 of 2)

[1] Bessede A, Marabelle A, Guégan JP, et al. Impact of acetaminophen on the efficacy of immunotherapy in cancer patients. Ann Oncol 2022;33:909-915.

Note: All recommendations are category 2A unless otherwise indicated.

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

NSAIDs and Toxicities

- **Monitoring for NSAID toxicities**
  - **Baseline blood pressure, blood urea nitrogen (BUN), creatinine, liver function studies (ie, alkaline phosphatase, lactate dehydrogenase [LDH], serum glutamic-oxaloacetic transaminase [SGOT], serum glutamic-pyruvic transaminase [SGPT]), and complete blood count (CBC). Repeat these evaluations as clinically indicated.**
- **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 PO NSAIDs.**
  - **Toxicity of anti-cancer treatment may increase the risk profile of anti-inflammatory treatment.**

Cardiac Toxicities

- **Patients at high risk: history of cardiovascular disease or at risk for cardiovascular disease or complications.[2]**
- **The use of concomitant NSAID with prophylactic aspirin may reduce the effectiveness of aspirin. Therefore, it is recommended to either avoid use or take separately to avoid this possibility.**
- **Treatment: Discontinue NSAID if congestive heart failure or hypertension develops or worsens. All NSAIDs have been associated with cardiac toxicities.**

Hematologic Toxicities

- **NSAIDs taken with prescribed anticoagulants, such as warfarin or heparin, may significantly increase the risk of bleeding complications.**
- **Avoid the use of PO NSAIDs in the setting of prophylactic or therapeutic anticoagulation. Celecoxib or topical NSAIDs such as diclofenac gel or patch may be useful in this population.**

Renal Toxicities

- **Patients at high risk: age >60 years, compromised fluid status, multiple myeloma, diabetes, interstitial nephritis, papillary necrosis, and concomitant administration of other nephrotoxic drugs (including cyclosporine, cisplatin) and renally excreted chemotherapy.**
- **Treatment: Reevaluate NSAID use if renal function deteriorates or if hypertension develops or worsens.**
- **All NSAIDs, including COX-2 inhibitors, with systemic administration have been associated with renal toxicities.**

GI Toxicities

- **Patients at high risk: age >60 years, 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, cardioprotective dose of daily aspirin, and concomitant use of selective serotonin reuptake inhibitor (SSRI) antidepressants.**
- **Treatment:**
  - **If patient develops gastric upset or nausea, consider discontinuing NSAID, adding proton pump inhibitors, 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.**
  - **As prophylaxis for NSAID peptic ulceration, consider adding misoprostol or proton pump inhibitors. 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.**

[2] 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.

Note: All recommendations are category 2A unless otherwise indicated.

ADJUVANT ANALGESICS FOR NEUROPATHIC PAIN (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 also be used in combination with opioids, for patients whose pain is otherwise inadequately controlled.**
- **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 etiology of neuropathic pain and the individual patient. Failure to control pain with one agent in a particular class does not mean the entire class of medications will not work.**
- **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.**
- **For information on cannabinoids and medical marijuana/cannabis, see Discussion.**
- **Expectations for onset of effect of adjuvant analgesics should be discussed with patients.**

Examples of Adjuvant Analgesics Use for Neuropathic Pain (PAIN-F, 2 of 2)

Note: All recommendations are category 2A unless otherwise indicated.

ADJUVANT ANALGESICS FOR NEUROPATHIC PAIN (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.

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 2–3 times a day. Dose increments of 50%–100% may occur as often as every 3 days. Slower titration is needed for those who are older or medically frail. Dose adjustment is required for those with renal insufficiency.
  - Pregabalin- Starting dose 75 mg twice a day, with increasing dose increments of 50%–100% every 3 days to a maximum daily dose of 600 mg. Slower titration is needed for the those who are older or medically frail. Dose adjustment is required for those with renal insufficiency. Pregabalin is more efficiently absorbed through the GI tract than gabapentin.
  - Consider other anticonvulsant agents, many of which have been shown to have efficacy in non-cancer neuropathic 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.
- Check for drug interactions with special regard to serotonergic medications due to risk for serotonin syndrome.
- Serotonin-norepinephrine reuptake inhibitors (SNRIs) (dose adjustment is required for those with renal and/or hepatic insufficiency):
  - Duloxetine- Starting dose 20–30 mg daily; after 1 week, increase to 60 mg daily as needed/tolerated (doses up to 120 mg per day may be useful for mood disorders) (there are data supporting use of duloxetine for chemotherapy-induced peripheral neuropathy)
  - Venlafaxine- Starting dose 37.5 mg daily, increase every 4 days as needed, up to 75–225 mg daily (dose must be at least 150 mg per day to achieve SNRI effects/analgesia)
- Tricyclic antidepressants (TCAs) (eg, amitriptyline, imipramine, nortriptyline, desipramine)
  - TCAs should be used with caution in patients with conduction abnormalities, including QTc prolongation, or ischemic heart disease
  - TCAs should be used with caution in older adults due to increased risk for falls, confusion, and anticholinergic adverse effects.
  - Start with low dose and increase every 5–7 days if tolerated (eg, nortriptyline and desipramine starting dose 10–25 mg nightly with increase to 50–150 mg nightly). The tertiary amines (ie, amitriptyline, imipramine) may be more efficacious but secondary amines (ie, 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.

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. Continuous application to a given area may increase likelihood of cutaneous damage over time.
  - Topical NSAIDs - See PAIN-E 1 of 2

Corticosteroids: Typically dexamethasone (due to less mineralocorticoid effect). Long half-life of these drugs allows for once-daily dosing, preferably in the morning due to their stimulating effect and to prevent nighttime insomnia. Useful in the acute management of a pain crisis when neural structures or bones are involved. Long-term adverse effects are significant.

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

Note: All recommendations are category 2A unless otherwise indicated.

OPIOID PRINCIPLES, PRESCRIBING, INITIATION, TITRATION, MAINTENANCE, AND SAFETY

Note: All recommendations are category 2A unless otherwise indicated.

OPIOID PRINCIPLES, PRESCRIBING, INITIATION, TITRATION, MAINTENANCE, AND SAFETY

General Principles

- Review prescription drug monitoring program (PDMP) databases as appropriate based on clinical necessity and regulatory requirements.
- Document opioid and controlled substance agreement as appropriate per regulatory requirements.
- UDT should be strongly considered at baseline (prior to opioid therapy initiation) and during treatment (at least annually) for all patients receiving opioid analgesics for subacute or chronic pain (PAIN-G 7 of 21).
- Dose and 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.
- The appropriate opioid dose is the lowest dose that relieves the patient's pain and maximizes function throughout the dosing interval without causing unmanageable adverse effects.
- Generally, PO route is most common; however, other routes (i.e., IV, [SC], rectal, transdermal, transmucosal) can be considered as indicated to maximize patient comfort (especially in context of unreliable GI absorption). 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 hours and increase both around-the-clock and as-needed dose as required. The rapidity of dose escalation should be related to the severity of the symptoms, expected analgesic onset and duration, and ability to monitor during dose titration.
  - When initiating opioid therapy or making significant dose adjustments, close follow-up should be considered.
- 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 allow for optimized titration of both agents (PAIN-E).
- Steady state drug levels will be achieved when a stable drug dose has been routinely administered for a period equal to 5 times the drug elimination half life.
- Consider opioid rotation if pain is inadequately controlled and further dose titration is limited by adverse effects. Other indications for switching to a different opioid include: out-of-pocket costs, limitations based on insurance formularies, or change in a patient's condition (eg, dysphagia, NPO [nothing by mouth] status, initiation of tube feeding, renal and/or hepatic function).
- For breakthrough pain, see PAIN-G, 2 of 21.
- For opioid dose reduction, see PAIN-G, 3 of 21.
- Patient evaluations should include assessment of risk factors for aberrant use of pain medications (PAIN-G, 6 of 21).
- Educate patients and caregivers about safe use, storage, and disposal of opioids (PAIN-I).
- Use caution when combining opioid medications with other medications that have a sedating effect (eg, benzodiazepines) due to increased risk for sedation and respiratory depression. See http://www.fda.gov/downloads/drugs/drugsafety/ucm518672.pdf.
- Consider pain or palliative care consult. See Management of Pain in Opioid-Tolerant Patients (PAIN-4).

Continued
References

Note: All recommendations are category 2A unless otherwise indicated.

OPIOID PRINCIPLES, PRESCRIBING, INITIATION, TITRATION, MAINTENANCE, AND SAFETY

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% to 100% of the daily requirement, depending on expected pain trajectory.
  - If using different forms of long-acting and short-acting opioids, particular care must be taken with conversions and appropriate dosing.
- When using methadone as a long-acting opioid, a short-acting opioid should also be provided for breakthrough pain as needed.
- Increase dose of regularly scheduled 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.
- Breakthrough pain (pain that fails to be controlled or "breaks through" a regimen of regularly scheduled analgesic) may require additional doses of analgesic for pain not relieved by regular schedule of long-acting (eg, extended-release) analgesic. 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 (eg, physical therapy, exercise, routine procedures that may induce pain)
  - 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
- Recommend using a single short-acting agent for breakthrough pain.
- Allow rescue doses of short-acting opioids (10%–20% of the 24-hour total of long-acting or regularly scheduled PO opioid dose) up to every 3–4 hours as needed. Titrate rescue dose as needed.
  - If pain is inadequately controlled, to allow for dose titration, the short-acting opioids could be given as often as once per hour as needed (if hourly dosing is needed for more than 3 cycles, reassessment or other intervention is recommended).
- Consider rapidly acting transmucosal fentanyl (various formulations and delivery systems are available) in opioid-tolerant patients for brief episodes of incident pain not relieved by traditional immediate-release opioids and not attributed to inadequate dosing of around-the-clock opioid (transmucosal fentanyl requires REMS certification for both prescriber and pharmacist [PAIN-G 4 of 21]).
  - Initiate transmucosal fentanyl with lowest dose in chosen formulation and titrate to effect. See specific transmucosal prescribing information for appropriate dosing intervals and initial dosing recommendations.
- Continue to monitor patients for opioid adverse effects and patients/caregiver/family for abnormal patterns of opioid use that may suggest aberrant drug use and/or diversion (PAIN-G, 6 of 21).
- Consider potential drug interactions (Table 1 in the Discussion).
- Renal insufficiency has the least impact on pharmacology of transdermal fentanyl, methadone, and buprenorphine. These medications should be considered in this setting.

Continued
References

Note: All recommendations are category 2A unless otherwise indicated.

OPIOID PRINCIPLES, PRESCRIBING, INITIATION, TITRATION, MAINTENANCE, AND SAFETY

Principles of Opioid Dose Reduction

- **Consider opioid dose reduction by 5% to 20% (https://www.cms.gov/About-CMS/Story-Page/CDCs-Tapering-Guidance.pdf) when:**
  - **Patient never or rarely needs breakthrough analgesic.**
  - **There is completion of acute pain event or response to cancer-directed therapies.**
  - **There is improvement of pain control through use of non-opioid pain management therapies.**
- **If patient is experiencing unmanageable opioid-related adverse effects, see PAIN-H. If pain is 3 (mild), consider downward dose titration by approximately 10% to 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.**
  - **If patient has rapid clinical deterioration (eg, marked sedation due to sepsis), temporary opioid dose reduction by 50% to 75% may be necessary (PAIN-H 3 of 3).**
- **Review expected trajectory of pain and goals of care/pain management when considering opioid dose reduction.**
- **Opioid dose reduction must be individualized to meet patient goals of care and minimize symptoms of withdrawal. If patient experiences withdrawal, slower taper may be needed.**

Continued
References

Note: All recommendations are category 2A unless otherwise indicated.

OPIOID PRINCIPLES, PRESCRIBING, INITIATION, TITRATION, MAINTENANCE, AND SAFETY

Opioids and Risk Evaluation and Mitigation Strategy (REMS)

- **Opioids are the principal analgesics for moderate to severe pain, yet opioids pose risks to patients and society. In 2021, 106,699 drug overdose deaths occurred in the United States, including 80,411 deaths involving opioids. Drug poisoning still remains the number one cause of injury-related deaths.[1] Most people who overdose on prescription opioids not prescribed to them have been given (not bought or stolen) opioids from friends or family. See CDC Drug Overdose Death Data (December 2022).**
- **Responding to the "public health crisis of addiction, misuse, abuse, overdose, and death," the FDA established REMS programs for all potent opioid products. See Opioid Drugs and Risk Evaluation and Mitigation Strategies (REMS). Provider and patient education are the principal recommendations of proposed opioid REMS programs. Highlights include:**
  - ◊ **Patient's therapeutic response to opioid therapy should be regularly evaluated as to patient treatment goals of therapy.**
  - ◊ **Prescriber should routinely evaluate each patient for risk factors associated with opioid misuse/diversion.**
  - ◊ **Prescriber should educate each patient on safe use, storage, and disposal of opioid (PAIN-I).**
  - ◊ **Prescriber should routinely monitor patients for opioid misuse. Different screening tools have been described for this purpose but have yet to be evaluated in cancer-related pain.[2]**
  - ◊ **Make use of state PDMPs. The National Association of State Controlled Substances Authorities (https://www.nascsa.org) maintains a database of state PDMP contacts.**
- **REMS programs are currently in place for all opioid analgesics (https://opioidanalgesicrems.com).**
  - ▸ **Registration is required in order to prescribe transmucosal fentanyl products (https://www.tirfremsaccess.com).**
- **It is important for prescribers to be aware of the range of opioid use patterns to detect potential aberrant behaviors (PAIN-G, 6 of 21).**
  - ▸ **Potential risk factors for non-medical use of analgesics (as established in the treatment plan) and/or increased risk of opioid use disorder (OUD) include:**
    - ◊ **Patients with a history of prescription, illicit drug, or SUD**
    - ◊ **Patients who have a history of binge drinking or peers who binge drink**
    - ◊ **Patients who have a family history of SUD**
    - ◊ **Patients with a history of psychiatric disorder, including anxiety, depression, attention deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), bipolar disorder, or schizophrenia**
    - ◊ **Patients who have a history of sexual abuse victimization may be at increased risk for prescribed medication misuse**
    - ◊ **Young age (<45 years)**
    - ◊ **Patients with a history of legal problems or incarceration**
- **Patients receiving treatment for SUD should be encouraged to continue with therapy and pain management should be carried out in coordination with a SUD specialist and consider referral to a pain specialist.**
- **As of June 27, 2023, as part of the Consolidated Appropriations Act of 2023, the Drug Enforcement Administration (DEA) requires that all prescribers applying for a new or renewed DEA registration will have to attest to having completed a total of at least 8 hours of training on the treatment and comprehensive care of patients with OUD or other SUD.**

Continued
References

Note: All recommendations are category 2A unless otherwise indicated.

OPIOID PRINCIPLES, PRESCRIBING, INITIATION, TITRATION, MAINTENANCE, AND SAFETY

Table 1. Glossary of Terms Related to Opioid Misuse[2]

Addiction	**See Substance use disorders (SUD)**
Chemical coping[3]	**Misuse of medication in a non-prescribed way to cope with the various stressful events associated with the diagnosis and management of cancer**
Diversion	**The transfer of a prescribed medication from the person for whom it was prescribed to another person**
Misuse	**The inappropriate use of a prescription drug, whether intentional or unintentional, and regardless of motivation**
Physical dependence	**Pharmacologic property of some drugs, defined solely by the occurrence of an abstinence syndrome after abrupt dose reduction, discontinuation of dosing, or administration of an antagonist drug**
Pseudoaddiction	**Distress and perceived drug-seeking behaviors that occur in the context of unrelieved pain. These behaviors subside when analgesia is achieved**
Substance use disorders (including OUD)	**A cluster of cognitive, behavioral, and psychological symptoms indicating that the individual continues using the substance despite significant substance-related problems[4]**
Tolerance	**Diminution of one or more drug effects (either favorable or adverse effects) caused by exposure to the drug; may be pharmacologic or associative (related to learning)**

Continued
References

Note: All recommendations are category 2A unless otherwise indicated.

OPIOID PRINCIPLES, PRESCRIBING, INITIATION, TITRATION, MAINTENANCE, AND SAFETY

Opioid Risk Mitigation Strategies During Chronic Opioid Use[2]

- Use caution when combining opioid medications with other medications that have a sedating effect (eg, benzodiazepines) (http://www.fda.gov/downloads/drugs/drugsafety/ucm518672.pdf).
- Risk assessment prior to and during treatment is recommended, although current assessment tools have not been validated in the setting of cancer care and clinical judgment should be exercised.
  - The Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP®-R)
  - The Opioid Risk Tool (ORT)
  - Current Opioid Misuse Measure (COMM)
  - CAGE-AID
  - Comprehensive psychological evaluation can be helpful in assessing risk for SUD.
- Educate regarding the potential risks and benefits of opioid therapy; educate regarding not sharing opioids with family members or friends.
  - Discuss the purpose of the assessment and reassure that responses will not prevent receiving appropriate treatment.
  - Provide guidance and education about the potential for diversion and misuse of opioids.
- Educate regarding safe manipulation, storage, and disposal of controlled substances. These interventions contribute to maintaining a safe community and minimize opioid misuse in the community (PAIN-I).
  - Encourage use of community take-back programs for disposal of unneeded controlled substances where available; otherwise, FDA regulations recommend flushing unneeded opioids down the toilet: https://www.fda.gov/drugs/safe-disposal-medicines/disposal-unused-medicines-what-you-should-know#Flush_List

Risk Mitigation for All Patients Receiving Opioid Analgesics

- Review PDMP databases as appropriate based on clinical necessity and regulatory requirements.
- Discuss the role of naloxone for administration by caregivers in the event of respiratory depression and sedation and make available as indicated or as required by local and/or state regulations.
  - Ensure education of caregivers in the proper indications and usage of naloxone (https://store.samhsa.gov/system/files/sma18-4742.pdf).
  - Instruct caregivers to call emergency services (911) if naloxone is administered.
  - After patient stabilization, in-person reevaluation is recommended. In the interim, if additional analgesics are required, consider reduced dose and frequency, as well as evaluation of other contributing respiratory depressants.
- Pain medication diaries are recommended for patients to document the dose and/or number of tablets and the date and time taken.
- Pill counts may be used at outpatient visits or by home health/hospice to assist in correct use of medication.

Patients with increased risk for OUD may benefit from additional education and support services. Behavioral and cognitive-behavioral interventions may increase a patient's ability to implement problem-solving strategies and reduce the impact of modifiable risk factors.

- Increase frequency of outpatient visits weekly, if possible, and/or reduce quantity of drug prescribed per prescription.
- Consider earlier referral to interventional pain specialist to maximize non-opioid options for pain control.
- Consider referral to multidisciplinary team including a specialist for SUD.
- Counsel patients at high risk for OUD that continuation of opioid therapy is contingent upon appropriate, safe use of prescribed analgesics.
- Consider utilizing programmable electronic medication dispensers.

Continued
References

Note: All recommendations are category 2A unless otherwise indicated.

OPIOID PRINCIPLES, PRESCRIBING, INITIATION, TITRATION, MAINTENANCE, AND SAFETY
URINE DRUG TESTING

Urine Drug Testing (UDT) in Cancer Pain Management

General Principles

- The goal of UDT is to improve patient outcomes and safety. Care must be taken in applying UDT to limit bias in test application/interpretation, and avoid excessive patient burden (eg, financial impact, delay of care) and/or negative impacts on patient care (punitive, judgmental response to unexpected results).[5]
- Published studies in patients with cancer found through random UDT that 1 in 4 patients receiving opioids had one or more abnormal results compared to results expected from prescribed therapy.[6]
- UDT should be strongly considered at baseline (prior to opioid therapy initiation) and during treatment (at least annually) for all patients receiving opioid analgesics for subacute or chronic cancer pain to aid in evaluation of opioid analgesic adherence, detect illicit substance use, and identify opioid diversion.
- UDT should also be considered during opioid therapy, if patients exhibit risk factors for opioid misuse, as part of analgesic therapy reassessment, to ensure patient safety and minimize risk of drug diversion.

Urine Drug Screen Monitoring in Cancer Pain Management

- UDT should be part of a comprehensive safety monitoring program for patients receiving opioids for subacute and/or chronic cancer pain. This program should include periodic review of state PDMPs, as required by local/state laws, opioid prescribing patient agreement, and informed consent for opioid therapy.
- Current published literature does not support UDT based on opioid risk stratification questionnaires (ie, ORT, SOAPP-R), especially in patients with OUD and/or those engaging in non-medical opioid use (NMOU).[7,8] Therefore, it is recommended that, for all patients receiving opioids for subacute and/or chronic cancer-related pain, strong consideration be given to UDT prior to initiating opioid therapy and periodically while opioids and other controlled substances are utilized for cancer pain management.

