National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Adult Cancer Pain

Version 1.2018 — January 22, 2018

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Σ Pharmacology
Ψ Neurology/neuro-oncology
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NCCN Guidelines Panel Disclosures

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

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

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

See NCCN Categories of Evidence and Consensus.

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Updates in Version 1.2018 of the NCCN Guidelines for Adult Cancer Pain from Version 2.2017 include:

PAIN-1

- **Principles of Cancer Pain Management**
  - General
    - ◊ 1st bullet was revised: "There is increasing evidence in oncology that survival is linked to symptom *reporting and* control and that pain management contributes to broad quality-of-life improvement. To maximize patient outcomes, pain management is an essential part of oncologic management."
    - ◊ 2nd bullet was revised: "Analgesic therapy is *often* done in conjunction with management of multiple symptoms or symptom clusters. *Treatment must consider the interaction* of complex pharmacologic therapies that *a* patient~~s~~ *is* prescribed *and the risk for analgesic misuse.*"
    - ◊ 5th bullet was revised: "Specific educational material, *including information about the role of opioids in cancer pain management*, must be provided to the patient and family/caregiver in an understandable language and format. (See PAIN-I)
- Assessment
  - 2nd bullet was revised: "Pain intensity must be routinely quantified *and documented*, and quality must be characterized by the patient (whenever possible based on patient communication capacity). *Also include patient reporting of breakthrough pain, treatments used and their impact on pain, patient reporting of adequate comfort, patient reporting of satisfaction with pain relief, provider assessment of impact on function, and any special issues for the patient relevant to pain treatment. If necessary, get additional information from family/caregiver regarding pain and impact on function."*
  - 4th bullet was revised: "Evaluate patient for risk factors ~~of~~ *for* opioid abuse/misuse/diversion."
  - A bullet was removed: "Assessment of patient's pain is essential, including patient reporting of qualities of the pain, breakthrough pain, treatments used and their impact on pain, patient reporting of adequate comfort, patient reporting of satisfaction with pain relief, provider assessment of impact on function, and any special issues for the patient relevant to pain treatment. If necessary, get additional information from family/caregiver regarding pain and impact on function."

PAIN-1 continued

- Management/Intervention
  - 5th bullet for "Goals of pain management" was added: "Affect (relationship between pain and mood)."
  - 2nd bullet was revised: "Comprehensive pain management (addressing the ~~physical and~~ biopsychosocial elements of pain using pharmacologic and non-pharmacologic modalities) is needed as most patients have multiple pathophysiologies and multiple symptoms."

PAIN-2

- Assessment
  - Comprehensive pain assessment
    - ◊ 1st sub-bullet was added: "Pain experience"
    - ◊ 6th sub-bullet was added: "Risks for substance use disorder (see PAIN-E)"
- Management of Pain
  - Pathway statements were removed: "Painful events and procedures" and "See Procedure-Related Pain and Anxiety (PAIN-B)."
  - Footnote "d" was revised and added to "Opioid tolerant patients" statement: "Opioid naïve ~~includes~~ patients ~~who~~ 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-3, PAIN-4, PAIN-5 and PAIN-6)
  - A footnote was removed: "Opioid tolerant includes patients who are chronically receiving opioid analgesic on a daily basis. The FDA identifies tolerance as receiving at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer." (Also for PAIN-5)

PAIN-3

- Management of Pain In Opioid-Naive Patients page was extensively revised.

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PAIN-4

- Pathway statements for Opioid-naive patients were revised:
  - "Oral *analgesic* (peak effect 60 min)"
  - *"Oral analgesics require a minimum of* 60 min *to reach peak effect"*

PAIN-5

- Title was revised: "Management of Pain *Crisis* in Opioid-Tolerant Patients"
- A statement was revised: "Oral *analgesic* (peak effect 60 min)"
- A footnote was removed: "Opioid tolerant includes patients who are chronically receiving opioid analgesic on a daily basis. The FDA identifies tolerance as receiving at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer."

PAIN-6

- Subsequent Pain Management page was extensively revised.

PAIN-7

- Ongoing care
  - 1st bullet was revised: "Convert from parenteral to oral/transdermal ~~medications~~ *opioids* (if feasible) including extended-release or long-acting agent with rescue doses (Conversion details, See PAIN-E)"
  - 2nd bullet was revised: "~~Routine follow-up~~ *Have regular follow-up schedule to monitor pain therapy outcomes"*
  - 5th bullet was revised: "Ensure ~~adequate access to prescribed medications, especially~~ *continuity of care* during transition between sites of care"
  - 1st sub-bullet under "Ensure continuity of care during transition between sites of care" was revised: "Collaborate with patient's pharmacist *and insurance company if needed"*
  - 6th bullet was revised: "Address system barriers, ~~including assistance from~~ *and recruit assistance from* social services as needed"

PAIN-B

- Procedure-Related Pain and Anxiety
  - 1st bullet under "Anxiolytics" was revised: "Anxiolytics should be given preemptively when feasible. *Examples include midazolam if experienced with its administration and provided onsite, or oral lorazepam or alprazolam. Oral 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."*

PAIN-C (1 of 3)

- Pain experience
  - 1st sub-bullet under "Intensity" was revised: "Last 24 hours *worst and least pain and pain now"*

PAIN-C (2 of 3)

- Risk factors for abberant use or diversion of pain medication
  - 1st sub-bullet was revised: "Patient, environmental, and social factors as identified by a detailed patient evaluation and/or screening tools at initiation of care (eg, SOAPP-R, ORT) and monitoring of ongoing analgesic use (eg, COMM). *(Specific screening tools have not been validated in the setting of cancer care).* ~~See PAIN-E (2 of 12)~~ *See PAIN-E (6 of 13)"*
  - Reference "5" was added: "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."
- 3rd bullet was revised: "*Clinical assessment,* physical examination, and *laboratory and imaging studies to evaluate for disease progression"*
- A bullet was removed: "Laboratory and imaging studies to evaluate for disease progression"

PAIN-D

- Title was revised: "~~Interventions For Cancer~~ *Management Strategies For Specific Cancer Pain* Syndromes"
- 1st statement was revised: "~~In general~~, *Moderate to severe* cancer pain is treated with opioids as indicated ~~on~~ (PAIN-3); 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 (See PAIN-J)"*

PAIN-D continued

- Bone pain without oncologic emergency
  - 1st bullet was revised: "NSAIDs ~~and titrate analgesic to effect~~, *acetaminophen, or steroids* See Non-Opioid Analgesic (Nonsteroidal Anti-Inflammatory Drugs [NSAIDs] and Acetaminophen) Prescribing (PAIN-K)"
  - 2nd bullet was revised: "Consider ~~trial of~~ bone-modifying agents (eg, bisphosphonates, denosumab)"
- 2nd bullet under local pain was added: "Assess for impending fracture with plain radiographs."
- Bowel Obstruction
  - 1st bullet was revised: "Evaluate etiology of bowel obstruction. If resulting from cancer, consider *surgical intervention.* ~~palliative surgery~~, ~~radiation, and/or chemotherapy for symptomatic bowel obstruction~~."
  - 2nd bullet was added: "For medical management of partial bowel obstruction consider corticosteroids and/or metoclopramide."
- Last bullet was revised: "For severe refractory pain in the imminently dying, *consider palliative sedation* (see NCCN Guidelines for Palliative Care)."
- A reference was removed: "Clark K, Lam L, Currow D. Reducing gastric secretions--a role for histamine 2 antagonists or proton pump inhibitors in malignant bowel obstruction? Support Care Cancer. 2009;17:1463-1468."

PAIN-E (1 of 13)

- General Principles
  - 2nd bullet was added: "Consider documentation of opioid and controlled substance agreement."
  - 6th bullet was revised: "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. Consider pain or palliative care consult if pain is poorly controlled despite opioid dose titration."
  - 9th bullet was revised: "Consider opioid rotation if pain is inadequately controlled ~~despite~~ *and* ~~adequate~~ *further* dose titration *is limited by adverse effects* ~~or there are persistent adverse effects from currenttherapy~~. Other indications for switching to a different opioid include: Other indications for switching to a different opioid include: out-of-pocket costs, limitations based upon insurance formularies, or change in a patient's condition (eg, dysphagia, NPO status, initiation of tube feeding, renal and/or hepatic function). Consider referral to palliative medicine or pain specialist."
  - 12th bullet was added: "For opioid dose reduction, See (Pain-E 5 of 13)."

PAIN-E (1 of 13) continued

  - 14th bullet was revised: "Monitor for aberrant drug-taking behaviors or evidence of diversion. May include patient survey tool (eg, COMM). See PAIN E (3 of 13). *Educate the patients and caregivers about safe use, storage, and disposal of opioids.*"
  - 15th bullet was revised: "~~Be mindful of~~ *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"
  - A bullet was removed: "If opioid dose reduction is desired or indicated consider opioid dose reduction by 50% to 75% with subsequent reevaluation and further dose adjustment."
  - A bullet was removed: "If patient is experiencing unmanageable adverse effects and 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."

PAIN-E (2 of 13)

- Opioids And Risk Evaluation And Mitigation Strategy (REMS)
  - 1st bullet was revised: "Opioids are the principal analgesics for moderate to severe pain, yet opioids pose risks to patients and society. In ~~2013~~ *2014* there were ~~43,982~~ *47,055* drug-poisoning deaths in the United States, including ~~16,235~~ *28,647* drug-poisoning deaths involving opioid analgesics. ~~The opioid analgesic overdose deaths have plateaued, decreasing between 2011 and 2013; however,~~ Drug poisoning still remains the number one cause of injury-related deaths. 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 Morbidity and Mortality Weekly Report, Increases in Drug and Opioid-Involved Overdose Deaths—United States, 2010-2015. *https://www.cdc.gov/mmwr/volumes/65/wr/pdfs/mm655051e1.pdf*"
  - 2nd bullet was revised: "Responding to the "public health crisis of addiction, misuse, abuse, overdose, and death," the FDA ~~is in the process of~~ has establish*ed* 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."
  - 5th bullet was revised: " "Make use of state PDMPs if available. *The National Association of State Controlled Substances Authorities (http://www.nascsa.org/index.htm) maintains a database of state PDMP contacts."*
  - A reference was removed: "Hedegaard H, Chen LH, Warner M - Drug-poisoning deaths involving heroin: United States, 2000-2013 - NCHS Data Brief. 2015 Mar http://www.cdc.gov/nchs/products/databriefs/db190.htm"

PAIN-E (4 of 13)

- Principles of Maintenance Opioid Therapy
  - 6th bullet was revised: "Allow rescue doses of short-acting opioids of 10% to 20% of the 24-hour total of long-acting or regularly scheduled oral opioid dose up to every 1 hour as needed. ~~Ongoing need for repeated rescue doses may indicate a need for adjustment of regularly scheduled opioid dose~~."
  - A bullet was removed: "Taper opioids and other treatments when no longer needed."

PAIN-E (5 of 13)

- "Principles of Opioid Dose Reduction" is a new page to the guideline.

PAIN-E (6 of 13)

- Strategies to Maintain Patient Safety and Minimize the Risk of Opioid Misuse and Abuse During Chronic Opioid Use
  - 1st bullet was revised: "~~Be mindful of~~ *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"
  - 2nd bullet was revised: "Risk assessment prior to *and during* treatment is recommended, ~~using assessment tools with adequate predictive validity and reliability~~ *although current assessment tools have not been validated in the setting of cancer care and clinical judgment should be exercised"*
  - 4th sub-bullet was added: "Comprehensive psychological evaluation can be helpful in assessing risk for substance use disorders."
  - 3rd bullet was revised: "Educati~~on~~*e* regarding the potential risks and benefits of opioid therapy; *educate regarding not sharing opioids with family members or friends*."
- Support for high-risk patients
  - 1st bullet was added: "Consider referral to multidisciplinary team including an addiction specialist."
  - 1st sub-bullet was revised: "Ensure education of caregivers in the proper indications and usage of naloxone. *https://www.samhsa.gov/capt/tools-learning-resources/opioid-overdose-prevention-toolkit"*
  - 4th sub-bullet was revised: "Pill counts may be used at outpatient visits *or by home health/hospice to assist in correct use of medication* ~~and verify the information documented in the pain medication diary~~."
  - 7th bullet was added: "Consider utilizing programmable, electronic medication dispensers."
  - 8th bullet was added: "Consider earlier referral to interventional pain specialist to maximize non-opioid options for pain control."
  - A bullet was removed: "In high-risk situations, consider the following steps to facilitate close monitoring"
- Educate regarding safe manipulation, storage, and disposal of controlled substances
  - A bullet was removed: "Educate regarding not sharing opioids with family members or friends."

PAIN-E (7 of 13)

- Opioid Agonists
  - Fentanyl
    - ◊ Parental dose was added: "0.1 mg"
  - Tramadol
    - ◊ Parental dose was added: "100 mg"
    - ◊ Oral dose was added: "300 mg"
    - ◊ Factor (IV to PO) was added: "3"
    - ◊ Footnote "10" was added: "The manufacturer recommends a maximum single dose of tramadol not to exceed 100 mg, with a maximum daily dose of 400 mg for IR formulations (300 mg/d in older adults, 200 mg/d for renal impairment) or 300 mg/d for ER formulations."
  - Tapentadol
    - ◊ Oral dose was added: "75–100 mg."
    - ◊ Footnote "11" was added: "The maximum daily dose for tapentadol ER is 500 mg, or 600 mg IR (lower doses are recommended for moderate hepatic impairment, avoid with severe impairment)."

PAIN-E (8 of 13)

- Mixed-mechanism drugs
  - 3rd bullet was revised: "Tramadol and tapentadol should be used with caution or avoided in patients taking other serotonergic or MAOI-like medications (eg, *tricyclic antidepressants* [TCAs], *selective serotonin reuptake inhibitors* [SSRIs], *monoamine oxidase inhibitors* [MAOIs]) due to risk of serotonin syndrome."
- Partial agonists
  - 1st statement was revised: "Transdermal buprenorphine, a partial mu-agonist, has been approved for chronic pain. ~~Although experience with this drug in the management of cancer pain is limited, anecdotal reports, a few small prospective uncontrolled studies, and at least one randomized trial support its use in cancer-related pain.~~ *Buprenorphine patch at lowest dose (5 mcg/h) may be used in opioid-naive patients requiring initiation of long-acting opioid therapy.* Because buprenorphine is a partial mu-receptor agonist, it exhibits a ceiling to analgesic efficacy and may precipitate withdrawal symptoms if administered to individuals currently taking a high-dose opioid. FDA guidelines recommend limiting dose to 20 mcg per hour due to concern for QT prolongation. Conversion to buprenorphine from other opioids may be complex; consider a pain specialty consultation."
- Non-opioid analgesic
  - 2nd bullet was added: "Intravenous lidocaine infusion may be a useful therapy for refractory pain."
  - Reference "18" was added: "Ferrini R, Paice JA. How to initiate and monitor infusional lidocaine for severe and/or neuropathic pain. J Support Oncol 2004;2:90-94."

PAIN E (9 of 13)
- Convert or rotate from one opioid to another opioid
  - 3rd sentence was revised: "If pain was effectively controlled, *and the patient is opioid tolerant*, reduce the dose by 25%–50% to allow for incomplete cross-tolerance between different opioids. During the first 24 hours, titrate liberally and rapidly to analgesic effect."

PAIN E (10 of 13)
- Special Notes Regarding Transdermal Fentanyl
  - 7th bullet was revised: "The fentanyl patch analgesic duration is usually 72 hours, but ~~some~~ patients *experiencing end-of-dose failure may* require fentanyl patch replacement every 48 hours."

PAIN E (12 of 13)
- Special notes regarding oral methadone
  - 1st bullet was revised by moving 2nd sentence from second bullet: "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."
  - 9th bullet was revised: "American Pain Society (APS) Guidelines for methadone safety recommend a methadone starting dose that is ~~75% to 90% less than the calculated equianalgesic dose,~~ no more than 30 to 45 mg/d. See APS guidelines: (http://www.jpain.org/article/S1526-5900(14)00522-7/fulltext)"

PAIN E (13 of 13)
- Table 2. Dose Conversion Ratios for Total 24-hour Oral Morphine to Oral Methadone
  - Statement was revised: "Note: If the total daily dose equivalent of morphine is greater than ~~800~~ *400* mg, ~~a higher dose ratio is necessary and dose titration is recommended.~~ a pain or palliative care specialist should be consulted."
  - Reference "25" was added: "Ripamonti C, Groff L, Brunelli C et al. Switching from morphine to oral methadone in treating cancer pain: what is the equianalgesic dose ratio? J Clin Oncol 1998;16(10):3216-21."

PAIN-F (1 of 3)
- Constipation
  - 1st bullet under preventive measures was added: "Educate patient and family on the need for bowel movements despite minimal intake of food."
  - 2nd bullet under preventive measures was added: "Set goals of treatment and explain to patient and family (eg, soft stool, ease of defecation, bowel movement every 2 days or less)."

