Adult Cancer Pain, Version 3.2019

Robert A. Swarm, MD[1,*]; Judith A. Paice, PhD, RN[2,*]; Doralina L. Anghelescu, MD[3,*]; Madhuri Are, MD[4]; Justine Yang Bruce, MD[5]; Sorin Buga, MD[6,*]; Marcin Chwistek, MD[7,*]; Charles Cleeland, PhD[8]; David Craig, PharmD[9,*]; Ellin Gafford, MD[10]; Heather Greenlee, PhD, ND[11,*]; Eric Hansen, MD[12]; Arif H. Kamal, MD, MBA, MHS[13]; Mihir M. Kamdar, MD[14]; Susan LeGrand, MD[15]; Sean Mackey, MD, PhD[16]; M. Rachel McDowell, MSN, ACNP-BC[17]; Natalie Moryl, MD[18,*]; Lisle M. Nabell, MD[19]; Suzanne Nesbit, PharmD, BCPS[20]; Nina O'Connor, MD[21]; Michael W. Rabow, MD[22,*]; Elizabeth Rickerson, MD[23]; Rebecca Shatsky, MD[24]; Jill Sindt, MD[25,*]; Susan G. Urba, MD[26]; Jeanie M. Youngwerth, MD[27,*]; Lydia J. Hammond, MBA[28,*]; and Lisa A. Gurski, PhD[28,*]

ABSTRACT

In recent years, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Adult Cancer Pain have undergone substantial revisions focusing on the appropriate and safe prescription of opioid analgesics, optimization of nonopioid analgesics and adjuvant medications, and integration of nonpharmacologic methods of cancer pain management. This selection highlights some of these changes, covering topics on management of adult cancer pain including pharmacologic interventions, nonpharmacologic interventions, and treatment of specific cancer pain syndromes. The complete version of the NCCN Guidelines for Adult Cancer Pain addresses additional aspects of this topic, including pathophysiologic classification of cancer pain syndromes, comprehensive pain assessment, management of pain crisis, ongoing care for cancer pain, pain in cancer survivors, and specialty consultations.

J Natl Compr Canc Netw 2019;17(8):977–1007
doi: 10.6004/jnccn.2019.0038

[1]Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; [2]Robert H. Lurie Comprehensive Cancer Center of Northwestern University; [3]St. Jude Children's Research Hospital/The University of Tennessee Health Science Center; [4]Fred & Pamela Buffett Cancer Center; [5]University of Wisconsin Carbone Cancer Center; [6]City of Hope National Medical Center; [7]Fox Chase Cancer Center; [8]The University of Texas MD Anderson Cancer Center; [9]Moffitt Cancer Center; [10]The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute; [11]Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance; [12]Roswell Park Comprehensive Cancer Center; [13]Duke Cancer Institute; [14]Massachusetts General Hospital Cancer Center; [15]Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute; [16]Stanford Cancer Institute; [17]Vanderbilt-Ingram Cancer Center; [18]Memorial Sloan Kettering Cancer Center; [19]O'Neal Comprehensive Cancer Center at UAB; [20]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; [21]Abramson Cancer Center at the University of Pennsylvania; [22]UCSF Helen Diller Family Comprehensive Cancer Center; [23]Dana-Farber/Brigham and Women's Cancer Center; [24]UC San Diego Moores Cancer Center; [25]Huntsman Cancer Institute at the University of Utah; [26]University of Michigan Rogel Cancer Center; [27]University of Colorado Cancer Center; and [28]National Comprehensive Cancer Network

*Discussion Writing Committee Member

NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

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

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

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

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

All recommendations are category 2A unless otherwise noted.

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

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

The complete NCCN Guidelines for Adult Cancer Pain are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.

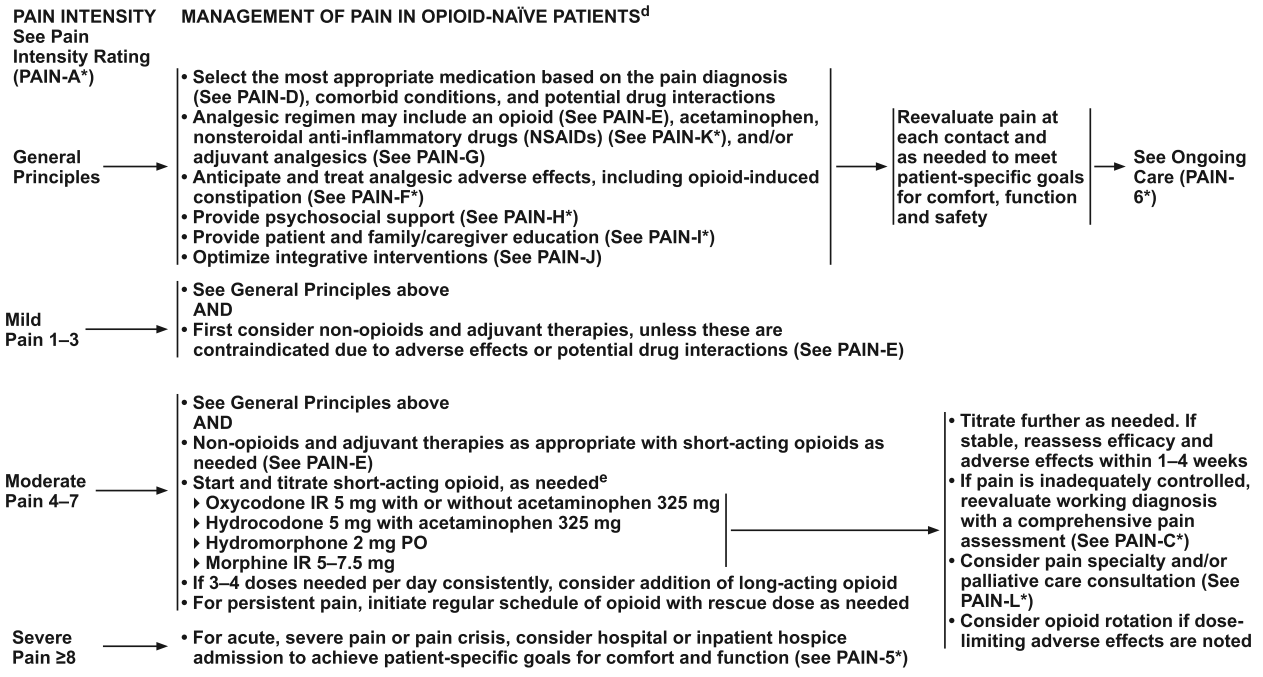
Disclosures for the NCCN Adult Cancer Pain Panel

At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Adult Cancer Pain Panel members can be found on page 1007. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.

Adult Cancer Pain



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

*Available online, in these guidelines, at NCCN.org.

PAIN-3

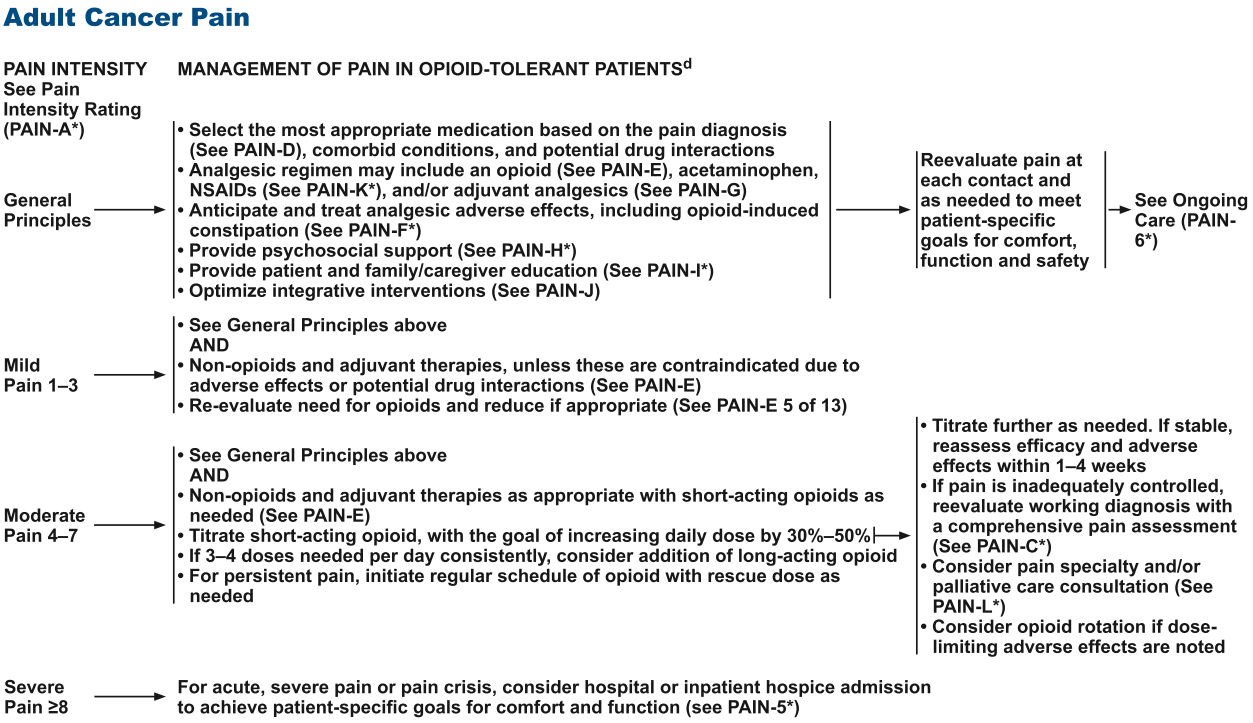
Overview

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] Evidence is mounting in oncology that quality of life and survival are 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 and this issue may be exacerbated by the inappropriate application of recommendations against the use of opioids to patients with cancer in the setting of the United States opioid epidemic.[10,11]

Goals of pain management are to optimize pain treatment outcomes in 5 dimensions, frequently referred to as the "5 As" of pain management outcomes (the "4 As" originally proposed by Passik and Weinreb[12] 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

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.[13–15] 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



[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.

*Available online, in these guidelines, at NCCN.org.

PAIN-4

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.[16,17] It suggests that patients with pain be started on acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). If this is not sufficient, therapy should be escalated to a "weak opioid" such as codeine and subsequently to a "strong opioid" such as morphine. Although this algorithm has served as an excellent teaching tool, the management of cancer pain is considerably more complex than this 3-tiered "cancer pain ladder" suggests.

These NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Adult Cancer Pain are unique in several important ways. The NCCN Guidelines identify central principles for assessing and managing cancer pain in adults. First, they list general principles of pain management, followed by guiding principles for assessment, management/intervention, and reassessment. The NCCN Guidelines acknowledge the range of complex decisions faced in the management of these patients. As a result, they provide dosing guidelines for opioids, nonopioid 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.

Management of Adult Cancer Pain

For management of cancer-related pain in adults, the algorithm distinguishes 3 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 3 levels of pain intensity referred to in the algorithm are mild pain (1–3); moderate pain (4–7); and severe pain (8–10).

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 consider 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

Adult Cancer Pain

MANAGEMENT STRATEGIES FOR SPECIFIC CANCER PAIN SYNDROMES

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

- **Pain from mucositis, pharyngitis, and esophagitis:**
  - **Gabapentin**
  - **Cryotherapy**
  - **Local anesthetic formulations/oral care protocols**
  - **For more information, see https://www.ons.org/pep/mucositis**

- **Bone pain without oncologic emergency:**
  - **NSAIDs, acetaminophen, or steroids[a]**
    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[a], 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[a] and/or metoclopramide.**
  - **Palliative management of bowel obstruction could include bowel rest, nasogastric suction (or percutaneous gastrostomy drainage), corticosteroids,[a] H2 blockers, anticholinergics (ie, scopolamine, hyoscyamine, glycopyrrolate), and/or octreotide.**

- **Nerve pain**
  - **Nerve compression or inflammation:**
    - **Trial of corticosteroids[a]**
  - **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†).**

[a]Due to potential impact on immunotherapies or other treatments, the use of steroids should be coordinated with the oncology care team.

*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

PAIN-D

hospital admission to achieve patient-specific goals for comfort and function. It is important to separate pain related to an oncologic emergency from pain not related to an oncologic emergency.

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

Opioid-tolerant patients are those chronically taking opioids for pain, defined by the US FDA as "patients who are taking at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, or an equianalgesic dose of another opioid for one week or longer."[18,19] Therefore, patients who do not meet these criteria of opioid tolerance, based on not having had exposure to opioid doses at least as much as those listed 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 the treatment of the underlying condition proceeds concurrently.

Management of Pain Not Related to Oncologic Emergency

For all patients experiencing pain, care providers should offer psychosocial support and begin educational activities. Psychosocial support is needed to ensure that patients encountering common barriers to appropriate pain management (eg, fear of addiction or side effects, inability to obtain opioids) or needing assistance in managing additional problems (eg, depression, rapidly declining functional status) receive appropriate aid.

Adult Cancer Pain

OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY

Opioids and Risk Evaluation and Mitigation Strategy (REMS)

- **Opioids are the principal analgesics for moderate to severe pain, yet opioids pose risks to patients and society. In 2017, 70,237 drug overdose deaths occurred in the United States, including 47,600 deaths involving opioids. Drug poisoning still remains the number one cause of injury-related deaths.[1] Most people who overdose on prescription opioids not prescribed to them have been given (not bought or stolen) opioids from friends or family. See CDC Drug Overdose Death Data (December 2018).**
- **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 (>45 years)**
  - **Patients with a history of legal problems or incarceration**
  - **Medication-assisted treatment for substance use disorder. Patients receiving treatment for addiction should be encouraged to continue with therapy and pain management should be carried out in coordination with an addiction specialist.**

[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 2013;11:1023-1031.

*Available online, in these guidelines, at NCCN.org.

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

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

When deciding on 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 nonopioid (eg, NSAIDs, acetaminophen) analgesics.[22]

For opioid-naïve patients (as defined previously) experiencing mild pain intensity (rating of 1–3), treatment with nonopioid analgesics such as NSAIDs or acetaminophen and adjuvant analgesics should be considered before opioid analgesics unless they are contraindicated due to adverse effects or potential drug interactions. Opioid-naïve patients experiencing moderate pain (ie, pain intensity rating, 4–7) should receive nonopioid and adjuvant therapies, as appropriate, with titration of short-acting opioids as needed (see PAIN-3, page 978). Short-acting formulations have the advantage of rapid onset of analgesic effect. The route of administration of opioid is decided (oral vs intravenous) based on what is best suited to the patient's ongoing analgesic needs.