Limitations of Monitoring

- UDT by immunoassay (often used in point of care testing) can identify naturally occurring opioids (PAIN-G 8 of 21) such as codeine and morphine, including diacetylmorphine (ie, heroin); however, synthetic or semisynthetic opioids are not reliably detected, unless specific drug assays are utilized. UDT via immunoassay is also susceptible to false positives/negatives.
  - For unexpected results from immunoassay testing, prescribers should request confirmatory testing (ie, gas chromatography–mass spectrometry [GC-MS], liquid chromatography–mass spectrometry [LC-MS]), and/or input from a certified laboratory professional or toxicologist (expert consensus/expert opinion).
- More specific mass spectrometry and/or quantitative UDT significantly increases drug costs and generally prolongs turnaround times for results compared with immunoassay (point of care) testing.
  - Urine drug screen testing costs may not be fully reimbursed by insurers and are sometimes passed on to patients with severe financial impact.
  - Mass spectrometry and or quantitative results may take 1 to 2 weeks, whereas immunoassay results may be available within 24 to 72 hours.
- Urine is the preferred route for routine drug testing, but other alternatives do exist such as saliva, blood or plasma, hair, and sweat. These alternatives may be options for patients unable to provide adequate urine samples, but may not provide comparable results.[9]
- For any unexpected results from either qualitative or quantitative testing, prescribers should seek input from a clinical pharmacist familiar with UDT interpretation, a certified laboratory professional, or toxicologist.[10]

Continued
References

Note: All recommendations are category 2A unless otherwise indicated.

OPIOID PRINCIPLES, PRESCRIBING, INITIATION, TITRATION, MAINTENANCE, AND SAFETY
URINE DRUG TESTING

Common Opioids and Metabolites Potentially Identified in Urine Drug Screen Testing[10-14]

Green (naturally occurring opioids, including diacetylmorphine), Yellow (semi-synthetic opioids), Blue (synthetic opioids)

Opioid	Metabolite(s) – Identified with Confirmatory Testing*	Detection Time (days) †	Comments
Codeine	Morphine (active), norcodeine, hydromorphone, norhydrocodone, hydrocodone, dihydrocodeine, codeine-6-glucuronide	1–4	Morphine is the active/major metabolite of codeine metabolism
Morphine	Morphine 6-glucuronide (active), morphine 3-glucuronide (inactive), hydromorphone, codeine**	1–4	Codeine is a pharmaceutical contaminant of morphine manufacturing
Heroin (Diacetylmorphine)	6-Monoacetylmorphine (6-MAM), morphine, normorphine, codeine**	<1	Heroin (diacetylmorphine) is rapidly metabolized to 6-MAM, which is quickly hydrolyzed to morphine. Due to the rapid elimination of 6-MAM, morphine is commonly reported
Oxycodone	Oxymorphone (active), noroxycodone, hydrocodone**	1–4	Hydrocodone is a pharmaceutical contaminant of oxycodone manufacturing
Hydrocodone	Hydromorphone (active), dihydrocodeine, norhydrocodone	1–4	
Hydromorphone	Hydromorphone-3-glucuronide	1–4	
Oxymorphone	Noroxymorphone, oxymorphone 3-glucuronide, 6-hydroxy oxymorphone	1–4	
Buprenorphine	Norbuprenorphine, buprenorphine 3-glucuronide	1–7	Low does of buprenorphine may not reach detectable levels in urine
Fentanyl	Norfentanyl	1–3	
Levorphanol	Levorphanol glucuronide, dextrorphan	1–5	LC–MS assays are unable to distinguish between stereoisomers of levorphanol and dextrorphan (metabolite of dextromethorphan); additional confirmatory testing may be needed
Methadone	EDDP (2-ethylene-1,5-dimethyl-3-3-diphenylpyrrolidine)	1–14	
Meperidine	Normeperidine, meperidinic and normeperidinic acid	1–2	
Tapentadol	Tapentadol-o-sulfate, nortapentadol (N-desmethyltapentadol) hydroxyl-tapentadol	1–3	
Tramadol	O-desmethyl tramadol (active), N-desmethyl tramadol	1–4	

Note: Not all metabolites listed above may be reported, but if no metabolites or high concentrations of parent drug alone are found, this may indicate tampering or spiking (adding drug to urine sample). Immunoassay, or point-of-care testing, cannot identify metabolites or detect spiking. Patients taking opioids as needed may have negative results based on infrequent patterns of use (outside of the detection window) or recent drug initiation.

* GC-MS, LC-MS, tandem mass spectrometry (LC-MS/MS)
** May be present in very small amounts due to impurities (due to manufacturing or contamination)
† Estimated detection in urine (days)

Continued
References

Note: All recommendations are category 2A unless otherwise indicated.

OPIOID PRINCIPLES, PRESCRIBING, INITIATION, TITRATION, MAINTENANCE, AND SAFETY
URINE DRUG TESTING

Non-opioid Drugs and Common Drugs of Abuse Potentially Identified in Urine Drug Screen Testing[15-18]

Drug	Urine (days)
Alcohol (ethanol)	<1
Amphetamine/Dextroamphetamine	1–5
Barbiturates	1–10
Benzodiazepines	1–10
Cathinones (Bath Salts)	1–5
Cocaine	1–5
Fentanyl	3–5
Heroin	<1
Ketamine	<3
Kratom	1–7
Marijuana/THC (chronic use)	≥3 weeks
Marijuana/THC (light use)	1–3
Methamphetamine	1–5
MDMA (Ecstasy)	1–3
Nicotine	1–7
Spice/K2	1–3

Note: Detection times listed above are variable and may be influenced by frequency of use and patient-specific variables.

Continued
References

Note: All recommendations are category 2A unless otherwise indicated.

OPIOID PRINCIPLES, PRESCRIBING, INITIATION, TITRATION, MAINTENANCE, AND SAFETY

Table 2. Oral and Parenteral Opioid Equivalences and Relative Potency of Drugs as Compared with Morphine Based on Single-Dose Studies
Drug conversions below are estimates; institutional variations should be considered

Opioid Agonists	Parenteral Dose	Oral Dose	Factor (IV to PO)	Duration of Action[j]
Morphine[a,b]	10 mg	30 mg	3	3–4 h
Hydromorphone[a]	1.5 mg	7.5 mg	2.5–5	2–3 h
Fentanyl[c]	0.1 mg	–	–	–
Methadone[d,e]	–	–	–	–
Oxycodone	–	15–20 mg	–	3–5 h
Hydrocodone[a,f]	–	30–45 mg	–	3–5 h
Oxymorphone[a]	–	10 mg	10	3–6 h
Codeine[a,g]	–	200 mg	–	3–4 h
Tramadol[h]	–	300 mg	3	6 h
Tapentadol[i]	–	75–100 mg	–	–

NOT RECOMMENDED
Meperidine[k]
Mixed agonist-antagonists[l] (pentazocine, nalbuphine, butorphanol)

Miscellaneous Analgesics (PAIN-G, 19 of 21)

[a] Codeine, morphine, hydromorphone, hydrocodone, and oxymorphone should be used with caution in patients with fluctuating renal function due to potential accumulation of renally cleared metabolites—monitor for neurologic adverse effects.
[b] Conversion factor listed for chronic dosing.
[c] In single-dose administration, 10 mg IV morphine is equivalent to approximately 100 mcg IV fentanyl; however, 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-G,13 of 21.
[d] Long half-life with marked variability (may be between 15–120 hours [Chou R, et al. J Pain 2014;15:321-137]); observe for drug accumulation and adverse effects, especially over first 4–5 days. In some individuals, steady state may not be reached for several days to 2 weeks. Methadone is typically dosed every 8–12 hours (PAIN-G 17 of 21).
[e] The PO 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-G, 17 of 21).
[f] Equivalence data have not been substantiated. Clinical experience suggests use as a mild, initial-use opioid but effective dose may vary. Immediate-release hydrocodone is only available commercially combined with acetaminophen (325 mg/tablet) or ibuprofen (200 mg/tablet). The FDA has limited 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 acetylsalicylic acid or acetaminophen.
[g] Codeine has no analgesic effect unless it is metabolized into morphine by hepatic enzyme CYP2D6 and then to its active metabolite morphine-6-glucuronide by phase II metabolic pathways (PAIN-N).
[h] The manufacturer recommends a maximum single dose of tramadol not to exceed 100 mg, with a maximum daily dose of 400 mg for immediate-release formulations (300 mg/day in older adults, 200 mg/day for renal impairment) or 300 mg/day for extended-release formulations (PAIN-N).
[i] The maximum daily dose for tapentadol extended-release is 500 mg, or 600 mg immediate-release (lower doses are recommended for moderate hepatic impairment; avoid with severe impairment).
[j] Shorter time generally refers to parenterally administered opioids (except for controlled-release products, which have some variability); longer time generally applies to PO dosing.
[k] Not recommended for cancer pain management because of central nervous system (CNS) toxic metabolite, normeperidine.
[l] Mixed agonists-antagonists have limited usefulness in cancer pain; however, they can be used to treat opioid-induced pruritus. 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.

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References

OPIOID PRINCIPLES, PRESCRIBING, INITIATION, TITRATION, MAINTENANCE, AND SAFETY

Convert or Rotate From One Opioid to Another Opioid

1. Determine the amount of current opioid(s) taken in a 24-hour period.
2. Calculate the equianalgesic dose of the new opioid. See Table 2 on PAIN-G, 10 of 21.
3. If pain was effectively controlled, and the patient is opioid tolerant,[m] reduce the dose by 25%–50% to allow for incomplete cross-tolerance between different opioids. During the first 24 hours, titrate as needed to analgesic effect.
4. If previous dose was ineffective, may begin with 100% of equianalgesic dose.
5. Lastly, for PO opioids divide the total daily dose of new opioid needed by the number of doses per day to determine the individual dose (eg, if using short-acting opioid: 6 doses for regular PO morphine every 4 hours; if using long-acting opioid, dose and frequency would depend on formulation used). Monitor closely for end-of-dose failure between doses of long-acting opioid. In addition, consider as-needed doses for breakthrough pain of 10% to 20% of the total daily dose.
6. Data do not support a specific transmucosal fentanyl dose equianalgesic to other opioids or between different transmucosal formulations. See package insert of specific transmucosal formulations for appropriate dosing information (https://www.tirfremsaccess.com/TirfUI/rems/home.action).
7. Consider the impact of impaired liver and renal function (if present) on metabolism and clearance of the new opioid. See Table 2 on PAIN-G, 10 of 21.

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-hour period for this patient
   (8 mg/h x 24 hours) = 192 mg/day
2. From Table 2 on PAIN-G, 10 of 21, 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)

[m] Opioid-naïve patients are those not chronically receiving opioid analgesic on a daily basis and therefore have not developed significant tolerance. Opioid tolerant includes patients who are chronically receiving opioid analgesic on a daily basis. The FDA identifies tolerance as receiving at least 25 mcg/h fentanyl patch, at least 60 mg of morphine daily, at least 30 mg of PO oxycodone daily, at least 8 mg of PO hydromorphone daily, or an equianalgesic dose of another opioid for a week or longer.

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References

OPIOID PRINCIPLES, PRESCRIBING, INITIATION, TITRATION, MAINTENANCE, AND SAFETY
TRANSDERMAL FENTANYL

General Comments Regarding Transdermal Fentanyl:

- **Pain should be relatively well-controlled on an opioid prior to initiating the fentanyl patch.**
  - **Use fentanyl patch only in patients tolerant to opioid therapy.[m]**
  - **Patches are NOT recommended for unstable pain requiring frequent dose changes or dose titration.**
- **Fever, topical application of heat (or external heat sources), or strenuous exertion may accelerate transdermal fentanyl absorption and are contraindications for transdermal fentanyl. Avoid exposing the fentanyl transdermal system application site and surrounding area to direct external heat sources. Temperature-dependent increases in fentanyl release from the system may result in overdose and death.**
- **Transdermal fentanyl patch should not be punctured or cut.**
- **An as-needed 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 to 3 days, increase the patch dosage based on the average amount of stable daily 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[19] 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). Decrease basal rate of infusion by 50% at 6 hours after placing fentanyl patch, then stop the basal infusion 12 hours after patch placement. An alternative method is to stop the basal infusion 6 hours after patch placement.[20] In some patients, additional dose titration of the fentanyl patch may be necessary.**
- **The fentanyl patch analgesic duration is usually 72 hours, but patients experiencing end-of-dose failure may require fentanyl patch replacement every 48 hours.**

Convert or Rotate From Another Opioid to Transdermal Fentanyl (PAIN-G 13 of 21)

[m] Opioid-naïve patients are those not chronically receiving opioid analgesic on a daily basis and therefore have not developed significant tolerance. Opioid tolerant includes patients who are chronically receiving opioid analgesic on a daily basis. The FDA identifies tolerance as receiving at least 25 mcg/h fentanyl patch, at least 60 mg of morphine daily, at least 30 mg of PO oxycodone daily, at least 8 mg of PO hydromorphone daily, or an equianalgesic dose of another opioid for a week or longer.

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References

OPIOID PRINCIPLES, PRESCRIBING, INITIATION, TITRATION, MAINTENANCE, AND SAFETY
TRANSDERMAL FENTANYL

Convert or Rotate From Another Opioid to Transdermal Fentanyl

1. Determine the 24-hour analgesic requirement of morphine.
2. For conversion from PO morphine to transdermal fentanyl, consider ratio of 200 mg/day PO morphine = 100 mcg/h fentanyl patch.
   See Table 2 PAIN-G, 10 of 21 for converting other opioids to morphine equivalent with subsequent conversion to transdermal fentanyl.[21]
3. Clinical data are unavailable to recommend a specific ratio to convert from fentanyl patch to PO morphine. (Common clinical practice is to use a similar conversion ratio as when switching from PO morphine to transdermal fentanyl. Titrate with caution.)

NOTE: Due to patient variability the doses suggested by this conversion are approximate and clinical judgment must be used to titrate to the desired response.

Case Example of Converting Oral Morphine to Transdermal Fentanyl Patch

A patient is taking 30 mg of sustained-release PO morphine every 12 hours and needs to be converted to transdermal fentanyl patch.

1. Calculate the total amount of current PO morphine in a 24-hour period.
   (PO morphine 30 mg x 2 = 60 mg/day PO morphine)
2. Using the conversion ratio of 200 mg/day PO morphine = 100 mcg/h fentanyl patch:
   60 mg/day PO morphine is ≈ 30 mcg/h transdermal fentanyl patch.
   Round down (for incomplete cross tolerance) to the closest equivalent patch, in this case 25 mcg/h.
   Fentanyl patch is available in 12, 25, 50, 75, and 100 mcg/h; therefore, begin with 25 mcg/h patch.

Case Example of Converting Oral Oxymorphone to Transdermal Fentanyl Patch

A patient is taking 10 mg of sustained-release PO oxymorphone every 12 hours and needs to be converted to transdermal fentanyl patch.

1. Calculate the total amount of current PO oxymorphone in a 24-hour period
   (PO oxymorphone 10 mg x 2 = 20 mg/day PO oxymorphone)

2. From Table 2 on PAIN-G, 10 of 21, convert to the equianalgesic dose of PO morphine:
   10 mg PO oxymorphone = 30 mg PO morphine; therefore,
   (20 mg/day PO oxymorphone x 3) = 60 mg total daily dose PO morphine

3. Using the conversion of 2 mg/day PO morphine: 1 mcg/h transdermal fentanyl:
   60 mg/day PO morphine is ≈ 30 mcg/h transdermal fentanyl patch.
   Round down (for incomplete cross tolerance) to the closest equivalent patch, in this case 25 mcg/h.
   Fentanyl patch is available in 12, 25, 50, 75, and 100 mcg/h; therefore, begin with the 25 mcg/h patch.

See transdermal fentanyl package insert for conversion tables from morphine and other opioids to transdermal fentanyl.

Continued
References

Note: All recommendations are category 2A unless otherwise indicated.

OPIOID PRINCIPLES, PRESCRIBING, INITIATION, TITRATION, MAINTENANCE, AND SAFETY

BUPRENORPHINE

Potential Advantages of Buprenorphine:

- Lower misuse potential than other potent opioids.[22]
- Causes less analgesic tolerance and less constipation when compared to other mu-receptor agonists with no effects on the sphincter of Oddi.[23]
- Has a ceiling effect for respiratory depression.[24]
- Can affect QTc interval, although not to the same degree as methadone.[25]
- May cause less cognitive impairment and has been safely used in older adults.[26]
- No dose adjustment required for patients with renal failure or renal insufficiency.[27]
- Less drug dependence and milder withdrawal symptoms.[28]

Buprenorphine for Cancer Pain:

- Buprenorphine is increasingly recognized as an effective analgesic with an improved therapeutic index relative to certain potent opioids; however, it has not been extensively studied in cancer pain. Its use in cancer pain is extrapolated from data on its effectiveness in non-malignant chronic pain.[29]
- Buprenorphine transdermal has been suggested to be safe and effective in patients with cancer pain and can be started in opioid-naive patients as a long-acting opioid.[30,31]
  - Due to its long-duration of effect, it is best used in patients with stable and predictable opioid requirements.
  - Immediate-release opioid formulations may be used to treat breakthrough pain.

Buprenorphine for Chronic Pain:

- Buprenorphine is a Schedule III opioid analgesic, considered a partial agonist with very high binding affinity for the μ-opioid receptor, an antagonist with high binding affinity for the delta- and kappa-opioid receptors, and an agonist with low binding affinity for the opioid receptor-like 1 receptor. It has a potential for better tolerability as well as safety advantages compared with full μ-opioid receptor agonists. It can also be used with supplemental dosing.[32]
- Buprenorphine use has been associated with better pain control without precipitating opioid withdrawal in patients with pain and on long-term opioid therapy.[33]

Buprenorphine for OUD:

- It is essential to continue addressing and treating OUD while treating cancer pain.[34,35]
- The majority of cancer hospitals do not offer treatment for OUD.[36]
  - Patients with OUD may be at higher risk for poorly controlled cancer-associated pain. Further, patients with OUD may face challenges accessing clinical support and psychosocial services.[34]
  - Clinicians treating cancer pain are encouraged to collaborate and coordinate care with local experts in SUD/buprenorphine prescribers already involved in the patient's care.
    - ◊ If a patient with OUD is admitted on buprenorphine, continue buprenorphine unless clinically contraindicated.
    - ◊ If a patient with OUD comes to an outpatient clinic on buprenorphine, ask the buprenorphine prescriber to continue prescribing buprenorphine for OUD and to continue mental health/counseling/support.
      - – If a local buprenorphine prescriber is not available, consult with your institution's pain, palliative care, or mental health clinicians certified to prescribe buprenorphine for OUD.
      - – Buprenorphine may be considered as a first-line opioid for cancer pain management in patients with OUD.

Continued
References

Note: All recommendations are category 2A unless otherwise indicated.

OPIOID PRINCIPLES, PRESCRIBING, INITIATION, TITRATION, MAINTENANCE, AND SAFETY

BUPRENORPHINE

Regulatory Requirements for Use of Buprenorphine (Note: revised with DEA regulation changes early 2023)[37,38]

- Special training and/or a DEA "X-waiver" is no longer required to prescribe any formulation for pain or OUD (only standard DEA registration is required).
- Consultation with a pain or palliative care specialist is recommended.[39]
- There are no longer any DEA limits or patient caps on the number of patients a prescriber may treat for OUD with buprenorphine.
- State laws or regulations limiting buprenorphine prescription for OUD may still be applicable.
- The FDA strongly encourages health care providers to complete a REMS-compliant education program when prescribing these products.

Adding an Opioid (full mu-agonist) to Treat Pain in a Patient Receiving Buprenorphine for OUD:

- Buprenorphine reduces morbidity and mortality in patients with OUD.[40]
- Short-acting full opioid agonist may be added if needed for breakthrough pain after initiating buprenorphine.
- Data and consensus statements are lacking in oncology.
  - In select patients with cancer pain, buprenorphine-naloxone alone may be an effective analgesic. In general, the formulations used for OUD may be used interchangeably.[41]
- Continue the patient's home buprenorphine dose perioperatively.[42]
  - Patients on buprenorphine perioperatively used significantly less opioids than those whose buprenorphine was stopped.[43]
  - Consult with institutional anesthesiologist, pain, or palliative care providers if the patient is on buprenorphine products for OUD.
- Continuing buprenorphine when admitted to the hospital reduces opioid requirements during the hospital stay.[44]
  - ◊ In patients who stopped therapy, 50% relapse into OUD.[45]

Pitfalls of Adding Buprenorphine to a Full Opioid Agonist:

- Abrupt initiation of buprenorphine in an opioid-tolerant patient receiving full agonist opioid may precipitate acute opioid withdrawal[46,47] (PAIN-G 16 of 21).
- Reduce the risk of opioid withdrawal, according to FDA recommendations, by decreasing the dose of the current opioid to no more than 30 mg/day PO morphine mg equivalents (MME) (immediate-release only) before starting buprenorphine. Those with experience in buprenorphine conversion may recommend other dosing strategies.
- Discontinue all around-the-clock and long-acting opioids when initiating buprenorphine.

Continued
References

Note: All recommendations are category 2A unless otherwise indicated.

OPIOID PRINCIPLES, PRESCRIBING, INITIATION, TITRATION, MAINTENANCE, AND SAFETY

BUPRENORPHINE

Buprenorphine Buccal Film for Chronic Pain:[46]

- Titrate individually in increments of up to 150 mcg every 12 hours no more frequently than every 4 days to a dose that provides adequate analgesia and minimizes adverse reactions.
- Film strengths of 600 mcg, 750 mcg, and 900 mcg are only for use following titration from lower doses. Do not exceed 900 mcg due to risk of QTc interval prolongation.

Transdermal Buprenorphine Patch for Chronic Pain:[47]

- Start with 5 mcg/h patch transdermal; change every 7 days (can be started in an opioid-naïve patient).
- Individually titrate by 5 mcg/h to a dose that provides adequate analgesia and minimizes adverse reactions up to the maximum dose of 20 mcg/h; minimal titration interval is 72 hours.
- Transdermal patches of 7.5, 10, 15, and 20 mcg/h are only for use in patients who are opioid-tolerant.