PAIN-F (1 of 3) continued
- If constipation persists
  - 7th bullet was revised: "When response to laxative therapy has not been sufficient for opioid-induced constipation ~~in patients with advanced illness~~, consider oral methylnaltrexone or naloxegol (FDA approved for opioid-induced constipation). Other second-line agents include injectable methylnaltrexone, 0.15 mg/kg subcutaneously, maximum one dose per day, lubiprostone and linaclotide (FDA approved for idiopathic constipation). These agents will not be of benefit and should not be used in patients with known or suspected mechanical bowel obstruction."

PAIN-F (2 of 3)
- If nausea develops
  - 3rd bullet was revised: "As an alternative, serotonin antagonists should be considered due to lower risk of CNS adverse effects (eg, ondansetron, 4–8 mg PO 3 times daily oral tablet or orally disintegrating tablet; granisetron, 2 mg PO daily). Use with caution as constipation is an adverse effect. *Also consider alternative agents such as scopolamine, dronabinol, or olanzapine for nausea management.*"
- Delirium
  - 4th bullet was revised: "Consider initial titration with haloperidol, 0.5–2 mg PO or IV every 4–6 hours; or olanzapine, 2.5–5 mg PO or sublingual every 6–8 hours; or risperidone, 0.25–0.5 mg 1–2 times per day. *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."

PAIN-G (2 of 2)
- TCAs (eg, amitriptyline, imipramine, nortriptyline, desipramine)
  - 1st bullet was added: "TCAs should be used with caution in patients with conduction abnormalities or ischemic heart disease"
  - 2nd bullet was revised: "Start with low dose and increase every ~~3–5 days~~ *5–7 days* if tolerated (eg, nortriptyline and desipramine starting dose 10–25 mg nightly 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."
- Anticonvulsants examples
  - 2nd bullet was revised: "Pregabalin- Starting dose ~~50~~ 25 mg *nightly, with increasing dose frequency, to* 2-3 times a day, *and increasing dose increments of 50%–100% every 3 days* ~~three times a day~~ *to* a maximum daily dose of ~~, increase to 100~~ 600 mg. ~~times a day.~~ Slower titration for the elderly or medically frail. Dose adjustment required for those with renal insufficiency. Pregabalin is more efficiently absorbed through the GI tract than gabapentin. ~~May increase further to a maximum dose of 600 mg in divided doses 2–3 times a day~~."

PAIN-H

- **Skills training**
  - 3rd sub-bullet was revised: "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*."

PAIN-I (1 of 2)

- To assess for patient and family/caregiver educational needs regarding pain treatment:
  - 1st bullet was added: "Assess for literacy to ensure understanding of education."
  - 3rd bullet was revised: "Assess *patient and family expectations for* ~~existing knowledge of~~ pain *management*, *knowledge of pain*, and pain treatment ~~to aid in developing appropriate patient and family/caregiver education plan~~."
  - 4th bullet was added: "Assess for meaning and understanding of the use and risks of opioid analgesics."
  - A bullet was removed: "Assess for literacy to ensure understanding of education."
- Messages to be conveyed to patient and family/caregiver regarding opioid analgesics
  - 4th tertiary bullet: "For potential risk factors for misuse/abuse, see (PAIN-E, 2 of 13*) and see (PAIN-E, 5 of 13), for information on naloxone*."

PAIN-J

- Cognitive modalities
  - 10th bullet was revised: "Cognitive behavioral therapy, *cognitive restructuring*"
  - 11th bullet was added: "Behavioral activation"

PAIN-K (1 of 2)

- **NSAIDS**
  - 1st sub-bullet was revised: "The FDA warns that ~~long-term use of~~ NSAID *use* increases the risk of heart attack or stroke."
- Compounds that do not inhibit platelet aggregation
  - A bullet was removed: "Choline + magnesium salicylate combinations, 1.5–4.5 g/d in three divided doses"

PAIN-K (2 of 2)

- **Cardiac toxicities**
  - 1st bullet was revised: "Patients at high risk: history of cardiovascular disease or at risk for cardiovascular disease or complications. ~~NSAIDs taken with prescribed anticoagulants, such as warfarin or heparin, may significantly increase the risk of bleeding complications.~~*"*
  - 2nd bullet was added: "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."
  - 3rd bullet was revised: "Treatment: discontinue NSAID if congestive heart failure or hypertension develops or worsens. ~~Naproxen and ibuprofen are preferred NSAIDs for individuals at high risk for cardiac toxicities.~~ *All NSAIDs have been associated with cardiac toxicities."*
- "Hematologic toxicities" is a new category.
  - 1st bullet was moved from "further NSAID considerations": "NSAIDs taken with prescribed anticoagulants, such as warfarin or heparin, may significantly increase the risk of bleeding complications."
  - 2nd bullet was moved from "further NSAID considerations": "Avoid the use of oral NSAIDs in the setting of prophylactic or therapeutic anticoagulation. Topical NSAIDs such as diclofenac gel or patch may be useful in this population."

PAIN-L

- **Provide psycho-education**
  - A bullet was removed: "Brain-reward pathway and neurobiology of addictions/medication misuse"

MS-1

- The discussion section has been updated to reflect the changes to the algorithm.

Pain Definition

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

Principles of Cancer Pain Management

General

- There is increasing evidence in oncology that survival is linked to symptom reporting and control and that pain management contributes to broad quality-of-life improvement. To maximize patient outcomes, pain management is an essential part of oncologic management.
- Analgesic therapy is often done in conjunction with management of multiple symptoms or symptom clusters. Treatment must consider the interaction of complex pharmacologic therapies that a patient is prescribed and the risk for analgesic misuse.
- A multidisciplinary team is optimal.
- Psychosocial support must be available including both emotional and informational support and coping skills training. (See PAIN-H)
- Specific educational material, including information about the role of opioids in cancer pain management, must be provided to the patient and family/caregiver in an understandable language and format. (See PAIN-I)
- Consider the multidimensional impact of "suffering" on patients and their families and address these concerns in a culturally respectful manner.

Assessment

- All patients must be screened for pain at each contact. (See PAIN-2)
- Pain intensity must be routinely quantified and documented, and quality must be characterized by the patient (whenever possible based on patient communication capacity). Also include patient reporting of breakthrough pain, treatments used and their impact on pain, patient reporting of adequate comfort, patient reporting of satisfaction with pain relief, provider assessment of impact on function, and any special issues for the patient relevant to pain treatment. If necessary, get additional information from family/caregiver regarding pain and impact on function.
- Comprehensive pain assessment must be performed if new or worsening pain is present and regularly performed for persisting pain. (See PAIN-C)
- Evaluate patient for risk factors for opioid abuse/misuse/diversion.

Management/Intervention

- Goals of pain management are highlighted by the "5 A's" of pain management outcomes:[b]
  - 1. Analgesia (optimize analgesia)
  - 2. Activites (optimize activities of daily living)
  - 3. Adverse effects (minimize adverse effects) (see PAIN-E)
  - 4. Aberrant drug taking (avoid aberrant drug taking) (see PAIN-F)
  - 5. Affect (relationship between pain and mood)
- Comprehensive pain management (addressing the biopsychosocial elements of pain using pharmacologic and non-pharmacologic modalities) is needed as most patients have multiple pathophysiologies and multiple symptoms.
- Prevention of expected analgesic side effects, especially constipation in the setting of opioid use, is key to effective pain treatment.
- Optimize patient and family education (See PAIN-I) and physical and cognitive integrative interventions (See PAIN-H and PAIN-J).
- For acute, severe pain or pain crisis, consider hospital or inpatient hospice admission to achieve patient-specific pain goals.
- Persistent cancer pain often requires treatment with regularly scheduled analgesics, and supplemental doses of analgesics are often required to manage breakthrough pain.
- For chronic pain in cancer survivors, See NCCN Guidelines for Survivorship.

Reassessment

- Pain reassessment must be performed at specified intervals to ensure that analgesic therapy is providing maximum benefit with minimal adverse effects, and that the treatment plan is appropriately followed.

[a]Merskey H, Bugduk N. Classification of Chronic Pain. Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms. 2nd ed. Seattle, WA: IASP Press; 1994.
[b]Passik SD, Kirsh KL, Whitcomb L et al. A new tool to assess and document pain outcomes in chronic pain patients receiving opioid therapy. Clin Ther 2004; 26(4):552-61. http://www.ncbi.nlm.nih.gov/pubmed/15189752.

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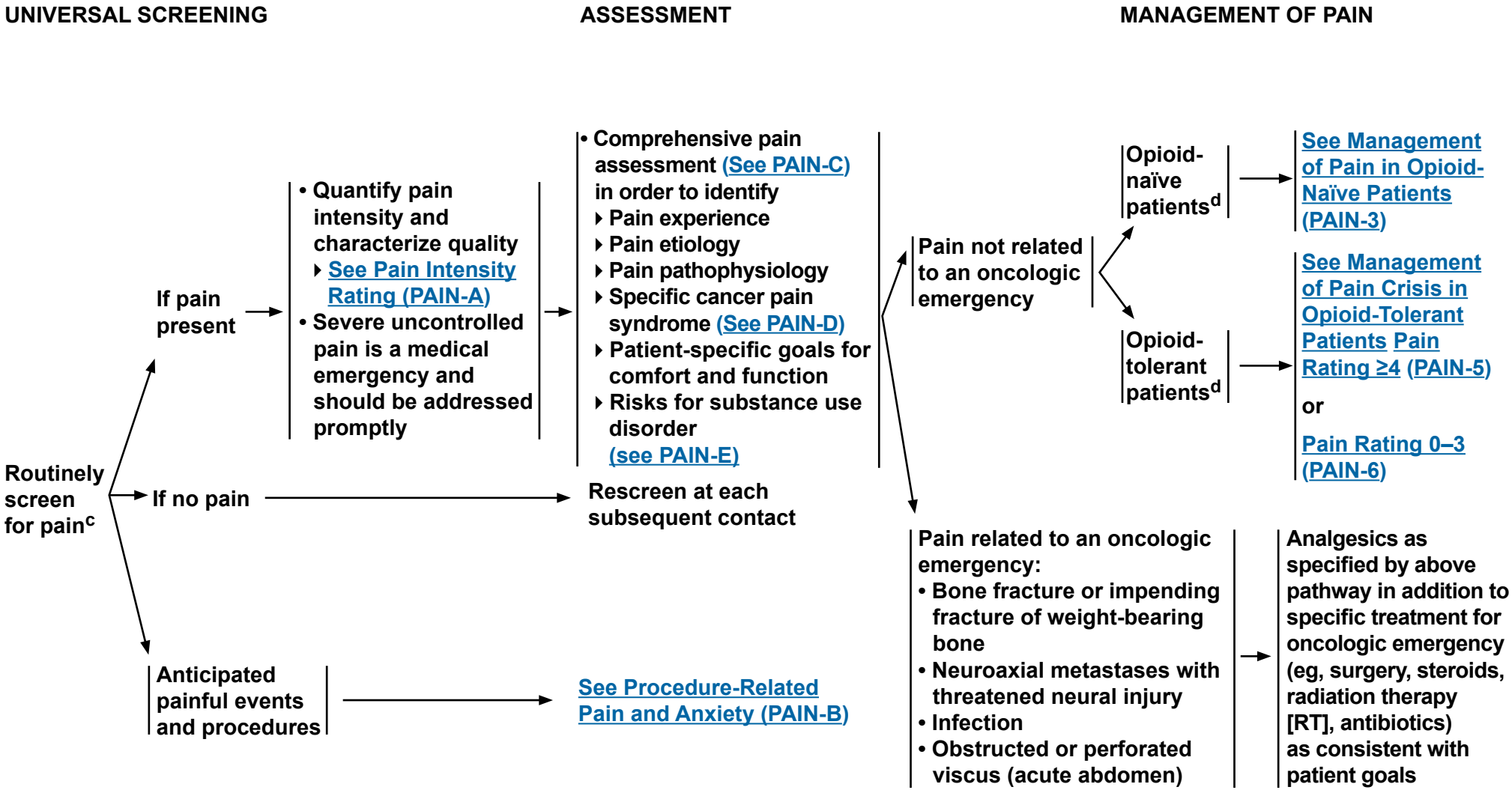
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

See Universal Screening (PAIN-2)



[c]For chronic pain in cancer survivors, see NCCN Guidelines for Survivorship.

[d]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.

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PAIN INTENSITY
See Pain Intensity Rating (PAIN-A)

MANAGEMENT OF PAIN IN OPIOID-NAÏVE PATIENTS[d]

General Principles →

- Select the most appropriate medication based on the pain diagnosis (See PAIN-D), comorbid conditions, and potential drug interactions
- Analgesic regimen may include an opioid (See PAIN-E), acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs) (See PAIN-K), and/or adjuvant analgesics (See PAIN-G)
- Anticipate and treat analgesic adverse effects, including opioid-induced constipation (See PAIN-F)
- Provide psychosocial support (See PAIN-H)
- Provide patient and family/caregiver education (See PAIN-I)
- Optimize integrative interventions (See PAIN-J)

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

Moderate to Severe Pain ≥4 →

- For acute, severe pain or pain crisis, consider hospital or inpatient hospice admission to achieve patient-specific goals for comfort and function

AND

- See General Principles above

AND

- Start and rapidly titrate short-acting opioid, (see PAIN-4)

Mild Pain 1–3 →

- See General Principles above

AND

- First consider non-opioids and adjuvant therapies, then short-acting opioids for patients who require further intervention (See PAIN-E)

[d]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.

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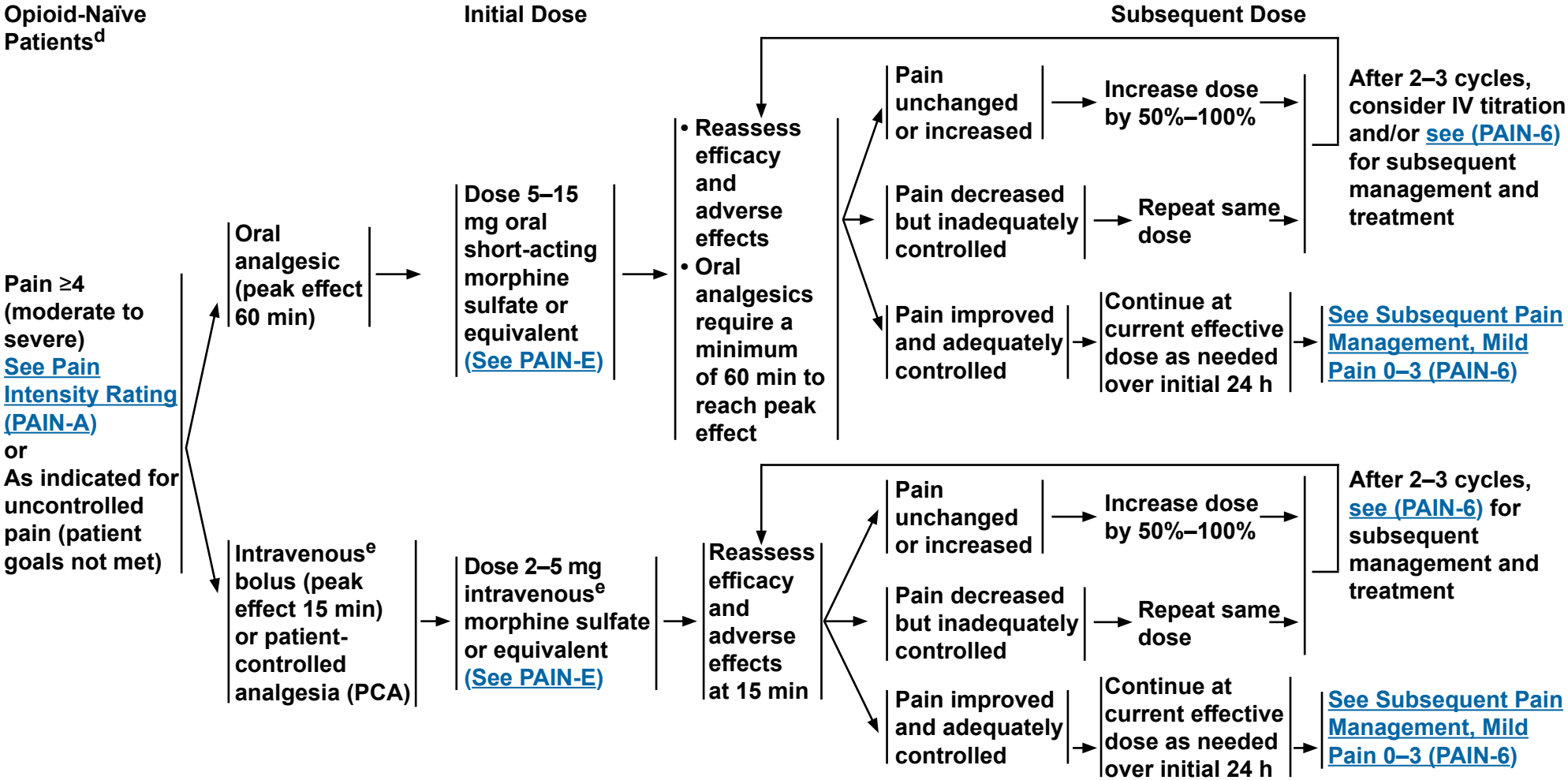
INITIATING SHORT-ACTING OPIOIDS IN OPIOID-NAÏVE PATIENTS[d]

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



[d]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.