Opioid-tolerant patients (as defined previously) who are experiencing mild pain (rating, 1–3) should continue to receive nonopioid and adjuvant therapies as appropriate. The need for opioid analgesics should be reevaluated and gradual dose reduction may be initiated, if indicated. Opioid-tolerant patients who are experiencing moderate pain (rating, 4–7) should continue nonopioid and adjuvant therapies, as appropriate, with short-acting opioids, as needed. Short-acting opioids should be titrated with the goal of increasing the daily dose by

Adult Cancer Pain

OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY

Principles of Opioid Dose Reduction

- **Consider opioid dose reduction by 10% to 20% when possible; situations that may warrant dose reduction include:**
  - **Patient never or rarely 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.**

30%–50% until pain relief is achieved (see PAIN-4, page 979).

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 (see "Management of Pain Crisis" in the complete version of these guidelines, at NCCN.org).

The use of opioid analgesics is potentially associated with substantial adverse effects. The management of common opioid-induced adverse effects should be started simultaneously with the start of opioid therapy. Opioid-induced bowel dysfunction should be anticipated and treated prophylactically with a stimulating laxative to increase bowel motility, as indicated.[23]

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%–20% of the total opioid daily consumption and may be given every hour as needed during severe exacerbations of pain. Opioids with a rapid onset and short duration are preferred as rescue doses. The repeated need for numerous rescue doses per day may indicate the need to adjust baseline treatment.

Subsequent Management of Cancer Pain

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

If pain at any time is severe, not improved, or increased, the working diagnosis must be reevaluated and comprehensive pain assessment must be performed. 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 reevaluated to either enhance the analgesic

Adult Cancer Pain

OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY

Strategies to Maintain Patient Safety and Minimize the Risk of Opioid Misuse and Abuse During Chronic Opioid Use

- 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 exhibit 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
  - Counsel high-risk patients that continuation of opioid therapy is contingent upon appropriate, safe use of prescribed analgesics.
  - 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

effect of the opioids or in some cases to counter the adverse effects associated with the opioids.[23] 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 7, with inadequate pain relief on the ongoing opioid regimen, the titration of the opioid may be continued or increased. In addition, as with patients experiencing severe pain, addition of adjuvant analgesics, additional interventions for specific cancer pain syndromes, and specialty consultation must be considered.

For patients experiencing mild pain, if they have adequate analgesia but intolerable or unmanageable adverse effects, the analgesic dose may be reduced by 10% to 25% of the current opioid dose. Addition of adjuvant analgesics may be considered. The need for opioid analgesics should be frequently reassessed and the dose reduced if appropriate.

Pharmacologic Interventions for Cancer Pain Management

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

Nonopioid Analgesics

Acetaminophen

Acetaminophen has analgesic and antipyretic, but not anti-inflammatory properties.[24] Recent attention has been drawn toward the relative limited efficacy and significant adverse effects of acetaminophen, particularly hepatic toxicity and possibly renal impairment.[25,26] Concerns are compounded by the inclusion of acetaminophen in a variety of prescription opioid preparations (eg, in combination with hydrocodone or codeine), as well as in a wide selection of over-the-counter products. Due to concerns about liver toxicity, the NCCN panel advises that

Adult Cancer Pain

OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY

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 acetylsalicylic acid (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 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 pruritus. They should NOT be used in combination with opioid agonist drugs. Converting from an agonist to an agonist-antagonist could precipitate a withdrawal crisis in the opioid-dependent patient.

*Available online, in these guidelines, at NCCN.org.

acetaminophen should be used with caution or not used at all with combination opioid-acetaminophen products to prevent excess acetaminophen dosing (see PAIN-K 1 of 2, available online, in these guidelines, at NCCN.org).

The FDA recommends that patients be advised to limit daily acetaminophen intake to a maximum of 4 g, and imposes a limit of 325 mg of acetaminophen per tablet, capsule, or other dosage unit in prescription products to reduce the risk of severe liver injury from acetaminophen overdosing, an adverse event that can lead to liver failure and death.[27] The FDA has issued a boxed warning to communicate the risk of severe liver injury associated with acetaminophen to health care professionals. In addition, 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.[27] Due to concerns of hepatic toxicity, the NCCN panel suggests that providers consider limiting chronic administration of acetaminophen to 3 g or less per day.

NSAIDs

NSAIDs produce analgesia by blocking the biosynthesis of prostaglandins, inflammatory mediators that initiate, cause, intensify, or maintain pain. History of peptic ulcer disease or gastrointestinal bleeding, advanced age (>60 years old), male gender, and concurrent corticosteroid or anticoagulant therapy should be considered before NSAID administration to prevent upper gastrointestinal tract bleeding and perforation. The risk of gastrointestinal bleeding is increased in patients with untreated *H. pylori* infection and with chronic, rather than short-term, use of NSAIDs. As prophylaxis for NSAID peptic ulceration, consider adding misoprostol or proton pump inhibitors. Well-tolerated proton pump inhibitors are recommended to reduce 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,[28] and concomitant use of an NSAID and low-dose (or cardioprotective) aspirin may increase the risk of gastrointestinal bleeding.[29,30] The NCCN panel recommends avoiding concurrent use or administering these agents separately (see PAIN-K 1 of 2, available online, in these guidelines, at NCCN.org).

NSAIDs should be prescribed with caution in patients older than 60 years of age or in those having compromised fluid status, renal insufficiency, concomitant

Adult Cancer Pain

OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY
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 years) and those with hepatic and/or renal dysfunction, to reduce the risk of seizures. Even at a maximum dose of 100 mg four times 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 monoamine oxidase inhibitor (MAOI)-like medications (eg, tricyclic antidepressants [TCAs], selective serotonin reuptake inhibitors [SSRIs]) 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/hour) 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 pain specialty and/or palliative care consultation.**

Non-opioid analgesic (given in collaboration with a pain/palliative care specialist):
- **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.

administration of other nephrotoxic drugs, and renally excreted chemotherapy to prevent renal toxicities. The addition of NSAIDs to opioids has the potential benefit of reducing the opioid dose when sedation, cognitive function, or other central nervous system (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 may increase the risk of heart attack or stroke.[31] This risk is present even with short-term use of NSAIDs and increases with higher doses.[32] 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. See "page PAIN-K 2 of 2" in the complete version of these guidelines, at NCCN.org, for more information.

Adjuvant Analgesics

The term *adjuvant analgesics* refers to medications that are coadministered to enhance opioid analgesia and possibly reduce adverse effects of opioids by allowing the use of lower doses of opioids. These drugs can be helpful for patients whose pain is only partially responsive to opioids. Clinically, adjuvant analgesics consist of a diverse range of drug classes, including anticonvulsants[33] (eg, gabapentin, pregabalin), antidepressants (eg, selective serotonin reuptake inhibitors [SSRIs], serotonin–norepinephrine reuptake inhibitors, triglyceride antidepressants [TCAs]), corticosteroids, and local anesthetics/topical agents (eg, topical lidocaine patch). Adjuvant analgesics are commonly used to help manage bone pain, neuropathic pain, and visceral pain and, if desired or indicated, to reduce the opioid requirement. They are particularly important in treating neuropathic pain (see PAIN-D, page 980 and PAIN-G 2 of 2, page 987).[34,35]

Physicians should check for drug interactions when prescribing antidepressants, paying particular attention to serotonergic medications (eg, SSRIs) due to risk of serotonin syndrome. Several antidepressants are known

Adult Cancer Pain

OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY

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

Convert from Oral Morphine to Oral Methadone[23]

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 to determine the appropriate dose conversion ratio and calculate the oral methadone dose. These ratios take into account the potential for incomplete cross-tolerance and are based on expert consensus.
3. Divide the total daily oral methadone dose into 2–4 daily doses.

Table 2. Dose Conversion Guidelines for Total 24-hour Oral Morphine to Oral Methadone[24]

ORAL MORPHINE	DOSE CONVERSION GUIDELINES
<60 mg	2–7.5 mg methadone per day
60–199 mg	10:1 (and patient <65 years of age)
≥200 mg	20:1 (and/or patient >65 years of age)

Case example converting oral morphine to oral methadone:

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

1. Calculate the total amount of current oral morphine in a 24-hour period for this patient: (30 mg x 6) = 180 mg/day
2. From Table 2 above, calculate equianalgesic dose of oral methadone.
   For 180 mg/day of oral morphine : oral methadone, the dose conversion ratio is 10:1. (180 mg/day morphine ÷ 10) = 18 mg/day oral methadone, which is ≈ 15 mg/day oral methadone.
3. Divide the total daily oral methadone dose into 3 daily doses.
   (reduced dose of 15 mg/day oral methadone ÷ 3 daily doses) = 5 mg oral methadone every 8 hours.
   Discontinue oral morphine 30 mg every 4 hours by a 3-day switch or rapid conversion method when methadone is initiated.

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

*Available online, in these guidelines, at NCCN.org.

[23] Manfredi PL, Houde RW. Prescribing methadone, a unique analgesic. J Support Oncol 2003;1:216-220.
[24] McPherson ML, Walker KA, Davis MP, et al. Safe and appropriate use of methadone in hospice and palliative care: expert consensus white paper, Journal of Pain and Symptom Management (2019), doi: https://doi.org/10.1016/j.jpainsymman.2018.12.001.[Epub ahead of print.]

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. Although 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,[36] other studies have not shown this effect.[37,38] 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).[36]

The most commonly used anticonvulsant drugs for the treatment of cancer pain are gabapentin and pregabalin.[39] They have been studied primarily in noncancer neuropathy syndromes,[40] although data exist supporting their use for treatment of cancer pain in conjunction with opioids.[41,42] Gabapentin has been reported to reduce mucositis pain in patients receiving concomitant radiotherapy and chemotherapy.[43] When compared in a prospective, randomized, open-label trial, pregabalin relieved neuropathic cancer-related pain more effectively than transdermal fentanyl.[44]

Corticosteroids have long been used to relieve neuropathic pain syndromes and have also been effective for treating bone pain due to their anti-inflammatory effects and use in relieving malignant intestinal obstruction.[22,45] A 2015 Cochrane review summarized the existing data for corticosteroid use in cancer pain.[46]

Cannabinoids and Medical Marijuana/Cannabis

In the context of shifting legality, many patients with cancer are using cannabinoids or medical marijuana for treatment of cancer- or cancer treatment-related symptoms.[47,48] To date, the FDA has approved 3 cannabinoids: dronabinol, nabilone, and cannabidiol.[49] Dronabinol and nabilone (both tetrahydrocannabinol [THC] or THC-mimics) have been approved to treat refractory nausea and vomiting associated with cancer treatment, dronabinol has also been approved to treat anorexia and weight loss related to AIDS. Cannabidiol has

Adult Cancer Pain

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

Examples of Adjuvant Analgesics Use

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

- 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, including QTc prolongation, 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 with 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 2–3 times a day. Dose increments of 50%–100% should occur every 3 days. Slower titration is needed for the elderly or medically frail. Dose adjustment is 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 is needed for the elderly or medically frail. Dose adjustment is required for those with renal insufficiency. Pregabalin is more efficiently absorbed through the GI tract than gabapentin.
    - Consider other anticonvulsant agents, many of which have been shown to have efficacy in non-cancer neuropathic pain.

- 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.

PAIN-G 2 OF 2

been approved to treat seizures associated with rare forms of severe epilepsy. Although medical marijuana has been legalized in many states, it has not been FDA-approved for any indication.[49] Furthermore, the US Drug Enforcement Administration classifies marijuana as a Schedule I substance, meaning that it has a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision.[50] Regardless, use of medical marijuana is common among patients with cancer, with some recent studies reporting that as many as 24% to 40% of patients with cancer in the United States use marijuana.[51,52] Therefore, providers should assess for cannabinoid/medical marijuana use and provide education on state and federal regulations, as appropriate.

Data supporting the use of cannabinoids as adjuvant analgesics for treatment of cancer pain are extremely limited and the results from what little data exist are somewhat conflicting. Although 2 randomized, placebo controlled trials have shown that nabiximols (cannabis extract that contains both THC and cannabidiol; it is not approved for use in the United States) significantly reduced cancer-related pain compared with placebo in patients with inadequate analgesia despite chronic opioid administration,[53,54] THC extract alone did not show a significant benefit compared with placebo.[53] Another randomized study reported no significant benefit of nabiximols compared with placebo for treatment of chemotherapy-induced neuropathic pain.[55] In these studies, the most commonly reported adverse events associated with nabiximols were somnolence, fatigue, dizziness, confusion, nausea, dry mouth, and hypotension, although these were noted to be dose-dependent and generally manageable.[53–55] The route of administration can also affect the safety profile of medical marijuana. A recent observational study in a state with legalized marijuana reported that although edible cannabis products accounted for only 0.32% of sales between 2014 and 2016, they accounted for 10.7% of emergency department visits during that time period.[56] The adverse effects that prompted the emergency department visits also differed by route of exposure, with cannabinoid hyperemesis syndrome more common for inhaled cannabis and acute psychiatric symptoms, intoxication, and cardiovascular symptoms more common

Adult Cancer Pain

INTEGRATIVE INTERVENTIONS

Consider integrative interventions in conjunction with pharmacologic interventions as needed. Integrative interventions may be especially important in vulnerable populations (eg, frail, elderly) 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 cognitive, physical, or interventional modalities:

- **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**
  - **CBT, cognitive restructuring**
  - **Behavioral activation**
- **Spiritual care (See NCCN Guidelines for Distress Management†)**
- **Physical modalities**
  - **Bed, bath, and walking supports**
  - **Positioning instruction**
  - **Instruction in therapeutic and conditioning exercise**
  - **Energy conservation, pacing of activities**
  - **Massage**
  - **Heat and/or ice**
  - **Transcutaneous electrical nerve stimulation (TENS)**
  - **Acupuncture or acupressure**
  - **Ultrasonic stimulation**
- **See Interventional Strategies (PAIN-M)**

†To view the most recent version of these guidelines, visit NCCN.org. *Available online, in these guidelines, at NCCN.org.

PAIN-J

for edible cannabis.[56] The authors propose that the delayed onset of effect associated with the edible route may lead users to repeat the dose, potentially resulting in delayed higher plasma concentrations.