Table 3. Dose Conversion Guidelines for Daily Oral Morphine Equivalents to Buprenorphine

- Reduce opioid dose to maximum 30 mg/day PO morphine equivalent before initiating buprenorphine at low dose and then proceeding with gradual dose titration.
- Other low-dose initiation protocols have been described.[48,49] Consider consultation with pain management specialist or OUD specialist familiar with buprenorphine initiation.

Daily Oral MME Before Starting Buprenorphine Buccal Film/Patch	Buprenorphine Buccal Film	Transdermal Buprenorphine Patch
<30 mg/day including opioid naive	75 mcg daily or every 12 hours	5 mcg/h every 7 days
30–80 mg/day	150 mcg every 12 hours	Taper around-the-clock opioids for up to 7 days to no more than 30 MME/day; then initiate transdermal buprenorphine 10 mcg/h at next dosing interval; may use short-acting analgesics as needed until analgesic efficacy is attained
81–89 mg/day		Consider alternative analgesic
90–160 mg	300 mcg every 12 hours	
>160 mg	Consider alternative analgesic	

Continued
References

Note: All recommendations are category 2A unless otherwise indicated.

OPIOID PRINCIPLES, PRESCRIBING, INITIATION, TITRATION, MAINTENANCE, AND SAFETY

METHADONE

Please note: 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. Due to the unique nature of methadone with a long and variable half-life (may be between 15–120 hours[50]) (and variability within a patient over time and variability between patients), caution should be used and frequent and careful evaluation should be performed.

Cautions Regarding Oral Methadone Use:

- 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.
- 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 should not be titrated more frequently than every 5 to 7 days or longer, usually by 5 mg/dose or less. If more rapid titration is desired, consult with a pain or palliative care specialist or experienced methadone prescriber.
  - 5–7 days is the time to steady state, and therefore, marked improvement in pain in the first 2–3 days of methadone or any significant sedation, may indicate the dose is too high and the patient may be at risk of oversedation or respiratory depression by day 5–7 if the dose is not immediately adjusted.
- Methadone should be reserved for the management of chronic, not acute, pain.
- Electrocardiogram (ECG) should be considered prior to initiation and when methadone doses exceed 30–40 mg/day and again with a dose of 100 mg/day and should be performed prior to initiation of methadone in patients who have risk factors for increased QTc, including medications that may lengthen QTc (including some chemotherapies and biologic agents).[50]
  - If QTc is abnormally prolonged, consider adjusting other factors, including other medications, that may impact QTc.
  - Methadone should not be used with QTc >500.
  - With QTc 450–500, consider alternate opioids and/or adjusting other factors that could prolong QTc.
  - For patients at the end of life, ECG may not be indicated based on prognosis, goals of care, and risk/benefit ratios.

Indications for Oral Methadone Use:

- Methadone may be a viable option for pain relief in patients experiencing hyperalgesia or unrelieved pain with current opioid use.
- Consider using methadone when a long-acting opioid that can be crushed or given in a liquid solution is needed.
- Methadone may be an option when opioid rotation is indicated.
- Methadone may have superior tolerability compared to other opioids in patients experiencing chronic pain.
- Methadone is a cost-effective alternative to other opioids.
- PO methadone has very good bio-availability.
- Methadone may be preferred over other opioids for pain control in certain circumstances (eg, in patients with a history of SUD, neuropathic pain related to malignancy, renal insufficiency due to the absence of renally cleared active metabolites).

Special Notes Regarding Oral Methadone Use:

- Methadone is commercially available in 5-mg and 10-mg tablets and 1 mg/mL, 2 mg/mL, and 10 mg/mL PO solution.
- Methadone tablets can be given sublingually, and may be crushed to facilitate PO, transmucosal, or enteral administration without affecting absorption.
- 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 SUD treatment and be unaware of its utility as a potent opioid analgesic.
- Methadone is typically given on a regular schedule with additional doses of a short-acting opioid, as needed.

Convert from Oral Morphine to Oral Methadone (PAIN-G 18 of 21)
References

Note: All recommendations are category 2A unless otherwise indicated.

OPIOID PRINCIPLES, PRESCRIBING, INITIATION, TITRATION, MAINTENANCE, AND SAFETY

METHADONE

Please note: The conversion ratios in Table 2 should NOT be used when converting FROM methadone to other opioids. Methadone conversion can be complex and must be individualized for each patient. Assistance from a practitioner familiar with prescribing methadone or a pain/palliative care specialist is recommended.

Convert from Oral Morphine to Oral Methadone:[51]

1. Calculate the total daily PO morphine dose (or morphine-equivalent dose) the patient is using.
2. Based on the PO morphine dose, use Table 3 to determine the appropriate dose conversion ratio and calculate the PO methadone dose. These ratios take into account the potential for incomplete cross-tolerance and are based on expert consensus.
3. Divide the total daily PO methadone dose into 2–4 daily doses.

Table 4. Dose Conversion Guidelines for Total 24-hour Oral Morphine to Oral Methadone[52]

ORAL MORPHINE	DOSE CONVERSION GUIDELINES
<60 mg	2–7.5 mg methadone per day
60–199 mg	10:1 (and patient <65 years of age)
≥200 mg	20:1 (and/or patient >65 years of age) Caution: not to exceed an initial dose of 45 mg/day

Case Example Converting Oral Morphine to Oral Methadone:

A 50-year-old patient is taking PO morphine at 30 mg every 4 hours around the clock for 3–5 days or longer, prior to conversion to methadone. (Please note that methadone should be reserved for the management of chronic, not acute, pain.)

1. Calculate the total amount of current PO morphine in a 24-hour period for this patient: (30 mg x 6) = 180 mg/day
2. From Table 3 above, calculate equianalgesic dose of PO methadone. (This conversion includes appropriate dose reduction for cross tolerance.) For 180 mg/day of PO morphine: PO methadone, the dose conversion ratio is 10:1. (180 mg/day morphine ÷ 10) = 18 mg/day PO methadone, which is ≈ 15 mg/day PO methadone.
3. Divide the total daily PO methadone dose into 3 daily doses. (reduced dose of 15 mg/day PO methadone ÷ 3 daily doses) = 5 mg PO methadone every 8 hours.
4. Consider continuing breakthrough dosing of short-acting opioid.

See special notes regarding oral methadone (PAIN-G, 17 of 21)

Continued
References

Note: All recommendations are category 2A unless otherwise indicated.

OPIOID PRINCIPLES, PRESCRIBING, INITIATION, TITRATION, MAINTENANCE, AND SAFETY

Mixed-Mechanism Drugs:

- **Tramadol is a weak μ-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 years) and those with hepatic and/or renal dysfunction, to reduce the risk of seizures. Even at a maximum dose of 100 mg four times daily, tramadol is less potent than other opioid analgesics such as morphine.**
  - **Tramadol should be used with caution due to marked variability with drug metabolism (see PAIN-N for pharmacogenetic considerations).**
- **Tapentadol[53] is a μ-opioid analgesic with norepinephrine reuptake inhibition for treatment of moderate to severe pain. Typical doses would start at 50 to 100 mg PO every 4 hours as needed, with a maximal daily dose of 500 mg per day (if using extended release) or 600 mg per day (if using IR only) due to lack of published data regarding higher doses. Some comparative data suggest tapentadol may have a lower incidence of GI adverse effects than oxycodone.**
- **Tramadol and tapentadol should be used with caution or avoided in patients taking other serotonergic or monoamine oxidase inhibitor (MAOI)-like medications (eg, TCAs, SSRIs, SNRIs) due to risk of serotonin syndrome.**

Non-Opioid Analgesic (given in collaboration with a pain/palliative care specialist):

- **Ketamine[54] 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.**
- **IV lidocaine infusion may be a useful therapy for refractory pain.[55]**

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Note: All recommendations are category 2A unless otherwise indicated.

OPIOID PRINCIPLES, PRESCRIBING, INITIATION, TITRATION, MAINTENANCE, AND SAFETY
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[52] McPherson ML, Walker KA, Davis MP, et al. Safe and appropriate use of methadone in hospice and palliative care: expert consensus white paper. J Pain Symptom Manage 2019;57:635-645.
[53] Hartrick CT, Rodriguez Hernandez JR. Tapentadol for pain: a treatment evaluation. Expert Opin Pharmacother 2012;13:283-286.
[54] Bell RF, Eccleston C, Kalso EA. Ketamine as an adjuvant to opioids for cancer pain. Cochrane Database of Systematic Reviews 2017;6:CD003351.
[55] Ferrini R, Paice JA. How to initiate and monitor infusional lidocaine for severe and/or neuropathic pain. J Support Oncol 2004;2:90-94.

Note: All recommendations are category 2A unless otherwise indicated.

MANAGEMENT OF OPIOID ADVERSE EFFECTS

Principles of Managing Opioid Adverse Effects

- Adverse effects to opioids are common, should be anticipated, and should be managed aggressively.
- 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.
- Patient and family/caregiver education is essential for successful anticipation and management of pain and opioid adverse effects.
- Information from patient and family/caregiver about adverse effects is essential for appropriate opioid dose adjustment and treatment.
- Recognize that pain is rarely treated in isolation in cancer and adverse effects also may be from other treatments or cancer itself.
- Chronic opioid therapy may depress hypothalamic–pituitary–adrenal (HPA) axis and cause hypogonadism.[1]
- Multisystem assessment is necessary.

Constipation

- Preventive measures
  - Educate patient and family on the need for bowel movements despite minimal food intake.
  - Set goals of treatment and explain to patient and family (eg, soft stool, ease of defecation, bowel movement every 2 days or less, adjusted per individual bowel habits).
  - Patients taking daily opioids almost always require agents for management of constipation.
  - Prophylactic medications
    - ◊ Stimulant laxative (eg, senna, 2 tablets daily; FDA-recommended maximum 8 tablets per day of senna)
    - ◊ Polyethylene glycol 17 gm = 1 heaping tablespoon in 8 oz water PO 1–2 times daily
    - ◊ 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 is unlikely to control opioid-induced constipation and may worsen constipation.
  - Docusate, which is a stool softener, may have limited benefit for constipation.
  - Exercise, if feasible.
- If constipation develops
  - Assess for cause and severity of constipation, including impact of other contributing medications.
  - Rule out obstruction.
  - Titrate laxatives as needed with goal of one non-forced bowel movement every 1 to 2 days.
  - 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/impaction and hypercalcemia, and evaluate for impact of other medications potentially associated with constipation.
  - Consider adding another agent, such as magnesium hydroxide 30–60 mL daily; bisacodyl 5–15 mg PO daily; 10-mg suppository per rectum (PR) daily; lactulose 30–60 mL daily; sorbitol 30 mL every 2 hours x 3, then as needed; magnesium citrate 8 oz PO daily; or polyethylene glycol (17 g/8 oz water PO two times daily).
  - PO sodium phosphate should only be used with extreme caution in patients with acute renal insufficiency.
  - Sodium phosphate, saline, or tap water enema should be used sparingly with awareness of possible electrolyte abnormalities.
  - The use of rectal suppositories and/or enemas is contraindicated in patients with neutropenia or thrombocytopenia.
  - When response to laxative therapy has not been sufficient for opioid-induced constipation, consider peripherally acting μ-opioid receptor antagonists (PAMORAs) such as methylnaltrexone, naloxegol, or naldemedine (FDA-approved for opioid-induced constipation).
    - ◊ Other agents including lubiprostone (FDA-approved for opioid-induced constipation) could also be considered.
    - ◊ These agents should not be used in patients with known or suspected mechanical bowel obstruction, recent bowel surgery, transmural bowel metastases, or other processes affecting integrity of GI lumen due to potential increased risk of perforation.
  - For intractable chronic constipation, consider opioid rotation to transdermal fentanyl, buprenorphine, or methadone. These medications may have less risk of constipation.
  - Consider neuraxial analgesics, neuroablative techniques, or other interventions to decrease pain, alleviate constipation, and/or reduce opioid dose.

[1] Rajagopal A, Vassilopoulou-Sellin R, Palmer JL, et al. Symptomatic hypogonadism in male survivors of cancer with chronic exposure to opioids. Cancer 2004;15:100:851-858.

Note: All recommendations are category 2A unless otherwise indicated.

MANAGEMENT OF OPIOID ADVERSE EFFECTS

Nausea (NCCN Guidelines for Antiemesis)

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, CNS pathology, chemotherapy, RT, hypercalcemia, bowel obstruction).
  - Consider prochlorperazine, 10 mg PO every 6 hours as needed; or metoclopramide, 10–15 mg PO 4 times daily as needed; or haloperidol, 0.5–1 mg PO every 6–8 hours as needed. Chronic use of any of these agents may be associated with development of tardive dyskinesia, especially in patients who are older and frail.
  - Alternative agents to consider include:
    - ◊ Serotonin antagonists (lower risk of CNS adverse effects; however, use with caution as constipation is an adverse effect)
      - – Ondansetron, 4–8 mg PO 3 times daily PO tablet or orally disintegrating tablet
      - – Granisetron, 2 mg PO daily
    - ◊ Olanzapine 2.5–5 mg QHS (every night at bedtime)
    - ◊ Scopolamine (especially indicated for motion-related nausea; may cause or worsen constipation)
    - ◊ Dexamethasone
    - ◊ FDA-approved cannabinoids, such as dronabinol
    - ◊ Mirtazapine
  - If nausea persists despite as-needed regimen, administer antiemetics around the clock for 1 week, then change as needed. There may be utility in using multiple agents from different classes to maximize effect.
- Opioid-induced nausea may resolve with continued exposure; if nausea persists for more than 1 week:
  - 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.
- Consider side effect profile when selecting an antiemetic, as some side effects may be of benefit to other symptoms (eg, metoclopramide for constipation, olanzapine for insomnia).

Pruritus

- If pruritus develops:
  - If pruritus is associated with rash, hives, or shortness of breath, consider true allergy and reconsider selection of opioid therapy.
  - Consider antihistamines such as cetirizine, 5–10 mg PO once daily or 10 mg IV daily; diphenhydramine, 25–50 mg PO or IV every 6 hours; promethazine, 12.5–25 mg PO every 6 hours; or hydroxyzine, 25–50 mg every 6 hours PO or intramuscularly (IM).
  - Assess for other causes (eg, other medications).
- 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 hours 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.
  - Consider ondansetron, 4–8 mg PO every 8 hours, as needed.

Delirium

- Assess for other contributing factors for delirium (eg, infection, hypercalcemia, CNS, metastases, other psychoactive medications, uncontrolled pain).
- If other possible causes of delirium are excluded, consider lowering the dose of the current opioid or consider changing the opioid.
- Consider non-opioid analgesic to allow reduction of the opioid dose.
- If delirious behavior necessitates medical intervention, consider:
  - Initial titration with haloperidol, 0.5–2 mg PO or IV every 4–6 hours
  - Olanzapine, 2.5–5 mg PO or sublingual every 6–8 hours
  - Risperidone, 0.25–0.5 mg 1–2 times per day
  - Consider quetiapine, especially in patients with Parkinson's syndrome.
  - Consider initially dosing on an as-needed basis.
  - With prolonged administration of these agents, it may be necessary to decrease dose due to long elimination half-life.
  - Antipsychotics may prolong QTc interval and ECG monitoring should be considered.
- For further information about delirium, including non-pharmacologic management, see NCCN Guidelines for Palliative Care.

Note: All recommendations are category 2A unless otherwise indicated.

MANAGEMENT OF OPIOID ADVERSE EFFECTS

Motor and Cognitive Impairment

- 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.
- Exercise caution regarding concurrent therapies and additive sedative effects, especially with benzodiazepines and gabapentin.
- Consider evaluation for driving impairment, often done through occupational therapy.

Respiratory Depression

- Sedation typically precedes respiratory depression; therefore, progressive sedation should be noted and adjustments in care should be made.
- Respiratory rate <10 breaths per minute may be an early sign of respiratory depression.
- Patients with limited cardiopulmonary reserve are more susceptible.
- Hypercarbia occurs before hypoxia.
- For concerns about respiratory depression:
  - Reduce opioid dose
  - Increase interval of opioid administration
  - Assess for transdermal preparations (eg, a forgotten fentanyl patch)
  - Monitor closely
- If respiratory depression or opioid-induced sedation occur, and patient is medically stable, consider providing noninvasive respiratory support and hold additional doses of opioid until respiratory status improves.
- If patient is unstable or response is inadequate, 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 or sustained-release preparation, 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.
- Slowed respiration is expected in patients at end of life receiving comfort measures only. Naloxone administration may be inconsistent with goals of care, and, if so, its use should be discouraged.

Sedation

- Sedation may be assessed using a tool such as the Pasero Opioid-induced Sedation Scale (POSS): https://pubmed.ncbi.nlm.nih.gov/19500754/
- It is critical to recognize the difference between cancer-related fatigue and opioid-induced sedation (NCCN Guidelines for Cancer-Related Fatigue).
- If significant or unexpected sedation develops:
  - Rule out other causes of sedation (eg, CNS pathology, other sedating medications, hypercalcemia, dehydration, infection, hypoxia)
  - If sedation is due to opioids, 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 non-opioid analgesic to allow reduction of the opioid dose
  - Consider the addition of caffeine, 100–200 mg PO every 6 hours; 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; or armodafinil 150–200 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.

Note: All recommendations are category 2A unless otherwise indicated.

PATIENT AND FAMILY/CAREGIVER EDUCATION

To assess for patient and family/caregiver educational needs regarding pain treatment, the health care team should:

- **Provide educational materials.**
- **Assess for literacy to ensure understanding of education.**
- **Assess for meaning and consequences of pain for patient and family/caregiver.**
- **Assess patient and family expectations for pain management, knowledge of pain, and pain treatment.[1,2]**
- **Assess for meaning and understanding of the use and risks of analgesics, including opioids.**

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, anxiety, constipation, nausea, fatigue, insomnia, depression) that need to be controlled; management of these other symptoms may facilitate control of pain.**
- **Educate patient and families on the processes contributing to their pain.**

Messages to be conveyed to patient and family/caregiver regarding opioid analgesics:

- **Morphine and morphine-like medications are principal 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.**
  - **Opioid analgesics should only be used to treat pain and not to assist with sleep, anxiety, or other mood issues.**
- **When working closely with health care providers these medications can be used to safely and adequately provide cancer pain relief and avoid untoward side effects.**
  - **For potential risk factors for misuse, see (PAIN-G, 4 of 21) and (PAIN-G, 6 of 21) for information on naloxone.**
  - **Patients/caregivers/family with a history of prescription, illicit drug, or SUD are at increased risk.**
  - **Patients with a history of OUD may also have increased tolerance, which may require higher doses for optimal pain control (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 increase dosage or frequency; advise patients to contact their health care provider if the pain management regimen is not controlling their pain.**
  - **Analgesics must be in a secured location, preferably in a locked box and not in a medicine cabinet to avoid danger to others/diversion.**
  - **Unused or unneeded medications (especially opioid analgesics) must be properly disposed of:**
    - **Per the FDA, unless a take-back drug program is immediately available, the recommendation is to flush excess opioids down the sink or toilet.**
    - **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, et al. The impact of patient-centered care on outcomes. J Fam Pract 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.

Note: All recommendations are category 2A unless otherwise indicated.

PATIENT AND FAMILY/CAREGIVER EDUCATION

Communication with the health care provider is critical for the patient and family/caregiver to assist in meeting goals of care.

- Be certain that patient/family know how to contact physician/hospital.
- 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 writing on a dated form:

- A list of each medication prescribed, a description of what each medication is for, and instructions on how and when to take each one
  - Plan for obtaining prescription refills, especially for potent opioids, because schedule II narcotics 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 obtaining 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 (PAIN-I, 1 of 2)

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PROCEDURE-RELATED PAIN AND ANXIETY

- **Anticipate and offer analgesic (topical, local, and/or systemic) and anxiolytic therapy for procedures that are frequently accompanied by pain and/or anxiety. See PAIN-G, 2 of 21 for incident pain/breakthrough pain.**
- **Make every effort to create a calm, comfortable procedural environment.**
- **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 patients with incident pain, merit pretreatment with an analgesic intervention.**
- **Providing information regarding 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 the information, ask questions, and learn self-management techniques to reduce 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 (60 minutes prior for PO or 15 minutes for IV).**
    - **If procedure or transportation precludes continuation of IV PCA, give the prescribed IV bolus dose 10 minutes before procedure/transport and consider administering a single SC dose equivalent to 2-hour basal infusion rate.**
    - **Additional analgesics and/or local anesthetics should be available for further titration as needed.**
  - **Anxiolytics**
    - **Anxiolytics should be given preemptively when feasible. Examples include midazolam if experienced with its administration and provided onsite, or PO lorazepam or alprazolam. PO anxiolytics should be administered at least 30 minutes before a procedure, up to an hour before.**
    - **Patients should be cautioned to avoid driving or operating machinery if taking an anxiolytic prior to a procedure.**
    - **Use caution when combining anxiolytic medications with other medications that have a sedating effect (eg, opioids). See http://www.fda.gov/downloads/drugs/drugsafety/ucm518672.pdf.**
  - **Local anesthetics such as:**
    - **Topical local anesthetic creams (containing lidocaine, prilocaine, or tetracaine) applied to intact skin with sufficient time for effectiveness as per package insert.**
    - **SC administration of lidocaine with a 27-gauge needle.**
  - **Administration of sedatives/analgesics/general anesthesia by trained personnel.**
  - **Integrative and nonpharmacologic interventions for relief of pain and/or anxiety (PAIN-D).**

Note: All recommendations are category 2A unless otherwise indicated.