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

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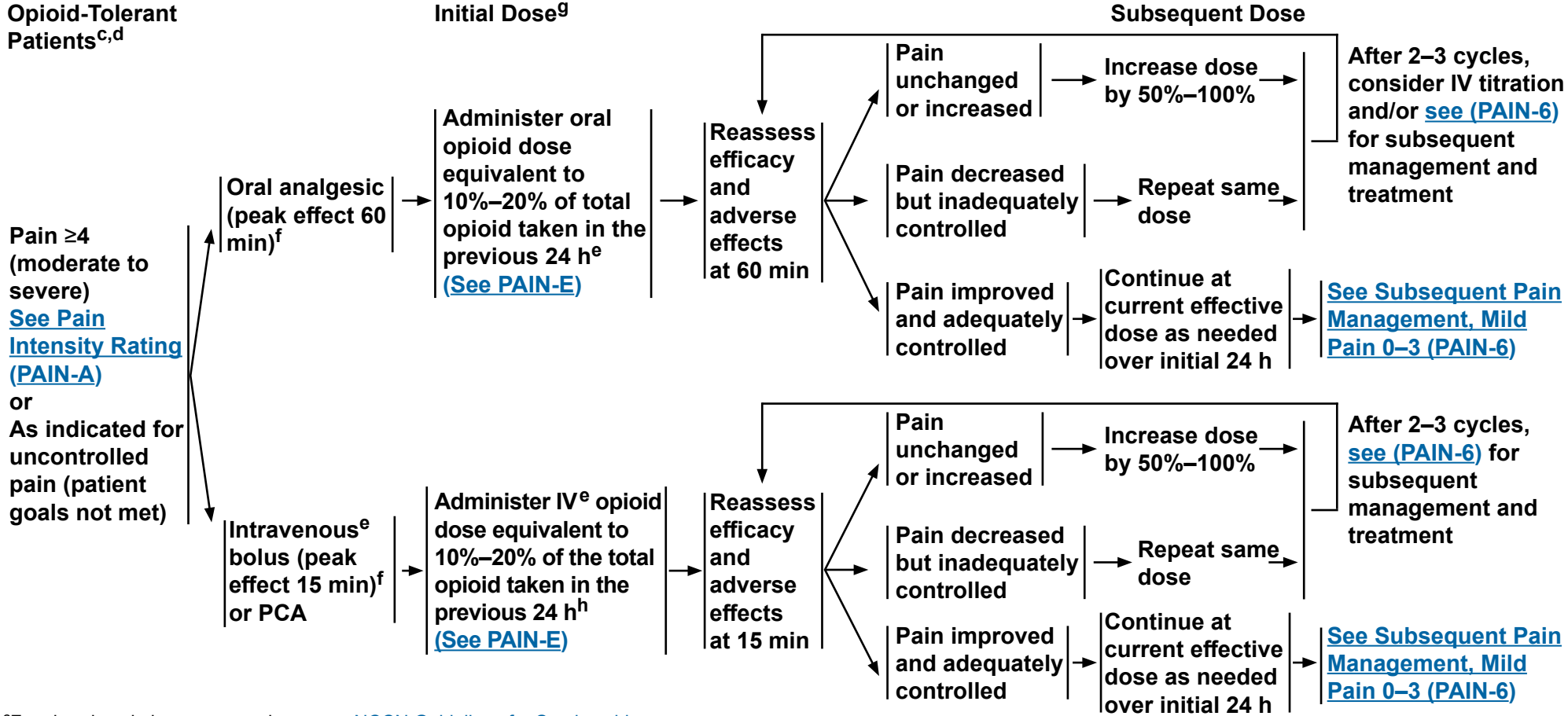
MANAGEMENT OF PAIN CRISIS IN OPIOID-TOLERANT PATIENTS[d]

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



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[e]Subcutaneous can be substituted for intravenous; however, peak effect subcutaneously is usually 30 min.
[f]Continuation of patient's previous opioid could be considered or upward titration to accomodate dose requirements could be warranted.
[g]Doses are supplemental to long-acting (chronic) opioid dose.
[h]Not including transmucosal fentanyl dose.

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PAIN INTENSITY See Pain Intensity Rating (PAIN-A)

SUBSEQUENT PAIN MANAGEMENT[d]

GOALS OF TREATMENT

General Principles

- For persistent pain, initiate regular schedule of opioid with rescue dose as needed
- Continue management of constipation (See PAIN-F) and other adverse effects
- Provide psychosocial support (See PAIN-H)
- Provide patient and family/caregiver education (See PAIN-I)
- Optimize integrative interventions (See PAIN-J)
- Consider adding/adjusting adjuvant analgesics (See PAIN-G)

Moderate to Severe Pain ≥4

- See General Principles above
  AND
- If pain is inadequately controlled reevaluate opioid titration (See PAIN-E)
- If pain is inadequately controlled reevaluate working diagnosis with a comprehensive pain assessment (See PAIN-C)
- Consider specific pain syndrome problems (See PAIN-D)
- Consider pain specialty consultation (See PAIN-L)
- Consider opioid rotation if dose limiting adverse effects are noted

Mild Pain 0–3

- See General Principles above
  AND
- Reassess and modify regimen to minimize adverse effects; taper opioids and other treatments when no longer needed (See PAIN-E and See PAIN-F)

Routinely reevaluate pain at each contact and as needed to meet patient-specific goals for comfort, function, and safety

Achieved → See Ongoing Care (PAIN-7)

Not achieved

- See Universal Screening and Assessment (PAIN-2)
- Consider pain management specialty consultation.
- Consider interventional strategies (PAIN-M) or other treatments
- Consider palliative care consultation (See NCCN Guidelines for Palliative Care)

[d]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.

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ONGOING CARE

- Convert from parenteral to oral/transdermal opioids (if feasible) including extended-release or long-acting agent with rescue doses (Conversion details, See PAIN-E)
  - Simplify analgesic regimen for improved patient compliance, if feasible.
- 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 abuse/diversion or cognitive dysfunction
- Provide written follow-up pain plan, including prescribed medications (See 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
- 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: (See 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
- Reevaluate patient-centered goals of care in the context of current disease and available therapies
- Maintain communication and coordinate care with pain specialist and relevant providers, especially during transition between sites of care

GOALS OF TREATMENT

Routinely reevaluate pain at each contact and as needed to meet patient-specific goals for comfort, function, and safety

Achieved → **Continue routine follow-up**

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

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PAIN INTENSITY RATING (1 of 2)

- **Pain intensity rating scales can be used as part of universal screening and comprehensive pain assessment. At minimum, patients should be asked about "current" pain, as well as "worst" pain, "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-C) for more details.**

Table 1: Numerical Rating Scale

Numerical rating scale:

- **Verbal: "What number describes your pain from 0 (no pain) to 10 (worst pain you can imagine)?"**
- **Written: "Circle the number that describes your pain."**

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

Categorical scale:

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

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

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

[1]Hicks CL, von Baeyer CL, Spafford P, et al. The Faces Pain Scale - Revised: Toward a common metric in pediatric pain measurement. Pain 2001;93:173-183.
[2]Ware LJ, Epps CD, Herr K, Packard A. Evaluation of the Revised Faces Pain Scale, Verbal Descriptor Scale, Numeric Rating Scale, and Iowa Pain Thermometer in older minority adults. Pain Manag Nurs 2006;7:117-125.

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Continued on next page
PAIN-A 2 of 2

PAIN INTENSITY RATING (2 of 2)

Pain assessment in the nonverbal patient[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 (See NCCN Guidelines for Distress Management). Potential causes and the context of the behavior must be considered when making pain treatment decisions.**
- **A multi-faceted approach is recommended that combines direct observation, family/caregiver input, and evaluation of response to pain medicines or nonpharmacologic interventions.**
- **For patients with advanced dementia, a comprehensive review of currently published tools, including those available at http://prc.coh.org/pain_assessment.asp, is recommended. These tools are in varying stages of development and validation and include, but are not limited to:**
  - **The Assessment of Discomfort in Dementia (ADD) protocol: http://www.ncbi.nlm.nih.gov/pubmed/11893998[4]**
  - **Checklist of Nonverbal Pain Indicators (CNPI): http://www.ncbi.nlm.nih.gov/pubmed/11706452[5]**
  - **The Pain Assessment in Advanced Dementia (PAINAD) scale: http://www.ncbi.nlm.nih.gov/pubmed/12544460[6]**
- **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 and intensive care: http://www.ncbi.nlm.nih.gov/pubmed/11801819[7]**
  - **Critical-Care Pain Observation Tool (CPOT) tested in adults and intensive care: http://www.ncbi.nlm.nih.gov/pubmed/17575489[8]**
- **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.**

Cultural and linguistic assessment[9,10]

- **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]Kovach CR, Noonan PE, Griffie J, Muchka S, Weissman DE. The assessment of discomfort in dementia protocol. Pain Manag Nurs 2002;3:16-27.
[5]Feldt KS. Checklist of nonverbal pain indicators. Pain Manag Nurs 2000;1:13-21.
[6]Lane P, Kuntupis M, MacDonald S, et al. A pain assessment tool for people with advanced Alzheimer's and other progressive dementias. Home Healthc Nurse 2003;21:32-37.
[7]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.
[8]Gélinas C, Johnston C, et al. Pain assessment in the critically ill ventilated adult: validation of the Critical-Care Pain Observation Tool and physiologic indicators. Clin J Pain 2007;23:497-505.
[9]Al-Atiyyat HNM. Cultural diversity and cancer pain. Journal of Hospice & Palliative Nursing 2009;11:154-164.
[10]Ezenwa MO, Ameringer S, Ward SE, Serlin RC. Racial and ethnic disparities in pain management in the United States. J Nurs Scholarsh 2006;38:225-233.

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PROCEDURE-RELATED PAIN AND ANXIETY

- **Anticipate and offer analgesic (topical, local, and/or systemic) and anxiolytic therapy for procedures that are frequently accompanied by pain and/or anxiety. (See PAIN-E, 4 of 13 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 all of the analgesic techniques described below prior to the procedure is ideal as it allows the patient and family/caregiver the time they may need to assimilate all of the information, ask questions, and master the techniques while reducing anticipatory anxiety.**
- **Intervention may be multimodal and potentially include one or more of the following as appropriate.**
  - **Analgesics**
    - ◊ **Supplemental doses of analgesics should be given in anticipation of procedure-related pain.**
    - ◊ **If procedure or transportation precludes continuation of IV PCA, give the prescribed IV bolus dose 10 minutes before procedure/transport and consider administering a single subcutaneous 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 oral lorazepam or alprazolam. Oral 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.**
  - **Local anesthetics such as:**
    - ◊ **Topical local anesthetics creams (containing lidocaine, prilocaine, or tetracaine) applied to intact skin with sufficient time for effectiveness as per package insert.**
    - ◊ **Subcutaneous administration of lidocaine with a 27-gauge needle.**
  - **Administration of sedatives/analgesics/general anesthesia by trained personnel.**
  - **Integrative and nonpharmacologic interventions for relief of pain and/or anxiety (See PAIN-J).**

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COMPREHENSIVE PAIN ASSESSMENT

- Patient's self report of pain is the standard of care. If the patient is unable to verbally report pain, an alternative method to obtain pain rating and response should be utilized. (See PAIN-A 2 of 2).
- The goal of 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, the patient's clinical condition, and patient-centered goals of care.
- The etiology and pathophysiology of the pain should be investigated, including medical history (including psychosocial factors), physical exam, laboratory tests, and imaging studies.
  - Etiology factors may include direct involvement of cancer itself, cancer therapy (chemotherapy, RT, surgery) or procedures, and coincidental or noncancer pain (eg, arthritis).
  - Pathophysiology factors may include nociceptive, neuropathic, visceral, affective, behavioral, and cognitive components.
- Pain experience
  - Location, referral pattern, radiation of pain(s)
  - Intensity See Pain Intensity Rating (PAIN-A)
    - ◊ Last 24 hours worst and least pain and pain now
    - ◊ At rest and with movement
  - Interference with activities
    See Impact of Pain Measurement (PAIN-C 3 of 3)
    - ◊ General activity, mood, walking ability, work ability, relationship with others, sleep, appetite, and enjoyment of life
  - Timing: onset, duration, course, persistent, or intermittent
  - Description or quality
    - ◊ Aching, stabbing, throbbing, or pressure often associated with somatic pain in skin, muscle, and bone
    - ◊ Gnawing, cramping, aching, or sharp pain often associated with visceral pain in organs or viscera
    - ◊ Burning, tingling, shooting, or electric/shocking pain often associated with neuropathic pain caused by nerve damage
  - Aggravating and alleviating factors
  - Other current symptoms; symptom clusters
  - Current pain management plan, both pharmacologic and non-pharmacologic. If medications are used, determine:
    - ◊ What medication(s), prescription and/or over the counter?
    - ◊ Dose, route of administration, 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 see (PAIN-E 4 of 13).
- Prior pain therapies
  - ◊ Reason for use, length of use, response, reasons for discontinuing, and adverse effects encountered
- Special issues relating to pain
  - ◊ Meaning and consequences of pain for patient and family/caregiver
  - ◊ Patient and family/caregiver knowledge and beliefs surrounding pain and pain medications
  - ◊ Cultural beliefs toward pain, pain expression, and treatment
  - ◊ Spiritual, religious considerations, and existential suffering
  - ◊ Patient goals and expectations regarding pain management
  - ◊ Assess for use of integrative therapies (See PAIN-J)
  - ◊ Screen for potential adverse interactions or effects
  - ◊ Assess risk of opioid abuse/misuse/diversion

List of potential risk factors for misuse/abuse see (PAIN-E 2 of 13)

Continued on (PAIN-C 2 of 3)

Return to Universal Screening (PAIN-2)

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COMPREHENSIVE PAIN ASSESSMENT

- **Psychosocial Support** (See PAIN-H)
  - **Patient distress** (See NCCN Guidelines for Distress Management)
  - **Family and other support; assess impact and burden on caregiver and recommend resources as appropriate**
  - **Psychiatric history including current or prior patient, family/caregiver, or household history of substance abuse**
  - **Risk factors for aberrant use or diversion of pain medication** See PAIN-E (2 of 13)
    - ◊ **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]) and monitoring of ongoing analgesic use (eg, COMM).[4] (Specific screening tools have not been validated in the setting of cancer care).[5]** See PAIN-E (6 of 13)
  - **Risk factors for undertreatment of pain**
    - ◊ **Being a pediatric, geriatric, minority, or female patient; communication barriers; history of substance abuse; neuropathic pain; and cultural factors**
- **Medical history**
  - **Oncologic treatment including current and prior chemotherapy, hormonal therapy, radiation therapy, and surgery**
  - **Other significant illnesses, conditions**
  - **Pre-existing chronic pain**
- **Clinical assessment, physical examination, and laboratory and imaging studies to evaluate for disease progression**

[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]Meltzer EC, et al. Identifying prescription opioid use disorder in primary care: diagnostic characteristics of the current opioid misuse measure (COMM). PAIN 2011; 152(2):397-402.
[5]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.