Opioids and Miscellaneous Analgesics

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

Pure agonists (such as morphine, oxycodone, oxymorphone, and fentanyl) are the most commonly used medications in the management of cancer pain. The short half-life opioid agonists (morphine, hydromorphone, fentanyl, and oxycodone) are preferred, because they can be more easily titrated than the long half-life opioids (methadone and levorphanol).[57] 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 2 treatment groups, and overall well-being/symptom burden was rated as significantly better in the low-dose morphine arm.[58]

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.[59–61]

Morphine

Morphine is a mu-opioid receptor agonist and weak kappa receptor agonist. Morphine is available in a wide range of formulations and routes, including oral, parenteral, and rectal delivery.[62] In a patient who has not been exposed to opioids in the past, morphine is generally considered the standard starting drug of choice.[63,64] Oral administration is the preferred route. An initial oral

Adult Cancer Pain

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.

PAIN-M

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 intravenous or subcutaneous route. If given parenterally, the equivalent dose is one-third of the oral dose.[65] An initial dose of 2 to 5 mg of intravenous 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 because it accumulates in patients with renal insufficiency.[66,67]

Fentanyl

Fentanyl is a highly lipid-soluble mu-opioid receptor agonist that can be administered by the parenteral, spinal, transdermal, transmucosal, buccal, and intranasal routes.[68,69] Transdermal fentanyl is not indicated for rapid opioid titration and should be recommended only after pain is adequately managed by other opioids in opioid-tolerant patients.[70] 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.[71] Another meta-analysis of randomized controlled trials reported similar results, showing similar effectiveness of cancer pain management between transdermal fentanyl and oral morphine, but lower rates of constipation, nausea, vomiting, drowsiness, and urinary retention with transdermal fentanyl.[72] Conversion from intravenous fentanyl continuous infusion basal rate via patient-controlled analgesia to transdermal fentanyl can be accomplished effectively using a 1:1 conversion ratio.[73] 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 transmucosal immediate release fentanyl is effective in treatment of breakthrough pain in patients with cancer.[74–76]

Hydrocodone

Hydrocodone is a mu- and delta-opioid receptor agonist that may be approximately equipotent with oral morphine; however, its equivalence data are not substantiated.[68] Clinical experience suggests use as a mild, initial use opioid, but effective dose may vary. Hydrocodone is available in immediate-release (IR) formulations mixed with acetaminophen or ibuprofen. Hydrocodone ER preparations (without added nonopioid analgesics) are available.

Codeine

Codeine is a weak mu- and delta-opioid receptor agonist with little direct analgesic effect; it is a prodrug that is hepatically metabolized to codeine-6-glucuronide, norcodeine, morphine, morphine-3-glucuronide, morphine-6-glucuronide, and normorphine.[68,77] 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.[78] Conversely, rapid metabolizers may experience toxicity after codeine administration from more rapid morphine production.[78]

Hydromorphone

Hydromorphone is primarily a mu-opioid receptor agonist and weak delta-opioid receptor agonist that has properties similar to morphine and is available in oral tablets, liquids, suppositories, and parenteral formulations.[68,79] Some evidence suggests that the metabolite of hydromorphone may lead to opioid neurotoxicity, including myoclonus, hyperalgesia, and seizures.[80] This metabolite may be more neurotoxic than the morphine metabolite.[81] In a prospective, open-label trial of 879 patients with cancer, hydromorphone effectively reduced pain that was inadequately controlled by other analgesics.[82] Additionally, randomized controlled trials (RCTs) have shown the clinical noninferiority of once-daily hydromorphone ER compared with twice-daily oxycodone controlled-release[83] and 4 times daily hydromorphone IR compared with 4 times daily oxycodone IR[84] for relieving moderate to severe cancer pain. A Cochrane review found evidence that hydromorphone provides similar effect on pain management as reported for oxycodone or morphine.[85]

Oxycodone and Oxymorphone

Oxycodone is an opioid with agonist activity at the mu-, delta-, and kappa-opioid receptors and is available in IR and ER formulations.[86–88] Oxycodone is also available in combination with acetaminophen; therefore, the acetaminophen dose must be monitored for safe limits to avoid potential hepatic toxicity. Recent Cochrane reviews 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.[89,90] Studies of oxycodone/naloxone formulations showed effective analgesia with reduced opioid-induced constipation for long-term use in cancer-related pain.[91,92]

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

Methadone

Methadone is a mu-opioid receptor agonist and an antagonist at N-methyl-D-aspartate receptors; it is commercially available in multiple strength oral tablets or in an oral or intravenous solution.[68] Individual variations in methadone pharmacokinetics (long half-life ranging from 8 to more than 120 hours) make its usage complex in patients with cancer.[93] Due to its long half-life, high potency, and interindividual variations in pharmacokinetics, methadone, when indicated, should be started by or in consultation with an experienced pain or palliative care specialist. Although many recommendations for methadone rotation exist, the NCCN panel members find the recommendations on the starting doses of methadone outlined in the "Hospice and Palliative Medicine White Paper" to be the easiest to implement.[94] Because the starting dose may need to be titrated up, it is essential to provide the patient with access to adequate, short-acting, breakthrough pain medications during the titration period. The NCCN Guidelines recommend monitoring for drug accumulation and adverse effects, particularly over the first 4 to 7 days, and caution that a steady state may not be reached for several days to 2 weeks. Furthermore, these recommendations should not be applied when converting from methadone to morphine (see PAIN-E 13 of 13, page 986).

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.[95] Studies show that outpatient initiation and rotation to methadone can be successfully done in patients with cancer without serious adverse effects.[96] Retrospective studies have also reported that low-dose methadone may improve pain control when used as a coanalgesic in patients with cancer-related pain that were receiving a different, regularly scheduled opioid analgesic.[97,98]

There is evidence suggesting that high doses of methadone (120 mg and above) may lead to QTc prolongation and torsades de pointes, which may lead to sudden cardiac death.[99–101] 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.[102] The NCCN panel supports the use of baseline and follow-up electrocardiogram for patients treated with methadone as outlined in published recommendations and for patients with cardiac disease, or when methadone is used in patients taking other medications also known to prolong QTc (including TCAs).[94,103] electrocardiogram monitoring should be considered within the patient's goals of care and risk/benefit ratio as discussed with the patient. The following measures may be considered to correct QTc prolongation:

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

Alternate opioids are needed for patients with QTc greater than 500 msec, and are recommended for those with QTc of 450 to 500 msec, concurrently with interventions to correct any reversible causes of prolonged QTc.[103] The decision must be tailored to the individual clinical situation and goals of care. Good communication among the patient, family, and care providers is a critical component of the decision process.

Patients and their families may need to be educated about analgesic utility of methadone. Some may only be familiar with methadone use for maintenance of addiction and be unaware of its utility as a potent opioid analgesic. Patients and caregivers should be educated on the signs of delayed sedation and respiratory depression that may occur 4 to 7 days or longer after initiation of methadone or after titrating the dose upwards.

Levorphanol

Levorphanol is a mu-, delta-, and kappa-opioid receptor agonist. Like methadone, levorphanol also acts as an antagonist at N-methyl-D-aspartate receptors, but it has a shorter half-life and more predictable metabolism.[104] 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.[104] For certain populations (eg, the elderly), levorphanol may offer similar benefits to methadone but with lessened prescribing complexities and adverse effects.[105] One study also demonstrated potential efficacy of levorphanol for treating neuropathic pain.[106]

Miscellaneous Analgesics and Mixed Mechanism Drugs

Tramadol and tapentadol

Tramadol and tapentadol are atypical opioids with a dual mechanism of action on opioid receptors and neurotransmitter reuptake (eg, norepinephrine, serotonin). Tramadol and tapentadol should be used with caution or avoided in patients taking other serotonergic or monoamine oxidase inhibitors (MAOI)-like medications (eg, TCAs, SSRIs, and MAOIs) due to risk of serotonin syndrome.[107] See "Opioid Principles, Prescribing, Titration, Maintenance, and Safety, Miscellaneous Analgesics" (PAIN-E 8 of 13, page 985).

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.[108] Tramadol is available as IR and ER formulations. The NCCN panel recommends a maximum daily dose of 400 mg for IR formulations (100 mg 4 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.[108] 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.[109] However, in a double-blind study of patients with cancer, tramadol produced more adverse effects, including vomiting, dizziness, and weakness, than hydrocodone and codeine.[110] 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.[111]

Tapentadol is an opioid that binds to the mu-opioid receptor and inhibits norepinephrine reuptake.[112,113] It is available as ER and IR formulations and is used for treatment of moderate to severe pain as well as for neuropathic pain. Typical doses start at 50 to 100 mg orally every 4 hours as needed, with a maximal daily dose of 500 mg per day (if using the ER) or 600 mg per day (if using the IR only) due to lack of published data regarding higher doses. Lower doses are recommended for patients with moderate hepatic impairment, and tapentadol should be avoided in patients with severe hepatic or renal impairment. In comparative phase 2–3 studies, the efficacy and safety of tapentadol have been shown as compared with placebo and oxycodone for noncancer

pain.[114–116] Data on tapentadol for treating noncancer pain have also suggested that it may have a lower incidence of gastrointestinal adverse effects than oxycodone.[114] Limited data suggest that there may be a roll for tapentadol in the management of cancer pain,[117,118] but further clinical trials are needed.

Buprenorphine

Buprenorphine, a partial mu-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.[119–123] Therefore, transdermal buprenorphine may be used at a dose of 5 mcg/hour in opioid-naïve patients requiring initiation of LA opioid therapy. In some instances, transmucosal buprenorphine may be more appropriate given a wider range of available doses, a higher maximum dose, and a lower likelihood of causing skin reactions compared with transdermal buprenorphine.

Based on its pharmacokinetics, buprenorphine may be especially appropriate for treating cancer pain in patients with renal impairment.[122] 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.[124] Although transdermal buprenorphine may have some advantages over methadone in the context of cancer treatments that prolong QT, FDA guidelines recommend limiting dose to a maximum of 20 mcg/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

Ketamine is a noncompetitive N-methyl D-aspartate receptor antagonist that blocks glutamate. Low (subanesthetic) 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.[125] A double-blind, randomized, placebo-controlled trial found no significant difference between the outcomes of patients treated for cancer pain with ketamine versus placebo.[126] 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.[127] Some data also suggest that ketamine may improve mood in individuals with depressive disorders.[128–130]

Lidocaine

Although 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 intravenous lidocaine for treatment of cancer pain are limited, case reports and smaller studies have been published that support its use for opioid-refractory cancer pain or postsurgical pain.[131–134] One phase 2, randomized, double-blind crossover study of 50 patients with opioid-refractory cancer pain found that pain relief was better with intravenous lidocaine compared with placebo ($P<.001$). Additionally, more patients were able to decrease their analgesic requirements after administration of intravenous 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.[131] Intravenous 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 intravenous lidocaine may be started at 0.5 to 2 mg/kg/hr (maximum 100 mg/hour), using the lowest dose that controls the patient's pain.[133] Some reports suggest that intravenous lidocaine may be especially useful for cancer-related neuropathic pain.[132–134]

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

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

Oral is the preferred route of administration for chronic opioid therapy.[135–137] 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, intravenous or subcutaneous, is recommended for patients who cannot swallow or absorb opioids enterally. Opioids, given parenterally, may produce fast and effective plasma concentrations in comparison with oral or transdermal opioids. Intravenous route is considered for faster analgesia because of the short lag-time between injection and effect (peak 15 minutes) in comparison with oral dosing (peak 60 minutes).[138] The subcutaneous route has a slower onset and lower peak (30 minutes) effect when compared with the intravenous route.

Analgesic Agents That Are Not Recommended

The following agents are not recommended for patients with cancer: (1) mixed agonist-antagonists (eg, butorphanol, pentazocine); (2) meperidine; and (3) placebos. Mixed agonist-antagonists should not be

used in combination with opioid agonist drugs for cancer pain management. Converting from an agonist to an agonist-antagonist could precipitate 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.[135] Use of placebo in the treatment of pain is unethical.

Opioid Prescription, Titration, and Maintenance

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

The physicians should be aware of potential drug-drug and drug-disease interactions while determining the treatment plan. For a summary of common drug-drug interactions between chemotherapeutics, analgesics, and other commonly prescribed medications, see Table 1 in the complete version of these guidelines, at NCCN.org. 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, long-acting 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. See PAIN-E 7 of 13 (page 984) for oral and parenteral opioid equivalences and relative potency of drugs as compared with morphine based on single-dose studies.

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).[139] 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 1,000 oncology patients, 44% reported incident pain, 41.5% reported spontaneous pain, and 14.5% reported both incident-related and spontaneous breakthrough pain.[140] 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.[141–144]

Initiating Short-Acting Opioids in Opioid-Naïve Patients

The route of administration of an opioid (oral or intravenous) 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 intravenous morphine sulfate or equivalent is recommended. Assessment of efficacy and adverse effects should be performed every 60 minutes for orally administered opioids and every 15 minutes for intravenous opioids to determine a subsequent dose. On 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 intravenously. On reassessment after 2 to 3 cycles of the opioid,

if inadequate response is seen in patients with moderate to severe pain, changing the route of administration from oral to intravenous 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 Dose Reduction

The NCCN panel recommends monitoring patients for situations that may warrant opioid dose reduction. Scenarios where opioid dose reduction may be considered include the patient rarely or never needing breakthrough analgesics, completion of an acute pain event, improvement of pain control through use of nonopioid 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 reevaluated 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. For more information on tapering opioids, see PAIN-E 5 of 13 (page 982) and the VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain.[145]

Preventing Opioid Misuse and Abuse

The NCCN panel 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.[146,147] It examines concurrent misuse; in contrast, SOAPP-R (Screener and Opioid Assessment for Patients with Pain-Revised) or ORT (Opioid Risk Tool) are helpful in predicting which patients being considered for long-term opioid therapy may exhibit aberrant medications behaviors in the future. Potential risk factors for opioid abuse/misuse include the following patient characteristics[148]:

- History of prescription, illicit drug, or alcohol dependence or misuse before cancer diagnosis/treatment
- 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, posttraumatic 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
- History of medication-assisted therapy for substance use disorder

If signs of aberrant opioid use are present, providers should consider limiting or restricting use to avoid risk of diversion. Patients who are actively receiving treatment of addiction should be encouraged to continue with therapy, and care should be coordinated with their addiction specialist. See additional recommendations in "Strategies to Maintain Patient Safety and Minimize the Risk of Opioid Misuse and Abuse During Chronic Opioid Use," (PAIN-E 6 of 13, page 983).

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.[149–154] Chronic opioid therapy may depress the hypothalamic-pituitary axis and cause hypogonadism.[155] Each adverse effect requires a careful assessment and treatment strategy. Management of opioid-induced adverse effects is integral to opioid pain management.[149,156–164]

The details of prophylactic regimens and other measures to prevent opioid-induced adverse effects are provided in "Management of Opioid Adverse Effects," available in the complete version of these guidelines, at NCCN.org.