MANAGEMENT STRATEGIES FOR SPECIFIC CANCER PAIN SYNDROMES

Moderate to severe cancer pain is treated with opioids as indicated (PAIN-3 and PAIN-4); these interventions are meant to complement opioid management. Adjuvant analgesics are used depending on the pain diagnosis, comorbidities, and potential for drug interactions. Integrative interventions should also be optimized (PAIN-D).

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

- **Disease-specific pain: Refer to tumor-specific guidelines for details on palliative RT as applicable.**

- **Pain from PO mucositis:**
  - **Gabapentin PO or in liquid preparation**
  - **Local anesthetic formulations/PO care protocols**
  - **For more information on the prevention and treatment of mucositis, see**
    - **https://www.ons.org/pep/mucositis**
    - **MASCC Guidelines**
    - **ESMO Guidelines**

- **Nerve pain**
  - **Nerve compression or inflammation:**
    - **Trial of corticosteroids[a]**
    - **Optimize local disease control as appropriate; consider RT or other treatments**
  - **Neuropathic pain:**
    - **Trial of antidepressant (SNRI or TCA) (PAIN-F) and/or**
    - **Trial of anticonvulsant (PAIN-F) and/or**
    - **Consider trial of topical agent (PAIN-F)**
    - **For refractory pain, consider referral to a pain specialist and/or the use of interventional strategies (Interventional Strategies (PAIN-M)**

- **Bone pain without oncologic emergency:**
  - **NSAIDs, acetaminophen, or steroids[a]; See Non-Opioid Analgesic (Nonsteroidal Anti-Inflammatory Drugs [NSAIDs] and Acetaminophen) Prescribing (PAIN-E).**
  - **Consider bone-modifying agents (eg, bisphosphonates, denosumab[b]).**
  - **Diffuse bone pain: Consider hormonal therapy or chemotherapy, corticosteroids,[a] and/or systemic administration of radioisotopes.**
  - **Local bone pain:**
    - **Consider local RT, nerve block (eg, rib pain), vertebral augmentation, or percutaneous ablation techniques.**
    - **Assess for impending fracture with plain radiographs.**
  - **Consider physical medicine evaluation. See Specialty Consultations for Improved Pain Management (PAIN-L).**
  - **Consider orthopedic consultation for stabilization, if feasible.**

Consider referral to a pain specialist or interventional therapist for interventional pain therapies including percutaneous ablation techniques for bone lesions. See Interventional Strategies (PAIN-M).

- **For severe refractory pain in the imminently dying, consider palliative sedation (NCCN Guidelines for Palliative Care).**

- **Immunotherapy-related polyarthralgias (NCCN Guidelines for Management of Immunotherapy-Related Toxicities)**

[a] Due to potential impact on immunotherapies or other treatments, the use of steroids should be coordinated with the oncology care team.
[b] An FDA-approved biosimilar is an appropriate substitute.

Note: All recommendations are category 2A unless otherwise indicated.

SPECIALTY CONSULTATIONS FOR IMPROVED PAIN MANAGEMENT

Major Indication for Referral:
- 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/or Palliative Care Specialty Consultation
(NCCN Guidelines for Palliative Care)
- Consider interventional strategies (PAIN-M)
- Management of symptoms refractory to initial treatment
- Management of sleep disturbances
- Diagnosis and treatment of underlying condition
- Consider PO or IV ketamine for pain resistant to other analgesics
- Consider methadone for pain resistant to other opioids
- Consider palliative sedation for intractable pain
- Adjustment of drugs and doses beyond the expertise of the primary team/oncologist
- Management of complicated psychosocial issues
- Clarity of goals of care, especially regarding pain and medication side effects

Physical/Occupational Therapy, Rehabilitation/Mobility, Integrative Medicine Consultation
- Physical modalities
  - Bed, bath, and walking supports
  - Positioning instruction
  - Energy conservation, pacing of activities
  - Lymphedema management
  - Massage
  - Heat and/or ice
  - TENS
  - Acupuncture or acupressure
  - Ultrasonic stimulation

Social Worker Consultation
- Caregiver burden and support needs
- Recommend use of community care resources

SUD Specialist (Addiction Medicine) Consultation
- Management of aberrant drug behavior

Mental Health Consultation
(NCCN Guidelines for Distress Management)
- Assessment
  - Diagnostic interview: assess for depression, anxiety, psychiatric disease, and SUD
  - Ongoing evaluation for misuse/diversion and other defined problems
- Pharmacologic management and psychotherapy
- Adaptive coping skills
  - Imagery
  - Distraction
  - Relaxation training
  - Active coping
  - Graded task assignments, setting goals, pacing, and prioritizing
- Evidence-based treatment modalities
  - Integrative medicine practitioners, psychologists, and other mental health professionals can be used to deliver evidence-based treatment modalities (eg, cognitive behavioral therapy [CBT], mindfulness-based stress reduction [MBSR], acceptance-based therapy, biofeedback, hypnosis, music therapy, yoga/meditation)
- Education
  - Communicate regarding need to accomplish pain relief but avoid misuse/diversion
  - Provide psycho-education
  - Discuss psychosocial factors that impact pain experience and perception
- Assist in establishing treatment agreements, limit setting, and single provider/pharmacy as needed

Spiritual Care Consultation
- Determine importance to patient and family/caregiver and current availability of support
- Manage spiritual and existential concerns

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INTERVENTIONAL STRATEGIES

Interventional Consultation[1]

- **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, chest with intercostal nerve block)**
  - **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)**
  - **Desire to avoid or limit systemic opioid administration**

- **Commonly used interventional procedures:**
  - **Regional infusions (requires infusion pump)**
    - ◊ **Epidural: easy to place, requires the use of an externalized catheter/pump; for infusions of opioids, local anesthetics, and clonidine; useful for acute postoperative pain; use beyond several days to a few weeks is limited by concerns for catheter displacement and infection**
    - ◊ **Intrathecal: easy to internalize to implanted pump; for infusions of opioids, local anesthetics, clonidine, and ziconotide; implanted infusion pumps may be costly, refills require technical expertise**
    - ◊ **Regional plexus: for infusions of local anesthetics, to anesthetize single extremity; use beyond several days to a few weeks is limited by concerns for catheter displacement and infection**
  - **Percutaneous vertebral augmentation and/or cementoplasty for bone lesions**
  - **Neurodestructive procedures for well-localized pain syndromes (spinal analgesics are used more frequently)[2]**
    - ◊ **Head and neck: peripheral neurolysis generally associated with sensory and/or motor deficit**
    - ◊ **Upper extremity: brachial plexus neurolysis**
    - ◊ **Dorsal root entry zone (DREZ) lesioning**
    - ◊ **Thoracic wall: epidural or intrathecal, intercostal, or dorsal root ganglion neurolysis**
    - ◊ **Upper abdominal pain (visceral): celiac plexus block, thoracic splanchnicectomy**
    - ◊ **Pelvic pain: superior hypogastric plexus block**
    - ◊ **Rectal/perineal pain: intrathecal neurolysis, midline myelotomy, superior hypogastric plexus block, or ganglion impar block**
    - ◊ **Unilateral pain syndromes: cordotomy**
    - ◊ **Consider intrathecal lumbar/sacral phenol block**
  - **Neurostimulation procedures (ie, spinal cord, dorsal root ganglion, peripheral nerve stimulation) for cancer-related symptoms (ie, peripheral neuropathy, plexitis, neuralgias, complex regional pain syndrome)**
  - **Percutaneous ablation techniques for bone lesions**
    - ◊ **Specific therapies for bone pain are outside the scope of this guideline. Other resources (eg, Filippiadis 2019) may be referred to for more information**

If interventional approaches are appropriate:
- **Evaluate which pain site can be relieved**
- **Verify that interventional technique will provide sufficient benefit**
  - **If interventional treatment is undertaken and is successful, patient may require significant reduction in systemic opioid**

If interventional approaches are not appropriate[3]:
- **Reassess therapeutic plan**

[1] Patient prognosis should be communicated to interventional pain colleagues as an important consideration when selecting interventional pain therapies.
[2] Most of these procedures can be performed in a non-neurodestructive manner as well (eg, a nerve block).
[3] Infection, coagulopathy, very short 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.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PHARMACOGENETICS

- **Patients may respond differently to the same drug given at the same dose for the same indication often as a result of inherent differences in drug disposition due to genetic alterations that impact drug metabolism. These differences may lead to little or no analgesic response or significant adverse effects.**
- **Genetic factors can influence the analgesic response to opioids via pharmacokinetic (metabolic enzymes, ie, CYP P450) or pharmacodynamic (receptors and signal transduction) pathways.[1]**
- **Pharmacogenomic testing may be considered prior to initiation or during analgesic pharmacologic treatment when concerns of toxicity or lack of analgesic response are demonstrated or suspected.**
- **Many commonly prescribed analgesics are metabolized via P450 (CYP) such as CYP2D6, CYP2C19, or CYP2C9.**
- **Opioid-mediated analgesia can be influenced by the *COMT* gene and the μ-opioid receptor (OPRM1) A118G single-nucleotide polymorphism; however, the clinical importance of these are unclear.**
- **FDA-approved pharmacogenetic tests for *CYP2D6, CYP2C19*, *and CYP2C9* are currently available; however, insurance reimbursement and availability of approved laboratories may be limited.**
- **Consider consulting a clinical pharmacist or clinical pharmacogenomics specialist to aid in drug selection and dose adjustments based on the interpretation and evaluation of pharmacogenomic test results.**
  - **CYP2D6: Codeine, Tramadol[1]**
    - **Avoid codeine and tramadol in patients who are known CYP2D6 ultrarapid metabolizers (UM) due to the risk of increased toxicity. If a patient is determined to be a CYP2D6 UM, rotate to another opioid (morphine, oxymorphone, or hydromorphone) and/or consider non-opioid analgesic alternatives.**
    - **Avoid codeine and tramadol in patients who are known poor metabolizers (PM) due to the lack of analgesic effect. If a patient is determined to be CYP2D6 PM, rotate to another opioid (morphine, oxymorphone, or hydromorphone). Tramadol is not recommended as an alternative to codeine.**
    - **Monitor codeine and tramadol use in patients who are intermediate metabolizers for less than optimal response and offer an alternative analgesic if warranted.**
  - **CYP2C19 and CYP2D6: Amitriptyline, Doxepin[2,3]**
    - **CYP2C19 PM and UM: Consider alternatives to doxepin and amitriptyline such as nortriptyline or desipramine.**
    - **CYP2D6 UM: Consider alternatives to amitriptyline. CYP2D6 PM: Consider lower starting doses of amitriptyline or a 50% dose reduction.**
  - **CYP2C9: Celecoxib, Meloxicam, Ibuprofen[4]**
    - **CYP2C9 PM: Consider alternatives to celecoxib or ibuprofen, or initiate therapy with 25%–50% of the lowest recommended starting dose (ie, 50%–75% dose reduction), and careful dose titration to effect.**
    - **CYP2C9 intermediate or PM: Consider alternatives to meloxicam.**

[1] Crews KR, et al. Clin Pharmacol Ther 2021;110:888-896.
[2] Hicks JK, et al. Clin Pharmacol Ther 2013;93:402-408.
[3] Hicks JK, et al. Clin Pharmacol Ther 2017;102:37-44.
[4] Theken KN, et al. Clin Pharmacol Ther 2020;108:191-200.

Note: All recommendations are category 2A unless otherwise indicated.

ABBREVIATIONS

ADHD	attention deficit hyperactivity disorder
BPS	Behavioral Pain Scale
BUN	blood urea nitrogen
CBC	complete blood count
CBT	cognitive behavioral therapy
CNS	central nervous system
COMM	current opioid misuse measure
CPOT	Critical-Care Pain Observation Tool
DEA	Drug Enforcement Administration
DREZ	dorsal root entry zone
ECG	electrocardiogram
GC-MS	gas chromatography–mass spectrometry
GI	gastrointestinal
HPA	hypothalamic–pituitary–adrenal
IASP	International Association for the Study of Pain
IM	intramuscular
IR	immediate release
LC-MS	liquid chromatography–mass spectrometry
LDH	lactate dehydrogenase
MAOI	monoamine oxidase inhibitor
MASCC	Multinational Association of Supportive Care in Cancer
MBSR	mindfulness-based stress reduction
MME	morphine mg equivalents
NMOU	non-medical opioid use
NPO	nothing by mouth
NSAID	nonsteroidal anti-inflammatory drug
ORT	Opioid Risk Tool
OTC	over the counter
OUD	opioid use disorder
PAMORA	peripherally acting mu-opioid receptor antagonist
PCA	patient-controlled analgesia
PDMP	prescription drug monitoring program
PM	poor metabolizers
POSS	Pasero Opioid-induced Sedation Scale
PR	per rectum
PTSD	post-traumatic stress disorder
QHS	every night at bedtime
QTc	corrected QT interval
REMS	risk evaluation and mitigation strategy
SC	subcutaneous
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SNRI	serotonin-norepinephrine reuptake inhibitor
SOAPP-R	revised Screener and Opioid Assessment for Patients with Pain
SSRI	selective serotonin reuptake inhibitor
SUD	substance use disorder(s)
TCA	tricyclic antidepressant
TENS	transcutaneous electrical nerve stimulation
UDT	urine drug testing
UM	ultrarapid metabolizers

Note: All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) 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 indicated.

NCCN Guidelines Version 3.2024
Adult Cancer Pain

Discussion

This discussion corresponds to the NCCN Guidelines for Adult Cancer Pain. Last updated November 25, 2024

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NCCN Guidelines Version 3.2024
Adult Cancer Pain

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 sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.[1] IASP defines chronic cancer-related pain as chronic pain caused by the primary cancer itself, or metastases (chronic cancer pain) or its treatment (chronic post-cancer treatment pain).[2] Cancer pain or cancer-related pain distinguishes pain experienced by patients with cancer from that experienced by patients without malignancies. A meta-analysis revealed that pain was reported in 59% of patients undergoing cancer treatment, in 64% of patients with advanced disease, and in 33% of patients after curative treatment.[3] In addition, this is one of the symptoms patients fear most. Unrelieved pain denies patients comfort and greatly affects their activities, motivation, interactions with family and friends, and overall quality of life.[4] There is mounting evidence in oncology that quality of life and survival are linked to early and effective palliative care, including pain management.[5-10] Although improvements have been observed, undertreatment of pain remains an issue in a significant subset of patients with cancer. This issue may be exacerbated by the inappropriate application of recommendations against opioid use for patients with cancer in the setting of the United States opioid epidemic.[11-13]

Goals of pain management are to optimize pain treatment outcomes in 5 dimensions, frequently referred to as the “5 A’s” of pain management outcomes (the “4 A’s” originally proposed by Passik and Weinreb[14] were later amended to include “Affect”):

- Analgesia: optimize analgesia (pain relief)
- Activities: optimize activities of daily living (psychosocial functioning)
- Adverse effects: minimize adverse events
- Aberrant behavior: monitor for aberrant drug-use behaviors
- Affect: relationship between pain and mood

The importance of relieving pain and the availability of effective therapies make it imperative that health care providers be adept at cancer pain assessment and treatment.[15-17] This requires familiarity with the pathogenesis of cancer pain, pain assessment techniques, and common barriers to the delivery of appropriate analgesia. Providers should be familiar with pertinent pharmacologic, anesthetic, neurosurgical, and behavioral interventions for treating cancer pain, as well as complementary approaches such as physical/occupational therapy. Early referral to palliative care may also be helpful in managing cancer pain, as well as other symptoms related to cancer and its treatment.

The most widely accepted algorithm for the treatment of cancer pain was developed by the World Health Organization (WHO).[18,19] It suggests that patients with pain be started on acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). If this is not sufficient, therapy 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.

These NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Adult Cancer Pain are unique in several important ways. The NCCN Guidelines identify central principles for assessing and managing cancer pain in adults. First, they list general principles of pain management, followed by guiding principles for assessment, management/intervention, and reassessment. The NCCN Guidelines acknowledge the range of complex decisions faced in the comprehensive care of these patients. As a result, they provide dosing guidelines for opioids, non-opioid analgesics, and adjuvant analgesics. They also provide specific suggestions for titration and rotation of 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.

Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Literature Search Criteria

Prior to the update of the NCCN Guidelines® for Adult Cancer Pain, an electronic search of the PubMed database was performed to obtain key literature in adult cancer pain published since the previous Guidelines update, using the following search terms: cancer pain, oncologic pain, cancer-related pain. The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[20]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Practice Guideline, Randomized Controlled Trial, Meta-analysis, Multi-center Study, Observational Study, Systematic Reviews, and Validation Studies. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines as discussed by the Panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.[21] NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Pathophysiologic Classification of Cancer Pain Syndromes

Different types of pain occur in patients with cancer. 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 which 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.[22,23]

Nociceptive pain is the result of injury to somatic and visceral structures and the resulting activation of nociceptors. Nociceptors are present in skin, viscera, muscle, and connective tissue. Nociceptive pain can further be divided into somatic pain and visceral pain.[24] 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 or 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), radiation therapy, or following surgical injury to the nerves.

Comprehensive Pain Assessment

A comprehensive evaluation is essential to ensure proper pain management. Inadequate assessment of pain frequently leads to poor pain management. 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 and quality of life during the initial evaluation, at each subsequent contact, 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, patients' self-reporting of pain is the current standard of care for assessment.

Selecting Tools for Assessing Pain

Various methods and tools exist to assess pain severity. Intensity of pain should be quantified using a numerical rating scale (ie, 0–10), visual analog scale, categorical scale, or pictorial scale (eg, The Faces Pain Rating Scale).[25-28] Although pain is commonly assessed using numerical or categorical ratings, some patients may experience difficulty with these scales. The Faces Pain Rating Scale may be successful with patients who have difficulty with other scales, for example, children, older adults, 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 (ie, aching, burning).

The Brief Pain Inventory (BPI) assesses pain severity in patients with cancer in two important dimensions: intensity of pain and interference of pain with a patient's life.[26,29,30] Studies suggest that pain may interfere with daily functions to a different extent in patients with cancer versus those with chronic noncancer pain.[31] As such, pain interference (ie, a measure of the impact of pain on daily functions) is of particular importance when assessing pain in patients with cancer. The BPI quantifies these measures using a 0 to 10 numerical scale. Based on these numerical ratings, cut-points have been established to categorize pain severity as mild, moderate, or severe for the purpose of treatment planning.[26,29,30]

Specialized assessment tools have been developed for specific cancer pain syndromes. For example, the Oral Mucositis Assessment Scale (OMAS) developed by the Mucositis Study Group[32] and the Patient-Reported Oral Mucositis Symptom (PROMS) scale[33,34] have been validated in patients with cancer who experienced mucositis as a result of chemotherapy, radiotherapy, or bone marrow transplantation. Several tools have been developed that include assessment for neuropathic pain, including the Neuropathic Pain Scale, Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), and the Neuropathic Pain Questionnaire, among others.[35,36] A validated clinical assessment tool for bone-related pain and its effect on quality of life is the Functional Assessment of Cancer Therapy – Bone Pain (FACT-BP) Quality of Life Measurement in Patients with Bone Pain.[37] The FACT-BP was developed specifically to assess cancer-related bone pain and reflected clinical change as evidenced by differences in performance status.

Assessment of both pain intensity and impact of pain on daily functions should be considered when establishing patient-specific goals for comfort and function.

An additional assessment tool that has undergone psychometric evaluation is the patient-reported outcomes measurement information system-pain interference (PROMIS-PI) bank; early validation studies suggest the potential utility of this approach to pain assessment as an alternative to standard-of-care assessment methods based on the BPI.[38] Additional studies are needed to assess the application of the PROMIS-PI for assessing cancer pain severity.

Assessing Pain

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 as cancer-related pain has been found to be highly dynamic for an individual patient over time.[39]

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 (eg, onset, duration, course); pain intensity (ie, pain experienced at rest; with movement); estimated trajectory of pain; location; referral pattern; radiation of pain; impact of pain (ie, interference with activities such as work, sleep, and interpersonal interactions); the associated factors that exacerbate or relieve the pain; current pain management plan; patient's pain experience and response to current therapy; prior pain therapies; breakthrough or episodic pain inadequately managed with existing pain regimen; important psychosocial factors (eg, patient distress, family/caregiver and other support, psychiatric history, risk factors for undertreatment of pain[12]); and other special issues relating to pain (eg, meaning of pain for patient and family/caregiver including patient experience of medical or other trauma; cultural beliefs toward pain, pain expression, and treatment; spiritual or religious considerations and existential suffering).[40,41] The patient's goals and expectations of pain management should be discussed, including level of comfort and function, with family/caregivers included.