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Return to Universal Screening (PAIN-2)

IMPACT OF PAIN MEASUREMENT[6,7]

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**

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

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MANAGEMENT STRATEGIES FOR SPECIFIC CANCER PAIN SYNDROMES

Moderate to severe cancer pain is treated with opioids as indicated (PAIN-3); 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. (See PAIN-J)

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

- **Bone pain without oncologic emergency:**
  - **NSAIDs, acetaminophen, or steroids**
    See Non-Opioid Analgesic (Nonsteroidal Anti-Inflammatory Drugs [NSAIDs] and Acetaminophen) Prescribing (PAIN-K)
  - **Consider bone-modifying agents (eg, bisphosphonates, denosumab)**
  - **Diffuse bone pain: Consider hormonal therapy or chemotherapy, corticosteroids, and/or systemic administration of radioisotopes**
  - **Local bone pain:**
    - ◊ **Consider local RT, nerve block (eg, rib pain), vertebral augmentation, or radiofrequency ablation.**
    - ◊ **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 for interventional consultation. See Interventional Strategies (PAIN-M)**

- **Bowel obstruction**
  - **Evaluate etiology of bowel obstruction. If resulting from cancer, consider surgical intervention.**
  - **For medical management of partial bowel obstruction consider corticosteroids and/or metoclopramide.**
  - **Palliative management of bowel obstruction could include bowel rest, nasogastric suction (or percutaneous gastrostomy drainage), corticosteroids, H2 blockers, anticholinergics (ie, scopolamine, hyoscyamine, glycopyrrolate), and/or octreotide**

- **Nerve pain**
  - **Nerve compression or inflammation:**
    - ◊ **Trial of corticosteroids**
  - **Neuropathic pain:**
    - ◊ **Trial of antidepressant, see (PAIN-G)**
      and/or
    - ◊ **Trial of anticonvulsant, see (PAIN-G)**
      and/or
    - ◊ **Consider trial of topical agent, see (PAIN-G)**
    - ◊ **For refractory pain, consider referral to a pain specialist and/or the use of interventional strategies.**
      See Interventional Strategies (PAIN-M)

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

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

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OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY (1 of 13)

GENERAL PRINCIPLES

- Periodically review prescription drug monitoring program (PDMP) databases.
- Consider documentation of opioid and controlled substance agreement.
- The appropriate opioid dose is the lowest dose that relieves the patient's pain and maximizes his or her function throughout the dosing interval without causing unmanageable adverse effects.
- Titrate with caution in patients with risk factors such as decreased renal/hepatic function, chronic lung disease, upper airway compromise, sleep apnea, and poor performance status.
- Generally, oral route is most common; however, other routes (ie, IV, subcutaneous, rectal, transdermal, transmucosal) can be considered as indicated to maximize patient comfort. For intrathecal route administration, See (PAIN-M).
- Calculate dosage increase based upon total opioid dose (around the clock/scheduled and as needed) taken in the previous 24 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. Consider pain or palliative care consult if pain is poorly controlled despite opioid dose titration.
  See Management of Pain in Opioid-Tolerant Patients (PAIN-5) and (PAIN-6).
- According to FDA guidelines, when higher doses of analgesic are needed, switch from preparations of opioid combined with other medications [such as aspirin or acetaminophen] to a pure opioid preparation to provide adequate analgesic to relieve pain while avoiding the toxicities of the non-opioid component of the combination. See (PAIN-K).
- Steady state 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 upon insurance formularies, or change in a patient's condition (eg, dysphagia, NPO status, initiation of tube feeding, renal and/or hepatic function).
- Consider referral to palliative medicine or pain specialist.
- For breakthrough pain, See (PAIN-E 4 of 13).
- For opioid dose reduction, See (PAIN-E 5 of 13).
- Initial patient evaluation should include the routine assessment of risk factors for aberrant use of pain medications by detailed patient evaluation and/or the use of screening tools (eg, SOAPP-R, ORT).
- Monitor for aberrant drug-taking behaviors or evidence of diversion. May include patient survey tool (eg, COMM). See PAIN E (3 of 13). Educate the patients and caregivers about safe use, storage, and disposal of opioids.
- 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

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OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY (2 of 13)

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 2014 there were 47,055 drug-poisoning deaths in the United States, including 28,647 drug-poisoning deaths involving opioid analgesics. 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 Morbidity and Mortality Weekly Report, Increases in Drug and Opioid-Involved Overdose Deaths—United States, 2010-2015.
- **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/abuse/diversion.**
  - ◊ **Prescriber should educate each patient on safe use, storage, and disposal of opioid. (See PAIN-I)**
  - ◊ **Prescriber should routinely monitor patients for opioid misuse or abuse. Different screening tools have been described for this purpose but have yet to be evaluated in cancer-related pain.[2] If signs of aberrant opioid use are observed, consider limiting or restricting use accordingly to avoid risk of diversion.**
  - ◊ **Make use of state PDMPs if available. The National Association of State Controlled Substances Authorities (http://www.nascsa.org/index.htm) maintains a database of state PDMP contacts.**
- **REMS programs are currently in place for:**
  - **All transmucosal fentanyl products (registration is required in order to prescribe these agents) (http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM289730.pdf)**
  - **Long-acting, extended-release formulations of opioids (eg, hydrocodone ER, hydromorphone ER, morphine ER, oxycodone ER, oxymorphone ER, tapentadol ER) (http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf)**
  - **Methadone tablets and solutions that are indicated for use as analgesics**
  - **Fentanyl or buprenorphine-containing transdermal delivery systems**
  - **It is important for doctors to be aware of the range of opioid use patterns to detect any potential aberrant behaviors. (See Pain E 3 of 13)**
- **Potential risk factors for misuse/abuse include:**
  - **Patients with a history of prescription, illicit drug, or alcohol dependence/substance abuse**
  - **Patients who have a history of binge drinking or peers who binge drink**
  - **Patients who have a family history of substance abuse**
  - **Patients with a history of psychiatric disorder, including anxiety, depression, ADHD, PTSD, bipolar disorder, or schizophrenia**
  - **Patients who have a history of sexual abuse victimization may be at increased risk for prescribed medication misuse/abuse**
  - **Young age less than 45 years**
  - **Patients with a history of legal problems or incarceration**

[1]Dart RC, Surratt HL, Cicero TJ, et al. Trends in opioid analgesic abuse and mortality in the United States. N Engl J Med 2015 Jan;372(3):241-8, http://www.nejm.org/doi/full/10.1056/NEJMsa1406143#t=article.
[2]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 013;11:1023-1031.

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OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY (3 of 13)

Table 1 Glossary of Terms Related to Opioid Use[2]

Abuse	**A maladaptive pattern of a prescription opioid use leading to clinically significant impairment and/or distress**
Addiction	**The aberrant use of a substance characterized by** **• loss of control, craving** **• compulsive use and preoccupation** **• continued use despite harm**
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 drug-seeking behaviors that occur in the context of unrelieved pain. These behaviors subside when analgesia is achieved**
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)**

[2]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.
[3]Kwon JH, Tanco K, Hui D, et al. Chemical coping versus pseudoaddiction in patients with cancer pain. Palliat Support Care. 2014;12(5):413-417.

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OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY (4 of 13)

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 natural history.
- When possible, use the same opioid for short-acting and extended-release forms. When using methadone as a long-acting opioid, consider supplementing with doses of short-acting opioid.
- Increase dose of extended-release opioid if patient persistently needs doses of as-needed opioids or when dose of around-the-clock opioid fails to relieve pain at peak effect or at end of dose.
- Breakthrough pain (pain that fails to be controlled or “breaks through” a regimen of regularly scheduled opioid) may require additional doses of opioid for pain not relieved by regular schedule of long-acting (eg, extended-release) opioid. Breakthrough pain may be further evaluated into the following categories, which have direct impact on treatment:
  - Incident pain: pain associated with or incident to specific activities or events, potentially managed with short-acting opioid given in anticipation of those events (eg, physical therapy, exercise, or 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
- Allow rescue doses of short-acting opioids of 10% to 20% of the 24-hour total of long-acting or regularly scheduled oral opioid dose up to every 1 hour as needed.
- Consider rapidly acting transmucosal fentanyl (various formulations and delivery systems are available) in opioid-tolerant patients for brief episodes of incident pain not attributed to inadequate dosing of around-the-clock opioid.
  - Data do not support a specific transmucosal fentanyl dose equianalgesic to other opioids or between different transmucosal formulations. Always initiate transmucosal fentanyl with lowest dose in chosen formulation and titrate to effect. (See specific transmucosal prescribing information for appropriate dosing intervals.)
- Continue to monitor patients/family for abnormal patterns of opioid use that may suggest misuse or abuse. (See Pain E 6 of 13)

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OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY (5 of 13)

PRINCIPLES OF OPIOID DOSE REDUCTION

- **Consider opioid dose reduction by 10% to 20% when possible; situations that may warrant dose reduction include:**
  - **Patient never needs breakthrough analgesic**
  - **Completion of acute pain event**
  - **Improvement of pain control through use of non-opioid pain management therapies**
  - **Well-controlled pain in the setting of stable disease**
- **If patient is experiencing unmanageable adverse effects and 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 significant safety issues (eg, marked sedation due to sepsis), opioid dose reduction by 50% to 75% may be necessary.**
- **If pain is worsened with increasing dose, consider opioid hyperalgesia; opioid dose reduction or rotation with attention to other pain therapies may be indicated.**

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STRATEGIES TO MAINTAIN PATIENT SAFETY AND MINIMIZE THE RISK OF OPIOID MISUSE AND ABUSE DURING CHRONIC OPIOID USE (6 of 13)

- 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)
  - Comprehensive psychological evaluation can be helpful in assessing risk for substance use disorders.
- 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 and the addictive potential associated with prescription opioids.
- Support for high-risk patients who endorse one or more opioid misuse and abuse risk factors 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.
  - Consider referral to multidisciplinary team including an addiction specialist.
  - Consider encouraging naloxone availability for administration by caregivers as needed for patients taking opioids who are at high risk for respiratory depression and sedation.
    - ◊ Ensure education of caregivers in the proper indications and usage of naloxone. https://www.samhsa.gov/capt/tools-learning-resources/opioid-overdose-prevention-toolkit
  - 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.
  - Urine drug testing at baseline and during treatment should be considered to help document opioid analgesic adherence, detect illegal drug use, and identify opioid diversion.
  - Increase frequency of outpatient visits weekly, if possible, and/or reduce quantity of drug prescribed per prescription.
  - Consider utilizing programmable electronic medication dispensers.
  - Consider earlier referral to interventional pain specialist to maximize non-opioid options for pain control.
- Educate regarding safe manipulation, storage, and disposal of controlled substances. These interventions contribute to maintaining a safe community and minimize opioid misuse and abuse in the community.
  - 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: http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/EnsuringSafeUseofMedicine/SafeDisposalofMedicines/ucm186187.htm#Flush_List

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OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY (7 of 13)

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

Opioid Agonists	Parenteral Dose	Oral Dose	Factor (IV to PO)	Duration of Action[13]
Morphine[4,5]	10 mg	30 mg	3	3–4 h
Hydromorphone[4]	1.5 mg	7.5 mg	5	2–3 h
Fentanyl[6]	0.1 mg	–	–	–
Methadone[7,8]	–	–	–	–
Oxycodone	–	15–20 mg	–	3–5 h
Hydrocodone[9]	–	30–45 mg	–	3–5 h
Oxymorphone	1 mg	10 mg	10	3–6 h
Codeine[4,10]	–	200 mg	–	3–4 h
Tramadol[11]	100 mg	300 mg	3	–
Tapentadol[12]	–	75–100 mg	–	–

NOT RECOMMENDED

Meperidine[14]

Mixed agonist-antagonists[15] (pentazocine, nalbuphine, butorphanol)

See Miscellaneous Analgesics (PAIN-E 8 of 13)

[4]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.

[5]Conversion factor listed for chronic dosing.

[6]6n single-dose administration, 10 mg IV morphine is equivalent to approximately 100 mcg IV fentanyl but with chronic fentanyl administration, the ratio of 10 mg IV morphine is equivalent to approximately 250 mcg IV fentanyl. For transdermal fentanyl conversions, (See PAIN-E 10 of 13).

[7]Long half-life, 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 h.

[8]The oral conversion ratio of methadone varies. PRACTITIONERS ARE ADVISED TO CONSULT WITH A PAIN OR PALLIATIVE CARE SPECIALIST IF THEY ARE UNFAMILIAR WITH METHADONE PRESCRIBING. (See Special Notes Regarding Oral Methadone, PAIN-E 12 of 13).

[9]Equivalence data not 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 ASA or acetaminophen.

[10]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. Individuals with low CYP2D6 activity may receive no analgesic effect from codeine, but rapid metabolizers may experience toxicity from higher morphine production. Dosage must be monitored for safe limits as it may be available in combination with acetylsalicylic acid (ASA) or acetaminophen. Dose listed refers only to opioid portion.

[11]The manufacturer recommends a maximum single dose of tramadol not to exceed 100 mg, with a maximum daily dose of 400 mg for IR formulations (300 mg/d in older adults, 200 mg/d for renal impairment) or 300 mg/d for ER formulations.

[12]The maximum daily dose for tapentadol ER is 500 mg, or 600 mg IR (lower doses are recommended for moderate hepatic impairment, avoid with severe impairment).

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

[14]Not recommended for cancer pain management because of CNS toxic metabolite - normeperidine.

[15]Mixed agonists-antagonists have limited usefulness in cancer pain; however, they can be used to treat opioid-induced pruritis. They should NOT be used in combination with opioid agonist drugs. Converting from an agonist to an agonist-antagonist could precipitate a withdrawal crisis in the opioid-dependent patient.

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OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY (8 of 13)

MISCELLANEOUS ANALGESICS

Mixed-mechanism drugs:

- **Tramadol is a weak mu-opioid agonist with some norepinephrine and serotonin reuptake inhibition used for mild to moderate pain. A maximum daily dose of 400 mg (100 mg four times daily) is recommended for adults with normal hepatic and renal function, and lower daily doses are recommended for older adults (≥75 y) and those with hepatic and/or renal dysfunction, to reduce the risk of seizures. Even at a maximum dose of 100 mg four times a day, tramadol is less potent than other opioid analgesics such as morphine.**
- **Tapentadol[16] is a mu-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 the extended release) or 600 mg per day (if using the immediate release only) due to lack of published data regarding higher doses. Some comparative data suggest tapentadol may have a lower incidence of GI adverse effects than oxycodone.**
- **Tramadol and tapentadol should be used with caution or avoided in patients taking other serotonergic or MAOI-like medications (eg, tricyclic antidepressants [TCAs], selective serotonin reuptake inhibitors [SSRIs], monoamine oxidase inhibitors [MAOIs]) due to risk of serotonin syndrome.**

Partial agonists:

- **Transdermal buprenorphine,[17] a partial mu-agonist, has been approved for chronic pain. Buprenorphine patch at lowest dose (5 mcg/h) may be used in opioid-naive patients requiring initiation of long-acting opioid therapy. Because buprenorphine is a partial mu-receptor agonist, it exhibits a ceiling to analgesic efficacy and may precipitate withdrawal symptoms if administered to individuals currently taking a high-dose opioid. FDA guidelines recommend limiting dose to 20 mcg per hour due to concern for QT prolongation. Conversion to buprenorphine from other opioids may be complex; consider a pain specialty consultation.**

Non-opioid analgesic:

- **Ketamine[18] 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.**
- **Intravenous lidocaine infusion may be a useful therapy for refractory pain.[19]**

[16]Hartrick CT, Rodriguez Hernandez JR: Tapentadol for pain: a treatment evaluation. Expert Opin Pharmacother 2012;13:283-286.
[17]Pergolizzi JV Jr, Mercadante S, Echaburu AV, et al. Euromed Communications meeting. The role of transdermal buprenorphine in the treatment of cancer pain: an expert panel consensus. Curr Med Res Opin 2009;25:1517-1528.
[18]Bell RF, Eccleston C, Kalso EA. Ketamine as an adjuvant to opioids for cancer pain. Cochrane Database of Systematic Reviews 2012, Issue 11. Art. No.: CD003351. DOI: 10.1002/14651858.CD003351.pub2.
[19]Ferrini R, Paice JA. How to initiate and monitor infusional lidocaine for severe and/or neuropathic pain. J Support Oncol 2004;2:90-94.

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OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY (9 of 13)

CONVERT OR ROTATE FROM ONE OPIOID TO ANOTHER OPIOID

1. Determine the amount of current opioid(s) taken in a 24-hour period that effectively control pain.
2. Calculate the equianalgesic dose of the new opioid. See Table 1 PAIN-E (7 of 13).
3. If pain was effectively controlled, and the patient is opioid tolerant, reduce the dose by 25%–50% to allow for incomplete cross-tolerance between different opioids. During the first 24 hours, titrate liberally and rapidly to analgesic effect.
4. If previous dose was ineffective, may begin with 100% or 125% of equianalgesic dose.
5. Lastly, for oral opioids divide the total daily dose of new opioid needed by the number of doses per day to determine the individual dose (eg, 6 doses for regular PO morphine every 4 hours; 2 doses for extended-release morphine every 12 hours).
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 impact of impaired renal function (if present) on clearance of new opioid. See Table 1 on PAIN-E (7 of 13)

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/d)
   (Total amount of IV morphine this patient is taking is 192 mg/d)

2. From Table 1 on PAIN-E (7 of 13), calculate the equianalgesic dose of IV hydromorphone
   (10 mg IV morphine = 1.5 mg IV hydromorphone; therefore,
   192 mg/d IV morphine = 28.8 mg/d IV hydromorphone = 1.2 mg/h IV hydromorphone)

3. If patient was effectively controlled with IV morphine (192 mg/d), reduce the dose of hydromorphone by 25%–50%.
   (28.8 mg/d reduced by 25% = 21.6 mg/d IV hydromorphone = 0.9 mg/h IV hydromorphone)
   (28.8 mg/d reduced by 50% = 14.4 mg/d IV hydromorphone = 0.6 mg/h IV hydromorphone)

   If dose of IV morphine was ineffective in controlling pain, may begin with 100% of equianalgesic hydromorphone dose (28.8 mg/d IV hydromorphone = 1.2 mg/h IV hydromorphone) or increase that by 25% (36 mg/d IV hydromorphone = 1.5 mg/h IV hydromorphone)

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OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY (10 of 13)

CONVERT OR ROTATE FROM ANOTHER OPIOID TO TRANSDERMAL FENTANYL

1. **Determine the 24-h analgesic requirement of morphine.**
2. **For conversion from oral morphine to transdermal fentanyl, consider ratio of 200 mg/d oral morphine = 100 mcg/h fentanyl patch. See Table 1 PAIN-E (7 of 13) for converting other opioids to morphine equivalent with subsequent conversion to transdermal fentanyl.[20]**
3. **Clinical data are unavailable to recommend specific ratio to convert from fentanyl to oral morphine.**

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.