Constipation

Constipation can almost always be anticipated with opioid treatment, and patients do not develop tolerance to constipation; therefore, administration of a prophylactic bowel regimen is recommended for nearly all patients taking opioids. However, there is limited evidence on which to base the selection of the most appropriate prophylactic bowel regimen. One study showed that addition of the stool softener, docusate, to the laxative, sennosides, was less effective than administering sennosides alone.[165] More recently, an RCT in hospice patients showed that there was no benefit in adding docusate to sennosides compared with sennosides alone.[166] 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 with 8 oz of water 2 times daily along with maintaining adequate fluid intake. Based on the available literature, docusate has not shown benefit and is, therefore, not recommended. Although 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 polyethylene glycol) may be helpful. Opioid rotation to fentanyl or methadone may be considered. Enema with sodium phosphate, saline, or tap water may be helpful because it dilates the bowel, stimulates peristalsis, and lubricates the stool to encourage a bowel movement. However, these types of enemas should be used sparingly with awareness of possible electrolyte abnormalities. The use of rectal suppositories or enemas should be avoided in patients with neutropenia or thrombocytopenia. Additionally, oral laxatives or enemas that contain sodium phosphate should be limited to a maximum dose of once daily in patients at risk for renal dysfunction; optimally, alternative agents can be used.

When response to laxative therapy has not been sufficient, peripherally acting mu opioid receptor antagonists such as oral methylnaltrexone,[167–172] naloxegol,[173] or naldemedine,[174] opioid antagonists that work on receptors in the gastrointestinal system, can be used as a rescue when constipation is clearly related to opioid therapy[175] (methylnaltrexone is FDA approved for opioid-induced constipation in adults with advanced illness who are receiving palliative care; naloxegol and naldemedine are FDA approved for opioid-induced constipation in adults with chronic noncancer pain, including those with chronic pain related to previous cancer or treatment). Other second-line agents include lubiprostone (FDA approved for opioid-induced constipation in adults with noncancer pain including those with chronic pain related to prior cancer or treatment),[176,177] and linaclotide[178] (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.

Nausea and Vomiting

For patients with a prior history of opioid-induced nausea, prophylactic treatment with antiemetic agents is highly recommended. If nausea develops, other causes of nausea (eg, constipation, CNS pathology, chemotherapy, radiation therapy, hypercalcemia) must be assessed. Effective agents that may be considered include phenothiazines such as prochlorperazine or thiethylperazine or dopamine receptor antagonists such as metoclopramide or haloperidol.

If nausea persists despite an as-needed regimen, administer antiemetics around the clock for 1 week and then change dosing as needed. When managing opioid-induced persistent nausea, instead of replacing one antiemetic with another, adding therapies that target different mechanisms of action, resulting in a synergistic effect, may be helpful. Adding serotonin receptor antagonists such as granisetron or ondansetron may be helpful and have a lower rate of CNS effects. Alternative agents such as scopolamine, dronabinol, or olanzapine may also be considered for management of nausea. Olanzapine may be especially helpful for patients with bowel obstruction.[179,180] 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.[181]

If nausea persists for longer than a week, the cause of nausea needs to be reassessed and opioid rotation must be considered. If opioid rotation and the previously described measures have been tried and nausea still persists, neuraxial analgesics, neuroablative techniques, and other interventions could be performed to potentially reduce the opioid dose. Cannabinoids that have been FDA-approved for chemotherapy-induced nausea and vomiting (eg, dronabinol, nabilone) may also be considered in this situation.[182–185] It should be noted that in the context of shifting legality, many patients with cancer are using medical cannabis for treatment of nausea and other cancer- or cancer treatment-related symptoms.[47,48] Although medical cannabis has been legalized in many states, it has not been FDA-approved.[48] Education on state and federal regulations for medical cannabis should be provided (see "Adjuvant Analgesics, Cannabinoids and Medical Marijuana", page 986, for more information).

Pruritus

Pruritus or itchiness is a particularly common and distressing complaint. Pruritus occurs in 10% to 50% of patients receiving opioids. Even in the presence of attentive skin care, opioids can produce recalcitrant pruritus. If pruritus develops, other causes of pruritus such as use of any other medication must first be assessed. Pruritus is more likely to occur early in the course of treatment. If it is persistent despite attempted symptom management, consider changing to another opioid. Careful titration of mixed opioid agonist-antagonists (eg, nalbuphine) or mu-opioid receptor antagonists (eg, naloxone) may help reduce opioid-induced adverse

effects while maintaining analgesic efficacy. The mu-receptor antagonists (eg, naloxone) are also used to reverse the effects of opioid-induced adverse effects,[186] 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 (nonsedating), diphenhydramine (sedating), or promethazine (sedating) may be beneficial. Hydroxyzine, administered by mouth or intramuscular injection, may also be useful.

Delirium

Delirium is a pathophysiologic condition characterized by altered consciousness and inattention, cognitive dysfunction, and disturbed psychomotor behavior. Delirium may be prevented or decreased with various nonpharmacologic interventions or, when delirium is severe and hyperactive, may be managed with a neuroleptic drug such as haloperidol, olanzapine, or risperidone on an as needed basis or by switching to another opioid.[187–190] 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.[191] Patients taking opioids may be screened for driving impairment, if indicated. Driving fitness screens are often performed through occupational therapy.

Sedation

Recognizing the difference between cancer-related fatigue and opioid-induced sedation is critical, because 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 (available at NCCN.org). Sedation may hinder the achievement of dose titration of opioids to levels that provide adequate analgesia.[23] If opioid-induced sedation develops and persists for more than a week, it may be managed by administration of psychostimulants such as methylphenidate, dextroamphetamine, modafinil, or armodafinil, or by adding caffeine. When using CNS stimulants for sedation, the dosing should be limited to morning and early afternoon to avoid insomnia at night. Sedation often precedes respiratory depression; therefore, progressive sedation should be noted and adjustments in care should be made.

Use caution when combining opioid medications with other medications that have a sedating effect (eg, benzodiazepines). The FDA has issued a black box warning about possible serious effects from this combination, including slowed or difficult breathing and death.[192]

Respiratory Depression

Respiratory depression is another adverse effect that is a concern for both physicians and patients. Physicians should be aware that patients with limited cardiopulmonary reserve are more susceptible 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.[193] 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. Although no RCTs have been published, the results of a nonrandomized intervention study showed that patients receiving long-term opioid analgesia who were coprescribed naloxone had fewer opioid-related emergency department visits compared with those who were not prescribed naloxone.[194] 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. Naloxone may be available without a prescription in some localities.

Opioid Rotation

No single opioid is optimal for all patients.[195] If opioid adverse effects are significant, an improved balance between analgesia and adverse effects might be achieved by changing to an alternative opioid. This approach is known as opioid rotation.[149,196,197] Establishing equianalgesic dosing can be challenging; studies have sought to establish safe conversion ratios and methods.[198–202] 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" (PAIN-E 7 of 13, page

984) as well as in the complete version of these guidelines, at NCCN.org.

Opioids and Risk Evaluation and Mitigation Strategy

Although opioids are the principal analgesics for management of moderate to severe pain in the context of a cancer diagnosis, they pose risks to patients and society. The abuse of opioids is an increasing concern. In 2017, 70,237 drug overdose deaths occurred in the United States, including 47,600 drug overdose deaths involving opioid analgesics.[203] Drug poisoning remains the number one cause of injury-related death in the United States.[204] Although ensuring that opioids continue to be prescribed for patients for whom they are appropriate is important, 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.[205] 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.

On September 18, 2018, the FDA approved the Opioid Analgesic REMS program, which covers all opioid analgesics intended for use in an outpatient setting.[206] This program requires that training be made available to all healthcare providers who are involved in the management of patients with pain (eg, nurses, pharmacists) and requires that education cover broader information about pain management, including nonopioid analgesics and nonpharmacologic interventions.[207] The complete list of currently approved REMS programs is available on the FDA website.[208]

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.[148] One exception is the Opioid Risk Tool, the use of which was evaluated in a retrospective chart review of 114 patients with cancer.[209] More research is warranted to determine the best practice for screening methods.

The panel recommends that clinicians use 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 (available at www.nascsa.org). Written agreements or guidelines may help to clarify expectations and parameters for safe use of opioid analgesics. Although further research is needed to evaluate their utility in patients with cancer, such agreements are consistent with evolving CDC and FDA recommendations and may be required in certain states.

Management Strategies for Specific Cancer Pain Syndromes

Moderate to severe cancer pain is treated with opioids as indicated; however, opioids alone may not provide optimal analgesia. When a specific cancer pain syndrome is suspected or documented, additional interventions may be targeted to that pain syndrome (see "Management Strategies for Specific Cancer Pain Syndromes," PAIN-D, page 980). Nonopioid analgesics (such as an NSAID), adjuvant analgesics (antidepressants, anticonvulsants, topical agents, and corticosteroids), integrative interventions (psychologic and physical approaches), and/or interventional strategies may be used in conjunction with opioids to help to improve patient outcomes.[23]

Neuropathic Pain

Cancer-related neuropathic pain is common and can be related to the cancer itself or the acute or chronic effects of cancer treatment.[210] Adjuvant analgesics are particularly important in treating neuropathic pain.[34,35] The most common adjuvant analgesics used for treating neuropathic cancer pain include anticonvulsants, antidepressants, and topical treatments. See previous section on "Adjuvant Analgesics"(page 985) for more information on these agents, including important cautions for their use. Corticosteroids have also long been used to relieve neuropathic pain syndromes, particularly radiculopathies associated with vertebral body compression fractures.

Although a limited number of RCTs support the role of antidepressants as adjuvant analgesics for neuropathic cancer pain, the effectiveness of TCAs for relief of neuropathic cancer pain may be extrapolated from studies conducted in non-cancer-related neuropathic pain.[211–213] Several RCTs have shown that anticonvulsants (pregabalin or gabapentin) provided relief of neuropathic cancer-related pain.[44,214] Likewise, some systematic reviews of trials of patients with cancer pain suggest that adjuvant analgesics (antidepressants and antiepileptics) added to opioids provided additional neuropathic pain relief,[215] although another concluded that combining opioid analgesia with gabapentinoids did not provide significantly improved pain relief (data on amitriptyline, fluvoxamine, and

phenytoin were inconclusive).[216] The likelihood of benefit should be balanced with the risk of adverse effects by clinicians considering adjuvant analgesics for neuropathic pain.

Topical local anesthetic agents can be useful in preventing procedural pain and in relieving some types of cancer-related neuropathic pain. They act locally and are also thought to have some central inhibitory effect on pain. They may be used as an analgesic in combination with an opioid, antidepressant, and/or an anticonvulsant. Both the gel and patch forms of lidocaine have been shown to reduce the pain of postherpetic neuropathy and cancer-related pain.[217–219]

Management of Bone Pain Without an Oncologic Emergency

The clinical complications of bone metastases include debilitating bone pain, which tends to be most prominent with movement, pathologic fractures, spinal cord compression, neurologic complications, and hypercalcemia of malignancy. The term skeletal-related events (SREs) refers to a constellation of skeletal complications including fracture, need for surgery to bone, need for radiation to bone, and spinal cord compression. In some situations, hypercalcemia of malignancy is also included as an SRE. Administration of NSAIDs, acetaminophen, or steroids may improve bone pain control when combined with opioid analgesics.[220–222] Topical diclofenac, including gel or patch, may provide relief for pain due to bone metastases with minimal system effects.[220]

Although bone-modifying agents such as bisphosphonates and RANKL (receptor activator of nuclear factor-kappa-B 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)[223–227] and denosumab (a RANKL inhibitor)[225,228] 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,[225,228,229] although evidence is insufficient to recommend one of these agents over the others.[230] 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.[230]

Surgical and radiation treatment of bone metastases is performed to relieve local bone pain, provide stabilization, and prevent impending fracture or spinal cord compression.[231] In some situations, interventions such as vertebral augmentation provide a greater likelihood of return to ambulatory status than radiation alone. Plain radiographs may be used to identify impending fractures so that the patient can be referred to an orthopedic specialist for stabilization. Consultation with a pain or palliative care specialist for interventional consultation is recommended to determine optimal management strategy for vertebral augmentation.

Ablative strategies such as radiofrequency (RF) ablation or ultrasound 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 who do not attain adequate analgesia without intolerable effects.[232–235] Several small studies have also demonstrated the palliative effects of high-intensity focused ultrasound (HIFU) treatment of bone lesions.[236–238]

Physical and occupational therapy may also be beneficial in the prevention of complications associated with SREs.[239–241]

Management of Pain From Mucositis, Pharyngitis, and Esophagitis

Certain treatments for cancer–including systemic therapy, head and neck radiation, or hematopoietic stem cell transplant; can cause pain in the mouth, pharynx, and esophagus.[242] To prevent mucositis, cryotherapy may be performed by having the patient suck on ice chips or hold ice water in their mouths before, during, and/or after rapid infusions of systemic therapies that are associated with mucositis. Studies have shown this approach to be effective in patients receiving melphalan for multiple myeloma and 5-fluorouracil for solid tumors.[243,244] Gabapentin may be used in combination with opioid or nonopioid analgesics for treatment of mucositis, although studies on the effectiveness of this approach have reported mixed results.[43,245]

Oral care protocols, consisting of good oral hygiene and prophylactic mouth rinses may be used for prevention of mucositis.[246] Prophylactic mouth rinses (also called "magic mouthwash") compositions vary significantly, including ingredients such as antibiotics, antihistamines, antifungals, corticosteroids, and antacids.[247,248] The effectiveness of these ingredients for preventing or treating mucositis and the evidence supporting their use varies. Because of this, bland mouth rinses using ingredients such as sodium bicarbonate are often recommended.[242] The NSAID benzydamine also has some data supporting its use in an oral rinse for the prevention and treatment of mucositis.[249,250] Local anesthetics (eg, lidocaine) may be used to treat mucositis either as component of a mouth rinse or separately, in a liquid or gel formulation.

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. These measures include bowel rest, nasogastric suction, venting gastrostomy, corticosteroids, anticholinergic agents (eg, scopolamine, hyoscyamine, glycopyrrolate), and/or octreotide (see the NCCN Guidelines for Palliative Care). Although metoclopramide should not be used in the setting of full bowel obstruction, it may be considered for partial obstructions. Although evidence supporting the use of H2 blockers for malignant bowel obstruction is lacking,[251] H2 blockers are 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.