It is important to keep in mind that due to the biopsychosocial nature of pain, health inequities and disparities influence the pain experience and access to pain evaluation and care. A report from the American Cancer Society's Study of Cancer Survivors-II (SCS-II) concluded that "inequalities in pain management remain a persistent, yet understudied, public health epidemic." The report states that data from multiple sources demonstrate that there are sociodemographic and health-related inequalities that contribute to barriers to cancer pain management. Barriers exist across patient, provider, and system levels and are multifaceted. These findings support the recommendation that providers perform routine assessment of pain using standardized measures, as well as utilize patient education and engagement to promote shared decision making between patients and providers.[42]

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 with pain from impending spinal cord compression. Without glucocorticoids and local radiation therapy, the pain is unlikely to be well-managed, and the patient will remain at high risk for spinal cord injury. Patients with pain that is determined to be unrelated to cancer or cancer treatment should be referred to an appropriate pain provider or program or care should be coordinated as such.

The NCCN Panel recommends monitoring risk factors for aberrant use or diversion of pain medication, which might be identified at initiation of care using screening tools such as Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R), Opioid Risk Tool (ORT), or the Cut Down-Annoyed-Guilty-Eye Opener (CAGE) questionnaire Adapted to Include Drug use tool (CAGE-AID).[43,44] Although specific screening tools have not been validated in the cancer care setting, their validated efficacy for evaluating risk in patients with non-malignant pain supports their use in this setting.[45] The SOAPP was developed to predict which patients, being considered for long-term opioid therapy, may exhibit aberrant medications behaviors in the future.[46] SOAPP-R is a revised version of the SOAPP.[47] Similar to the SOAPP-R, the ORT assesses the risk of aberrant behaviors when patients are prescribed opioid medication for chronic pain with a high degree of sensitivity and specificity for determining which individuals are at risk for opioid misuse.[48,49] SOAPP-R and ORT differentiate between patients who are at high risk or low risk for opioid misuse.[50] A high-risk score on the SOAPP-R or ORT correlates with an increased likelihood of drug misuse.[51] The CAGE-AID questionnaire is used to screen patients for the possibility of alcoholism and illicit drug use. It is helpful in screening for maladaptive behavior in patients who present with a seemingly exaggerated need for opioid medication.[44,52]

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. The clinician should also evaluate for factors that could impact equitable access to pain therapies.

Management of Adult Cancer Pain

For management of cancer-related pain in adults, the algorithm distinguishes three levels of pain intensity determined by a numerical or pictorial rating scale used as part of the comprehensive pain assessment. The three levels of pain intensity referred to in the algorithm are mild pain, moderate pain, and severe pain.

The NCCN Panel recommends that providers consider all pain management interventions in the context of patient-specific goals for comfort and function, as well as safety. Individualized pain treatment should also take into account the etiology and characteristics of pain and the patient's clinical condition. Patients presenting with an acute, severe pain or pain crisis may be candidates for hospital admission to achieve patient-specific goals for comfort and function. It is important to separate pain related to an oncologic emergency from pain not related to an oncologic emergency.

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

Patients who are opioid-tolerant are those chronically taking opioids for pain, defined by the U.S. Food and Drug Administration (FDA) as "patients who are taking at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, or an equianalgesic dose of another opioid for 1 week or longer."[53] Therefore, patients who do not meet the above criteria of opioid tolerance, based on not having had exposure to opioid doses at least as much as those listed above for ≥1 week, are considered to be opioid naïve.

Management of Pain Related to Oncologic Emergency

An oncologic emergency is defined as a life-threatening event directly or indirectly related to a patient's cancer or cancer treatment. Pain related to

an oncologic emergency includes pain due to bone fracture or impending fracture of weight-bearing bone; neuraxial metastases with threatened injury; infection; obstructed or perforated viscus (acute abdomen); or thromboembolic emergency. Pain associated with oncologic emergency should be treated directly while concurrently proceeding with the treatment of the underlying condition.

Management of Pain Not Related to Oncologic Emergency

For all patients experiencing pain, care providers should offer psychosocial support and begin educational activities. Psychosocial support is needed to ensure that patients encountering common barriers to appropriate pain management (eg, fear of substance use disorders or side effects, inability to obtain opioids) or needing assistance in managing additional problems (eg, depression, rapidly declining functional status) receive appropriate aid. The patient and the family/caregiver must be educated regarding pain management and related issues.[54,55] Patients should be reevaluated at each contact and as needed to meet their goals for comfort and function.

Although pharmacologic analgesics, including non-opioids (such as NSAIDs or acetaminophen), opioids, and adjuvant analgesics (such as antidepressants, anticonvulsants, topical agents, and corticosteroids) are the cornerstone of cancer pain management, they are not always adequate and are associated with adverse effects. Optimal use of nonpharmacologic integrative interventions (physical, cognitive, and spiritual) and multidisciplinary care may serve as valuable additions to pharmacologic interventions.

When deciding upon the most appropriate analgesic regimen, the patient's pain diagnosis, comorbid conditions, safety, potential drug interactions, estimated pain trajectory, medication availability, and expense or financial toxicity should be considered. Addition of adjuvant analgesics for specific pain syndromes should be considered for all groups of patients. Adjuvant analgesics may be used as the main analgesics (especially for neuropathic pain), or to enhance the effects of opioid- or non-opioid (eg, NSAIDs, acetaminophen) analgesics.[56]

For patients who are opioid-naïve (as defined above) who are experiencing mild pain intensity, treatment with non-opioid analgesics such as NSAIDs or acetaminophen as well as adjuvant analgesics should be considered prior to opioid analgesics unless they are contraindicated due to adverse effects, potential drug interactions, or comorbid conditions. Patients who are opioid-naïve who are experiencing moderate pain should receive non-opioid and adjuvant therapies, as appropriate, with titration of short-acting opioids as needed (see section below on *Opioid Prescription, Initiation, Titration, and Maintenance*). Short-acting formulations have the advantage of rapid onset of analgesic effect. The route of administration of opioid is decided (oral vs. intravenous [IV]) based on what is best suited to the patient's ongoing analgesic needs. If multiple doses of a short-acting opioid are consistently needed throughout the day, the addition of a long-acting (LA) opioid may be considered.

Patients who are opioid-tolerant (as defined above) who are experiencing mild pain should continue to receive non-opioid and adjuvant therapies, as appropriate. The need for opioid analgesics should be reevaluated and gradual dose reduction may be initiated, if indicated. Patients who are opioid-tolerant who are experiencing moderate pain should continue non-opioid and adjuvant therapies, as appropriate, with short-acting opioids, as needed. Short-acting opioids may be titrated by increasing the daily dose by 30% to 100%, until pain relief is achieved. If multiple doses of a short-acting opioid are consistently needed throughout the day, the addition or increase in dose of a LA opioid may be considered.

In cases of acute, severe pain or pain crisis, hospital or inpatient hospice admission may be considered to rapidly titrate analgesic and quickly

achieve patient-specific goals for comfort and function (see section below on *Management of Pain Crisis*).

The use of opioid analgesics is potentially associated with substantial adverse effects. The management of 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, as indicated.[57]

Patients with chronic persistent pain treated with stable doses of short-acting opioids should be provided with around-the-clock extended-release (ER) or LA formulation opioids with provision of a "rescue dose" to manage breakthrough or transient exacerbations of pain. The rescue dose is usually equivalent to 10% to 20% of the total opioid daily consumption, and may be given every hour as needed during severe exacerbations of pain. Opioids with a rapid onset and short duration are preferred as rescue doses. The repeated need for numerous rescue doses per day may indicate the necessity to adjust the baseline treatment.

Management of Pain Crisis

In order to achieve adequate analgesia, an initial dose of short-acting opioid should be determined and administered in patients who are experiencing severe pain (or uncontrolled pain when goals of pain management and function are not met).[58] For patients who are opioid-naïve, this dose should be 5 to 15 mg oral or 2 to 5 mg IV morphine sulfate or equivalent. A subcutaneous (SC) route of administration can be substituted for IV; however, the time to peak effect is generally longer (~30 minutes). For patients who are opioid-tolerant, a rescue dose equivalent to 10% to 20% of the total opioid taken in the previous 24 hours should be given in supplement to the patient's LA (chronic) opioid dose. However, a retrospective cohort study of 216 patients with cancer who were opioid-tolerant who presented to the emergency department with acute pain found that while 77.4% of those taking <200 oral morphine equivalent received adequate rescue doses, only 3.2% of those taking >400 oral morphine equivalent received adequate breakthrough medication.[59] Continuation of a patient's previous opioid could be considered or upward titration to accommodate dose requirements could be warranted.[60,61] In patients with risk factors such as decreased renal or hepatic function, chronic lung disease, upper airway compromise, sleep apnea, or poor performance status, the initial dosing and upward titration of opioid analgesia should be approached with caution.

Efficacy and adverse effects should be assessed approximately every 60 minutes for orally administered opioids and every 15 minutes for IV/SC opioids to determine a subsequent dose. Upon assessment, if the pain score remains unchanged or is increased, further increase in opioid rescue dose by 50% to 100% is recommended. If the pain is reduced but still inadequately controlled, the same opioid dose is repeated and reassessment is performed at 60 minutes for orally administered opioids and every 15 minutes for opioids administered by IV/SC. If pain score remains unchanged upon reassessment after 2 to 3 cycles of the opioid, in patients with moderate to severe pain, changing the route of administration from oral to IV/SC or alternate management strategies should be considered. If the pain score decreases to a level where it is adequately controlled, the current effective dose can be continued "as needed" over an initial 24 hours before proceeding to subsequent management strategies.

Management of Procedure-Related Pain and Anxiety

Procedure-related pain represents an acute short-lived experience that may be accompanied by a great deal of anxiety. Procedures reported as painful include bone marrow aspirations; wound care; lumbar puncture; skin and bone marrow biopsies; and injections into or manipulations of an

IV line, arterial line, or central line. 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, and other individual characteristics of the patient, such as age and physical condition. The interventions may be multimodal and may include pharmacologic and/or nonpharmacologic approaches. Supplemental doses of analgesics should be given in anticipation of procedure-related pain; topical, local, and/or systemic formulations can be considered. Anxiolytics, such as midazolam, lorazepam, or alprazolam, are drugs used for the treatment of anxiety and its related psychologic and physical symptoms. Anxiolytics should be given between 30 and 60 minutes before a procedure to manage procedure-related anxiety when feasible. Patients should be cautioned to avoid driving or operating machinery when taking an anxiolytic.

Local anesthetics can be used to manage procedure-related pain with sufficient time for effectiveness as per package inserts. Examples of local anesthetics include lidocaine, prilocaine, and bupivacaine. Physical approaches such as cutaneous warming, laser or jet injection, and ultrasound (US) 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 nonpharmacologic interventions may be valuable in managing procedure-related pain and anxiety. The major goal of nonpharmacologic interventions that include physical and cognitive modalities is to promote a sense of control, thus increasing hope and reducing helplessness that many patients with pain from cancer experience. Creating a calm, comfortable procedural environment can help achieve this.

Patients usually tolerate procedures better when they know what to expect. Therefore, patients and family members/caregivers should receive written instructions for managing pain. Pre-procedure patient education that includes procedure details and pain management strategies is essential to allow time for assimilating the information, asking questions, and learning self-management techniques to reduce anticipatory anxiety.

Subsequent Management of Cancer Pain

The subsequent treatment is based on the patient's continued pain rating score as well as its function and evidence of appropriate use of prior treatments. Approaches for all pain intensity levels must include psychosocial support and education for patients and their families/caregivers. For all levels of pain requiring ongoing use of an opioid, opioid doses should be administered on a routine schedule with rescue doses as needed. Constipation should be routinely evaluated and managed.

If pain at any time is severe, not improved, 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.[57] Optimal use of nonpharmacologic integrative interventions (physical, cognitive, and spiritual) may serve as valuable additions to pharmacologic interventions. 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 pain of moderate intensity, with inadequate pain relief on the ongoing opioid regimen, the 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 10% to 25% of the current opioid dose. Addition of adjuvant analgesics may be considered. The need for opioid analgesics should be frequently reassessed and the dose reduced, if appropriate.

Ongoing Care

Although pain intensity ratings may be obtained frequently during analgesic titration, formal pain re-evaluation is required at each contact to ensure that pain management therapies are successfully meeting patient-specific goals for comfort, function, and safety.

If an acceptable level of comfort and function has been achieved for the patient, and 24-hour opioid requirement is stable, the NCCN Panel recommends converting to an ER oral medication (if feasible) or other ER formulation (ie, transdermal fentanyl). The subsequent treatment is based on the patient's continued pain rating score. Rescue doses of the short-acting formulation of the same LA opioid may be provided during maintenance therapy for the management of pain in patients with cancer not relieved by ER opioids.

A regular follow-up schedule should be initiated to monitor outcomes of analgesic therapy, including adverse effects. Pain should be assessed during each outpatient contact or at least each day for inpatients depending on patient conditions, institutional standards, and regulatory requirements.

System-related barriers exist that include cost of analgesics and a lack of access to/availability of analgesics, particularly in low-income neighborhoods or for those who are economically disadvantaged. Studies have documented the inequities that persist since those with financial burdens or from historically marginalized racial and ethnic groups have less access to pain treatment.[41,62] The NCCN Panel recommends addressing these system barriers, including recruiting assistance from social services as needed.[63-66]

The patients must be provided with a written follow-up pain plan, including prescribed medications. It is important to ensure that the patient has adequate access to prescribed medications, particularly as research shows that patients with cancer and cancer survivors are having increasing difficulty in accessing their opioid prescriptions.[67] Therefore, the patient should be encouraged to maintain communication and coordination of care with relevant providers, especially during transitions between sites of care. Collaboration with the patient's pharmacist and insurance company is helpful in achieving this. It should be clarified with the patient which clinician will be prescribing their ongoing pain care and confirmed that the patient/caregiver(s) know how to contact the providers and hospital. The use of a pain diary may facilitate communication between the patient and their providers.[68]

Equally important is monitoring for the use of analgesics as prescribed, especially in patients with risk factors for or history of substance use disorders, diversion, or cognitive dysfunction. Particular attention should be paid to early recognition of ineffective analgesia despite rapid escalation of opioid analgesics, which may indicate opioid misuse. Patients and the family/caregiver should be informed that opioids should only be used to treat pain and are not intended for the treatment of sleep, anxiety, or other mood issues. However, if working closely with health care providers, opioid medications can be used to safely and effectively relieve cancer-related pain.

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 must be considered. Other sources of distress (eg, psychological, social, spiritual) should also be recognized, documented, and treated as these may contribute to poorly controlled

physical pain. See the NCCN Guidelines for Distress Management for more information.

Pain in Cancer Survivors

Chronic pain in cancer survivors may have a unique etiology and symptomatology compared with pain experienced by patients with cancer. Up to one third of post-treatment cancer survivors experience chronic pain, which can cause psychological distress and impact quality of life.[69,70] In 2016, ASCO issued a guideline on chronic pain management in adult cancer survivors.[71] A qualitative study demonstrated unmet needs related to cancer survivor and clinician communication about chronic pain. It highlighted that often cancer survivors with chronic pain have challenges in receiving adequate management of their pain due to a lack of clarity about which health care provider's role it is to take on the responsibility of providing long-term pain management. Additionally, it was shown that there is an apparent lack of recognition in clinicians regarding the frequency of chronic pain in cancer survivors. Whether this is due to under-reporting by patients or due to inadequate screening by clinicians was not investigated in this study.[72] For more information on pain in cancer survivors as well as other survivor-related issues, please see the NCCN Guidelines for Survivorship.

Pharmacologic Interventions for Cancer Pain Management

Optimal management of cancer pain is often accomplished by using a combination of pharmacologic and non-pharmacologic therapies. Pharmacologic therapies may include nonopioid analgesics (such as acetaminophen or an NSAID), adjuvant analgesics (antidepressants, anticonvulsants, topical agents, and corticosteroids), and/or opioid analgesics.

Non-Opioid Analgesics

Acetaminophen

Acetaminophen has analgesic and antipyretic, but not anti-inflammatory properties.[73] Attention has been drawn towards the relative limited efficacy and significant adverse effects of acetaminophen, particularly hepatic toxicity and possibly renal impairment.[74,75] Concerns are compounded by the inclusion of acetaminophen in a variety of prescription opioid preparations (eg, in combination with hydrocodone or codeine), as well as in a wide selection of over-the-counter products. A randomized blinded clinical trial involving hospitalized patients with cancer who were treated with opioids for moderate or severe acute pain, looked to determine if the addition of acetaminophen to their opioid regimen would improve pain control or decrease total opioid use. Among 112 randomized patients, the percentage of patients reporting improvement in pain control after 48 hours was similar between acetaminophen and placebo. The study concluded that addition of acetaminophen to an opioid regimen for cancer-related pain may not improve pain control or decrease total opioid use.[76]

Due to concerns about 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 recommends that patients be advised to limit daily acetaminophen intake to a maximum of 4 g, and imposes a limit of 325 mg of acetaminophen per tablet, capsule, or other dosage unit in prescription products to reduce the risk of severe liver injury from acetaminophen overdosing, an adverse event that can lead to liver failure and death.[77] The FDA has issued a boxed warning to communicate the risk of severe liver injury associated with acetaminophen to health care 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.[77] Due to concerns of hepatic toxicity, the NCCN Panel suggests that providers consider limiting chronic administration of acetaminophen or use of acetaminophen in older adults to ≤3 g per day.

Additionally, data have demonstrated concerns over possible impacts of the efficacy of immunotherapy in the setting of concurrent acetaminophen use. In one study, 600 patients with advanced cancer took acetaminophen prior to the start of immunotherapy and the response of immune checkpoint inhibitors was assessed after initiation of immunotherapy. The response of immune checkpoint inhibitors was significantly reduced, suggesting that acetaminophen has immunosuppressive effects.[78,79] Therefore, the NCCN Panel recommends using acetaminophen with caution in the setting of immunotherapy. There also may be concerns about the risk of masking fever in patients who are immunocompromised.

NSAIDs

NSAIDs produce analgesia by blocking the biosynthesis of prostaglandins, inflammatory mediators that initiate, cause, intensify, or maintain pain. History of peptic ulcer disease or gastrointestinal (GI) bleeding, advanced age (>60 years old), male sex, and concurrent selective serotonin reuptake inhibitor (SSRI) antidepressants,[80] corticosteroids, or anticoagulant therapy should be considered before NSAID administration to prevent upper GI tract bleeding and perforation. The risk of GI bleeding is increased in patients with untreated *H. pylori* infection and with chronic, rather than short-term, use of NSAIDs. As prophylaxis for NSAID peptic ulceration, consider adding misoprostol or proton pump inhibitors. Well-tolerated proton pump inhibitors are recommended to reduce GI adverse effects induced by NSAIDs. The FDA cautions that the concomitant use of an NSAID with aspirin may reduce the cardioprotective efficacy of aspirin,[81] and concomitant use of an NSAID and low-dose (or cardioprotective) aspirin may increase the risk of GI bleeding.[82,83] The NCCN Panel recommends avoiding concurrent use or administering these agents separately.

NSAIDs should be prescribed with caution in patients >60 years of age or in those having compromised fluid status, renal insufficiency, concomitant administration of other nephrotoxic drugs, and renally excreted chemotherapy to prevent renal toxicities.[84] NSAID use should be coordinated with other oncologic therapies. While there is a paucity of high-quality evidence supporting the role of NSAIDs in analgesia of cancer pain,[85,86] the addition of NSAIDs to opioids has the potential benefit of reducing the opioid dose when sedation, cognitive function, or other CNS effects of opioid analgesic therapy become burdensome.

In patients at high risk for cardiac toxicities such as those with a history of cardiovascular disease or at risk for cardiovascular disease or complications, NSAIDs should be discontinued if congestive heart failure or hypertension develop or worsen.[84] The FDA has issued a warning that NSAID use may increase the risk of heart attack or stroke.[87] This risk is present even with short-term use of NSAIDs and increases with higher doses.[88] NSAIDs taken with prescribed anticoagulants, such as warfarin or heparin, may significantly increase the risk of bleeding complications. Topical NSAIDs such as diclofenac gel or patch may be useful for treatment of peripheral joint pain in this population, due to reduced systemic absorption.

The NSAID and acetaminophen prescribing guidelines are listed in the algorithm under *Non-Opioid Analgesic (NSAIDs and Acetaminophen) Prescribing*.