See next page for case examples

Special Notes Regarding Transdermal Fentanyl:

- **Pain should be relatively well-controlled on a short-acting opioid prior to initiating the fentanyl patch. Patches are NOT recommended for unstable pain requiring frequent dose changes. Use fentanyl patch only in patients tolerant to opioid therapy.**
- **Fever, topical application of heat, or extreme 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[21] is appropriate, (ie, the number of mcg of parenteral fentanyl per hour should be approximately equal to the number of mcg of transdermal fentanyl per hour). In some patients, additional dose titration of the fentanyl patch may be necessary.**
- **The fentanyl patch analgesic duration is usually 72 hours, but patients experiencing end-of-dose failure may require fentanyl patch replacement every 48 hours.**

[20]Breitbart W, Chandler S, Eagel B, et al. An alternative algorithm for dosing transdermal fentanyl for cancer-related pain. Oncology 2000;14:695-702.
[21]Kornick CA, Santiago-Palma J, Khojainova N, et al. A safe and effective method for converting patients from intravenous to transdermal fentanyl. Cancer 2001;92:3056-3061.

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OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY (11 of 13)

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

Case example of converting oral morphine to transdermal fentanyl patch

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

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

2. **Using the conversion ratio of 200 mg/d oral morphine = 100 mcg/h fentanyl patch; 60 mg/d oral morphine is approximately 30 mcg/h transdermal fentanyl patch. Round down 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 oral oxymorphone every 12 hours and needs to be converted to transdermal fentanyl patch.

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

2. **From Table 1 on PAIN-E (7 of 13), convert to the equianalgesic dose of oral morphine**
   (Based on Table 1, 10 mg oral oxymorphone = 30 mg oral morphine; therefore,
   20 mg/d oral oxymorphone x 3 = total daily dose oral morphine of 60 mg/d)

3. **Using the conversion of 2 mg/d oral morphine: 1 mcg/h transdermal fentanyl:**
   60 mg/d oral morphine is approximately 30 mcg/h transdermal fentanyl patch.
   Fentanyl patch is available in 12, 25, 50, 75, and 100 mcg/h; therefore, begin with the 25 mcg/h patch.

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OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY (12 of 13)

Special Notes Regarding Oral Methadone:

- **Due to the unique nature of methadone with a long and variable half-life (and variability within a patient over time and variability between patients), caution should be used and frequent and careful evaluation should be performed. 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.**
- **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 is commercially available in 5 mg and 10 mg tablets and 1 mg/mL, 2 mg/mL, and 10 mg/mL oral solution.**
- **Without a consultation with a pain or palliative care specialist, methadone may be titrated up every 5 to 7 days, usually by 5 mg/dose. If more rapid titration is desired, consult with pain or palliative care specialist.**
- **Methadone is typically given at a regular schedule with additional doses of a short-acting opioid given as needed.**
- **EKG should be considered prior to initiation of methadone and should always be performed prior to initiation of methadone in patients who have risk factors for increased QTc. Also, methadone should not be used with QTc > 500 and alternate opioids are recommended with QTc 450–500. Consider EKG when doses exceed 30–40 mg/d and again with dose of 100 mg/d. Obtain follow-up EKGs in patients with risk factors for prolonged QTc after initiation of methadone.[22] (http://www.jpain.org/article/S1526-5900(14)00522-7/fulltext)**
- **The conversion ratios in Table 2 (Pain-E 13 of 13) should NOT be used in converting from methadone to other opioids. Methadone conversion can be complex and must be individualized for each patient, and assistance from a practitioner familiar with opioid prescribing or a pain specialist is recommended.**
- **American Pain Society (APS) Guidelines for methadone safety recommend a methadone starting dose that is no more than 30 to 45 mg/d. See APS guidelines: (http://www.jpain.org/article/S1526-5900(14)00522-7/fulltext)**
- **It may be necessary to educate patients and families about analgesic utility of methadone. Some may only be familiar with methadone use for maintenance of addiction and be unaware of its utility as a potent opioid analgesic.**

See Convert from Oral Morphine to Oral Methadone (PAIN-E 13 of 13)

[22]Chou R, Cruciani RA, Fiellin DA, et al. Methadone safety: A clinical practice guideline from the American Pain Society and college on problems of drug dependence, in collaboration with the Heart Rhythm Society. J Pain. 2014;15(4):321-337.

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OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY (13 of 13)

CONVERT FROM ORAL MORPHINE TO ORAL METHADONE[23]

See Special Notes Regarding Oral Methadone (PAIN-E 12 of 13)

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

Table 2. Dose Conversion Ratios for Total 24-hour Oral Morphine to Oral Methadone[24,25,26]

ORAL MORPHINE	DOSE CONVERSION RATIO (total 24-hour oral morphine:oral methadone)
30–90 mg	4:1
91–300 mg	8:1
300–600 mg	10:1
600–800 mg	12:1
800–1000 mg	15:1
>1000	20:1

Note: If the total daily dose equivalent of morphine is greater than 400 mg, a pain or palliative care specialist should be consulted.

Case example of converting oral morphine to oral methadone

A patient is taking oral morphine at 30 mg every 4 h and needs to be converted to oral methadone

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

2. From Table 2 above, calculate equianalgesic dose of oral methadone
   (For 180 mg/d of oral morphine: oral methadone, the dose conversion ratio is 8:1; therefore, 180 mg/d morphine = 22.5 mg/d methadone)

3. Reduce the calculated equianalgesic dose of oral methadone by at least 50% to account for incomplete cross-tolerance, dosing ratio variability, and patient variability (for example, 22.5 mg/d oral methadone reduced by 50% = 11.25 mg/d oral methadone, which is equal to approximately 15 mg/d oral methadone)

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

[23]Manfredi PL, Houde RW. Prescribing methadone, a unique analgesic. J Support Oncol 2003;1:216-220.
[24]Ayonrinde OT, Bridge DT. The rediscovery of methadone for cancer pain management. Med J Aust 2000; 173(10):536-540. ©Copyright 2000 The Medical Journal of Australia-adapted with permission. The *Medical Journal of Australia* does not accept responsibility for any errors in adaptation.
[25]The suggested conversion ratios are general recommendations. Those with clinical expertise in prescribing methadone for management of pain in advanced cancer may use a different conversion.
[26]Ripamonti C, Groff L, Brunelli C et al. Switching from morphine to oral methadone in treating cancer pain: what is the equianalgesic dose ratio? J Clin Oncol 1998;16(10):3216-21.

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MANAGEMENT OF OPIOID ADVERSE EFFECTS (1 of 3)

Principles of Management of Opioid Adverse Effects

- Adverse effects to opioids are common, should be anticipated, and should be managed aggressively.
- Patient and family/caregiver education is essential for successful anticipation and management of pain and opioid adverse effects.
- Recognize that pain is rarely treated in isolation in cancer and adverse effects also may be from other treatments or cancer itself.
- Opioid adverse effects generally improve over time, except with constipation. Maximize non-opioid and nonpharmacologic interventions to limit opioid dose and treat adverse effects. If adverse effects persist, consider opioid rotation.
- Multisystem assessment is necessary.
- Information from patient and family/caregiver about adverse effects is essential for appropriate opioid dose adjustment and treatment of adverse effects.
- Chronic opioid therapy may depress HPA axis and cause hypogonadism in males[1] and females.

Constipation

- Preventive measures
  - Educate patient and family on the need for bowel movements despite minimal intake of food.
  - Set goals of treatment and explain to patient and family (eg, soft stool, ease of defecation, bowel movement every 2 days or less).
  - Patients taking daily opioids almost always require agents for management of constipation
  - Prophylactic medications
    - ◊ Stimulant laxative (eg, senna, 2 tablets every morning; maximum 8 tablets per day of senna)
    - ◊ Polyethylene glycol 17 gm = 1 heaping tablespoon in 8 oz water PO twice 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 may not provide benefit
  - Exercise, if feasible
- If constipation develops
  - Assess for cause and severity of constipation
  - 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 and hypercalcemia, and evaluate for impact of other medications potentially associated with constipation
  - Check for impaction
  - Consider adding another agent, such as magnesium hydroxide, 30–60 mL daily; bisacodyl, 2–3 tablets PO daily; 1 rectal suppository daily; lactulose, 30–60 mL daily; sorbitol, 30 mL every 2 hours x 3, then as needed; magnesium citrate, 8 oz PO daily; or polyethelene glycol (17 g/8 oz water PO two times a day)
  - Oral 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 are contraindicated in neutropenic or thrombocytopenic patients
  - When response to laxative therapy has not been sufficient for opioid-induced constipation, consider oral methylnaltrexone or naloxegol (FDA approved for opioid-induced constipation). Other second-line agents include injectable methylnaltrexone, 0.15 mg/kg subcutaneously, maximum one dose per day, lubiprostone and linaclotide (FDA approved for idiopathic constipation). These agents will not be of benefit and should not be used in patients with known or suspected mechanical bowel obstruction
  - For intractable chronic constipation, consider opioid rotation to fentanyl or methadone
  - Consider neuraxial analgesics, neuroablative techniques, or other interventions to decrease pain, alleviate constipation, and/or reduce opioid dose

[1]Rajagopal A, Vassilopoulou-Sellin R, Palmer JL, et al. Symptomatic hypogonadism in male survivors of cancer with chronic exposure to opioids. Cancer 200415:100(4):851-858.

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MANAGEMENT OF OPIOID ADVERSE EFFECTS (2 of 3)

Nausea

- Preventive measures
  - Ensure that patient is having bowel movements consistently.
  - For patients with a prior history of opioid-induced nausea, prophylactic treatment with antiemetic agents (see below) is highly recommended.
- If nausea develops
  - Assess for other causes of nausea (eg, central nervous system [CNS] pathology, chemotherapy, RT, hypercalcemia).
  - 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 frail, elderly patients.
  - As an alternative, serotonin antagonists should be considered due to lower risk of CNS adverse effects (eg, ondansetron, 4–8 mg PO 3 times daily oral tablet or orally disintegrating tablet; granisetron, 2 mg PO daily). Use with caution as constipation is an adverse effect. Also consider alternative agents such as scopolamine, dronabinol, or olanzapine for nausea management.
  - Consider orally disintegrating olanzapine, 2.5–5 mg PO daily, for patients with bowel obstruction. Olanzapine has lower risk of extrapyramidal reactions than typical antipsychotics such as haloperidol.
  - If nausea persists despite as-needed regimen, administer antiemetics around the clock for 1 week, then change as needed.
  - Dexamethasone can be considered.
- 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.

Pruritus

- If pruritus develops
  - Consider changing to another opioid if symptomatic management has failed.
  - Assess for other causes (eg, other medications)
  - If pruritus is associated with rash, hives, or shortness of breath, consider true allergy and reconsider selection of opioid therapy.
- If pruritus persists
  - Consider adding to analgesic regimen: small doses of mixed agonist-antagonist, nalbuphine, 0.5–1 mg IV every 6 h as needed.
  - Consider continuous infusion of naloxone, 0.25 mcg/kg/h and titrate up to 1 mcg/kg/h for relief of pruritus without decreasing effectiveness of the analgesic.
  - Consider ondansetron at doses comparable for use in antinausea
  - Consider antihistamines such as cetirizine, 5–10 mg PO once 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 IM.

Delirium

- Assess for other causes of delirium (eg, infection, hypercalcemia, CNS, metastases, other psychoactive medications).
- If other possible causes of delirium are excluded, consider lowering the dose of the current opioid or consider changing the opioid.
- Consider nonopioid analgesic to allow reduction of the opioid dose.
- Consider initial titration with haloperidol, 0.5–2 mg PO or IV every 4–6 hours; or olanzapine, 2.5–5 mg PO or sublingual every 6–8 hours; or risperidone, 0.25–0.5 mg 1–2 times per day. 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.
- For further information about delirium, See NCCN Guidelines for Palliative Care.

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MANAGEMENT OF OPIOID ADVERSE EFFECTS (3 of 3)

Motor and Cognitive Impairment

- Studies have shown that stable doses of opioids (>2 week) are not likely to interfere with psychomotor and cognitive function, but these functions should be monitored during analgesic administration and titration.
- Consider evaluation for driving impairment, often done through occupational therapy.

Respiratory Depression

- Sedation often precedes respiratory depression; therefore, progressive sedation should be noted and adjustments in care should be made.
- Patients with limited cardiopulmonary reserve are more susceptible.
- Hypercarbia occurs before hypoxia.
- If respiratory problems or opioid-induced sedation occur, 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.
- At end of life in patients receiving comfort measures only, slowed respiration is expected. Naloxone administration may be inconsistent with goals of care.

Sedation

- It is critical to recognize the difference between cancer-related fatigue and opioid-induced sedation. (See NCCN Guidelines for Fatigue)
- If significant or unexpected sedation develops and persists for more than 2–3 days after initiating or a significant upward titration of an opioid
  - Assess for other causes of sedation (eg, CNS pathology, other sedating medications, hypercalcemia, dehydration, infection, hypoxia)
  - Consider a lower dose of opioid given more frequently to decrease peak concentrations
  - Decrease the dose of opioid if pain control can be maintained at a lower dose
  - Consider opioid rotation
  - Consider nonopioid analgesic to allow reduction of the opioid dose
  - Consider the addition of caffeine, 100–200 mg PO every 6 h; or methylphenidate, 5–10 mg 1–3 times per day; or dextroamphetamine, 5–10 mg PO 1–3 times per day; or modafinil, 100–200 mg per day.
    - ◊ When using CNS stimulants for sedation, limit dosing to morning and early afternoon to avoid insomnia at night.
- If sedation persists despite several changes of opioids and the above measures
  - Reassess cause and severity of sedation
  - Consider neuraxial analgesics, neuroablative techniques, and other interventions to potentially reduce opioid dose
- If the patient has had marked sleep deprivation related to poor pain control, adjustments of analgesics to improve pain control may result in “catch up” sleep lasting 2–3 days. Therefore, extreme fatigue can result in somnolence that may be difficult to differentiate from opioid-induced sedation. If related to fatigue, patients generally can be fully aroused, although this may require some effort.

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

Principles of Adjuvant Analgesic Use

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

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

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

Examples of Adjuvant Analgesics Use

- Extrapolated from non-cancer neuropathic pain management
- Both antidepressants and anticonvulsants are frequently used as an adjuvant analgesic in combination with an opioid to treat neuropathic components of pain.
- Antidepressants: Analgesic effectiveness is not dependent on its antidepressant activity. Effective analgesic dose 1) may be lower than that required to treat depression; and 2) the onset of analgesic relief may occur earlier than anti-depressive effects.
- Frequently used as an adjuvant analgesic in combination with an opioid for the neuropathic component of the pain.
  - Check for drug interactions with special regard to serotonergic medications due to risk for serotonin syndrome.
  - TCAs (eg, amitriptyline, imipramine, nortriptyline, desipramine)
    - ◊ TCAs should be used with caution in patients with conduction abnormalities or ischemic heart disease
    - ◊ Start with low dose and increase every 5–7 days if tolerated (eg, nortriptyline and desipramine starting dose 10–25 mg nightly 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.
  - Other examples:
    - ◊ Duloxetine- Starting dose 20–30 mg daily, increase to 60–120 mg daily
    - ◊ Venlafaxine- Starting dose 37.5 mg daily, increase to 75–225 mg daily
- Anticonvulsants: Frequently used as an adjuvant analgesic in combination with an opioid for the neuropathic component of the pain.
  - Anticonvulsants examples:
    - ◊ Gabapentin- Starting dose 100–300 mg nightly, increase to 900–3600 mg daily in divided doses 2 to 3 times a day. Dose increments of 50%–100% every 3 days. Slower titration for the elderly or medically frail. Dose adjustment required for those with renal insufficiency.
    - ◊ Pregabalin- Starting dose 25 mg nightly, with increasing dose frequency, to 2-3 times a day, and increasing dose increments of 50%–100% every 3 days to a maximum daily dose of 600 mg. Slower titration for the elderly or medically frail. Dose adjustment 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.
- 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.
- 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

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PSYCHOSOCIAL SUPPORT

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

Support

- **Inform patient and family/caregiver that emotional reactions to pain are normal and are evaluated and treated as part of pain treatment.**
- **Provide emotional support to patient and family/caregiver that acknowledges that the pain is a problem to be addressed.**
- **Assist in accessing treatment as needed.**
- **State that you will work together with the patient and family/caregiver as part of the team to address the pain problem.**
- **Describe the 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 that there is always something else that can be done to try to adequately manage pain and other noxious symptoms.**
- **Assess impact upon family and significant others; provide education and support as indicated.**
- **Verbally repeat your concern and the plan of action to be taken.**

Skills training

- **Teach coping skills (to be used in conjunction with and not in lieu of appropriate analgesia) to provide pain relief, enhance a sense of personal control, and refocus energy on optimizing quality of life.**
  - **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 Lamaze-type breathing exercises, distraction techniques**
  - **Coping skills for chronic pain (not pain emergency) include all of the above plus relaxation techniques, guided imagery, graded task assignments, hypnosis to maximize function, cognitive restructuring, and behavioral activation.**
  - **Training to encourage assertiveness to maximize comfort**
- **Educate patient and family/caregiver that in pain management a team effort is necessary to comprehensively assess and treat the impact of pain. Members of the team may include: oncologist, nurse, pain specialist, palliative care clinician, physiatrist, neurologist, psychologist, social worker, psychiatrist, physical therapist, and spiritual counselor. See Patient and Family/Caregiver Education (PAIN-I)**

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PATIENT AND FAMILY/CAREGIVER EDUCATION (1 of 2)

- **To assess for patient and family/caregiver educational needs regarding pain treatment, the health care team should:**
  - **Assess for 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 opioid analgesics.**
- **Educational materials should be provided.**
- **Messages to be conveyed to patient and family/caregiver regarding management of pain**
  - **Relief of pain is medically important and there is no medical benefit to suffering with pain.**
  - **Pain can usually be well-controlled with pain medications. For persistent pain, taking an analgesic on a regular schedule will improve pain control.**
  - **Patients with pain often have other symptoms (eg, constipation, nausea, fatigue, insomnia, depression) that need to be controlled; management of these other symptoms may facilitate control of pain.**
- **Messages to be conveyed to patient and family/caregiver regarding opioid analgesics**
  - **Morphine and morphine-like medications are 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/abuse, see (PAIN-E, 2 of 13) and see (PAIN-E, 6 of 13) for information on naloxone.**
    - ◊ **Patients with a history of prescription, illicit drug, or alcohol dependence/substance abuse are at increased risk.**
    - ◊ **Patients with a history of opioid use/abuse may also have increased tolerance, which may require higher doses for optimal pain control (see PAIN-L).**
  - **These medications are controlled substances and must be used with caution:**
    - ◊ **These medications should not be mixed with alcohol or illicit substances.**
    - ◊ **Potent analgesics should be taken only as prescribed and by the person for whom the medication is prescribed; advise patients not to self increase dosage or frequency; and advise patients to contact 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.**
    - ◊ **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, McWhinney I, 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.