Nonpharmacologic 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 nonpharmacologic interventions. A growing body of evidence suggests that the use of nonpharmacologic interventions (physical, cognitive, psychosocial, and spiritual) may serve as valuable additions to pharmacologic interventions.[252–254] The integration of physical, cognitive, psychosocial, and spiritual modalities should be based on assessment of cultural and financial considerations, and are best presented as part of joint and informed decision making (see PAIN-J, page 988).

Physical Interventions

Physical interventions include, but are not limited to, therapeutic or conditioning exercise, physical or occupational therapy, massage, use of heat and/or cold, acupuncture, and acupressure.[255–258]

Cognitive-behavioral Interventions

Cognitive interventions are aimed at enhancing a sense of control over the pain or underlying disease. Mindfulness-based stress reduction, breathing exercises, relaxation, imagery, hypnosis, biofeedback, music, and other behavioral therapies can be very useful.[259–264] Patient-based educational interventions have a significant impact in providing pain relief.[265] 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 mindfulness-based stress reduction. Education provides patients and family/caregivers with the knowledge to use analgesics correctly and to address side effects or unrelieved pain.

Psychosocial interventions

Attention should focus on psychosocial support and providing education to patients and families.[266,267] Psychosocial support can greatly enhance patients' sense of control as well as greatly reduce the family/caregivers' feeling of helplessness.[263] 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.[268]

Spiritual Interventions

In cancer care, there is growing interest in attention to spiritual needs and the existential concerns often associated with pain. Many patients hold cultural beliefs about such treatments, and home remedies, rituals, prayer, and other spiritual practices may be most helpful in relieving or coping with pain. Involvement of spiritual care providers from a range of culturally appropriate spiritual backgrounds is essential.[269] Spiritual needs should be routinely assessed and spiritual care should be incorporated as a component of comprehensive pain management.

Interventional Strategies

Some patients experience inadequate pain 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 shown, in some cases, to eliminate or significantly reduce the level of pain, and they may allow a significant decrease in systemic analgesics (see PAIN-M, page 989). 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.[23,234,235,270–274]

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 it is generally associated with a reduction in adverse effects.[275,276]

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.[277] This approach is a valuable tool to improve analgesia for patients who have pain from a variety of anatomic locations (eg, head and neck, upper and lower extremities, trunk).[278–281] 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.[282–287] 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, ultrasound ablation) for bone lesions can also be helpful in reducing pain.[232–238] See "Management Strategies for Specific Cancer Pain Syndromes, Bone Pain Without an Oncologic Emergency" (PAIN-D, page 980) for more information.

Neurostimulation procedures have been suggested as useful for painful chemotherapy-induced peripheral neuropathies, neuralgias, and complex regional pain syndrome.[288]

The interventional strategies listed previously are not appropriate if patients are unwilling or in patients with infections, coagulopathy, or with very short life expectancies. Also, 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], antiangiogenesis agents [bevacizumab]). The patient may need to stop taking the medication for an appropriate amount of time before 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, uses 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.

References

1. Merskey H, Bugduk N. Classification of Chronic Pain. Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms, 2nd Ed. IASP Press, Seattle, WA. 1994.
2. van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, et al. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. Ann Oncol 2007;18:1437–1449.
3. Te Boveldt N, Vernooij-Dassen M, Burger N, et al. Pain and its interference with daily activities in medical oncology outpatients. Pain Physician 2013;16:379–389.
4. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733–742.
5. Zimmermann C, Swami N, Krzyzanowska M, et al. Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. Lancet 2014;383:1721–1730.
6. Grudzen CR, Richardson LD, Johnson PN, et al. Emergency department-initiated palliative care in advanced cancer: a randomized clinical trial. JAMA Oncol 2016;2:591–598.
7. Ferrell B, Sun V, Hurria A, et al. Interdisciplinary palliative care for patients with lung cancer. J Pain Symptom Manage 2015;50:758–767.
8. Bakitas MA, Tosteson TD, Li Z, et al. Early versus delayed initiation of concurrent palliative oncology care: patient outcomes in the ENABLE III randomized controlled trial. J Clin Oncol 2015;33:1438–1445.
9. Bakitas M, Lyons KD, Hegel MT, et al. Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: the Project ENABLE II randomized controlled trial. JAMA 2009;302:741–749.
10. Greco MT, Roberto A, Corli O, et al. Quality of cancer pain management: an update of a systematic review of undertreatment of patients with cancer. J Clin Oncol 2014;32:4149–4154.
11. Fairchild A. Under-treatment of cancer pain. Curr Opin Support Palliat Care 2010;4:11–15.
12. Passik SD, Weinreb HJ. Managing chronic nonmalignant pain: overcoming obstacles to the use of opioids. Adv Ther 2000;17:70–83.
13. Cleeland CS, Gonin R, Hatfield AK, et al. Pain and its treatment in outpatients with metastatic cancer. N Engl J Med 1994;330:592–596.

14. Martin LA, Hagen NA. Neuropathic pain in cancer patients: mechanisms, syndromes, and clinical controversies. J Pain Symptom Manage 1997;14: 99–117.
15. Mercadante S. Malignant bone pain: pathophysiology and treatment. Pain 1997;69:1–18.
16. Stjernswärd J. WHO cancer pain relief programme. Cancer Surv 1988;7: 195–208.
17. Stjernswärd J, Colleau SM, Ventafridda V. The World Health Organization Cancer Pain and Palliative Care Program. Past, present, and future. J Pain Symptom Manage 1996;12:65–72.
18. U.S. Food and Drug Administration. Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Stratgey (REMS). Silver Spring, MD: 2014. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM289730.pdf. Accessed March 7, 2019.
19. U.S. Food and Drug Administration. Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS). Silver Spring, MD: 2015. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf. Accessed March 7, 2019.
20. Stewart M, Brown JB, Donner A, et al. The impact of patient-centered care on outcomes. J Fam Pract 2000;49:796–804.
21. 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.
22. Mercadante SL, Berchovich M, Casuccio A, et al. A prospective randomized study of corticosteroids as adjuvant drugs to opioids in advanced cancer patients. Am J Hosp Palliat Care 2007;24:13–19.
23. American Pain Society. Principles of Analgesic Use, 7th Ed. American Pain Society, Glenview, IL. 2016.
24. Stockler M, Vardy J, Pillai A, et al. Acetaminophen (paracetamol) improves pain and well-being in people with advanced cancer already receiving a strong opioid regimen: a randomized, double-blind, placebo-controlled cross-over trial. J Clin Oncol 2004;22:3389–3394.
25. American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. J Am Geriatr Soc 2009;57:1331–1346.
26. Israel FJ, Parker G, Charles M, et al. Lack of benefit from paracetamol (acetaminophen) for palliative cancer patients requiring high-dose strong opioids: a randomized, double-blind, placebo-controlled, crossover trial. J Pain Symptom Manage 2010;39:548–554.
27. U.S. Food and Drug Administration. FDA Drug Safety Communication: Prescription acetaminophen products to be limited to 325 mg per dosage unit; boxed warning will highlight potential for severe liver failure. 2011. Available at: http://www.fda.gov/drugs/drugsafety/ucm239821.htm. Accessed March 7, 2019.
28. U.S. Food and Drug Administration. Information for Healthcare Professionals: concomitant use of ibuprofen and aspirin. 2006. Available at: https://www.fda.gov/downloads/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm161282.pdf. Accessed March 7, 2019.
29. Tielemans MM, Eikendal T, Jansen JB, et al. Identification of NSAID users at risk for gastrointestinal complications: a systematic review of current guidelines and consensus agreements. Drug Saf 2010;33: 443–453.
30. Laine L, Curtis SP, Cryer B, et al. Risk factors for NSAID-associated upper GI clinical events in a long-term prospective study of 34 701 arthritis patients. Aliment Pharmacol Ther 2010;32:1240–1248.
31. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes. 2015. Available at: https://www.fda.gov/drugs/drugsafety/ucm451800. Accessed April 12, 2019.
32. Bally M, Dendukuri N, Rich B, et al. Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. BMJ 2017;357:j1909.
33. Lussier D, Huskey AG, Portenoy RK. Adjuvant analgesics in cancer pain management. Oncologist 2004;9:571–591.
34. Manfredi PL, Gonzales GR, Sady R, et al. Neuropathic pain in patients with cancer. J Palliat Care 2003;19:115–118.
35. Jongen JL, Huijsman ML, Jessurun J, et al. The evidence for pharmacologic treatment of neuropathic cancer pain: beneficial and adverse effects. J Pain Symptom Manage 2013;46:581–590 e581.
36. Jin Y, Desta Z, Stearns V, et al. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. J Natl Cancer Inst 2005;97:30–39.
37. Haque R, Shi J, Schottinger JE, et al. Tamoxifen and antidepressant drug interaction in a cohort of 16,887 breast cancer survivors. J Natl Cancer Inst 2016;108:(3)
38. Azoulay L, Dell'Aniello S, Huiart L, et al. Concurrent use of tamoxifen with CYP2D6 inhibitors and the risk of breast cancer recurrence. Breast Cancer Res Treat 2011;126:695–703.
39. Johannessen Landmark C. Antiepileptic drugs in non-epilepsy disorders: relations between mechanisms of action and clinical efficacy. CNS Drugs 2008;22:27–47.
40. Baron R, Brunnmüller U, Brasser M, et al. Efficacy and safety of pregabalin in patients with diabetic peripheral neuropathy or postherpetic neuralgia: Open-label, non-comparative, flexible-dose study. Eur J Pain 2008;12:850–858.
41. Chen DL, Li YH, Wang ZJ, et al. The research on long-term clinical effects and patients' satisfaction of gabapentin combined with oxycontin in treatment of severe cancer pain. Medicine (Baltimore) 2016;95:e5144.
42. Dou Z, Jiang Z, Zhong J. Efficacy and safety of pregabalin in patients with neuropathic cancer pain undergoing morphine therapy. Asia Pac J Clin Oncol 2017;13:e57–e64.
43. Bar Ad V, Weinstein G, Dutta PR, et al. Gabapentin for the treatment of pain syndrome related to radiation-induced mucositis in patients with head and neck cancer treated with concurrent chemoradiotherapy. Cancer 2010;116:4206–4213.
44. Raptis E, Vadalouca A, Stavropoulou E, et al. Pregabalin vs. opioids for the treatment of neuropathic cancer pain: a prospective, head-to-head, randomized, open-label study. Pain Pract 2014;14:32–42.
45. Wooldridge JE, Anderson CM, Perry MC. Corticosteroids in advanced cancer. Oncology (Williston Park) 2001;15:225–234., discussion 234–236.
46. Haywood A, Good P, Khan S, et al. Corticosteroids for the management of cancer-related pain in adults. Cochrane Database Syst Rev 2015;4: CD010756.
47. Donovan KA, Chang YD, Oberoi-Jassal R, et al. Relationship of cannabis use to patient-reported symptoms in cancer patients seeking supportive/palliative care [published online February 22, 2019]. J Palliat Med. doi: 10.1089/jpm.2018.0533
48. Steele G, Arneson T, Zylla D. A comprehensive review of cannabis in patients with cancer: availability in the USA, general efficacy, and safety. Curr Oncol Rep 2019;21:10.
49. National Center for Complementary and Integrative Health. Marijuana and Cannabinoids. 2019. Available at: https://nccih.nih.gov/health/marijuana. Accessed April 25, 2019.
50. Drugs of Abuse: a DEA Resource Guide; 2017. Available at: https://www.dea.gov/sites/default/files/sites/getsmartaboutdrugs.com/files/publications/DoA_2017Ed_Updated_6.16.17.pdf.
51. Pergam SA, Woodfield MC, Lee CM, et al. Cannabis use among patients at a comprehensive cancer center in a state with legalized medicinal and recreational use. Cancer 2017;123:4488–4497.
52. Tringale KR, Huynh-Le MP, Salans M, et al. The role of cancer in marijuana and prescription opioid use in the United States: A population-based analysis from 2005 to 2014. Cancer 2019;125:2242–2251.
53. Johnson JR, Burnell-Nugent M, Lossignol D, et al. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. J Pain Symptom Manage 2010;39:167–179.
54. Portenoy RK, Ganae-Motan ED, Allende S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain 2012;13: 438–449.
55. Lynch ME, Cesar-Rittenberg P, Hohmann AG. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. J Pain Symptom Manage 2014;47:166–173.
56. Monte AA, Shelton SK, Mills E, et al. Acute illness associated with cannabis use, by route of exposure: an observational study. Ann Intern Med 2019;170:531–537.
57. Cherny NI. The pharmacologic management of cancer pain. Oncology (Williston Park) 2004;18:1499–1515., discussion 1516, 1520–1521., 1522, 1524.
58. Bandieri E, Romero M, Ripamonti CI, et al.Early Strong Opioid Treatment Study (ESOT) Investigators. Randomized trial of low-dose morphine

versus weak opioids in moderate cancer pain. J Clin Oncol 2016;34:436–442.