Adjuvant Analgesics

The term adjuvant analgesics refers to medications that are coadministered to enhance opioid analgesia and possibly reduce adverse

effects of opioids by allowing the use of lower doses of opioids. 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[89] (eg, gabapentin, pregabalin), antidepressants (eg, SSRIs, serotonin–norepinephrine reuptake inhibitors [SNRIs], tricyclic antidepressants [TCAs]), corticosteroids, and local anesthetics/topical agents (eg, topical lidocaine patch or topical NSAID). Adjuvant analgesics are commonly used to help manage bone pain, neuropathic pain, and visceral pain and, if desired or indicated, to reduce the opioid requirement. They are particularly important in treating neuropathic pain (see *Management Strategies for Specific Cancer Pain Syndromes, Neuropathic Pain*).[90,91]

Physicians should check for drug interactions when prescribing antidepressants, paying particular attention to serotonergic medications (eg, SSRIs) due to risk of serotonin syndrome. Several antidepressants are known inhibitors of hepatic drug metabolism via inhibition of cytochrome P450 (CYP450) 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. While some clinical studies indicate increased risk of breast cancer recurrence in patients with breast cancer treated with tamoxifen who are also treated with SSRI antidepressants versus those receiving tamoxifen alone,[92] other studies have not shown this effect.[93,94] If concomitant use of an SSRI is required in a patient receiving tamoxifen, use of a mild CYP2D6 inhibitor (ie, sertraline, citalopram, venlafaxine, escitalopram) may be preferred over a moderate-to-potent inhibitor ie, (paroxetine, fluoxetine, fluvoxamine, bupropion, duloxetine).[92]

The most commonly used anticonvulsant drugs for the treatment of cancer pain are gabapentin and pregabalin.[95] They have been studied primarily in noncancer neuropathy syndromes,[96] although there are data supporting their use for treatment of cancer pain in conjunction with opioids.[97,98] Gabapentin has been reported to reduce mucositis pain in patients receiving concomitant radiotherapy and chemotherapy.[99] When compared in a prospective, randomized, open-label trial, pregabalin relieved neuropathic cancer-related pain more effectively than transdermal fentanyl.[100]

Corticosteroids have long been used to relieve neuropathic pain syndromes and have also been effective for treating bone pain due to their anti-inflammatory effects as well as relieving malignant intestinal obstruction.[56,101] A 2015 Cochrane review summarized the existing data for corticosteroid use in cancer pain.[102]

Cannabinoids and Medical Cannabis

In the context of shifting legality, many patients with cancer are using cannabinoids or medical cannabis (also called “medical marijuana”) for treatment of cancer- or cancer treatment-related symptoms.[103,104] Current FDA-approved cannabinoids include dronabinol (THC) and cannabidiol (CBD).[105] At the time of this Discussion update, previously FDA-approved nabilone is no longer available in the United States.[106]

Dronabinol is a synthetic delta-9 tetrahydrocannabinol (THC), which is approved to treat refractory nausea and vomiting associated with cancer treatment and is also approved to treat anorexia and weight loss related to AIDS. CBD has been approved to treat seizures associated with rare forms of severe epilepsy. While medical cannabis has been legalized in many states, it has not been FDA-approved for any indication.[105] Furthermore, the U.S. Drug Enforcement Administration (DEA) classifies cannabis as a Schedule I substance, meaning that it has a high potential for misuse, no currently accepted medical use in treatment in the United

States, and a lack of accepted safety for use under medical supervision.[107] Regardless, use of medical cannabis is common among patients with cancer, with some studies reporting that as many as 22% to 40% of patients with cancer in the United States use cannabis.[108-110] Therefore, providers should assess for cannabinoid/medical cannabis use and provide education on state and federal regulations, as appropriate.

Data supporting the use of cannabinoids as adjuvant analgesics for treatment of cancer pain are extremely limited and the results from what little data exist are somewhat conflicting. While two randomized, placebo-controlled trials have shown that nabiximols (cannabis extract that contains both THC and CBD—it is not approved for use in the United States) significantly reduced cancer-related pain compared to placebo in patients with inadequate analgesia despite chronic opioid administration,[111,112] THC extract alone did not show a significant benefit compared to placebo,[111] and another randomized study reported no significant benefit of nabiximols compared to placebo for treatment of chemotherapy-induced neuropathic pain.[113] In these studies, the most commonly reported adverse events associated with nabiximols were somnolence, fatigue, dizziness, confusion, nausea, dry mouth, and hypotension, although these were noted to be dose-dependent and generally manageable.[111-113] Systematic reviews and meta-analyses of randomized controlled trials (RCTs) have also reported mixed results with some RCTs reporting little or no benefit of cannabinoids for cancer pain,[114-118] and another RCT reporting that some cannabinoids were able to reduce certain types of cancer pain (notably neuropathic pain) depending on route of administration.[119]

The route of administration can also affect the safety profile of medical cannabis. An observational study in a state with legalized cannabis reported that while edible cannabis products accounted for only 0.32% of sales between 2014 and 2016, they accounted for 10.7% of emergency department visits during that time period.[120] The adverse effects that prompted the emergency department visits also differed by route of exposure, with cannabinoid hyperemesis syndrome more common for inhaled cannabis, and acute psychiatric symptoms, intoxication, and cardiovascular symptoms more common for edible cannabis.[120] The authors propose that the delayed onset of effect associated with the edible route may lead users to repeat the dose, potentially resulting in delayed higher plasma concentrations.

Opioids and Miscellaneous Analgesics

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.

Pure agonists (such as morphine, 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 opioids (methadone and levorphanol).[121] A randomized trial compared the efficacy of low-dose morphine, a "strong" opioid agonist, to "weak opioids" (ie, codeine, codeine plus acetaminophen, tramadol) for treating moderate-intensity cancer pain. Among the 240 patients with cancer enrolled in the trial, low-dose morphine had a significantly higher response rate and earlier onset of response compared with weak opioids. Opioid-related adverse effects were comparable across the two treatment groups, and overall well-being/symptom burden was rated as significantly better in the low-dose morphine arm.[122]

Morphine, hydromorphone, hydrocodone, oxymorphone, and 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.[123-125]

Morphine

Morphine is a mu-opioid receptor agonist and weak kappa receptor agonist. Morphine is available in a wide range of formulations and routes, including oral, parenteral, and rectal delivery.[126] In a patient who has not been exposed to opioids in the past, morphine is generally considered the standard starting drug of choice.[127,128] Oral administration is the preferred route. An initial oral dose of 5 to 15 mg of oral short-acting morphine sulfate or equivalent is recommended for patients who are opioid-naïve with consideration of using a half tablet for lower dose titration in patients who are frail or older. Patients presenting with severe pain needing urgent relief should be treated with parenteral opioids, usually administered by the IV or SC route. If given parenterally, the equivalent dose is one-third of the oral dose.[129] An initial dose of 2 to 5 mg of IV morphine sulfate or equivalent is recommended for patients who are opioid-naïve. Morphine-6-glucuronide, an active metabolite of morphine, contributes to analgesia and may worsen adverse effects as it accumulates in patients with renal insufficiency.[130,131]

Fentanyl

Fentanyl is a highly lipid-soluble mu-opioid receptor agonist that can be administered by the parenteral, spinal, transdermal, transmucosal, buccal, and intranasal routes.[132,133] Transdermal fentanyl is not indicated for rapid opioid titration and should be recommended only after pain is adequately managed by other opioids in patients who are opioid-tolerant.[134] It is usually the treatment of choice for patients who are unable to swallow, patients with poor tolerance to morphine, and patients with poor adherence to treatment. Findings from a Cochrane Database review support the efficacy of transdermal fentanyl for relieving moderate to severe cancer pain and suggest a reduction in opioid-related constipation compared with oral morphine regimens.[135] Another meta-analysis of RCTs reported similar results, showing similar effectiveness of cancer pain management between transdermal fentanyl and oral morphine, but lower rates of constipation, nausea, vomiting, drowsiness, and urinary retention with transdermal fentanyl.[136] Conversion from IV fentanyl continuous infusion basal rate via patient-controlled analgesia to transdermal fentanyl can be accomplished effectively using a 1:1 conversion ratio.[137] The basal rate of infusion should be decreased by 50% at 6 hours after placing the fentanyl patch, followed by stopping the basal infusion 12 hours after patch placement. An alternative method is to stop the basal infusion 6 hours after patch placement.[138] Transmucosal fentanyl may be considered in patients who are opioid-tolerant for brief episodes of incident pain not attributed to inadequate dosing of an around-the-clock opioid. There are data showing that transmucosal immediate-release (IR) fentanyl is effective in treatment of breakthrough pain in patients with cancer.[139-141]

Hydrocodone

Hydrocodone is a mu- and delta-opioid receptor agonist that may be approximately equipotent with oral morphine; however, its equivalence data are not substantiated.[132] Clinical experience suggests use as a mild, initial-use opioid, but effective dose may vary. Hydrocodone is available in IR formulations mixed with acetaminophen or ibuprofen. Hydrocodone ER preparations (without added non-opioid analgesics) are available.

Codeine

Codeine is a weak mu- and delta-opioid receptor agonist with little direct analgesic effect; it is a prodrug that is hepatically metabolized to codeine-6-glucuronide, norcodeine, morphine, morphine-3-glucuronide, morphine-6-glucuronide, and normorphine.[132,142] This process is largely through the action of the CYP450 enzyme, CYP2D6. It is important to note

that CYP2D6 exhibits polymorphism between various ethnic groups and between individuals. A significant portion of individuals who are poor metabolizers would obtain reduced or no analgesic effects from codeine administration.[143] Conversely, rapid metabolizers may experience toxicity after codeine administration from more rapid morphine production.[143]

Hydromorphone

Hydromorphone is primarily a mu-opioid receptor agonist and weak delta-opioid receptor agonist that has properties similar to morphine and is available in oral tablets, liquids, suppositories, and parenteral formulations.[132,144] There is some evidence suggesting that the metabolite of hydromorphone may lead to opioid neurotoxicity, including myoclonus, hyperalgesia, and seizures.[145] This metabolite may be more neurotoxic than the morphine metabolite.[146] In a prospective, open-label trial of 879 patients with cancer, hydromorphone effectively reduced pain that was inadequately controlled by other analgesics.[147] Additionally, RCTs have demonstrated the clinical noninferiority of once-daily hydromorphone ER compared with twice-daily oxycodone controlled-release[148] and four-times-daily hydromorphone IR compared with four-times-daily oxycodone IR[149] for relieving moderate to severe cancer pain. A Cochrane review found evidence that hydromorphone provides similar effect on pain management as reported for oxycodone or morphine.[150] Another review of 18 RCTs with 2271 patients concluded that hydromorphone has similar efficacy to morphine and oxycodone in reducing cancer pain intensity, decreasing consumption of additional analgesics, and improving quality of life. Adverse effects were shown to be similar for hydromorphone compared to morphine or oxycodone. [151]

Oxycodone and Oxymorphone

Oxycodone is an opioid with agonist activity at the mu-, delta-, and kappa-opioid receptors and is available in IR and ER formulations.[152-154] Oxycodone is also available in combination with acetaminophen; therefore, the acetaminophen dose must be monitored for safe limits to avoid potential hepatic toxicity. Cochrane reviews and other meta-analyses found overall evidence that oxycodone provided similar analgesic and adverse effects to morphine, concluding that these agents could be interchangeable in the front-line treatment setting for cancer-related pain.[155-157] Studies of oxycodone/naloxone formulations showed effective analgesia with reduced opioid-induced constipation for long-term use in cancer-related pain.[158,159]

Oxymorphone is an opioid agonist that acts primarily at the mu-opioid receptor. It is available in an IR formulation.

Methadone

Methadone is a mu-opioid receptor agonist and an antagonist at N-methyl-D-aspartate (NMDA) receptors; it is commercially available in multiple strength oral tablets or in an oral or IV solution.[132] Individual variations in methadone pharmacokinetics (long and variable half-life ranging from 15–120 hours) make its usage complex in patients with cancer.[160] Due to its long half-life, high potency, and inter-individual variations in pharmacokinetics, methadone, when indicated, should be started by or in consultation with an experienced pain or palliative care specialist.

Although many recommendations for methadone rotation exist, the NCCN Panel members find the recommendations on the starting doses of methadone outlined in the Hospice and Palliative Medicine White Paper to be the easiest to implement.[161] The evidence is mixed regarding superiority of one method to initiate methadone. Some evidence supports lower adverse events with the 3-day switch method compared to the rapid conversion (stop-and-go) or ad libitum (as often as necessary) methods. In the 3-day switch method for methadone initiation, the original opioid is discontinued gradually by lowering the daily dose by one-third over a 3-day period. Simultaneously, methadone is initiated at one-third of the

calculated dose and increased by one-third over 3 days to the calculated amount.[162,163]

Because the starting dose may need to be titrated up, it is essential to provide the patient with access to adequate, short-acting, breakthrough pain medications during the titration period. The NCCN Guidelines recommend monitoring for drug accumulation and adverse effects, particularly over the first 5 to 7 days, and caution that a steady state may not be reached for several days to 2 weeks. Methadone should not be titrated more frequently than every 5 to 7 days or longer. If more rapid titration is desired, consult with a pain or palliative care specialist or experienced methadone prescriber. Any significant sedation or marked improvement in pain prior to the fifth day of methadone may indicate the dose is too high and the patient may be at risk of oversedation or respiratory depression by day 5 to 7 if the dose is not immediately adjusted.

Generally, RCT data have demonstrated that appropriately titrated methadone, although harder to manage than morphine, has similar efficacy and tolerability and has a role in treating cancer pain.[164] Studies show that outpatient initiation and rotation to methadone can be successfully done in patients with cancer without serious adverse effects.[165] Retrospective studies have also reported that low-dose methadone may improve pain control when used as a coanalgesic in patients with cancer-related pain that were receiving a different, regularly scheduled opioid analgesic.[166,167]

There is evidence suggesting that high doses of methadone (120 mg and above) may lead to corrected QT interval (QTc) prolongation and torsades de pointes, which may lead to sudden cardiac death.[168-170] A study conducted in patients with cancer suggests that QT interval changes exist commonly at baseline and are not changed with the addition of methadone.[171] The NCCN Panel supports the use of baseline and follow-up electrocardiogram (ECG) for patients treated with methadone at doses >30 to 40 mg/day as outlined in published recommendations and for patients with cardiac disease, or when methadone is used in patients taking other medications also known to prolong QTc (including TCAs).[160,161] ECG monitoring should be considered within the patient's goals of care and risk/benefit ratio as discussed with the patient. The following measures may be considered to correct QTc prolongation:

1) Correction of hypokalemia, hypomagnesemia, or hypocalcemia
2) Avoidance of other drugs that can prolong QTc
3) Avoidance of other drugs that can inhibit the biotransformation of methadone such as CYP3A4 inhibitors

Alternate opioids are needed for patients with QTc >500 msec, and are recommended for those with QTc of 450 to 500 msec, concurrently with interventions to correct any reversible causes of prolonged QTc.[160] The decision must be tailored to the individual clinical situation and goals of care. Good communication among the patient, family, and care providers is a critical component of the decision-making process.

Patients and their families may need to be educated about analgesic utility of methadone. Some may only be familiar with methadone use for maintenance treatment of opioid use disorder (OUD) and be unaware of its utility as a potent opioid analgesic. Patients and caregivers should be educated on the signs of delayed sedation and respiratory depression that may occur 5 to 7 days or longer after initiation of methadone or after titrating the dose upwards.

Levorphanol

Levorphanol is a mu-, delta-, and kappa-opioid receptor agonist. Like methadone, levorphanol also acts as an antagonist at NMDA receptors, but it has a shorter half-life and more predictable metabolism.[172] Similar to methadone, levorphanol varies in its dosing equivalence with morphine. In a case series of 20 patients receiving palliative or hospice care, the

morphine to levorphanol conversion factors were listed as 12:1 for morphine doses of <100 mg, 15:1 for morphine doses between 100 mg and 299 mg, 20:1 for morphine doses between 300 mg and 599 mg, and 25:1 for morphine doses >600 mg.[172] For certain populations (eg, patients who are older), levorphanol may offer similar benefits to methadone but with lessened prescribing complexities and adverse effects.[173] One study also demonstrated potential efficacy of levorphanol for treating neuropathic pain.[174]

Miscellaneous Analgesics *and Mixed Mechanism Drugs*

Tramadol and Tapentadol

Tramadol and tapentadol are atypical opioids with a dual mechanism of action on opioid receptors and neurotransmitter reuptake (eg, norepinephrine, serotonin). Tramadol and tapentadol should be used with caution or avoided in patients taking other serotonergic or monoamine oxidase inhibitor (MAOI)-like medications (eg, TCAs, SSRIs, SNRIs, and MAOIs) due to risk of serotonin syndrome.[175] Tramadol can also have marked variability in drug metabolism, and should be used with caution for this reason.[176] See *Principles of Pharmacogenetics* in the algorithm.

Tramadol is a weak mu-opioid receptor agonist with some norepinephrine and serotonin reuptake inhibition that is indicated for treating moderate to moderately severe pain.[177] Tramadol is available as IR and ER formulations. The NCCN Panel recommends a maximum daily dose of 400 mg for IR formulations (100 mg four times a day), or 300 mg/day for ER formulations, for adults with normal hepatic and renal function. Lower doses are recommended for adults aged ≥75 years and those with hepatic and/or renal dysfunction to reduce the risk of seizures. Tramadol is less potent than other opioids and is considered to be approximately one-tenth as potent as morphine.[177] One nonrandomized, observational study in patients with cancer found comparable analgesic efficacy of high-dose tramadol (ie, ≥300 mg/day) and low-dose morphine (ie, ≤60 mg/day), but observed higher rates of constipation, neuropsychological symptoms, and pruritus in patients receiving low-dose morphine.[178] However, in a double-blind study of patients with cancer, tramadol produced more adverse effects, including vomiting, dizziness, and weakness, than hydrocodone and codeine.[179] A Cochrane review of tramadol (with or without acetaminophen) concluded that limited evidence supports the use of tramadol for treatment of cancer pain and that tramadol is likely not as effective as morphine in this setting.[180]

Tapentadol is an opioid that binds to the mu-opioid receptor and inhibits norepinephrine reuptake.[181,182] It is available as ER and IR formulations and is used for treatment of moderate to severe pain as well as for neuropathic pain. Typical doses start at 50 to 100 mg orally every 4 hours as needed, with a maximal daily dose of 500 mg per day (if using the ER) or 600 mg per day (if using the IR only) due to a lack of published data regarding higher doses. Lower doses are recommended for patients with moderate hepatic impairment, and tapentadol should be avoided in patients with severe hepatic or renal impairment. In comparative phase II–III studies, the efficacy and safety of tapentadol have been demonstrated compared with placebo and oxycodone for non-cancer pain.[183-185] Data on tapentadol for treating non-cancer pain have also suggested that it may have a lower incidence of GI adverse effects than oxycodone.[183] Limited data suggest that there may be a roll for tapentadol in the management of cancer pain,[186-188] but further clinical trials are needed. A retrospective study showed that >90% of patients with moderate-to-severe cancer-related pain (those with neuropathic pain or mixed pain) and all patients with nociceptive pain responded to tapentadol. In this study most patients (93%) achieved clinically relevant pain relief within 4 days.[189]

Buprenorphine

Buprenorphine, a partial mu-agonist, has been approved for chronic pain in patients who are opioid-naïve or opioid-tolerant. Special training and/or

a DEA “X-Waiver” is no longer required to prescribe any formulation of buprenorphine for pain or OUD. Although RCT data on buprenorphine for treating cancer pain are somewhat limited, several case series, prospective uncontrolled studies, and a few randomized trials support its use in cancer-related pain.[190-194] Therefore, transdermal buprenorphine may be used at a dose of 5 mcg/h in patients who are opioid-naïve requiring initiation of LA opioid therapy. Due to its ER formulation, transdermal buprenorphine is best used in patients with predictable and stable opioid requirements.[191,195] In some instances, transmucosal buprenorphine may be more appropriate given a wider range of available doses, a higher maximum dose, and a lower likelihood of causing skin reactions compared to transdermal buprenorphine.

Potential advantages to using buprenorphine over other opioids include its lower potential for misuse,[196] less analgesic tolerance, and less constipation when compared to other mu-receptor agonists with no effects on the sphincter of Oddi.[197] Buprenorphine also has a ceiling effect on respiratory depression and may cause less cognitive impairment, physical dependence, and milder withdraw symptoms.[198,199]

Based on its pharmacokinetics, buprenorphine may be especially appropriate for treating cancer pain in patients with renal impairment.[193] Studies of buprenorphine suggest that, being 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.[200] While transdermal buprenorphine may have some advantages over methadone in the context of cancer treatments that prolong QT, FDA guidelines recommend limiting transdermal buprenorphine dose to a maximum of 20 mcg/h due to concern for QT prolongation. Dosing recommendations for transdermal and buccal buprenorphine can be found in the treatment algorithm under *Opioid Principles, Prescribing, Initiation, Titration, Maintenance, and Safety - Buprenorphine*. Because the dose conversion from other opioids to buprenorphine can be complex, the NCCN Panel suggests that providers consider a pain specialty consultation for complex cases. Microdosing and other low-dose buprenorphine initiation methods have been described.[201-203]

A systematic review and meta-analysis reported the prevalence of OUD in patients with cancer-related chronic pain to be 8% (95% CI, 1–20) and the prevalence of risk factors for OUD was 23.5% (95% CI, 19.5–27.8).[204] It is essential to continue treatment of OUD while still adequately treating cancer pain. Therefore, clinicians are encouraged to collaborate and coordinate care with specialists for substance use disorders and/or buprenorphine prescribers who may already be involved in the patient’s care.