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PATIENT AND FAMILY/CAREGIVER EDUCATION (2 of 2)

- **Communication with the health care provider is critical for the patient and family/caregiver to assist in meeting goals of care.**
  - **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 written form, which is dated:**
  - **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 refilled prescriptions, especially 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 in getting the prescriptions or taking the medication**
    - ◊ **New pain, change in pain, or pain not relieved with medication**
    - ◊ **Nausea and vomiting that prevents eating for 1 day**
    - ◊ **Problems with bowel movements, including no bowel movements for 3 days**
    - ◊ **Difficulty arousing the patient from sleep easily during the daytime**
    - ◊ **Confusion**
  - **A plan for follow-up visits and/or phone calls, including availability of after-hours assistance**
  - **A plan for proper storage and disposal** **(See PAIN-I 1 of 2)**

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

INTEGRATIVE INTERVENTIONS

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

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

- **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 or acupressure**
  - **Ultrasonic stimulation**
- **Cognitive modalities**
  - **Mindfulness-based stress reduction**
  - **Imagery**
  - **Hypnosis**
  - **Biofeedback**
  - **Acceptance-based training**
  - **Distraction training**
  - **Relaxation training**
  - **Active coping training**
  - **Graded task assignments, setting goals, pacing, and prioritizing**
  - **Cognitive behavioral therapy, cognitive restructuring**
  - **Behavioral activation**
- **Spiritual care (See NCCN Guidelines for Distress Management)**
- **See Interventional Strategies (PAIN-M)**

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

Acetaminophen

- Acetaminophen, 650 mg every 4 hours or 1 g every 6 hours (daily maximum 4 g/d) in adult patients with normal liver function. For chronic administration, consider limiting the maximum daily dose to 3 g/d 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.

NSAIDs

- Use NSAIDs with caution, especially for chronic use, as many oncology patients may be at high risk for renal, GI (ie, upper GI surgery, RT), or cardiac toxicities; thrombocytopenia; or bleeding disorder.
  - 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.
  - Ibuprofen, 400 mg four times a day (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
    - ◊ Salsalate, 2–3 g/d in two or three divided doses
    - ◊ Selective COX-2 inhibitor
- Consider topical NSAID - diclofenac gel 1% 4 times/d; or diclofenac patch 180 mg, 1–2 patches/d

See NSAIDs and toxicities on next page

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

NSAIDs and toxicities

- **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
- **GI toxicities**
  - Patients at high risk: age >60 years, history of peptic ulcer disease or significant alcohol use (3 or more alcoholic beverages/d), major organ dysfunction including hepatic dysfunction, high-dose NSAIDs given for long periods, concomitant steroid use, and cardioprotective dose of daily aspirin.
  - Treatment:
    - ◊ If patient develops gastric upset or nausea, consider discontinuing NSAID or changing to selective COX-2 inhibitor. COX-2 inhibitors are associated with lower incidence of GI adverse effects and do not inhibit platelet aggregation; however, they have not been demonstrated to have reduced renal adverse effects.
    - ◊ 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.
- **Cardiac toxicities**
  - Patients at high risk: history of cardiovascular disease or at risk for cardiovascular disease or complications.[1]
  - 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 oral NSAIDs in the setting of prophylactic or therapeutic anticoagulation. Topical NSAIDs such as diclofenac gel or patch may be useful in this population.
- **Monitoring for NSAID toxicities**
  - Baseline blood pressure, BUN, creatinine, liver function studies [alkaline phosphatase, LDH, SGOT, SGPT], CBC, and fecal occult blood test
  - Repeat every 3 mo to ensure lack of toxicity
- **Further NSAID considerations**
  - If two NSAIDs are tried in succession without efficacy, use another approach to analgesia.
  - If NSAIDs are effective but treatment is limited by toxicities that are not deemed serious, consider trial of another NSAID.
  - When systemic administration is not feasible, consider topical NSAID preparations in place of oral NSAIDs.
  - Toxicity of anti-cancer treatment may increase the risk profile of anti-inflammatory treatment.

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

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SPECIALTY CONSULTATIONS FOR IMPROVED PAIN MANAGEMENT

- Major indication for referral is:
  - Pain likely to be relieved or function improved through consultation delivered by a specialty service provider as suggested below. Note that the specific provider of these services may vary in different treatment settings.
- Pain and palliative care specialty consultation
  See NCCN Guidelines for Palliative Care
  - Consider interventional strategies (See PAIN-M)
  - Management of symptoms refractory to initial treatment
  - Management of sleep disturbances
  - Diagnosis and treatment of underlying condition
  - Consider oral or IV ketamine for pain resistant to other analgesics
  - Consider methadone in 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, including aberrant drug behavior
  - Clarity of goals of care, especially regarding pain and medication side effects
- Mental health consultation
  See NCCN Guidelines for Distress Management
  - Assessment
    - ◊ Diagnostic Interview: assess for depression, anxiety, psychiatric disease, and substance abuse disorder
    - ◊ Ongoing evaluation for misuse/abuse/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
    - ◊ CBT
    - ◊ MBSR
    - ◊ Acceptance-based therapy
  - Evidence-Based Treatment Modalities continued
    - ◊ Biofeedback
    - ◊ Hypnosis
  - 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, single provider/pharmacy as needed
- Social work consultation
  - Caregiver burden and support needs
  - Recommend use of community care resources
- Spiritual care consultation
  - Determine importance to patient and family/caregiver and current availability of support
  - Manage spiritual, existential concerns
- Physical/occupational therapy, rehabilitation/mobility specialty consultation
  - Physical modalities
    - ◊ Bed, bath, and walking supports
    - ◊ Positioning instruction
    - ◊ Energy conservation, pacing of activities
    - ◊ Massage
    - ◊ Heat and/or ice
    - ◊ TENS
    - ◊ Acupuncture or acupressure
    - ◊ Ultrasonic stimulation
- Lymphedema management

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INTERVENTIONAL STRATEGIES

Interventional consultation[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, intercostal nerve)**
  - **Failure to achieve adequate analgesia and/or the presence of intolerable adverse effects (may be handled with intraspinal agents, blocks, spinal cord stimulation, or destructive neurosurgical procedures)**
- **Commonly used interventional procedures:**
  - **Regional infusions (requires infusion pump)**
    - ◊ **Epidural: easy to place, requires 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 vertebroplasty/kyphoplasty**
  - **Neurodestructive procedures for well-localized pain syndromes (spinal analgesics are used more frequently)**
    - ◊ **Head and neck: peripheral neurolysis generally associated with sensory and/or motor deficit**
    - ◊ **Upper extremity: brachial plexus neurolysis**
    - ◊ **Thoracic wall: epidural or intrathecal, intercostal, or dorsal root ganglion neurolysis**
    - ◊ **Upper abdominal pain (visceral): celiac plexus block, thoracic splanchnicectomy**
    - ◊ **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 L/S phenol block**
  - **Neurostimulation procedures for cancer-related symptoms (ie, peripheral neuropathy, neuralgias, complex regional pain syndrome)**
  - **Radiofrequency ablation for bone lesions**

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

- **If interventional approaches are not appropriate**[2]
  - **Reassess therapeutic plan**

[1]Patient prognosis should be communicated to interventional pain colleagues as an important consideration when selecting interventional pain therapies.
[2]Infection, coagulopathy, very short or lengthy life expectancy, distorted anatomy, patient unwillingness, medications that increase risk for bleeding (eg, anti-angiogenesis agents such as bevacizumab), or technical expertise is not available.

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Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise indicated.

Table of Contents

Overview

Pain is one of the most common symptoms associated with cancer. Pain is defined by the International Association for the Study of Pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in relation to such damage.[1] Cancer pain or cancer-related pain distinguishes pain experienced by 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.[2] 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.[3] There is mounting evidence in oncology that quality of life and survival is linked to early and effective palliative care, including pain management.[4-9] Although improvements have been observed, undertreatment of pain remains an issue in a significant subset of patients with cancer.[10,11]

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.[12-14] 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.

The most widely accepted algorithm for the treatment of cancer pain was developed by the WHO.[15,16] It suggests that patients with pain be started on acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). If this is not sufficient, the patient should be escalated to a “weak opioid,” such as codeine, and subsequently to a “strong opioid,” such as morphine. Although this algorithm has served as an excellent teaching tool, the management of cancer pain is considerably more complex than this three-tiered “cancer pain ladder” suggests.

This NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Adult Cancer Pain 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.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version 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, using the following search terms: “cancer pain” (title/abstract) OR “oncologic pain” (title/abstract) OR "cancer-related pain.” The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.

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 potential relevance of the PubMed search results was examined. The data from key PubMed articles selected by the panel for review

during the Guidelines update meeting as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN webpage.

Principles of Cancer Pain Management

General

- There is increasing evidence in oncology that survival is linked to symptom reporting and control and that pain management contributes to broad quality-of-life improvement. To maximize patient outcomes, pain management is an essential part of oncologic management.
- Analgesic therapy is often done in conjunction with management of multiple symptoms or symptom clusters. Treatment must consider the interaction of complex pharmacologic therapies that a patient is prescribed and the risk for analgesic misuse.
- A multidisciplinary team is optimal.
- Psychosocial support must be available, including emotional and informational support and coping skills training.
- Specific educational material, including information about the role of opioids in cancer pain management, must be provided to the patient and family/caregiver in an understandable language and format.
- Consider the multidimensional impact of "suffering" on patients and their families and address these concerns in a culturally respectful manner.

Assessment

- All patients must be screened for pain at each contact.
- Pain intensity must be routinely quantified and documented and quality must be characterized by the patient (whenever possible based on patient communication capacity). Also, include patient reporting of breakthrough pain, treatments used and their impact on pain, patient reporting of adequate comfort, satisfaction with pain relief, provider assessment of impact on function, and any special issues for the patient relevant to pain treatment. If necessary, get additional information from the family/caregiver regarding pain and impact on function.
- Comprehensive pain assessment must be performed if new or worsening pain is present and regularly performed for persisting pain.
- Evaluate the patient for risk factors for opioid abuse/misuse/diversion.

Management/Intervention

- 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" were originally proposed by Passik and Weinreb[17]; these 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 drug taking: avoid aberrant drug taking (addiction-related outcomes)
    - Affect: relationship between pain and mood
- Comprehensive pain management (addressing the biopsychosocial elements of pain using pharmacologic and non-pharmacologic modalities) is needed, as most patients have multiple pathophysiologies and multiple symptoms.
- Prevention of expected analgesic side effects, especially constipation in the setting of opioid use, is key for effective pain treatment.

- Optimize patient and family education and physical and cognitive integrative interventions.
- For acute, severe pain or pain crisis, consider hospital or inpatient hospice admission to achieve patient-specific pain goals.
- Persistent cancer pain often requires treatment with regularly scheduled analgesics, and supplemental doses of analgesics are often required to manage breakthrough pain.
- For chronic pain in cancer survivors, see the NCCN Guidelines for Survivorship.

Reassessment

- Pain reassessment must be performed at specified intervals to ensure that analgesic therapy is providing maximum benefit with minimal adverse effects, and that the treatment plan is appropriately followed.

The NCCN Guidelines acknowledge the range of complex decisions faced in the management of these patients. As a result, they provide dosing guidelines for opioids, non-opioid analgesics, and adjuvant analgesics. They also provide specific suggestions for 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.

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.[18,19]

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.[20] 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. Failure to adequately assess 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 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).[21-24] 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, the elderly, and patients with language or cultural differences or other communication barriers. If the patient is unable to verbally report pain, an alternative method to obtain pain rating and pain assessment must be utilized. In addition to pain intensity, the patient should be asked to describe the characteristics of his/her 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.[22,25,26] Studies suggest that pain may interfere with daily functions to a different extent in patients with cancer versus those with chronic noncancer pain.[27] 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.[22,25,26] 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 PROMIS 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.[28] 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.

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); 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[11]); and other special issues relating to pain (eg, meaning of pain for patient and family/caregiver; cultural beliefs toward pain, pain expression, and treatment; spiritual or religious considerations and existential suffering).[29,30] Finally, the patient's goals and expectations of pain management should be discussed, including level of comfort and function, with family/caregivers included.

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.

The NCCN Panel recommends monitoring risk factors for aberrant use or diversion of pain medication, which might be identified at initiation of care using tools such as SOAPP-R (Screener and Opioid Assessment for Patients with Pain-Revised) or ORT (Opioid Risk Tool). Although specific screening tools have not been validated in the setting of cancer care, their validated efficacy for evaluating risk in patients with non-malignant pain supports their use in this setting.[31] The SOAPP was developed to predict which patients, being considered for long-term opioid therapy, may exhibit aberrant medications behaviors in the future.[32] SOAPP-R is a revised version of the SOAPP.[33] 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 abuse.[34] SOAPP-R and ORT discriminate between high-risk and low-risk patients.[35] A high-risk score on the SOAPP-R or ORT correlates with an increased likelihood of drug abuse.[36] Randomly administered urine drug screens and periodic review of prescription drug monitoring programs can also be used to monitor for aberrant use or diversion of pain medications.

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

Management of Adult Cancer Pain

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

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

Opioid-tolerant patients are those chronically taking opioids for pain relief. According to the U.S. Food and Drug Administration (FDA), "patients considered opioid tolerant are those who are taking at least: 60 mg oral morphine 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 one week or longer."[37,38] Therefore, patients who do not meet the above definition of opioid tolerant, and who have not had opioid doses at least as much as those listed above for a week or more, are considered to be opioid naïve.

Management of Pain 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; epidural or leptomeningeal metastases seen in patients with advanced cancers; pain related to infection; or obstructed or perforated viscus. Pain associated with oncologic emergency should be treated directly while proceeding with the treatment of the underlying condition.

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

For all patients experiencing pain, care providers should provide psychosocial support and begin educational activities. Psychosocial support is needed to ensure that patients encountering common barriers to appropriate pain management (eg, fear of addiction 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.[39,40] 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 many adverse effects. Optimal use of nonpharmacologic integrative interventions (physical, cognitive modalities, and spiritual) may serve as valuable additions to pharmacologic interventions.

When deciding upon the most appropriate medication, the patient's pain diagnosis, comorbid conditions, and potential drug interactions 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.[41]

Opioid-naïve patients (those who are not chronically receiving opioids on a daily basis) experiencing moderate to severe pain (ie, pain intensity rating 4–10) should receive rapid titration of short-acting opioids (see section below on *Opioid Prescription, 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. In cases of acute, severe pain or pain crisis, hospital or inpatient hospice admission may be considered to achieve patient-specific goals for comfort and function. For opioid-naïve patients experiencing mild pain intensity (rating of 1–3) treatment with nonopioid analgesics such as NSAIDs or acetaminophen as well as adjuvant analgesics should be considered first. Short-acting opioids may be subsequently considered if the patient requires further intervention.

The use of opioid analgesics is potentially associated with a number of 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.[42]

Patients with chronic persistent pain managed by stable doses of short-acting opioids should be provided with round-the-clock extended-release (ER) or long-acting (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 daily dose given every hour as needed. Opioids with a rapid onset and short duration are preferred as rescue doses. The repeated need for rescue doses per day may indicate the necessity to adjust the baseline treatment.