59. Andersen G, Jensen NH, Christrup L, et al. Pain, sedation and morphine metabolism in cancer patients during long-term treatment with sustained-release morphine. Palliat Med 2002;16:107–114.
60. Smith MT. Neuroexcitatory effects of morphine and hydromorphone: evidence implicating the 3-glucuronide metabolites. Clin Exp Pharmacol Physiol 2000;27:524–528.
61. Sande TA, Laird BJ, Fallon MT. The use of opioids in cancer patients with renal impairment-a systematic review. Support Care Cancer 2017;25:661–675.
62. Mercadante S. Intravenous morphine for management of cancer pain. Lancet Oncol 2010;11:484–489.
63. Klepstad P, Kaasa S, Borchgrevink PC. Start of oral morphine to cancer patients: effective serum morphine concentrations and contribution from morphine-6-glucuronide to the analgesia produced by morphine. Eur J Clin Pharmacol 2000;55:713–719.
64. Klepstad P, Kaasa S, Skauge M, et al. Pain intensity and side effects during titration of morphine to cancer patients using a fixed schedule dose escalation. Acta Anaesthesiol Scand 2000;44:656–664.
65. Foley KM. The treatment of pain in the patient with cancer. CA Cancer J Clin 1986;36:194–215.
66. Tiseo PJ, Thaler HT, Lapin J, et al. Morphine-6-glucuronide concentrations and opioid-related side effects: a survey in cancer patients. Pain 1995;61:47–54.
67. Portenoy RK, Foley KM, Stulman J, et al. Plasma morphine and morphine-6-glucuronide during chronic morphine therapy for cancer pain: plasma profiles, steady-state concentrations and the consequences of renal failure. Pain 1991;47:13–19.
68. Trescot AM, Datta S, Lee M, et al. Opioid pharmacology. Pain Physician 2008; 11(2, Suppl)S133–S153.
69. Mercadante S, Vellucci R, Cuomo A, et al. Long-term efficacy and tolerability of intranasal fentanyl in the treatment of breakthrough cancer pain. Support Care Cancer 2015;23:1349–1354.
70. Caraceni A, Hanks G, Kaasa S, et al.European Association for Palliative Care (EAPC). Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncol 2012;13:e58–e68.
71. Hadley G, Derry S, Moore RA, et al. Transdermal fentanyl for cancer pain. Cochrane Database Syst Rev 2013;10:CD010270.
72. Wang DD, Ma TT, Zhu HD, et al. Transdermal fentanyl for cancer pain: trial sequential analysis of 3406 patients from 35 randomized controlled trials. J Cancer Res Ther 2018; 14(8, Supplement)14–21.
73. Kornick CA, Santiago-Palma J, Khojainova N, et al. A safe and effective method for converting cancer patients from intravenous to transdermal fentanyl. Cancer 2001;92:3056–3061.
74. Portenoy RK, Taylor D, Messina J, et al. A randomized, placebo-controlled study of fentanyl buccal tablet for breakthrough pain in opioid-treated patients with cancer. Clin J Pain 2006;22:805–811.
75. Weinstein SM, Messina J, Xie F. Fentanyl buccal tablet for the treatment of breakthrough pain in opioid-tolerant patients with chronic cancer pain: A long-term, open-label safety study. Cancer 2009;115:2571–2579.
76. Kleeberg UR, Filbet M, Zeppetella G. Fentanyl buccal tablet for breakthrough cancer pain: why titrate? Pain Pract 2011;11:185–190.
77. Srinivasan V, Wielbo D, Tebbett IR. Analgesic effects of codeine-6-glucuronide after intravenous administration. Eur J Pain 1997;1:185–190.
78. Kirchheiner J, Schmidt H, Tzvetkov M, et al. Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. Pharmacogenomics J 2007;7:257–265.
79. Murray A, Hagen NA. Hydromorphone. J Pain Symptom Manage 2005;29(Suppl):57–66.
80. Thwaites D, McCann S, Broderick P. Hydromorphone neuroexcitation. J Palliat Med 2004;7:545–550.
81. Wright AW, Mather LE, Smith MT. Hydromorphone-3-glucuronide: a more potent neuro-excitant than its structural analogue, morphine-3-glucuronide. Life Sci 2001;69:409–420.
82. Han HS, Lee KH, Lee KH, et al. A prospective, open-label, multicenter study of the clinical efficacy of extended-release hydromorphone in treating cancer pain inadequately controlled by other analgesics. Support Care Cancer 2014;22:741–750.
83. Yu S, Shen W, Yu L, et al. Safety and efficacy of once-daily hydromorphone extended-release versus twice-daily oxycodone hydrochloride controlled-release in chinese patients with cancer pain: a phase 3, randomized, double-blind, multicenter study. J Pain 2014;15:835–844.
84. Inoue S, Saito Y, Tsuneto S, et al. A randomized, double-blind, non-inferiority study of hydromorphone hydrochloride immediate-release tablets versus oxycodone hydrochloride immediate-release powder for cancer pain: efficacy and safety in Japanese cancer patients. Jpn J Clin Oncol 2018;48:542–547.
85. Bao YJ, Hou W, Kong XY, et al. Hydromorphone for cancer pain. Cochrane Database Syst Rev 2016;10:CD011108.
86. Davis MP, Varga J, Dickerson D, et al. Normal-release and controlled-release oxycodone: pharmacokinetics, pharmacodynamics, and controversy. Support Care Cancer 2003;11:84–92.
87. Ordóñez Gallego A, González Barón M, Espinosa Arranz E. Oxycodone: a pharmacological and clinical review. Clin Transl Oncol 2007;9:298–307.
88. Gabrail NY, Dvergsten C, Ahdieh H. Establishing the dosage equivalency of oxymorphone extended release and oxycodone controlled release in patients with cancer pain: a randomized controlled study. Curr Med Res Opin 2004;20:911–918.
89. Schmidt-Hansen M, Bennett MI, Arnold S, et al. Oxycodone for cancer-related pain. Cochrane Database Syst Rev 2017;8:CD003870.
90. Schmidt-Hansen M, Bennett MI, Arnold S, et al. Efficacy, tolerability and acceptability of oxycodone for cancer-related pain in adults: an updated Cochrane systematic review. BMJ Support Palliat Care 2018;8:117–128.
91. Ahmedzai SH, Nauck F, Bar-Sela G, et al. A randomized, double-blind, active-controlled, double-dummy, parallel-group study to determine the safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate/severe, chronic cancer pain. Palliat Med 2012;26:50–60.
92. Ahmedzai SH, Leppert W, Janecki M, et al. Long-term safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate-to-severe chronic cancer pain. Support Care Cancer 2015;23:823–830.
93. Davis MP, Homsi J. The importance of cytochrome P450 monooxygenase CYP2D6 in palliative medicine. Support Care Cancer 2001;9:442–451.
94. McPherson ML, Walker KA, Davis MP, et al. Safe and appropriate use of methadone in hospice and palliative care: expert consensus white paper. J Pain Symptom Manage 2019;57:635–645.
95. Nicholson AB, Watson GR, Derry S, et al. Methadone for cancer pain. Cochrane Database Syst Rev 2017;2:CD003971.
96. Parsons HA, de la Cruz M, El Osta B, et al. Methadone initiation and rotation in the outpatient setting for patients with cancer pain. Cancer 2010;116:520–528.
97. Courtemanche F, Dao D, Gagné F, et al. Methadone as a coanalgesic for palliative care cancer patients. J Palliat Med 2016;19:972–978.
98. Fürst P, Lundström S, Klepstad P, et al. Improved pain control in terminally ill cancer patients by introducing low-dose oral methadone in addition to ongoing opioid treatment. J Palliat Med 2018;21:177–181.
99. Krantz MJ, Lewkowiez L, Hays H, et al. Torsade de pointes associated with very-high-dose methadone. Ann Intern Med 2002;137:501–504.
100. Krantz MJ, Kutinsky IB, Robertson AD, et al. Dose-related effects of methadone on QT prolongation in a series of patients with torsade de pointes. Pharmacotherapy 2003;23:802–805.
101. Kornick CA, Kilborn MJ, Santiago-Palma J, et al. QTc interval prolongation associated with intravenous methadone. Pain 2003;105:499–506.
102. Reddy S, Hui D, El Osta B, et al. The effect of oral methadone on the QTc interval in advanced cancer patients: a prospective pilot study. J Palliat Med 2010;13:33–38.
103. Chou R, Cruciani RA, Fiellin DA, et al.Heart Rhythm Society. 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;15:321–337.
104. McNulty JP. Can levorphanol be used like methadone for intractable refractory pain? J Palliat Med 2007;10:293–296.
105. Atkinson TJ, Fudin J, Pandula A, et al. Medication pain management in the elderly: unique and underutilized analgesic treatment options. Clin Ther 2013;35:1669–1689.
106. Rowbotham MC, Twilling L, Davies PS, et al. Oral opioid therapy for chronic peripheral and central neuropathic pain. N Engl J Med 2003;348:1223–1232.

107. Beakley BD, Kaye AM, Kaye AD. Tramadol, pharmacology, side effects, and serotonin syndrome: a review. Pain Physician 2015;18:395–400.
108. Grond S, Sablotzki A. Clinical pharmacology of tramadol. Clin Pharmacokinet 2004;43:879–923.
109. Grond S, Radbruch L, Meuser T, et al. High-dose tramadol in comparison to low-dose morphine for cancer pain relief. J Pain Symptom Manage 1999;18:174–179.
110. Rodriguez RF, Bravo LE, Castro F, et al. Incidence of weak opioids adverse events in the management of cancer pain: a double-blind comparative trial. J Palliat Med 2007;10:56–60.
111. Wiffen PJ, Derry S, Moore RA. Tramadol with or without paracetamol (acetaminophen) for cancer pain. Cochrane Database Syst Rev 2017;5: CD012508.
112. Wade WE, Spruill WJ. Tapentadol hydrochloride: a centrally acting oral analgesic. Clin Ther 2009;31:2804–2818.
113. Hartrick CT, Rodríguez Hernandez JR. Tapentadol for pain: a treatment evaluation. Expert Opin Pharmacother 2012;13:283–286.
114. Afilalo M, Etropolski MS, Kuperwasser B, et al. Efficacy and safety of tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study. Clin Drug Investig 2010;30:489–505.
115. Buynak R, Shapiro DY, Okamoto A, et al. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled phase III study. Expert Opin Pharmacother 2010;11: 1787–1804.
116. Schwartz S, Etropolski M, Shapiro DY, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. Curr Med Res Opin 2011;27:151–162.
117. Mercadante S, Porzio G, Ferrera P, et al. Tapentadol in cancer pain management: a prospective open-label study. Curr Med Res Opin 2012; 28:1775–1779.
118. Mercadante S, Porzio G, Adile C, et al. Tapentadol at medium to high doses in patients previously receiving strong opioids for the management of cancer pain. Curr Med Res Opin 2014;30:2063–2068.
119. Naing C, Aung K, Racloz V, et al. Safety and efficacy of transdermal buprenorphine for the relief of cancer pain. J Cancer Res Clin Oncol 2013;139:1963–1970.
120. 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.
121. Deandrea S, Corli O, Moschetti I, et al. Managing severe cancer pain: the role of transdermal buprenorphine: a systematic review. Ther Clin Risk Manag 2009;5:707–718.
122. Melilli G, Samolsky Dekel BG, Frenquelli C, et al. Transdermal opioids for cancer pain control in patients with renal impairment. J Opioid Manag 2014;10:85–93.
123. Lundorff L, Sjøgren P, Hansen OB, et al. Switching from high doses of pure μ-opioid agonists to transdermal buprenorphine in patients with cancer: a feasibility study. J Opioid Manag 2013;9:255–262.
124. Johnson RE, Fudala PJ, Payne R. Buprenorphine: considerations for pain management. J Pain Symptom Manage 2005;29:297–326.
125. Bell RF, Eccleston C, Kalso EA. Ketamine as an adjuvant to opioids for cancer pain. Cochrane Database Syst Rev 2017;6:CD003351.
126. Hardy J, Quinn S, Fazekas B, et al. Randomized, double-blind, placebo-controlled study to assess the efficacy and toxicity of subcutaneous ketamine in the management of cancer pain. J Clin Oncol 2012;30: 3611–3617.
127. Bredlau AL, Thakur R, Korones DN, et al. Ketamine for pain in adults and children with cancer: a systematic review and synthesis of the literature. Pain Med 2013;14:1505–1517.
128. DeWilde KE, Levitch CF, Murrough JW, et al. The promise of ketamine for treatment-resistant depression: current evidence and future directions. Ann N Y Acad Sci 2015;1345:47–58.
129. Fond G, Loundou A, Rabu C, et al. Ketamine administration in depressive disorders: a systematic review and meta-analysis. Psychopharmacology (Berl) 2014;231:3663–3676.
130. Lee EE, Della Selva MP, Liu A, et al. Ketamine as a novel treatment for major depressive disorder and bipolar depression: a systematic review and quantitative meta-analysis. Gen Hosp Psychiatry 2015;37:178–184.
131. Sharma S, Rajagopal MR, Palat G, et al. A phase II pilot study to evaluate use of intravenous lidocaine for opioid-refractory pain in cancer patients. J Pain Symptom Manage 2009;37:85–93.
132. Jendoubi A, Naceur IB, Bouzouita A, et al. A comparison between intravenous lidocaine and ketamine on acute and chronic pain after open nephrectomy: A prospective, double-blind, randomized, placebo-controlled study. Saudi J Anaesth 2017;11:177–184.
133. Ferrini R, Paice JA. How to initiate and monitor infusional lidocaine for severe and/or neuropathic pain. J Support Oncol 2004;2:90–94.
134. Carroll I. Intravenous lidocaine for neuropathic pain: diagnostic utility and therapeutic efficacy. Curr Pain Headache Rep 2007;11:20–24.
135. Bruera E, Kim HN. Cancer pain. JAMA 2003;290:2476–2479.
136. Portenoy RK, Lesage P. Management of cancer pain. Lancet 1999;353: 1695–1700.
137. Stevens RA, Ghazi SM. Routes of opioid analgesic therapy in the management of cancer pain. Cancer Contr 2000;7:132–141.
138. Harris JT, Suresh Kumar K, Rajagopal MR. Intravenous morphine for rapid control of severe cancer pain. Palliat Med 2003;17:248–256.
139. Nijland L, Schmidt P, Frosch M, et al. Subcutaneous or intravenous opioid administration by patient-controlled analgesia in cancer pain: a systematic literature review. Support Care Cancer 2019;27:33–42.
140. Davies A, Buchanan A, Zeppetella G, et al. Breakthrough cancer pain: an observational study of 1000 European oncology patients. J Pain Symptom Manage 2013;46:619–628.
141. Zeppetella G, Davies AN. Opioids for the management of breakthrough pain in cancer patients. Cochrane Database Syst Rev 2013;10: CD004311.
142. Mercadante S. Pharmacotherapy for breakthrough cancer pain. Drugs 2012;72:181–190.
143. Jandhyala R, Fullarton JR, Bennett MI. Efficacy of rapid-onset oral fentanyl formulations vs. oral morphine for cancer-related breakthrough pain: a meta-analysis of comparative trials. J Pain Symptom Manage 2013;46:573–580.
144. Zeppetella G, Davies A, Eijgelshoven I, Jansen JP. A network meta-analysis of the efficacy of opioid analgesics for the management of breakthrough cancer pain episodes. J Pain Symptom Manage 2014;47: 772–785.
145. VA/DoD clinical practice guideline for opioid therapy for chronic pain. Version 3.0. 2017. Available at: https://www.healthquality.va.gov/guidelines/Pain/cot/VADoDOTCPG022717.pdf. Accessed March 7, 2019.
146. Butler SF, Budman SH, Fernandez KC, et al. Development and validation of the Current Opioid Misuse Measure. Pain 2007;130:144–156.
147. Meltzer EC, Rybin D, Saitz R, et al. Identifying prescription opioid use disorder in primary care: diagnostic characteristics of the Current Opioid Misuse Measure (COMM). Pain 2011;152:397–402.
148. Anghelescu DL, Ehrentraut JH, Faughnan LG. Opioid misuse and abuse: risk assessment and management in patients with cancer pain. J Natl Compr Canc Netw 2013;11:1023–1031.
149. McNicol E, Horowicz-Mehler N, Fisk RA, et al.Americal Pain Society. Management of opioid side effects in cancer-related and chronic non-cancer pain: a systematic review. J Pain 2003;4:231–256.
150. Mercadante S. Comments on Wang et al., PAIN, 67 (1996) 407-416. Pain 1998;74:106–107.
151. Mercadante S. Pathophysiology and treatment of opioid-related myoclonus in cancer patients. Pain 1998;74:5–9.
152. Wilson RK, Weissman DE. Neuroexcitatory effects of opioids: patient assessment #57. J Palliat Med 2004;7:579–581.
153. Moryl N, Carver A, Foley KM. Pain and palliation. In: Holland JF, Frei E, eds. Cancer Medicine. Vol. I7th ed. Hamilton, ON: BC Decker Inc; 2006: 1113-1124.
154. Moryl N, Obbens EA, Ozigbo OH, et al. Analgesic effect of gefitinib in the treatment of non-small cell lung cancer. J Support Oncol 2006;4:111.
155. Rajagopal A, Vassilopoulou-Sellin R, Palmer JL, et al. Symptomatic hypogonadism in male survivors of cancer with chronic exposure to opioids. Cancer 2004;100:851–858.
156. Boettger S, Breitbart W. Atypical antipsychotics in the management of delirium: a review of the empirical literature. Palliat Support Care 2005;3: 227–237.
157. Breitbart W, Marotta R, Platt MM, et al. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. Am J Psychiatry 1996;153:231–237.