Ketamine

Ketamine is a non-competitive N-methyl D-aspartate receptor antagonist that blocks glutamate. Low (sub-anesthetic) doses produce analgesia and may limit 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.[205] A double-blind, randomized, placebo-controlled trial found no significant difference between the outcomes of patients treated for cancer pain with ketamine versus placebo.[206] However, a subsequent systematic review of the evidence on ketamine for treating cancer-related pain concluded that the data, although limited, did suggest modest analgesic potential for ketamine.[207] A systemic review and meta-analysis showed that ketamine could significantly reduce pain intensity in patients with cancer-related pain while also reducing adverse side effects typically reported with opioid pain medications.[208]There are also some data suggesting that ketamine may improve mood in individuals with depressive disorders.[209-211]

Lidocaine

While it is most often used as a local analgesic, lidocaine may also be administered intravenously in patients with refractory cancer pain. Although data supporting the use of IV lidocaine for treatment of cancer pain are limited, there are case reports and smaller studies that support its use for opioid-refractory cancer pain or postsurgical pain.[212-215] One phase 2, randomized, double-blind crossover study of 50 patients with opioid-refractory cancer pain found that pain relief was better with IV lidocaine compared to placebo ($P < .001$). Additionally, more patients were able to decrease their analgesic requirements following administration of IV lidocaine than placebo ($P = .0012$). Side effects including tinnitus, perioral numbness, sedation, lightheadedness, and headache were self-limiting and did not require intervention except for discontinuation of the lidocaine infusion in one patient.[212] A meta-analysis of pooled data from RCTs demonstrated a significant reduction in cancer pain with lidocaine infusion compared to placebo in 60 patients.[216] IV lidocaine may be started as a bolus infusion of 1 to 3 mg/kg over 20 to 30 minutes. If this bolus is tolerated and effective at reducing pain, a continuous infusion of IV lidocaine may be started at 0.5 to 2 mg/kg/h (maximum 100 mg/h), using the lowest dose that controls the patient's pain.[214] Some reports suggest that IV lidocaine may be especially useful for cancer-related neuropathic pain.[213-215]

Selecting a Route of Administration for Opioid Analgesics and Mixed Mechanism Drugs

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.[60,217,218] 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. IV 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).[219] The SC route has a slower onset and lower peak (30 minutes) effect when compared with IV route.

Analgesic Agents That Are Not Recommended

The following agents are not recommended for patients with cancer: 1) mixed agonist-antagonists (eg, butorphanol, pentazocine); 2) meperidine; and 3) placebos. Mixed agonist-antagonists should not be used in combination with opioid agonist drugs for cancer pain management. 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.[217] Use of placebo in the treatment of pain is unethical.

Opioid Prescription, Initiation, Titration, and Maintenance

The appropriate dose of opioid is based on the patient's pain intensity and goals, while limiting undesirable and unmanageable adverse drug effects.

The physicians should be aware of potential drug-drug and drug-disease interactions while determining the treatment plan. For a summary of common drug-drug interactions between chemotherapeutics, analgesics, and other commonly prescribed medications, see Table 1. 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, LA dosing should be used for continuous pain relief. Additional doses of opioid may be required for pain not relieved by a regular schedule of LA (eg, ER) opioid.

The NCCN Panel recommends considering opioid rotation if pain is inadequately managed despite adequate dose titration, or if persistent adverse effects from current therapy occur. Other indications for switching to a different opioid include a change in the patient’s condition (dysphagia, NPO [*nil per os*] status, or initiation of tube feeding), and out-of-pocket costs and limitations based on insurance formularies.

For patients who have intermittent pain with pain-free intervals, IR opioids can be administered on an “as needed” basis, with the exception of methadone due to its long duration of effect. 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).[220] However, if the patient persistently requires doses of “as-needed” opioids, or if the “around-the-clock” opioid regimen does not relieve pain at peak effect or at end of dose, increased dose of the regularly scheduled opioid should be considered.

Breakthrough pain is defined as pain that is not adequately managed or “breaks through” a regimen of regularly scheduled analgesic and may be further categorized as:

- incident pain that is associated with specific activities or events (eg, physical therapy, exercise, or routine procedures that may induce pain), potentially managed with “rescue doses” of short-acting opioid given in anticipation of those events;
- end-of-dose failure pain that recurs toward the end of dosing interval for regularly scheduled opioid, potentially managed by increasing the dose or frequency of regularly scheduled opioid; or
- persistent pain that is routinely inadequately managed by existing regularly scheduled opioid, potentially managed by adjusting dose of regularly scheduled opioid.

Breakthrough pain is commonly reported among patients with cancer. In a survey of 1000 oncology patients, 44% reported incident pain, 41.5% reported spontaneous pain, and 14.5% reported both incident-related and spontaneous breakthrough pain.[221] Although the literature on useful therapies for breakthrough cancer pain is relatively small, multiple RCTs suggest that buccal, sublingual, or oral/nasal transmucosal formulations of fentanyl are effective options for managing episodic breakthrough pain.[222-225]

Initiating Short-Acting Opioids in Patients Who are Opioid-Naïve

The route of administration of an opioid (oral or IV) must be selected based on the patient’s needs. The NCCN Guidelines for Adult Cancer Pain management provide guidance for initiating short-acting opioids in patients who are opioid-naïve.

For patients who are opioid-naïve who are experiencing moderate/severe pain, or mild pain when non-opioid therapies are contraindicated, an initial dose of 5 to 7.5 mg of oral morphine sulfate every 3 to 4 hours as needed, or equivalent, is recommended. The algorithm also recommends starting doses for oxycodone immediate release, hydrocodone, and hydromorphone in patients who are opioid-naïve. Pain should be reassessed regularly and the dose titrated further as needed. If ≥4 doses of a short-acting opioid are consistently needed each day, the addition of a long-acting opioid may be considered based on the total daily dose.

Opioid Dose Reduction

The NCCN Panel recommends monitoring patients for situations that may warrant opioid dose reduction. Scenarios where opioid dose reduction may be considered include the patient rarely or never needing breakthrough analgesics, completion of an acute pain event, response to cancer-directed therapies, or improvement of pain control through use of non-opioid or interventional pain management therapies.[226] In these situations, the dose of opioid may be reduced by 5% to 20% after which the adequacy of pain control may be re-evaluated and further dose reductions may be considered if appropriate. Opioid dose reduction may also be considered when the pain is mild and the patient is experiencing unmanageable opioid-related adverse effects and/or rapid clinical deterioration. The expected trajectory of pain and the goals of care and pain management should be carefully reviewed when considering opioid dose reduction. For more information on tapering opioids, see *Principles of Opioid Dose Reduction* in the algorithm and the VA/DoD Clinical Practice Guideline for the Use of Opioids in the Management of Chronic Pain.[227]

Preventing Opioid Misuse

The NCCN Panel recommends monitoring for aberrant medication drug-related behaviors over the course of treatment using tools such as Current Opioid Misuse Measure (COMM). The COMM tool helps clinicians identify whether a patient, currently on long-term opioid therapy, is exhibiting aberrant behaviors associated with misuse of opioid medications.[228,229] It examines concurrent misuse; in contrast, SOAPP-R, ORT, or CAGE-AID are helpful in predicting which patients being considered for long-term opioid therapy may exhibit aberrant medications behaviors in the future. Potential risk factors for misuse of prescribed analgesics include the following patient characteristics:[45]

- History of prescription, illicit drug, or alcohol use disorder or misuse prior to cancer diagnosis/treatment
- History of binge drinking or peers who binge drink
- Family history of substance use disorders
- History of psychiatric disorder including anxiety, depression, attention-deficit hyperactivity disorder, post-traumatic stress disorder, bipolar disorder, or schizophrenia
- History of sexual abuse victimization
- Young age (<45 years of age)
- History of legal problems or incarceration

If signs of aberrant opioid use are present, providers should consider limiting or restricting use to avoid risk of diversion. Patients who are actively receiving treatment for substance use disorders should be encouraged to continue with therapy and care should be coordinated with their specialist. See additional recommendations in *Opioid Risk Mitigation Strategies During Chronic Opioid Use* in the algorithm.

Randomly administered urine drug tests (UDT) and review of prescription drug monitoring programs (PDMPs, also known as PMPs) can be used to monitor for aberrant use or diversion of pain medications. The goal of UDT is to improve patient outcomes and safety. There are limited recommendations regarding use of UDT in patients with cancer-related pain receiving opioid therapy, and as a result UDT appears to be underutilized among this population.[230] Due to the lack of studies in this population, some recommendations are extrapolated from studies done on patients who do not have cancer. It is judicious that the prescriber takes caution in the utilization of UDT to limit bias in test application/interpretation and avoid excessive patient burden and/or negative impacts on patient care.[231]

Published studies in patients with cancer found through random UDT that 1 in 4 patients receiving opioids had one or more abnormal results compared to results expected from prescribed therapy.[232] Current data show that UDT ordering is infrequent for patients with cancer on opioid therapy and the majority of ordering is performed by palliative care

physicians, not oncologists. Furthermore, when definitive UDT results are found to be aberrant, clinicians rarely make prescribing changes reflectively. It is apparent that more definitive guidance related to UDT ordering and opioid management is needed for patients taking opioids for cancer-related pain. [233]

The NCCN Panel recommends the consideration of UDT as part of a comprehensive safety monitoring program for patients receiving opioids for subacute and/or chronic cancer pain. This program should also include periodic review of state PDMPs as required by local/state laws, opioid prescribing patient agreement, and informed consent for opioid therapy.

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.[234-239] Chronic opioid therapy may depress the hypothalamic-pituitary axis and cause hypogonadism.[240] Each adverse effect requires a careful assessment and treatment strategy. Management of opioid-induced adverse effects is integral to opioid pain management.[234,241-249]

The details of prophylactic regimens and other measures to prevent opioid-induced adverse effects are provided in *Management of Opioid Adverse Effects* in the algorithm.

Constipation

Constipation can almost always be anticipated with opioid treatment and patients do not develop tolerance to constipation; therefore, administration of a prophylactic bowel regimen is recommended for nearly all patients taking opioids. However, there is limited evidence on which to base the selection of the most appropriate prophylactic bowel regimen. One study showed that addition of the stool softener, docusate, to the laxative, sennosides, was less effective than administering sennosides alone.[250] An RCT in hospice patients showed that there was no benefit in adding docusate to sennosides compared to sennosides alone.[251] Therefore, for prophylaxis, the NCCN Guidelines for Adult Cancer Pain Panel members recommend a stimulant laxative or a heaping tablespoon (17 g) of polyethylene glycol (PEG) with 8 oz of water one to two times daily along with maintaining adequate fluid intake. Based on the available literature, the stool softener docusate may have limited benefit. While maintaining adequate dietary fiber intake is recommended, supplemental medicinal fiber, such as psyllium, has been shown to be useful in some studies, but may worsen constipation in certain patients. Other dietary modifications such as addition of prunes, prune juice, and/or kiwifruit may improve chronic constipation in some patients, although the studies were not specific to patients using opioids for pain.[252,253] Patients should be encouraged to stay adequately hydrated and maintain activity (gentle exercise) as tolerated/feasible.

Once constipation develops, the cause and severity of constipation must be assessed to rule out obstruction. Laxatives may be titrated as needed with the goal of achieving one non-forced bowel movement every 1 to 2 days. Adjuvant analgesics 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 and hypercalcemia. Providers should assess other medications with the potential to cause constipation. 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 transdermal fentanyl, buprenorphine, or methadone may be considered. These medications may have less risk of constipation. Enema with sodium phosphate, saline, or tap water may be helpful as it

dilates the bowel, stimulates peristalsis, and lubricates the stool to encourage a bowel movement. However, these types of enemas should be used sparingly with awareness of possible electrolyte abnormalities. The use of rectal suppositories or enemas should be avoided in patients with neutropenia or thrombocytopenia. Additionally, oral laxatives or enemas that contain sodium phosphate should be limited to a maximum dose of once daily in patients at risk for renal dysfunction; optimally, alternative agents can be used.

When response to laxative therapy has not been sufficient, peripherally acting mu-opioid receptor antagonists (PAMORAs) that work on receptors in the GI system, such as oral methylnaltrexone,[254-259] naloxegol,[260] or naldemedine,[261] can be used as a rescue when constipation is clearly related to opioid therapy[262] (methylnaltrexone is FDA-approved for opioid-induced constipation in adults with advanced illness who are receiving palliative care; naloxegol and naldemedine are FDA-approved for opioid-induced constipation in adults with chronic non-cancer pain, including those with chronic pain related to prior cancer or its treatment). Other second-line agents may be considered, including lubiprostone which is FDA-approved for opioid-induced constipation in adults with non-cancer pain including those with chronic pain related to prior cancer or its treatment.[263,264] These agents should not be used in patients with known or suspected mechanical bowel obstruction, recent bowel surgery, transmural bowel metastases, or other processes affecting integrity of the GI lumen due to the potential increased risk of perforation.[265] Guidelines from the American Gastroenterological Association Institute for the medical management of opioid-induced constipation may be referenced for more information and recommendations on use of these agents.[266]

Neuraxial analgesics, neuroablative techniques, or other interventions to decrease pain and/or reduce systemic opioid dose may also be considered to reduce opioid-related adverse effects.

Nausea and Vomiting

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, CNS pathology, chemotherapy, radiation therapy, hypercalcemia, bowel obstruction) must be assessed. Effective agents that may be considered include phenothiazines 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 and 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 and have a lower rate of CNS effects. Alternative agents such as scopolamine, olanzapine, or mirtazapine may also be considered for management of nausea. Olanzapine may be especially helpful for patients with bowel obstruction.[267,268] Corticosteroids, such as dexamethasone, 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.[269]

If nausea persists for >1 week, the cause of nausea needs to be reassessed and opioid rotation must be considered.[270] If opioid rotation and the above measures have been tried and nausea still persists, neuraxial analgesics, neuroablative techniques, and other interventions could be performed to potentially reduce the opioid dose. Dronabinol, a cannabinoid that has been FDA-approved for chemotherapy-induced nausea and vomiting, may also be considered in this situation.[271,272] It should be noted that in the context of shifting legality, many patients with cancer are using medical cannabis for treatment of nausea and other

cancer- or cancer treatment-related symptoms.[103,104] While medical cannabis has been legalized in many states, it has not been FDA-approved.[104] Education on state and federal regulations for medical cannabis should be provided (see *Adjuvant Analgesics* and *Cannabinoids and Medical Cannabis* for more information).

Pruritus

Pruritus or itchiness is a particularly common and distressing complaint. Pruritus occurs in 10% to 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 first be assessed. Pruritus is more likely to occur early in the course of treatment. If it is persistent despite attempted symptom management, consider changing to another opioid. Careful titration of mixed opioid agonist-antagonists (eg, nalbuphine) or mu-opioid receptor antagonists (eg, naloxone) may help reduce opioid-induced adverse effects while maintaining analgesic efficacy. The mu-receptor antagonists (eg, naloxone) are also used to reverse the effects of opioid-induced adverse effects,[273] and careful dose titration can produce relief without reversing analgesic efficacy. A serotonin antagonist such as ondansetron may also be considered. Antihistamines such as cetirizine (non-sedating), diphenhydramine (sedating), or promethazine (sedating) may be beneficial. Hydroxyzine, administered by mouth or intramuscular injection, may also be useful.

Delirium

Delirium is a pathophysiologic condition characterized by altered consciousness and inattention, cognitive dysfunction, and disturbed psychomotor behavior. Delirium may be prevented or decreased with various non-pharmacologic interventions or, when delirium is severe and hyperactive, may be managed with a neuroleptic drug such as haloperidol, olanzapine, or risperidone on an as-needed basis or by switching to another opioid.[274-277] 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.[278] Quetiapine may be useful, especially in patients with Parkinson's syndrome.[279] Patients taking opioids may be screened for driving impairment, if indicated. Driving fitness screens are often performed through occupational therapy.

Sedation

It is critical to recognize the difference between cancer-related fatigue and opioid-induced sedation, as some techniques to manage sedation may not work for fatigue. The Pasero Opioid-induced Sedation Scale (POSS) has been validated and is recommended for monitoring opioid-induced sedation, particularly for inpatient care and when increasing the dose of opioids.[280,281] For more information on managing cancer-related fatigue, see the NCCN Guidelines for Cancer-Related Fatigue. Sedation may hinder the achievement of dose titration of opioids to levels that provide adequate analgesia.[57] If opioid-induced sedation develops, it may be managed by administration of psychostimulants such as methylphenidate, dextroamphetamine, modafinil, or armodafinil 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. Sedation typically precedes respiratory depression; therefore, progressive sedation should be noted and adjustments in care should be made.

Use caution when combining opioid medications with other medications that have a sedating effect (eg, benzodiazepines) due to an increased risk for sedation and respiratory depression. The FDA has issued a black box warning about possible serious effects from this combination, including slowed or difficult breathing and death.[282]

Respiratory Depression

Respiratory depression is another adverse effect that is a concern for both physicians and patients. Physicians should be aware that patients with limited cardiopulmonary reserve are more susceptible to respiratory depression and that hypercarbia occurs before hypoxia. Initial steps that may be taken when there is a concern about respiratory depression include reducing the opioid dose, increasing the interval of opioid administration, confirming that the patient does not have any forgotten transdermal opioid patches, and providing close monitoring. If the patient is medically stable, noninvasive respiratory support may be considered and/or additional doses of opioid analgesic may be temporarily halted until the patient's respiratory status improves.

In cases where the patient is unstable or response to the above interventions is inadequate, naloxone remains a useful antidote for the reversal of opioid-induced respiratory and CNS depression. However, naloxone should be administered with caution so as not to precipitate acute opioid withdrawal syndrome in the patient who is opioid-tolerant. Abrupt reversal of opioid depression in patients who are opioid-tolerant may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, tremulousness, and seizures. Pulmonary edema, cardiac arrhythmias, and cardiac arrest have also been associated with naloxone administration.[283] At end-of-life in patients receiving comfort measures only, slowed respiration is expected. Naloxone administration may be inconsistent with goals of care in these patients.

Naloxone may be made available to caregivers of patients receiving opioid analgesics to administer in the event of respiratory depression and sedation. While there are no RCTs, the results of a nonrandomized intervention study showed that patients receiving long-term opioid analgesia who were co-prescribed naloxone had fewer opioid-related emergency department visits compared to those who were not prescribed naloxone.[284] Providers should become familiar with state regulations regarding the prescription of naloxone. The availability of needle-free naloxone preparations (eg, nasal spray) may facilitate use of naloxone in the outpatient setting. Importantly, caregivers who are provided naloxone must be educated in the proper indications and usage to prevent inappropriate administration. Caregivers should be instructed to call emergency services (911) if naloxone is administered. Naloxone may be available without a prescription in some localities.

Opioid Rotation

No single opioid is optimal for all patients.[285] If opioid adverse effects are significant, an improved balance between analgesia and adverse effects might be achieved by changing to an alternative opioid. This approach is known as opioid rotation.[234,286,287] A post hoc analysis of 498 patients from a randomized phase IV clinical trial found that the opioid was switched in 79 patients, with 51.45% of switches resulting in better pain control and 43.5% resulting in better control of opioid side effects.[288] Establishing equianalgesic dosing can be challenging; studies have sought to establish safe conversion ratios and methods.[163,289-293] It is important to consider relative effectiveness when switching between oral and parenteral routes to avoid subsequent overdosing or underdosing. Known equianalgesic dose ratios, opioid titration and maintenance, and clinical examples of converting from one opioid to another are listed in *Opioid Principles, Prescribing, Initiation, Titration, Maintenance, and Safety* in the algorithm.

Opioids and Risk Evaluation and Mitigation Strategy

While opioids are the principal analgesics for management of moderate to severe pain in the context of a cancer diagnosis, they pose risks to both individual patients and larger communities. The misuse of opioids is an increasing concern. In 2022, there were 107,941 drug overdose deaths in the United States, including 81,806 deaths due to opioid overdose.[294,295] Drug poisoning remains the number one cause of injury-related death in

the United States.[296] While it is important to ensure that opioids continue to be prescribed for patients for whom they are appropriate, it is also essential to ensure that these drugs are prescribed carefully and are appropriately managed, especially during prolonged usage. To reduce the risk of substance use disorders, misuse, overdose, and death, the FDA has established Risk Evaluation and Mitigation Strategy (REMS) programs for opioid products.[297] The principal recommendations of opioid REMS programs are educating the provider, patient, and family/caregiver.

The highlights of provider responsibilities included in the REMS are:

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

On September 18, 2018, the FDA approved the Opioid Analgesic REMS program, which covers all opioid analgesics intended for use in an outpatient setting.[298] This program requires that training be made available to all health care providers who are involved in the comprehensive care of patients with pain (eg, nurses, pharmacists) and requires that education cover broader information about pain management, including non-opioid analgesics and non-pharmacologic interventions.[299] The complete list of currently approved REMS programs is available on the FDA website.[300]

All prescribers are encouraged to discuss the risks and benefits of opioid products with their patients. A patient counseling document approved with the REMS will be made available by the manufacturers to assist the prescribers in having these discussions. Providers should also routinely screen for signs of opioid misuse or diversion. Various screening tools have been described for this purpose, but have not yet been evaluated in patients with cancer.[45] One exception is the ORT, the use of which was evaluated in a retrospective chart review of 114 patients with cancer.[301] More research is warranted to determine the best practice for screening methods. If signs of aberrant drug use are observed, patient counseling, UDT, and limiting or restricting use accordingly is strongly encouraged. However, UDT results can be challenging to interpret and are susceptible to false positives and negatives; therefore, unexpected results should be followed up with confirmatory testing and/or input from a certified laboratory professional or toxicologist.[230]

The Panel recommends that clinicians utilize state PDMPs. The National Association of State Controlled Substances Authorities (NASCA) maintains a database of state PMP contacts (see NASCA's website). Written agreements or guidelines may help to clarify expectations and parameters for safe use of opioid analgesics. While further research is needed to evaluate their utility in patients with cancer, such agreements are consistent with evolving CDC and FDA recommendations and may be required in certain states.