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

In opioid-tolerant patients who are experiencing breakthrough pain of intensity greater than or equal to 4 (or a pain intensity less than 4 but whose goals of pain management and function are not met), in order to achieve adequate analgesia, a rescue dose should be determined and administered. This dose is supplemental to the patient's LA (chronic) opioid dose. Continuation of a patient's previous opioid could be considered or upward titration to accommodate dose requirements could be warranted. The rescue dose should be 10% to 20% of the total opioid taken in the previous 24 hours. During this opioid titration, continuation of a patient's previous opioid should be considered and dose increase may be required.[43,44]

Efficacy and adverse effects should be assessed every 60 minutes for orally administered opioids and every 15 minutes for IV 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. 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 or alternate management strategies should be considered. If the pain score decreases to 0 to 3, the current effective dose of either oral or IV opioid is administered "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. Patients and family members/caregivers should receive written information regarding pain management options.

Subsequent Management of Cancer Pain

The subsequent treatment is based on the patient's continued pain rating score. 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 this time is severe, unchanged, or increased, the working diagnosis must be re-evaluated and comprehensive pain assessment must be carried out. For patients unable to tolerate dose escalation of their current opioid due to adverse effects, an alternate opioid must be considered. Addition of adjuvant analgesics should be re-evaluated to either enhance the analgesic effect of the opioids or in some cases to counter the adverse effects associated with the opioids.[42] Optimal use of nonpharmacologic integrative interventions (physical, cognitive modalities, 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 of 4 to 6 and if he/she has inadequate pain relief on his/her current opioid, the current titration of the opioid may be continued or increased. In addition, as with patients experiencing severe pain, addition of adjuvant analgesics; additional interventions for specific cancer pain syndromes; and specialty consultation must be considered.

For patients experiencing mild pain, if they have adequate analgesia but intolerable or unmanageable adverse effects, the analgesic dose may be reduced by 10% to 25% of the current opioid dose. Addition of adjuvant analgesics may be considered. Taper opioids and other treatments when they are no longer needed.

Ongoing Care

Although pain intensity ratings may be obtained frequently during analgesic titration, formal pain reevaluation is required at each contact

to insure 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 inequalities that persist since those with financial burdens or minorities have less access to pain treatment.[30,45] The NCCN Panel recommends addressing these system barriers, including recruiting assistance from social services as needed.[46-49]

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 and maintains 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 regarding which clinician will be prescribing his/her ongoing pain care and confirmed that the patient/caregiver(s) know how to contact the providers and hospital. Equally important is monitoring for the use of analgesics as prescribed, especially in patients with risk factors for or history of substance abuse, 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 or abuse. 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.

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 a third of post-treatment cancer survivors experience chronic pain, which can cause psychological distress and impact quality of life.[50,51] In 2016, ASCO issued a guideline on chronic pain management in adult cancer survivors.[52] For more information on pain in cancer survivors as well as other survivor-related issues, please see the NCCN Guidelines for Survivorship.

Pharmacologic Interventions

Opioids and Miscellaneous Analgesics

Selecting an Appropriate Opioid

While starting therapy, attempts should be made to determine the underlying pain mechanism and diagnose the pain syndrome. Optimal analgesic selection will depend on the patient's pain intensity, any current analgesic therapy, and concomitant medical illness(es). An individual approach should be used to determine opioid starting dose, frequency, and titration in order to achieve a balance between pain relief and medication adverse effects.

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 analgesics (methadone and levorphanol).[53] A randomized trial compared the efficacy of low-dose morphine, a "strong" opioid agonist, to "weak opioids" (ie, codeine, codeine plus acetaminophen, or 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.[54]

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.[55] In a patient who has not been exposed to opioids in the past, morphine is generally considered the standard starting drug of choice.[56,57] 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 opioid-naïve patients. Patients presenting with severe pain needing urgent relief should be treated with parenteral opioids, usually administered by the IV route or the subcutaneous (SC) route. If given parenterally, the equivalent dose is one-third of the oral dose.[58] An initial dose of 2 to 5 mg of IV morphine sulfate or equivalent is recommended for opioid-naïve patients. Morphine-6-glucuronide, an active metabolite of morphine, contributes to analgesia and may worsen adverse effects as it accumulates in patients with renal insufficiency.[59,60]

Fentanyl is a highly lipid-soluble mu-opioid receptor agonist that can be administered by the parenteral, spinal, transdermal, transmucosal, buccal, and intranasal routes.[61,62] Transdermal fentanyl is not indicated for rapid opioid titration and only should be recommended after pain is adequately managed by other opioids in opioid-tolerant patients.[63] It is usually the treatment of choice for patients who are unable to swallow, patients with poor tolerance to morphine, and patients with poor compliance. 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.[64] Conversion from IV fentanyl to transdermal fentanyl can be accomplished effectively using a 1:1 conversion ratio.[65] Transmucosal fentanyl may be considered in opioid-tolerant patients for brief episodes of incident pain not attributed to inadequate dosing of an around-the-clock opioid. Data do not support a specific transmucosal fentanyl dose equianalgesic to other opioids or between different transmucosal formulations. There are data showing that buccal fentanyl is effective in treatment of breakthrough pain in patients with cancer. [66-68]

Hydrocodone is a mu- and delta-opioid receptor agonist that may be approximately equipotent with oral morphine; however, its equivalence data are not substantiated.[61] Clinical experience suggests use as a mild, initial use opioid, but effective dose may vary. Hydrocodone is only available in immediate-release (IR) formulations mixed with acetaminophen or ibuprofen. Hydrocodone ER preparations (without added non-opioid analgesics) are available.

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.[61,69] This process is largely through the action of the cytochrome P450 enzyme, CYP2D6. It is important to note that CYP2D6 exhibits polymorphism between various ethnic groups and between individuals. A significant portion of individuals who are poor metabolizers would obtain reduced or no analgesic effects from codeine administration.[70] Conversely, rapid metabolizers may experience toxicity after codeine administration from more rapid morphine production.[70]

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.[61,71] There is some evidence suggesting that the metabolite of hydromorphone may lead to opioid neurotoxicity, including myoclonus, hyperalgesia, and seizures.[72] This metabolite may be more neurotoxic than the morphine metabolite.[73] In a prospective, open-label trial of 879 patients with cancer, hydromorphone effectively reduced pain that was inadequately controlled by other analgesics.[74] Additionally, a randomized controlled trial (RCT) demonstrated the clinical noninferiority of once-daily hydromorphone ER compared with twice-daily oxycodone controlled-release for relieving moderate to severe cancer pain.[75] A Cochrane review found evidence that hydromorphone provides similar effect on pain management as reported for oxycodone or morphine.[76]

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.[77-79]

Oxycodone is an opioid with agonist activity at the mu-, delta-, and kappa-opioid receptors and is available in IR and ER formulations.[80-82] Oxycodone is also available in combination with acetaminophen; therefore, the acetaminophen dose must be monitored for safe limits to avoid potential hepatic toxicity. A 2017 Cochrane review 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.[83] Studies of oxycodone/naloxone formulations showed effective analgesia with reduced opioid-induced constipation for long-term use in cancer-related pain.[84,85]

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

Methadone is a mu-opioid receptor agonist that also acts as an antagonist at NMDA receptors; it is commercially available in multiple strength oral tablets or oral solution.[61] Individual variations in methadone pharmacokinetics (long half-life ranging from 8 to more than 120 hours) make its usage very difficult in patients with cancer.[86] Due to its long half-life, high potency, and inter-individual variations in pharmacokinetics, methadone should be started at doses reduced by at least 50% from the calculated equianalgesic dose and slowly titrated

upwards with provision of 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 4 to 5 days, and caution that a steady state may not be reached for several days to 2 weeks. Conversion from morphine to methadone should be carried out cautiously as outlined in the NCCN Guidelines; however, the safety and efficacy of using a reciprocal technique for converting methadone dose to morphine, or conversion from another opioid to methadone, has not been documented.[87,88]

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.[89] Studies show that outpatient initiation and rotation to methadone can be successfully done in patients with cancer without serious adverse effects.[90] A retrospective, observational study suggested that very-low-dose methadone (ie, ≤15 mg/d), in conjunction with adjuvant haloperidol, provided pain management without opioid-induced hyperalgesia or required opioid dose escalation.[91] Currently, no prospective randomized trials have investigated this approach.

The NCCN Panel cautions and advises practitioners to consult a pain management specialist if they are unfamiliar with methadone prescribing or if individual patient considerations necessitate very rapid switching to or from methadone.

There is evidence suggesting that high doses of methadone (120 mg and above) may lead to QTc prolongation and torsades de pointes, which if uncorrected may lead to sudden cardiac death.[92-94] Oral methadone is commonly used for the treatment of cancer pain, and the average dosing appears to be much lower than is used to treat opioid dependency and chronic nonmalignant pain. A study conducted in patients with cancer suggests that QT interval changes exist commonly at baseline and are not changed with the addition of methadone.[95] However, physicians initiating methadone should be aware of the drug interactions. The NCCN Panel supports the use of baseline and follow-up electrocardiogram (ECG) for patients treated with methadone doses >30 to 40 mg/d (and again at 100 mg/d) and for patients with cardiac disease, or when methadone is used in patients taking other medications also known to prolong QTc (including tricyclic antidepressants [TCAs]).[96] ECG monitoring should be considered within the patient's goals of care and risk/benefit ratio as discussed with the patient. Alternate opioids are needed for patients with QTc greater than 500, and are recommended for those with QTc of 450 to 500.[96]

Methadone use should be initiated by physicians with experience and expertise in its use. Patients and their families may need to be educated about analgesic utility of methadone. Some may only be familiar with methadone use for maintenance of addiction and be unaware of its utility as a potent opioid analgesic.

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.[97] 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 less than 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 over 600 mg.[97] For certain populations (eg, the elderly), levorphanol may offer similar benefits to methadone but with lessened prescribing complexities and

adverse effects.[98] One study also demonstrated potential efficacy of levorphanol for treating neuropathic pain.[99]

Selecting Miscellaneous Analgesics

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 inhibitors (MAOI)-like medications (eg, TCAs, selective serotonin reuptake inhibitors [SSRIs], and MAOIs) due to risk of serotonin syndrome.[100]

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.[101] 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 older adults (75 years and older) 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.[101] One nonrandomized, observational study in patients with cancer found comparable analgesic efficacy of high-dose tramadol (ie, ≥300 mg/d) and low-dose morphine (ie, ≤60 mg/d), but observed higher rates of constipation, neuropsychological symptoms, and pruritus in patients receiving low-dose morphine.[102] However, in a double-blind study of patients with cancer, tramadol produced more adverse effects, including vomiting, dizziness, and weakness, than hydrocodone and codeine.[103] 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.[104]

Tapentadol is an opioid that binds to the μ opioid receptor and inhibits norepinephrine reuptake.[105,106] It is available as ER and IR formulations and is used for treatment of moderate to severe pain. Typical doses would 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 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 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.[107-109] Data on tapentadol for treating non-cancer pain have also suggested that it may have a lower incidence of gastrointestinal adverse effects than oxycodone.[107] Limited data suggest that there may be a roll for tapentadol in the management of cancer pain,[110,111] but further clinical trials are needed.

Transdermal buprenorphine, a partial μ-agonist, has been approved for chronic pain in opioid-naïve or opioid-tolerant patients. 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.[112-116] Therefore, transdermal buprenorphine may be used at a dose of 5 mcg/h in opioid-naïve patients requiring initiation of LA opioid therapy. Based on its pharmacokinetics, buprenorphine may be especially appropriate for treating cancer pain in patients with renal impairment.[115] 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.[117] FDA guidelines recommend limiting dose to a maximum of 20 µg per hour due to concern for QT prolongation. 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.

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.[118] A double-blind, randomized, placebo-controlled trial found no significant difference between the outcomes of patients treated for cancer pain with ketamine versus placebo.[119] 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.[120]

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.[121-124] 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.[121] 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 per hour (maximum 100 mg/hour), using the lowest dose that controls the patient's pain.[123] Some reports suggest that IV lidocaine may be especially useful for cancer-related neuropathic pain.[122-124]

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.[125] Use of placebo in the treatment of pain is unethical.

Selecting a Route of Administration

The least invasive, easiest, and safest route of opioid administration should be provided to ensure adequate analgesia.

Oral is the preferred route of administration for chronic opioid therapy.[43,125,126] 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).[127] The SC route has a slower onset and lower peak (30 minutes) effect when compared with IV route.

Opioid Prescription, Titration, and Maintenance

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

The physicians should be aware of potential drug-drug and drug-disease interactions while determining the treatment plan. 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, 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). However, if the patient persistently requires doses of "as-needed" opioids, or if the "around-the-clock" opioid regimen fails to relieve pain at peak effect or at end of dose, increased dose of ER opioid should be considered.

Breakthrough pain is defined as pain that fails to be adequately managed or "breaks through" a regimen of regularly scheduled opioid and may be further categorized as:

- incident pain that is associated with specific activities or events (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.[128] 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.[129-132]

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 never needing

breakthrough analgesics, completion of an acute pain event, improvement of pain control through use of non-opioid or interventional pain management therapies, or well-controlled pain in the setting of stable disease. In these situations, the dose of opioid may be reduced by 10% 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 patient is experiencing unmanageable adverse effects and/or significant safety concerns (see *Opioid Adverse Effects* in this Discussion). For more information on tapering opioids, see the VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain.[133]

Preventing Opioid Misuse and Abuse

The NCCN Panel also recommends monitoring for aberrant medication drug-related behaviors over the course of treatment using tools such as COMM (Current Opioid Misuse Measure). 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.[134,135] It examines concurrent misuse; in contrast, SOAPP-R or ORT is helpful in predicting which patients being considered for long-term opioid therapy may exhibit aberrant medications behaviors in the future. Potential risk factors for opioid abuse/misuse include the following patient characteristics:[31]

- History of prescription, illicit drug, or alcohol dependence or abuse
- History of binge drinking or peers who binge drink
- Family history of substance abuse
- 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 (younger than 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. See additional recommendations in *Strategies to Maintain Patient Safety and Minimize the Risk of Opioid Misuse and Abuse During Chronic Opioid Use* in the algorithm.

Initiating Short-Acting Opioids in Opioid-Naïve Patients

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 opioid-naïve and opioid-tolerant patients.

For opioid-naïve patients experiencing pain intensity greater than or equal to 4 or less than 4 but whose goals of pain management and function are not met, an initial dose of 5 to 15 mg of oral morphine sulfate or 2 to 5 mg of IV morphine sulfate or equivalent is recommended. Assessment of efficacy and adverse effects should be performed every 60 minutes for orally administered opioids and every 15 minutes for IV opioids to determine a subsequent dose. Upon assessment, if the pain score remains unchanged or is increased, to achieve adequate analgesia, it is recommended that the dose be increased by 50% to 100% of the previous opioid dose. If the pain score decreases to 4 to 6, 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. If inadequate response is seen in patients with moderate to severe pain, upon reassessment after 2 to 3 cycles of the opioid, changing the route of administration from oral to IV or subsequent management strategies can be considered. If the pain score decreases to 0 to 3, the current effective dose of opioid is administered "as needed" over an initial 24 hours before proceeding to subsequent management strategies.

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.[136-141] Chronic opioid therapy may depress the hypothalamic-pituitary axis and cause hypogonadism.[142] Each adverse effect requires a careful assessment and treatment strategy. Management of opioid-induced adverse effects is integral to opioid pain management.[136,143-151]

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. 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.[152] More recently, an RCT in hospice patients showed that there was no benefit in adding docusate to sennosides compared to sennosides alone.[153] 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 two times daily along with maintaining adequate fluid intake. Based on the available literature, docusate has not shown benefit and is, therefore, not recommended. While maintaining adequate dietary fiber intake is recommended, supplemental medicinal fiber, such as psyllium, is ineffective and may worsen constipation.

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 analgesic may be considered to allow reduction of the opioid dose.

If constipation persists, the cause and severity of constipation must be assessed again to rule out bowel obstruction 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 fentanyl or methadone may be considered. 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 employed.

When response to laxative therapy has not been sufficient, oral methylnaltrexone[154] or naloxegol,[155] opioid antagonists that work on receptors in the gastrointestinal system, can be used as a rescue when constipation is clearly related to opioid therapy (methylnaltrexone is FDA approved for opioid-induced constipation in adults with advanced illness who are receiving palliative care and naloxegol is 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 include injectable methylnaltrexone,[156-160] lubiprostone (FDA approved for opioid-induced constipation in adults with non-cancer pain and for idiopathic constipation),[161,162] and linaclotide[163] (FDA approved for idiopathic

constipation). These agents will not be of benefit and should not be used in patients with known or suspected mechanical bowel obstruction. 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.

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) must be assessed. Effective agents that may be considered include benzodiazepines such as prochlorperazine or thiethylperazine or dopamine receptor antagonists such as metoclopramide or haloperidol. Use caution when combining opioid medications with other medications that have a sedating effect (eg, benzodiazepines). The FDA has issued a black box warning about possible serious effects from this combination, including slowed or difficult breathing and death.[164] 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, dronabinol, or olanzapine may also be considered for management of nausea. Olanzapine may be especially helpful for patients with bowel obstruction.[165,166] Corticosteroids can also be quite beneficial for reducing opioid-induced nausea and vomiting, and in particular have been found to be effective in combination with metoclopramide and ondansetron.[167] If nausea persists for longer than a week, the cause of nausea needs to be reassessed and opioid rotation must be considered.