158. Bruera E, Belzile M, Neumann C, et al. A double-blind, crossover study of controlled-release metoclopramide and placebo for the chronic nausea and dyspepsia of advanced cancer. J Pain Symptom Manage 2000;19: 427–435.
159. Challoner KR, McCarron MM, Newton EJ. Pentazocine (Talwin) intoxication: report of 57 cases. J Emerg Med 1990;8:67–74.
160. Katcher J, Walsh D. Opioid-induced itching: morphine sulfate and hydromorphone hydrochloride. J Pain Symptom Manage 1999;17: 70–72.
161. Marinella MA. Acute colonic pseudo-obstruction complicated by cecal perforation in a patient with Parkinson's disease. South Med J 1997;90: 1023–1026.
162. Reissig JE, Rybarczyk AM. Pharmacologic treatment of opioid-induced sedation in chronic pain. Ann Pharmacother 2005;39:727–731.
163. Tarcatu D, Tamasdan C, Moryl N, et al. Are we still scratching the surface? A case of intractable pruritus following systemic opioid analgesia. J Opioid Manag 2007;3:167–170.
164. Prommer E. Modafinil: is it ready for prime time? J Opioid Manag 2006; 2:130–136.
165. Hawley PH, Byeon JJ. A comparison of sennosides-based bowel protocols with and without docusate in hospitalized patients with cancer. J Palliat Med 2008;11:575–581.
166. Tarumi Y, Wilson MP, Szafran O, et al. Randomized, double-blind, placebo-controlled trial of oral docusate in the management of constipation in hospice patients. J Pain Symptom Manage 2013;45:2–13.
167. Rauck R, Slatkin NE, Stambler N, et al. Randomized, double-blind trial of oral methylnaltrexone for the treatment of opioid-induced constipation in patients with chronic noncancer pain. Pain Pract 2017;17:820–828.
168. Michna E, Blonsky ER, Schulman S, et al. Subcutaneous methylnaltrexone for treatment of opioid-induced constipation in patients with chronic, nonmalignant pain: a randomized controlled study. J Pain 2011; 12:554–562.
169. Portenoy RK, Thomas J, Moehl Boatwright ML, et al. Subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with advanced illness: a double-blind, randomized, parallel group, dose-ranging study. J Pain Symptom Manage 2008;35:458–468.
170. Chappell D, Rehm M, Conzen P. Methylnaltrexone for opioid-induced constipation in advanced illness. N Engl J Med 2008;359:1071.
171. Sanz Rubiales A, del Valle Rivero ML. Methylnaltrexone for opioid-induced constipation in advanced illness. N Engl J Med 2008;359: 1070–1071.
172. Thomas J, Karver S, Cooney GA, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. N Engl J Med 2008;358: 2332–2343.
173. Chey WD, Webster L, Sostek M, et al. Naloxegol for opioid-induced constipation in patients with noncancer pain. N Engl J Med 2014;370: 2387–2396.
174. Katakami N, Harada T, Murata T, et al. Randomized phase III and extension studies of naldemedine in patients with opioid-induced constipation and cancer. J Clin Oncol 2017;35:3859–3866.
175. Nee J, Zakari M, Sugarman MA, et al. Efficacy of treatments for opioid-induced constipation: systematic review and meta-analysis. Clin Gastroenterol Hepatol 2018;16:1569–1584.
176. Cryer B, Katz S, Vallejo R, et al. A randomized study of lubiprostone for opioid-induced constipation in patients with chronic noncancer pain. Pain Med 2014;15:1825–1834.
177. Jamal MM, Adams AB, Jansen JP, et al. A randomized, placebo-controlled trial of lubiprostone for opioid-induced constipation in chronic noncancer pain. Am J Gastroenterol 2015;110:725–732.
178. Chang L, Lembo AJ, Lavins BJ, et al. The impact of abdominal pain on global measures in patients with chronic idiopathic constipation, before and after treatment with linaclotide: a pooled analysis of two randomised, double-blind, placebo-controlled, phase 3 trials. Aliment Pharmacol Ther 2014;40:1302–1312.
179. Kaneishi K, Kawabata M, Morita T. Olanzapine for the relief of nausea in patients with advanced cancer and incomplete bowel obstruction. J Pain Symptom Manage 2012;44:604–607.
180. Navari RM, Nagy CK, Gray SE. The use of olanzapine versus metoclopramide for the treatment of breakthrough chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy. Support Care Cancer 2013;21:1655–1663.
181. Bruera E, Seifert L, Watanabe S, et al. Chronic nausea in advanced cancer patients: a retrospective assessment of a metoclopramide-based antiemetic regimen. J Pain Symptom Manage 1996;11:147–153.
182. Herman TS, Einhorn LH, Jones SE, et al. Superiority of nabilone over prochlorperazine as an antiemetic in patients receiving cancer chemotherapy. N Engl J Med 1979;300:1295–1297.
183. Steele N, Gralla RJ, Braun DW Jr, et al. Double-blind comparison of the antiemetic effects of nabilone and prochlorperazine on chemotherapy-induced emesis. Cancer Treat Rep 1980;64:219–224.
184. Sallan SE, Cronin C, Zelen M, et al. Antiemetics in patients receiving chemotherapy for cancer: a randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. N Engl J Med 1980;302: 135–138.
185. Sallan SE, Zinberg NE, Frei E III. Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy. N Engl J Med 1975;293:795–797.
186. Chamberlain JM, Klein BL. A comprehensive review of naloxone for the emergency physician. Am J Emerg Med 1994;12:650–660.
187. Gagnon P, Allard P, Mâsse B, et al. Delirium in terminal cancer: a prospective study using daily screening, early diagnosis, and continuous monitoring. J Pain Symptom Manage 2000;19:412–426.
188. Agar MR, Lawlor PG, Quinn S, et al. Efficacy of oral risperidone, haloperidol, or placebo for symptoms of delirium among patients in palliative care: a randomized clinical trial. JAMA Intern Med 2017;177:34–42.
189. Hirst JM, Vaughan CL, Irwin SA. Delirium: use antipsychotics when appropriate and appropriately. J Palliat Med 2017;20:799.
190. Hui D, Frisbee-Hume S, Wilson A, et al. Effect of lorazepam with haloperidol vs haloperidol alone on agitated delirium in patients with advanced cancer receiving palliative care: a randomized clinical trial. JAMA 2017;318:1047–1056.
191. Bruera E, Macmillan K, Hanson J, et al. The cognitive effects of the administration of narcotic analgesics in patients with cancer pain. Pain 1989;39:13–16.
192. U.S. Food and Drug Administration. FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. 2016. Available at: https://www.fda.gov/downloads/drugs/drugsafety/ucm518672.pdf. Accessed March 7, 2019.
193. Prescribing information. NARCAN® (naloxone hydrochloride) nasal spray. 2017. Available at: https://www.narcan.com/pdf/NARCAN-Prescribing-Information.pdf. Accessed March 7, 2019.
194. Coffin PO, Behar E, Rowe C, et al. Nonrandomized intervention study of naloxone coprescription for primary care patients receiving long-term opioid therapy for pain. Ann Intern Med 2016;165:245–252.
195. Slatkin NE. Opioid switching and rotation in primary care: implementation and clinical utility. Curr Med Res Opin 2009;25:2133–2150.
196. Vissers KC, Besse K, Hans G, et al. Opioid rotation in the management of chronic pain: where is the evidence? Pain Pract 2010;10:85–93.
197. Schuster M, Bayer O, Heid F, et al. Opioid rotation in cancer pain treatment. Dtsch Arztebl Int 2018;115:135–142.
198. Reddy A, Yennurajalingam S, Desai H, et al. The opioid rotation ratio of hydrocodone to strong opioids in cancer patients. Oncologist 2014;19: 1186–1193.
199. Davis MP, McPherson ML. Tabling hydromorphone: do we have it right? J Palliat Med 2010;13:365–366.
200. Reddy A, Tayjasanant S, Haider A, et al. The opioid rotation ratio of strong opioids to transdermal fentanyl in cancer patients. Cancer 2016; 122:149–156.
201. Reddy A, Yennurajalingam S, Reddy S, et al. The opioid rotation ratio from transdermal fentanyl to "strong" opioids in patients with cancer pain. J Pain Symptom Manage 2016;51:1040–1045.
202. McLean S, Twomey F. Methods of rotation from another strong opioid to methadone for the management of cancer pain: a systematic review of the available evidence. J Pain Symptom Manage 2015;50:248–259.
203. Scholl L, Seth P, Kariisa M, et al. Drug and opioid-involved overdose deaths - United States, 2013-2017. MMWR Morb Mortal Wkly Rep 2018; 67:1419–1427.
204. Dart RC, Surratt HL, Cicero TJ, et al. Trends in opioid analgesic abuse and mortality in the United States. N Engl J Med 2015;372:241–248.
205. U.S. Food and Drug Administration. Risk Evaluation and Mitigation Strategy (REMS) for opioid analgesics. 2017. Available at: https://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm163647.htm. Accessed December 1, 2017.
206. FDA takes important steps to encourage appropriate and rational prescribing of opioids through final approval of new safety measures governing the use of immediate-release opioid analgesic medications;