Management Strategies for Specific Cancer Pain Syndromes

Moderate to severe cancer pain is treated with opioids as indicated; however, opioids alone may not provide optimal analgesia. When a specific cancer pain syndrome is suspected or documented, additional interventions may be targeted to that pain syndrome. Nonopioid analgesics (such as an NSAIDs), adjuvant analgesics (antidepressants, anticonvulsants, topical agents, and corticosteroids), integrative interventions (psychologic and physical approaches), and/or interventional strategies may be used in conjunction with opioids to help improve patient outcomes.[57]

Neuropathic Pain

Cancer-related neuropathic pain is common and can be related to the cancer itself or the acute or chronic effects of cancer treatment.[302,303]

Adjuvant analgesics are particularly important in treating neuropathic pain.[90,91] The most common adjuvant analgesics used for treating neuropathic cancer pain include anticonvulsants, antidepressants, and topical treatments. See *Adjuvant Analgesics* for more information on these agents, including important cautions for their use. Corticosteroids have also long been used to relieve neuropathic pain syndromes, particularly radiculopathies associated with vertebral body compression fractures.

While there are a limited number of RCTs supporting the role of antidepressants as adjuvant analgesics for neuropathic cancer pain, the effectiveness of TCAs for relief of neuropathic cancer pain may be extrapolated from studies conducted in non–cancer-related neuropathic pain.[304-306] Several RCTs have shown that anticonvulsants (pregabalin or gabapentin) provided relief of neuropathic cancer-related pain.[100,307,308] Likewise, some systematic reviews of trials of patients with cancer pain suggest that adjuvant analgesics (antidepressants and antiepileptics) added to opioids provided additional neuropathic pain relief,[309] although another concluded that combining opioid analgesia with gabapentinoids did not provide significantly improved pain relief (data on amitriptyline, fluvoxamine, and phenytoin were inconclusive).[310] The likelihood of benefit should be balanced with the risk of adverse effects by clinicians considering adjuvant analgesics for neuropathic pain.

Topical local anesthetic agents can be useful in preventing procedural pain and in relieving some types of cancer-related neuropathic pain. They act locally and are also thought to have some central inhibitory effect on pain. They may be used as an analgesic in combination with an opioid, antidepressant, and/or an anticonvulsant. Both the gel and patch forms of lidocaine have been shown to reduce the pain of postherpetic neuropathy and cancer-related pain.[311-313]

Management of Bone Pain Without an Oncologic Emergency

The clinical complications of bone metastases include debilitating bone pain, which tends to be most prominent with movement, pathologic fractures, spinal cord compression, neurologic complications, and hypercalcemia of malignancy. The term skeletal-related events (SREs) refers to a constellation of skeletal complications including fracture, need for surgery to bone, need for radiation to bone, and spinal cord compression. In some situations, hypercalcemia of malignancy is also included as an SRE. Administration of NSAIDs, acetaminophen, or steroids may improve bone pain control when combined with opioid analgesics.[314-316] Topical diclofenac, including gel or patch, may provide relief for pain due to bone metastases with minimal system effects.[314]

Although bone-modifying agents such as bisphosphonates and receptor activator of nuclear factor-kappa-B ligand (RANKL) inhibitors are primarily used for the reduction of overall SREs, clinical trials have established that these agents can have an analgesic effect on patients with metastatic bone pain from a variety of tumors. Clinical trials have demonstrated the palliative effects of bisphosphonates (eg, zoledronic acid, ibandronate)[317-321] and denosumab (a RANKL inhibitor)[319,322] on pain related to bone metastases. Randomized trials suggest that, compared with zoledronic acid, denosumab provides comparable palliation of existing bone pain and may be superior for preventing worsening of bone pain,[319,322,323] although evidence is insufficient to recommend one of these agents over the others.[324] Due to differences in patient populations and the methods for assessing bone pain, direct comparison of bisphosphonates to determine their relative effects on bone pain across studies is difficult. Review of the literature shows that the analgesic effects of bone-modifying agents are modest and, therefore, these agents should not be used as a primary therapy for treatment of bone pain.[324]

Surgical and radiation treatment for bone metastases is performed to relieve local bone pain, provide stabilization, and prevent impending fracture or spinal cord compression.[325] In some situations, interventions such as vertebral augmentation provide a greater likelihood of return to ambulatory status than radiation alone. Plain radiographs may be used to identify impending fractures so that the patient can be referred to an orthopedic specialist for stabilization. Consultation with a pain or palliative care specialist and/or an interventional therapist is recommended to determine optimal management strategy for vertebral augmentation.

Ablative strategies such as image-guided ablation may also be performed to reduce pain and prevent SREs. Image-guided ablation of bone lesions has proven successful in pain management, especially for those unable to achieve adequate analgesia without intolerable effects.[326-329] Several small studies have also demonstrated the palliative effects of high-intensity focused US (HIFU) treatment of bone lesions.[330-332]

Physical and occupational therapy may also be beneficial in the prevention of complications associated with SREs.[333-335]

Management of Pain from Mucositis

Certain treatments for cancer—including systemic therapy, head and neck radiation, or hematopoietic cell transplant—can cause pain in the mouth, pharynx, and esophagus.[336] Resources and guidelines from the Oncology Nursing Society (ONS),[337] Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO),[338] and European Society for Medical Oncology (ESMO)[339] detail strategies for prevention and management of oral and GI mucositis.

To prevent oral mucositis, cryotherapy may be performed by having the patient suck on ice chips or hold ice water in their mouth before, during, and/or after rapid infusions of systemic therapies that are associated with mucositis. Studies have shown this approach to be effective in patients receiving melphalan for multiple myeloma and 5-fluorouracil for solid tumors.[340,341] Gabapentin may be used in combination with opioid or non-opioid analgesics for treatment of mucositis, although studies on the effectiveness of this approach have reported mixed results.[99,342]

Oral care protocols, consisting of good oral hygiene and prophylactic mouth rinses, may be used for prevention of mucositis.[343] Prophylactic mouth rinses (also called “magic mouthwash”) compositions vary significantly, including ingredients such as antibiotics, antihistamines, antifungals, corticosteroids, and antacids.[344,345] The effectiveness of these ingredients for preventing or treating mucositis and the evidence supporting their use varies. Because of this, bland mouth rinses using ingredients such as sodium bicarbonate are often recommended.[336] The NSAID benzydamine also has some data supporting its use in an oral rinse for the prevention and treatment of mucositis.[346,347] Local anesthetics (eg, lidocaine) may be used to treat mucositis either as a component of a mouth rinse or separately, in a liquid or gel formulation.

Pharmacogenetic Considerations

Pharmacogenetics can be defined as the study of how genetic differences may determine drug metabolism, and therefore response to analgesics. On the other hand, pharmacogenomics generally refers to a broader understanding of how all the genes in the genome relate to pain perception and response to analgesic drugs. There is considerable overlap in these terms, however, and they are often used interchangeably.[348] For the purposes of this Guideline, the term pharmacogenetics will be used as it is referring to detection of specific allelic variants, rather than the entire genome. This terminology is in agreement with that which is used in the Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines.[349,350]

Several classes of analgesic drugs have pharmacogenetic implications that may lead to little or no analgesic response or significant adverse effects. Notable among these are opioids,[176] TCAs,[351,352] and NSAIDs,[353] which are all metabolized by the CYP450s, a family of enzymes that represent the major system for oxidative metabolism of drugs. In humans, there are at least 57 documented CYP genes across 18 different families and 44 subfamilies. CYP families 1–3 are most relevant to the pharmacogenetics of drug metabolism.[354] CYP enzymes are named with the letters "CYP" followed by a numeral designating the family, then a letter designating the sub-family, and finally another numeral that represents the individual gene or isoform. Evidence also supports the roles of *OPRM1* (mu receptor) and Catechol-O-methyltransferase (COMT) in response to opioids, although current implications for clinical practice are unclear.[176]

The FDA has published a table of pharmacogenetic associations that it believes have sufficient evidence to suggest that subgroups of patients with certain genetic variants have altered drug metabolism and/or therapeutic effects.[355] Of note for this guideline, codeine (*CYP2D6*), tramadol (*CYP2D6*), amitriptyline (*CYP2D6*), doxepin (*CYP2D6*, *CYP2C19*), celecoxib (*CYP2C9*), and meloxicam (*CYP2C9*) are included on this list. See Table 1 for potential drug-drug interactions of commonly prescribed medications and Table 2 for a more complete list of CYP450 opioid metabolic pathways and related drug-to-drug interactions. FDA-approved pharmacogenetic tests for *CYP2D6*, *CYP2C19*, and *CYP2C9* are currently available. However, insurance reimbursement, availability of pharmacogenetic tests, and other implementation barriers may limit their use in clinical practice.[356,357] See *Principles of Pharmacogenetics* in the algorithm for recommendations on how to adjust drug dosages or selection based on the results of specific pharmacogenetic tests.

The NCCN Panel recommends that pharmacogenetic testing may be considered either prior to initiation of therapy or when concerns of toxicity or lack of analgesic response arise during analgesic treatment. Consultation with a clinical pharmacist or clinical pharmacogenomics/pharmacogenetics specialist may be helpful in the interpretation of pharmacogenetic test results and to aid in drug selection and/or dose adjustments, when necessary.

Specialty Consultations

Continued pain assessments should be obtained and documented in the medical record to ensure that the patient's pain remains well-managed 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 and then providing specific treatment and education for patients. The specialties include physical/occupational therapy; integrative medicine; mental health support services (including psychiatric consultation, psychology consultation, and/or substance use disorders consultation, as needed); pain and palliative care services; depression/distress consultation; spiritual care consultation; or social work services. Consultation with a specialist in the treatment of substance use disorders may be helpful for managing aberrant drug behavior in patients with a history of or risk factors for misuse of pain medication.

Non-Pharmacologic Interventions for Cancer Pain Management

Integrative Interventions

Since pain encompasses physical, psychosocial, and spiritual dimensions, the treatment of cancer pain inherently requires integration of therapies

inclusive of non-pharmacologic interventions. There is a growing body of evidence suggesting that the use of nonpharmacologic interventions (physical, cognitive, psychosocial, and spiritual) may serve as valuable additions to pharmacologic interventions.[358-360] The integration of physical, cognitive, psychosocial, and spiritual modalities should be based on assessment of cultural and financial considerations, and are best presented as part of joint and informed decision-making. ASCO has published a guideline on Integrative Medicine for Pain Management in Oncology, which provides evidence-based recommendations to health care providers on integrative approaches to managing pain in patients with cancer.[361]

Physical Interventions

Physical interventions include, but aren't limited to, therapeutic or conditioning exercise, physical or occupational therapy, massage, use of heat and/or cold, acupuncture, electro-acupuncture, and acupressure.[361-369]

Cognitive-Behavioral Interventions

Cognitive interventions are aimed at enhancing a sense of control over the pain or underlying disease. Cognitive behavioral therapy (CBT), cognitive restructuring, mindfulness-based stress reduction (MBSR), breathing exercises, relaxation, yoga, imagery, hypnosis, biofeedback, music, and other behavioral therapies can be very useful.[361,370-376] Patient-based educational interventions have a significant impact in providing pain relief.[377] Skills training helps modify the patient's experience of pain and helps patients acquire techniques of pain management such as deep muscle relaxation.[378] Patients who may benefit from skills training may be referred to a licensed mental health professional trained in CBT, hypnosis, biofeedback, or MBSR. Education provides patients and family/caregivers with the knowledge to use analgesics correctly and to address side effects or unrelieved pain.

Psychosocial Interventions

Attention should focus on psychosocial support and providing education to patients and families.[379,380] Psychosocial support can greatly enhance patients' sense of control as well as greatly reduce the family/caregivers' feeling of helplessness.[374] A meta-analysis of the effect of psychosocial interventions on cancer pain highlights the importance of a multimodal approach to the management of cancer pain.[381]

Spiritual Interventions

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 helpful in relieving or coping with pain. Involvement of spiritual care providers from a range of culturally appropriate spiritual backgrounds is essential.[382] Spiritual needs should be routinely assessed and spiritual care should be incorporated as a component of comprehensive pain management.

Nutritional Interventions

Consultation with a nutritional care provider experienced in nutritional counseling of patients with cancer may be helpful in providing dietary recommendations to help patients maintain a healthy body weight and avoid malnutrition. Some studies have reported malnutrition in approximately 30% to 40% of patients with cancer[383,384] and malnutrition can increase treatment toxicities, diminish quality of life, and increase cancer mortality. A nutritional care provider can also help to assess and educate on herbal, botanical, and dietary supplements a patient may be taking and their potential impact on treatment effectiveness and side effects.

Interventional Strategies

Some patients experience inadequate pain management despite pharmacologic 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.[385] Interventional therapies that can be useful in the relief of cancer pain include nerve blocks, vertebral augmentation, regional infusion of analgesics, image-guided ablation, and other techniques.[57,328,329,386-391]

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 abdominal pain with celiac plexus block, lower abdominal pain with superior hypogastric plexus block, chest pain with intercostal nerve block, peripheral/plexus nerve) and/or patients unable 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 management over systemic analgesics but is generally associated with a reduction in adverse effects.[392,393]

Regional analgesics techniques potentially allow for targeted delivery of local anesthetics when pain control is required for specific (limited) areas of pain which can be addressed by neural blockade of appropriate peripheral nerves or nerve plexus. For broader areas of pain, epidural or intrathecal routes of administration of analgesics solutions (containing local anesthetic, opioid, and/or other analgesics suitable for neuraxial administration) may be considered.[394-399] Nerve blockade techniques may be especially important in patients with intolerable sedation, confusion, constipation, and/or inadequate pain control from systemic analgesics. Percutaneous catheters with external infusion pumps may be used for prolonged administration (days to a few weeks) for selected peripheral nerve/regional plexus blocks as well as epidural/intrathecal analgesics administration. For clinical settings requiring longer-term administration of epidural/intrathecal analgesics, implanted spinal pump systems are typically used to minimize the concern of catheter migration (displacement) and the risk of infection.

Percutaneous vertebral augmentation and/or cementoplasty 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. Vertebral augmentation helps restore mechanical stability while reducing pain and neurologic symptoms.[400-405] Ablation techniques may also be helpful for pain management in patients who receive inadequate relief from pharmacologic therapy. Prospective trials of percutaneous ablative techniques, many using thermal energy, have shown decreased patient pain from bone metastases in patients who did or did not receive prior radiation therapy.[406-415] Non-ionizing thermal ablative techniques may serve as an alternative and/or adjunct to radiation therapy or be offered in patients who refuse or cannot receive radiation therapy. Early data suggest a synergistic effect with radiation therapy and these different treatment modalities may prove to be complementary.[416,417] Similarly, vertebral augmentation/cementoplasty provides pain relief with the additional benefit of improved stabilization, which may prevent or halt pathologic fracture.[418]

Neurodestructive procedures may be used for well-localized pain syndromes (eg, back pain due to facet or sacroiliac joint arthropathy; visceral pain due to abdominal or pelvic malignancy). Ablation therapy (eg, image-guided ablation, US ablation) for bone lesions can also be helpful in reducing pain.[326-332] See *Management Strategies for Specific Cancer Pain Syndromes, Bone Pain Without Oncologic Emergency* in the algorithm for more information. Neurostimulation procedures have been suggested to

be useful for painful chemotherapy-induced peripheral neuropathies, neuralgias, and complex regional pain syndrome.[419]

Interventional strategies listed above are not appropriate if patients are unwilling or in patients with infections, coagulopathy, or with very short life expectancies. Also, the experts performing the interventions must be made aware of any medications that the patient is taking that might increase bleeding risk (ie, anticoagulants [warfarin, heparin], antiplatelet agents [clopidogrel, dipyridamole], anti-angiogenesis agents [bevacizumab]). If this occurs, 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. Additionally, if interventional treatment is undertaken and successfully improves pain control, significant opioid dose reduction may be required.

Summary

In most patients, cancer pain can be successfully managed 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 re-evaluation of the patient. The NCCN Adult Cancer Pain Guidelines Panel advises that cancer pain can be well managed in the vast majority of patients if the algorithms presented are systematically applied, carefully monitored, and tailored to the needs of the individual patient.

Recommended Readings

Brant JM, Rodgers BB, Gallagher E, Sundaramurthi T. Breakthrough cancer pain: A systematic review of pharmacologic management. Clin J Oncol Nurs 2017;21:71-80.

Cherny N. Cancer Pain Syndromes. In: Cherny N, Fallon M, Kaasa S, et al., eds. Oxford Textbook of Palliative Medicine (5th ed). Oxford: Oxford University Press; 2015:819-840.

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Wiffen PJ, Wee B, Derry S, et al. Opioids for cancer pain - an overview of Cochrane reviews. Cochrane Database Syst Rev 2017;7:CD012592.

Table 1: Potential Drug-Drug Interactions: Chemotherapeutics, Analgesics, and Other Commonly Prescribed Medications*,β

Drug	Buprenorphine, Fentanyl, Hydrocodone, Methadone, & Oxycodone	Methadone & Buprenorphine	Enzalutamide, Apalutamide, Repotrectinib, Mitotane, & Dexamethasone[ε,φ]
Interaction	Potential to <u>increase</u> plasma levels of the above opioids	Potential for QTc prolongation when used with above opioids	Potential to <u>decrease</u> plasma levels of the agents below
Interacting Drugs	Adagrasib Clarithromycin Cobicistat Conivaptan Erythromycin Fluconazole Idelalisib Imatinib Indinavir Itraconazole Ketoconazole (systemic) Nelfinavir Nefazodone Posaconazole Ritonavir Saquinavir Tucatinib Verapamil Voriconazole	Abarelix Adagrasib Amiodarone Anagrelide Arsenic trioxide Ceritinib Chlorpromazine Citalopram Clarithromycin Crizotinib Bortezomib Dabrafenib Dasatinib Degarelix Dolasetron Encorafenib Entrectinib Epirubicin Escitalopram Fluoroquinolones Granisetron Haloperidol Ivosidenib Lapatinib Lenvatinib Levofloxacin Metoclopramide Nilotinib Olanzapine Ondansetron Osimertinib Oxaliplatin Pazopanib Quizartinib Ribociclib Risperdal Romidepsin Rucaparib Ruxolitinib Selpercatinib Sorafenib Sunitinib Tazemetostat Toremifene Vandetanib Vemurafenib Voriconazole Vorinostat Ziprasidone	Aprepitant Buprenorphine Bortezomib Ceritinib Crizotinib Dabrafenib Erlotinib Everolimus Fentanyl Gefitinib Hydrocodone Ibrutinib Idelalisib Imatinib Lapatinib Methadone Naldemedine Naloxegol Oxycodone Pazopanib Ruxolitinib Sirolimus Sorafenib Sunitinib Tacrolimus Temsirolimus Vandetanib Vemurafenib

*Data within this table were obtained from the FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors, and Inducers,[420] UpToDate Lexidrug,[421] available published literature, and prescribing information for drug products.[106] Information updated on August 5, 2024.

β This list is not comprehensive and may not represent new data or other agents recently introduced into practice. Clinicians are advised to refer to the individual drug labeling or seek expert consultation.

ε Many chemotherapeutic agents produce immunosuppression that can be exacerbated by concomitant dexamethasone use; physicians should consider goals of care, rationale for dexamethasone use, duration of use, and other factors when considering use with other immunosuppressive agents.

φ Dexamethasone is a dose-dependent inducer of CYP3A4.[422]

Table 2: CYP450 Opioid Metabolism and Potential Drug-Drug Interactions

Opioid	CYP450 *Metabolic Pathway*[106,420,423]	CYP 3A4 Inducers[420]		CYP 3A4 Inhibitors[420]	
Buprenorphine	CYP3A4	Carbamazepine Ω	Rifampin Ω	Adagrasib	Telaprevir**
Codeine	CYP2D6	Efavirenz	Ritonavir	Ceritinib	Nelfinavir**
Fentanyl	CYP3A4	Oxcarbazepine	Repotrectinib	Cobicistat	Indinavir**
Hydrocodone	CYP2D6, CYP3A4	Phenobarbital	St John's wort	Idelalisib	Clarithromycin**
Methadone	CYP2B6, CYP3A4 CYP2C8, CYP2C19 CYP2D6, CYP2C9	Phenytoin Ω	Enzalutamide Ω	Itraconazole**	Verapamil*
Oxycodone	CYP2D6, CYP3A4	Primidone	Apalutamide	Ketoconazole**	Aprepitant*
		Rifabutin	Encorafenib	Nefazodone**	Conivaptan*
			Mitotane	Posaconazole**	Diltiazem*
			Dexamethasone	Voriconazole**	Dronedarone*
				Atazanavir**	Erythromycin*
				Boceprevir**	Fluconazole*
				Ritonavir**	Tucatinib
				Saquinavir**	
Tapentadol	CYP2C9, CYP2C19 CYP2D6β	**CYP 2D6 Inducers[420]**		**CYP 2D6 Inhibitors[420]**	
Tramadol	CYP2D6, CYP3A4	No Data		Quinidine**	
Morphine	None			Paroxetine**	
Hydromorphone	None			Fluoxetine**	
Oxymorphone	None			Bupropion**	

Created by David Craig, PharmD and reviewed by the NCCN Panel (last updated 08/05/2024)

**Denotes strong inhibitors (>5-fold increase in exposure, or >80% decrease in clearance of substrate).

*Denotes moderate inhibitors (>2 to <5-fold increase in exposure, or 50% to 80% decrease in clearance of substrate).

β Tapentadol is not extensively metabolized via CYP450 enzymes; therefore, clinically relevant interactions mediated by this metabolic pathway are unlikely to occur.

Ω Denotes strong inducer (>80% reduction in AUC of substrate).

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