Pruritus or itchiness is a particularly common and distressing complaint. Pruritus occurs in 10% 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 μ-opioid receptor antagonists (eg, naloxone) may help reduce opioid-induced adverse effects while maintaining analgesic efficacy. The μ-receptor antagonists (eg, naloxone) are also used to reverse the effects of opioid-induced adverse effects,[168] 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 only, may also be useful.

Delirium is a pathophysiologic condition characterized by altered consciousness and inattention, cognitive dysfunction, and disturbed psychomotor behavior. Delirium may be treated with various interventions, for example adding a neuroleptic drug such as haloperidol, olanzapine, or risperidone or switching to another opioid.[169,170] 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.[171] Patients taking opioids may be screened

for driving impairment, if indicated. Driving fitness screens are often performed through occupational therapy.

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. 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.[42] If opioid-induced sedation develops and persists for over a week, it may be managed by administration of psychostimulants such as methylphenidate, dextroamphetamine, or modafinil or by adding caffeine. When using CNS stimulants for sedation, the dosing should be limited to morning and early afternoon to avoid insomnia at night. Sedation often precedes respiratory depression; therefore, progressive sedation should be noted and adjustments in care should be made.

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 and hypercarbia occurs before hypoxia. Naloxone remains a useful antidote for the reversal of opioid-induced respiratory and CNS depression, but should be administered cautiously so as not to precipitate acute opioid withdrawal syndrome in the opioid-tolerant patient. Abrupt reversal of opioid depression in opioid-tolerant patients 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.[172] Therefore, naloxone should be administered with caution in opioid-tolerant patients. 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 to administer when needed for patients taking opioids who are at high risk for 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.[173] 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.

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.

Opioid Rotation

No single opioid is optimal for all patients.[174] If opioid adverse effects are significant, an improved balance between analgesia and adverse effects might be achieved by changing to an equivalent dose of an alternative opioid. This approach is known as opioid rotation.[136,175] Establishing equianalgesic dosing can be challenging; studies have sought to establish safe conversion ratios and methods.[176-180] 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, 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, they pose risks to patients and society. The abuse of opioids is an increasing concern. In 2014, there were 47,055 drug-poisoning deaths in the United States, including 28,647 drug-poisoning deaths involving opioid analgesics.[181] Drug poisoning remains the number one cause of injury-related death in the United States.[182] 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. To reduce addiction, misuse, abuse, overdose, and death the FDA has established Risk Evaluation and Mitigation Strategy (REMS) programs for opioid products.[183] 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 or abuse.
- Educating each patient on safe use, storage, and disposal of opioid.
- Routinely monitoring patients for opioid misuse, abuse, or diversion.

The REMS programs are currently in place for all transmucosal fentanyl, ER or LA opioid analgesics, sublingual buprenorphine, and tapentadol.[184,185] The FDA has approved shared-system REMS for all transmucosal IR fentanyl (TIRF) products and for all ER and LA opioid analgesics. The TIRF REMS was originally approved in December 2011 and has been subsequently updated.[37] The ER and LA Opioid Analgesics REMS was originally approved in July 2012 and has been subsequently updated.[38] In September 2017, the FDA extended the REMS requirements to IR opioid analgesics, such that all opioids will be covered under the REMS program.[183] These modified REMS programs will require additional educational content in pain management, the safe use of opioids, and opioid use disorders. Currently, the REMS for fentanyl products requires a patient-prescriber agreement that requires patient education, and the ER and LA Opioid Analgesics REMS includes a patient counseling document. The complete list of currently approved REMS programs is available on the FDA website.[185] It is expected that drug manufacturers of opioids will meet the REMS requirement by providing educational grants for accredited entities and providing continuing education programs to prescribers.

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, abuse, or diversion. Various screening tools have been described for this purpose, but have not yet been evaluated in patients with cancer.[31]

The panel recommends that clinicians utilize state prescription drug monitoring programs (PDMP, also known as PMP) when available. 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. Nonopioid analgesics (such as an NSAID), adjuvant analgesics (antidepressants, anticonvulsants, topical agents, and corticosteroids), and/or integrative interventions (psychologic and physical approaches) may be used in conjunction with opioids to help to improve patient outcomes.[42]

Adjuvant Analgesics for Neuropathic Pain

The term adjuvant refers to medications that are coadministered to manage an adverse effect of an opioid or to adjuvant analgesics that are added to enhance analgesia. These drugs can be helpful for patients whose pain is only partially responsive to opioids. Clinically, adjuvant analgesics consist of a diverse range of drug classes, including anticonvulsants[186] (eg, gabapentin, pregabalin), antidepressants (eg, SSRIs, serotonin–norepinephrine reuptake inhibitors [SNRIs], TCAs), corticosteroids, and local anesthetics/topical agents (eg, topical lidocaine patch). Systematic reviews of trials of patients with cancer pain found that adjuvant analgesics (antidepressants and antiepileptics) added to opioids provide additional neuropathic pain relief.[187,188]

Adjuvant analgesics are commonly used to help manage bone pain, neuropathic pain, and visceral pain and, if desired or indicated, to reduce systemic opioid requirement. They are particularly important in treating neuropathic pain.[189,190] Extrapolating from studies conducted in neuropathic pain, in non-cancer conditions, TCAs are believed to provide relief from neuropathic pain.[191-193]

Physicians should check for drug interactions when prescribing antidepressants, paying particular attention to serotonergic medications due to risk of serotonin syndrome. Several antidepressants are known inhibitors of hepatic drug metabolism via inhibition of cytochrome P450 enzymes, especially CYP2D6. Tamoxifen is an estrogen receptor blocker commonly used in patients with hormone receptor-positive breast cancer. Tamoxifen undergoes extensive hepatic metabolism, and inhibition of CYP2D6 decreases production of tamoxifen active metabolites, potentially limiting tamoxifen efficacy. While some clinical studies indicate increased risk of breast cancer recurrence in tamoxifen-treated patients with breast cancer also treated with SSRI antidepressants versus those receiving tamoxifen alone,[194] other studies have not shown this effect.[195,196] If concomitant use of an SSRI is required in a patient receiving tamoxifen, use of a mild CYP2D6 inhibitor (sertraline, citalopram, venlafaxine, escitalopram) may be preferred over a moderate-to-potent inhibitor (paroxetine, fluoxetine, fluvoxamine, bupropion, duloxetine).[194]

The most commonly employed anticonvulsant drugs for the treatment of cancer pain are gabapentin and pregabalin.[197] They have been studied primarily in noncancer neuropathy syndromes,[198] although there are data supporting their use for treatment of cancer pain in conjunction with opioids.[199,200] Gabapentin has been reported to reduce mucositis pain in patients receiving concomitant radiotherapy and chemotherapy.[201] When compared in a prospective, randomized, open-label trial, pregabalin relieved neuropathic cancer-related pain more effectively than transdermal fentanyl.[202]

Topical local anesthetic agents are useful in preventing procedural pain and in relieving 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. Topical agents include lidocaine or diclofenac patch. Both the gel and patch forms of lidocaine have been shown to reduce the pain of postherpetic neuropathy and cancer-related pain.[203-205]

Corticosteroids have long been used to relieve neuropathic pain syndromes. Corticosteroids have also been effective for treating bone pain due to their anti-inflammatory effects as well as relieving malignant intestinal obstruction.[41,206] A 2015 Cochrane review summarized the existing data for corticosteroid use in cancer pain.[207]

Non-Opioid Analgesics

The non-opioid analgesics include NSAIDs and acetaminophen.

Acetaminophen is analgesic and antipyretic but not anti-inflammatory.[208] Recent attention has been drawn towards the relative limited efficacy and significant adverse effects of acetaminophen, particularly hepatic and renal toxicity.[209,210] This concern is compounded by the inclusion of acetaminophen in a variety of prescription opioid preparations (eg, hydrocodone or codeine) as well as in a wide selection of over-the-counter products. Due to concerns 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 grams, and imposed 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, liver transplant, and death.[211] 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. In January 2014, the FDA recommended that health care professionals “discontinue prescribing and dispensing prescription combination drug products that contain more than 325 milligrams (mg) of acetaminophen per tablet, capsule, or other dosage unit.”[212] Due to concerns of hepatic toxicity, the NCCN Panel suggests that providers consider limiting chronic administration of acetaminophen to 3 grams or less per day.

NSAIDs produce analgesia by blocking the biosynthesis of prostaglandins, inflammatory mediators that initiate, cause, intensify, or maintain pain. History of peptic ulcer disease, advanced age (>60 years old), male gender, and concurrent corticosteroid therapy should be considered before NSAID administration to prevent upper gastrointestinal tract bleeding and perforation. As prophylaxis for NSAID peptic ulceration, consider adding misoprostol or proton pump inhibitors. Well-tolerated proton pump inhibitors are recommended to reduce gastrointestinal adverse effects induced by NSAIDs. The FDA cautions that the concomitant use of an NSAID with aspirin may reduce the cardioprotective efficacy of aspirin,[213] and concomitant use of an NSAID and low-dose (or cardioprotective) aspirin may increase the risk of gastrointestinal bleeding.[214,215] The NCCN Panel recommends avoiding concurrent use or administering these agents separately.

NSAIDs should be prescribed with caution in patients older than 60 years of age or in those having compromised fluid status, renal insufficiency, concomitant administration of other nephrotoxic drugs, and renally excreted chemotherapy in order to prevent renal toxicities. The addition of NSAIDs to opioids has the potential benefit of reducing the opioid dose when sedation, cognitive function, or other 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 develops or worsens. The FDA has issued a warning that NSAID use increases the risk of heart attack or stroke.[216] This risk is present even with short-term use of NSAIDS and increases with higher doses.[217] NSAIDs taken with prescribed anticoagulants, such as warfarin or heparin, may significantly increase the risk of bleeding complications. Oral NSAIDs should be avoided in the setting of prophylactic or therapeutic anticoagulation. Topical NSAIDs such as diclofenac gel or patch may be useful in this population.

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

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.

Although bone-modifying agents such as bisphosphonates and RANKL (receptor activator of nuclear factor-kappaB ligand) 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)[218-222] and denosumab (a RANKL inhibitor)[220,223] 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,[220,223,224] although evidence is insufficient to recommend one of these agents over the others.[225] 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.[225]

Surgical and radiation treatment for bone metastases is performed to relieve local bone pain, provide stabilization, and prevent impending fracture or spinal cord compression.[226] 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 specialist for interventional consultation is recommended to determine optimal management strategy for vertebral augmentation.

Ablative strategies such as radiofrequency (RF) ablation or US ablation may also be performed to reduce pain and prevent SREs. RF ablation of bone lesions has proven successful in pain management, especially for those failing to achieve adequate analgesia without intolerable effects.[227-230] Several small studies have also demonstrated the palliative effects of high-intensity focused US (HIFU) treatment of bone lesions.[231-233]

Physical and occupational therapy may also be beneficial in the prevention of complications associated with SREs.[234-236]

Management of Pain Due to Bowel Obstruction

Malignant bowel obstruction is a common complication in patients with abdominal or pelvic cancers. The initial management of patients presenting with bowel obstruction includes evaluation of the etiology of the obstruction. If the obstruction is resulting from cancer, surgical intervention should be considered. Patients with advanced disease or poor general condition who are unfit for surgery may require other palliative measures to relieve distressing symptoms such as bowel rest, nasogastric suction, corticosteroids, anticholinergic agents (eg, scopolamine, hyoscyamine, glycopyrrolate), and/or octreotide (see the NCCN Guidelines for Palliative Care). While metoclopramide should not be used in the setting of full bowel obstruction, it may be considered for partial obstructions. Although there is a lack of evidence supporting the use of H2 blockers for malignant bowel obstruction,[237] it is a reasonable consideration for reducing gastric secretions in this setting. Use of opioid analgesics to help manage pain related to malignant bowel obstruction is appropriate.

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; mental health support services (including psychiatric consultation, psychology consultation, and/or substance abuse consultation, as needed); pain and palliative care services; depression/distress consultation; spiritual care consultation; or social work services.

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 cognitive-behavioral interventions.

Use of nonpharmacologic integrative interventions (physical, cognitive, and spiritual) may serve as valuable additions to pharmacologic interventions. Physical measures include, but aren't limited to, therapeutic or conditioning exercise, massage, use of heat or cold, acupuncture, and acupressure. Cognitive interventions are aimed at enhancing a sense of control over the pain or underlying disease. Mindfulness-based stress reduction (MBSR), breathing exercises, relaxation, imagery, hypnosis, biofeedback, and other behavioral therapies can be very useful.[238-245] Attention should also be focused on psychosocial support and providing education to patients and families.[246,247] All of these can greatly enhance patients' sense of control as well as greatly reduce the family/caregivers' feeling of helplessness.[243] 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.[248] The integration of physical, psychosocial, and spiritual modalities should also be based on assessment of cultural considerations. In cancer care, there is growing interest in attention to spiritual needs and the existential concerns often associated with pain. Many patients hold cultural beliefs about such treatments, and home remedies, rituals, prayer, and other spiritual

practices may be most helpful in relieving or coping with pain. Involvement of chaplains and other spiritual care providers is essential.[249] Spiritual needs should be routinely assessed and spiritual care should be incorporated as a component of comprehensive pain management.

Patient-based educational interventions have a significant impact in providing pain relief.[250] Skills training helps modify the patient's experience of pain and helps patients acquire techniques of pain management such as deep muscle relaxation. Patients who may benefit from skills training may be referred to a licensed mental health professional trained in cognitive behavioral therapy, 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.

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. Interventional therapies that can be useful in the relief of cancer pain include nerve blocks, vertebral augmentation, regional infusion of analgesics, RF ablation, and other techniques.[42,229,230,251-255]

The major indications for referral for interventional therapies include a patient suffering from pain that is likely to be relieved with nerve block (eg, pancreas/upper abdomen with celiac plexus block, lower abdomen with superior hypogastric plexus block, intercostal nerve, 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.[256,257]

Regional infusion of analgesics (epidural, intrathecal, and regional plexus) minimizes the distribution of drugs to receptors in the brain, potentially avoiding adverse effects of systemic administration. The intrathecal route of opioid administration should be considered in patients with intolerable sedation, confusion, and/or inadequate pain management with systemic opioid administration.[258] This approach is a valuable tool to improve analgesia for patients who have pain from a variety of anatomical locations (eg, head and neck, upper and lower extremities, trunk).[259-262] However, due to the risk of catheter migration and infection risk, consider limiting the duration of use to several days.

Percutaneous vertebral augmentation 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.[263-268] Ablation techniques may also be helpful for pain management in patients who receive inadequate relief from pharmacologic therapy. Additionally, these approaches could be considered for patients who do not prefer or are not indicated for receiving additional pharmacologic interventions or radiation therapy. 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, RF ablation, US ablation) for bone lesions can

also be helpful in reducing pain.[227-233] See *Management of Bone Pain Without an Oncologic Emergency* for more information.

Neurostimulation procedures have been suggested to be useful for painful chemotherapy-induced peripheral neuropathies, neuralgias, and complex regional pain syndrome.[269]

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 reevaluation 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

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Table 1: Potential Drug-Drug Interactions: Chemotherapeutics, Analgesics, and Other Commonly Prescribed Medications[*,β]						
Drug	Buprenorphine, fentanyl, methadone, & oxycodone		Methadone & buprenorphine		Enzalutamide and dexamethasone[ε,φ]	
Interaction	Potential to increase plasma levels of the above opioids		Potential for QTc prolongation when used with above opioids		Potential to decrease plasma levels of the agents below	
Interacting Drugs	Clarithromycin Cobicistat Conivaptan Erythromycin Fluconazole Imatinib Indinavir Itraconazole	Ketoconazole (systemic) Nelfinavir Nefazodone Posaconazole Ritonavir Saquinavir Voriconazole	Abarelix Citalopram Bortezomib Bevacizumab Dasatinib Degarelix Dolasetron Doxorubicin Epirubicin Fluoroquinolones Granisetron	Lapatinib Metoclopramide Nilotinib Ondansetron Pazopanib Ribociclib Ruxolitinib Sorafenib Sunitinib Toremifene Voriconazole Ziprasidone	Aprepitant Buprenorphine Bortezomib Erlotinib Everolimus Fentanyl Gefitinib Ibrutinib Idelalisib Imatinib	Lapatinib Methadone Oxycodone Pazopanib Ruxolitinib Sirolimus Sorafenib Sunitinib Tacrolimus Temsirolimus

***Data within this table were obtained from the University of Washington Drug Interaction Database (DIDB®), available at www.druginteractioninfo.org[270] and Lexicomp Online (Hudson, Ohio: Lexi-Comp, Inc.), available published literature, and prescribing information for drug products. Information accessed on April 24, 2017.**

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 an inducer of cytochrome P450 3A4.

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