2018. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm620935.htm.
207. FDA Education Blueprint for health care providers involved in the treatment and monitoring of patients with pain. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/rems/Opioid_analgesic_2018_09_18_FDA_Blueprint.pdf.
208. U.S. Food and Drug Administration. Approved Risk Evaluation and Mitigation Strategies (REMS). Available at: http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm. Accessed January 28, 2019.
209. Barclay JS, Owens JE, Blackhall LJ. Screening for substance abuse risk in cancer patients using the Opioid Risk Tool and urine drug screen. Support Care Cancer 2014;22:1883–1888.
210. Fallon MT. Neuropathic pain in cancer. Br J Anaesth 2013;111:105–111.
211. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. Cochrane Database Syst Rev 2005; (3):CD005454.
212. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain: a Cochrane review. J Neurol Neurosurg Psychiatry 2010;81:1372–1373.
213. Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. Pain 2010;150:573–581.
214. Caraceni A, Zecca E, Bonezzi C, et al. Gabapentin for neuropathic cancer pain: a randomized controlled trial from the Gabapentin Cancer Pain Study Group. J Clin Oncol 2004;22:2909–2917.
215. Bennett MI. Effectiveness of antiepileptic or antidepressant drugs when added to opioids for cancer pain: systematic review. Palliat Med 2011; 25:553–559.
216. Kane CM, Mulvey MR, Wright S, et al. Opioids combined with antidepressants or antiepileptic drugs for cancer pain: Systematic review and meta-analysis. Palliat Med 2018;32:276–286.
217. Fleming JA, O'Connor BD. Use of lidocaine patches for neuropathic pain in a comprehensive cancer centre. Pain Res Manag 2009;14:381–388.
218. Gammaitoni AR, Alvarez NA, Galer BS. Safety and tolerability of the lidocaine patch 5%, a targeted peripheral analgesic: a review of the literature. J Clin Pharmacol 2003;43:111–117.
219. Garzón-Rodríguez C, Casals Merchan M, Calsina-Berna A, et al. Lidocaine 5 % patches as an effective short-term co-analgesic in cancer pain. Preliminary results. Support Care Cancer 2013;21:3153–3158.
220. Liu Z, Xu Y, Liu ZL, et al. Combined application of diclofenac and celecoxib with an opioid yields superior efficacy in metastatic bone cancer pain: a randomized controlled trial. Int J Clin Oncol 2017;22:980–985.
221. Sima L, Fang WX, Wu XM, et al. Efficacy of oxycodone/paracetamol for patients with bone-cancer pain: a multicenter, randomized, double-blinded, placebo-controlled trial. J Clin Pharm Ther 2012;37:27–31.
222. Chow E, Meyer RM, Ding K, et al. Dexamethasone in the prophylaxis of radiation-induced pain flare after palliative radiotherapy for bone metastases: a double-blind, randomised placebo-controlled, phase 3 trial. Lancet Oncol 2015;16:1463–1472.
223. Body JJ, Diel IJ, Lichinitzer M, et al. Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with metastatic bone disease: results from two randomised, placebo-controlled phase III studies. Br J Cancer 2004;90:1133–1137.
224. Body JJ, Diel IJ, Bell R, et al. Oral ibandronate improves bone pain and preserves quality of life in patients with skeletal metastases due to breast cancer. Pain 2004;111:306–312.
225. Cleeland CS, Body JJ, Stopeck A, et al. Pain outcomes in patients with advanced breast cancer and bone metastases: results from a randomized, double-blind study of denosumab and zoledronic acid. Cancer 2013;119:832–838.
226. Rosen LS, Gordon D, Kaminski M, et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. Cancer J 2001;7:377–387.
227. Wardley A, Davidson N, Barrett-Lee P, et al. Zoledronic acid significantly improves pain scores and quality of life in breast cancer patients with bone metastases: a randomised, crossover study of community vs hospital bisphosphonate administration. Br J Cancer 2005;92: 1869–1876.
228. Vadhan-Raj S, von Moos R, Fallowfield LJ, et al. Clinical benefit in patients with metastatic bone disease: results of a phase 3 study of denosumab versus zoledronic acid. Ann Oncol 2012;23:3045–3051.
229. Martin M, Bell R, Bourgeois H, et al. Bone-related complications and quality of life in advanced breast cancer: results from a randomized phase III trial of denosumab versus zoledronic acid. Clin Cancer Res 2012;18:4841–4849.
230. Van Poznak C, Somerfield MR, Barlow WE, et al. Role of bone-modifying agents in metastatic breast cancer: an American Society of Clinical Oncology–Cancer Care Ontario Focused Guideline Update. J Clin Oncol 2017;35:3978–3986.
231. Malviya A, Gerrand C. Evidence for orthopaedic surgery in the treatment of metastatic bone disease of the extremities: a review article. Palliat Med 2012;26:788–796.
232. Dupuy DE, Liu D, Hartfeil D, et al. Percutaneous radiofrequency ablation of painful osseous metastases: a multicenter American College of Radiology Imaging Network trial. Cancer 2010;116:989–997.
233. Lutz S, Berk L, Chang E, et al.American Society for Radiation Oncology (ASTRO). Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. Int J Radiat Oncol Biol Phys 2011;79: 965–976.
234. Goetz MP, Callstrom MR, Charboneau JW, et al. Percutaneous image-guided radiofrequency ablation of painful metastases involving bone: a multicenter study. J Clin Oncol 2004;22:300–306.
235. Kashima M, Yamakado K, Takaki H, et al. Radiofrequency ablation for the treatment of bone metastases from hepatocellular carcinoma. AJR Am J Roentgenol 2010;194:536–541.
236. Li C, Zhang W, Fan W, et al. Noninvasive treatment of malignant bone tumors using high-intensity focused ultrasound. Cancer 2010;116: 3934–3942.
237. Napoli A, Anzidei M, Marincola BC, et al. Primary pain palliation and local tumor control in bone metastases treated with magnetic resonance-guided focused ultrasound. Invest Radiol 2013;48:351–358.
238. Liberman B, Gianfelice D, Inbar Y, et al. Pain palliation in patients with bone metastases using MR-guided focused ultrasound surgery: a multicenter study. Ann Surg Oncol 2009;16:140–146.
239. Silver JK, Gilchrist LS. Cancer rehabilitation with a focus on evidence-based outpatient physical and occupational therapy interventions. Am J Phys Med Rehabil 2011; 90(5, Suppl 1)S5–S15.
240. Silver JK, Baima J, Mayer RS. Impairment-driven cancer rehabilitation: an essential component of quality care and survivorship. CA Cancer J Clin 2013;63:295–317.
241. Jones L, Fitzgerald G, Leurent B, et al. Rehabilitation in advanced, progressive, recurrent cancer: a randomized controlled trial. J Pain Symptom Manage 2013;46:315–325.
242. Eilers J, Harris D, Henry K, et al. Evidence-based interventions for cancer treatment-related mucositis: putting evidence into practice. Clin J Oncol Nurs 2014; 18(Suppl)80–96.
243. Riley P, Glenny AM, Worthington HV, et al. Interventions for preventing oral mucositis in patients with cancer receiving treatment: oral cryotherapy. Cochrane Database Syst Rev 2015; (12):CD011552.
244. Idayu Mat Nawi R, Lei Chui P, Wan Ishak WZ, et al. Oral cryotherapy: prevention of oral mucositis and pain among patients with colorectal cancer undergoing chemotherapy. Clin J Oncol Nurs 2018;22:555–560.
245. Kataoka T, Kiyota N, Shimada T, et al. Randomized trial of standard pain control with or without gabapentin for pain related to radiation-induced mucositis in head and neck cancer. Auris Nasus Larynx 2016;43:677–684.
246. McGuire DB, Fulton JS, Park J, et al.Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). Systematic review of basic oral care for the management of oral mucositis in cancer patients. Support Care Cancer 2013;21:3165–3177.
247. Kwong KK. Prevention and treatment of oropharyngeal mucositis following cancer therapy: are there new approaches? Cancer Nurs 2004;27: 183–205.
248. Shih A, Miaskowski C, Dodd MJ, et al. A research review of the current treatments for radiation-induced oral mucositis in patients with head and neck cancer. Oncol Nurs Forum 2002;29:1063–1080.
249. Chitapanarux I, Tungkasamit T, Petsuksiri J, et al. Randomized control trial of benzydamine HCl versus sodium bicarbonate for prophylaxis of concurrent chemoradiation-induced oral mucositis. Support Care Cancer 2018;26:879–886.
250. Epstein JB, Silverman S, Jr., Paggiarino DA, et al. Benzydamine HCl for prophylaxis of radiation-induced oral mucositis: results from a multicenter, randomized, double-blind, placebo-controlled clinical trial. Cancer 2001;92:875–885.
251. 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.
252. Deng GE, Rausch SM, Jones LW, et al. Complementary therapies and integrative medicine in lung cancer: Diagnosis and management of lung

cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e420S–e436S.

253. Greenlee H, DuPont-Reyes MJ, Balneaves LG, et al. Clinical practice guidelines on the evidence-based use of integrative therapies during and after breast cancer treatment. CA Cancer J Clin 2017;67:194–232.

254. Lyman GH, Greenlee H, Bohlke K, et al. Integrative therapies during and after breast cancer treatment: ASCO endorsement of the SIO Clinical Practice Guideline. J Clin Oncol 2018;36:2647–2655.

255. Chiu HY, Hsieh YJ, Tsai PS. Systematic review and meta-analysis of acupuncture to reduce cancer-related pain. Eur J Cancer Care (Engl) 2017;26:e12457.

256. Hershman DL, Unger JM, Greenlee H, et al. Effect of acupuncture vs sham acupuncture or waitlist control on joint pain related to aromatase inhibitors among women with early-stage breast cancer: a randomized clinical trial. JAMA 2018;320:167–176.

257. Pfister DG, Cassileth BR, Deng GE, et al. Acupuncture for pain and dysfunction after neck dissection: results of a randomized controlled trial. J Clin Oncol 2010;28:2565–2570.

258. Zick SM, Sen A, Hassett AL, et al. Impact of self-acupressure on co-occurring symptoms in cancer survivors. JNCI Cancer Spectr 2018;2: pky064.

259. Raphael J, Hester J, Ahmedzai S, et al. Cancer pain: part 2: physical, interventional and complimentary therapies; management in the community; acute, treatment-related and complex cancer pain: a perspective from the British Pain Society endorsed by the UK Association of Palliative Medicine and the Royal College of General Practitioners. Pain Med 2010;11:872–896.

260. Stoelb BL, Molton IR, Jensen MP, et al. The efficacy of hypnotic analgesia in adults: a review of the literature. Contemp Hypn 2009;26:24–39.

261. Huang ST, Good M, Zauszniewski JA. The effectiveness of music in relieving pain in cancer patients: a randomized controlled trial. Int J Nurs Stud 2010;47:1354–1362.

262. Kwekkeboom KL, Cherwin CH, Lee JW, et al. Mind-body treatments for the pain-fatigue-sleep disturbance symptom cluster in persons with cancer. J Pain Symptom Manage 2010;39:126–138.

263. Cassileth BR, Keefe FJ. Integrative and behavioral approaches to the treatment of cancer-related neuropathic pain. Oncologist 2010;15(Suppl 2):19–23.

264. Montgomery GH, Weltz CR, Seltz M, et al. Brief presurgery hypnosis reduces distress and pain in excisional breast biopsy patients. Int J Clin Exp Hypn 2002;50:17–32.

265. Bennett MI, Bagnall AM, José Closs S. How effective are patient-based educational interventions in the management of cancer pain? Systematic review and meta-analysis. Pain 2009;143:192–199.

266. Keefe FJ, Abernethy AP, C Campbell L. Psychological approaches to understanding and treating disease-related pain. Annu Rev Psychol 2005;56:601–630.

267. Lovell MR, Luckett T, Boyle FM, et al. Patient education, coaching, and self-management for cancer pain. J Clin Oncol 2014;32:1712–1720.

268. Sheinfeld Gorin S, Krebs P, Badr H, et al. Meta-analysis of psychosocial interventions to reduce pain in patients with cancer. J Clin Oncol 2012; 30:539–547.

269. Puchalski C, Ferrell B, Virani R, et al. Improving the quality of spiritual care as a dimension of palliative care: the report of the Consensus Conference. J Palliat Med 2009;12:885–904.

270. Brogan S, Junkins S. Interventional therapies for the management of cancer pain. J Support Oncol 2010;8:52–59.

271. Eidelman A, White T, Swarm RA. Interventional therapies for cancer pain management: important adjuvants to systemic analgesics. J Natl Compr Canc Netw 2007;5:753–760.

272. Tay W, Ho KY. The role of interventional therapies in cancer pain management. Ann Acad Med Singapore 2009;38:989–997.

273. Wong GY, Schroeder DR, Carns PE, et al. Effect of neurolytic celiac plexus block on pain relief, quality of life, and survival in patients with unresectable pancreatic cancer: a randomized controlled trial. JAMA 2004;291:1092–1099.

274. Cheville AL, Basford JR. Role of rehabilitation medicine and physical agents in the treatment of cancer-associated pain. J Clin Oncol 2014;32:1691–1702.

275. Arcidiacono PG, Calori G, Carrara S, et al. Celiac plexus block for pancreatic cancer pain in adults. Cochrane Database Syst Rev 2011; (3): CD007519.

276. Zhang CL, Zhang TJ, Guo YN, et al. Effect of neurolytic celiac plexus block guided by computerized tomography on pancreatic cancer pain. Dig Dis Sci 2008;53:856–860.

277. Zheng S, He L, Yang X, et al. Evaluation of intrathecal drug delivery system for intractable pain in advanced malignancies: a prospective cohort study. Medicine (Baltimore) 2017;96:e6354.

278. Smith TJ, Staats PS, Deer T, et al.Implantable Drug Delivery Systems Study Group. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival. J Clin Oncol 2002;20:4040–4049.

279. Deer TR, Prager J, Levy R, et al. Polyanalgesic Consensus Conference 2012: recommendations for the management of pain by intrathecal (intraspinal) drug delivery: report of an interdisciplinary expert panel. Neuromodulation 2012;15:436–466.

280. Gulati A, Puttanniah V, Hung J, et al. Considerations for evaluating the use of intrathecal drug delivery in the oncologic patient. Curr Pain Headache Rep 2014;18:391.

281. Lauretti GR, Rizzo CC, Mattos AL, et al. Epidural methadone results in dose-dependent analgesia in cancer pain, further enhanced by epidural dexamethasone. Br J Cancer 2013;108:259–264.

282. Rastogi R, Patel T, Swarm RA. Vertebral augmentation for compression fractures caused by malignant disease. J Natl Compr Canc Netw 2010;8: 1095–1102.

283. Tancioni F, Lorenzetti MA, Navarria P, et al. Percutaneous vertebral augmentation in metastatic disease: state of the art. J Support Oncol 2011;9:4–10.

284. Gofeld M, Bhatia A, Burton AW. Vertebroplasty in the management of painful bony metastases. Curr Pain Headache Rep 2009;13:288–294.

285. Berenson J, Pflugmacher R, Jarzem P, et al.Cancer Patient Fracture Evaluation (CAFE) Investigators. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial. Lancet Oncol 2011;12:225–235.

286. Eleraky M, Papanastassiou I, Setzer M, et al. Balloon kyphoplasty in the treatment of metastatic tumors of the upper thoracic spine. J Neurosurg Spine 2011;14:372–376.

287. Zou J, Mei X, Gan M, et al. Kyphoplasty for spinal fractures from multiple myeloma. J Surg Oncol 2010;102:43–47.

288. Flagg A II, McGreevy K, Williams K. Spinal cord stimulation in the treatment of cancer-related pain: "back to the origins". Curr Pain Headache Rep 2012;16:343–349.

Individual Disclosures for the NCCN Adult Cancer Pain Panel

Panel Member	Clinical Research Support/Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Specialties
Doralina L. Anghelescu, MD	None	None	None	Anesthesiology, and Supportive Care
Madhuri Are, MD	None	None	None	Supportive Care
Justine Yang Bruce, MD	Kura Oncology, Inc., and Merck & Co., Inc.	Bristol-Myers Squibb Company	None	Medical Oncology
Sorin Buga, MD	None	None	None	Supportive Care
Marcin Chwistek, MD	None	None	None	Supportive Care, and Internal Medicine
Charles Cleeland, PhD	Bayer HealthCare, and Genentech, Inc.	National Cancer Institute	Bayer HealthCare	Psychiatry, Psychology, and Supportive Care
David Craig, PharmD	None	None	Nektar Therapeutics, and SpecGx, LLC	Supportive Care
Ellin Gafford, MD	None	None	None	Internal Medicine, and Supportive Care
Heather Greenlee, PhD, ND	None	None	None	Complementary and Alternative Medicine
Eric Hansen, MD	None	None	None	Supportive Care
Arif H. Kamal, MD, MBA, MHS[a]	None	Insys Therapeutics; Medtronic, Inc.; and Pfizer Inc.	None	Medical Oncology, and Supportive Care
Mihir M. Kamdar, MD	ePAL	Amorsa Therapeutics; CompleteCare; and Vivtex	None	Internal Medicine, and Supportive Care
Susan LeGrand, MD	None	None	None	Medical Oncology, and Supportive Care
Sean Mackey, MD, PhD	None	None	None	Anesthesiology, and Supportive Care
M. Rachel McDowell, MSN, ACNP-BC	None	None	None	Nursing, and Medical Oncology
Natalie Moryl, MD	None	Plexus Communications	None	Internal Medicine, and Supportive Care
Lisle M. Nabell, MD	None	None	None	Hematology/Hematology Oncology, and Medical Oncology
Suzanne Nesbit, PharmD, BCPS	None	None	None	Supportive Care, and Pharmacology
Nina O'Connor, MD	None	None	None	Supportive Care
Judith A. Paice, PhD, RN	None	None	None	Nursing, and Supportive Care
Michael W. Rabow, MD	None	None	None	Internal Medicine, and Supportive Care
Elizabeth Rickerson, MD	None	None	None	Anesthesiology, and Supportive Care
Rebecca Shatsky, MD	Pending	Pending	Pending	Medical Oncology
Jill Sindt, MD	None	None	None	Anesthesiology, and Supportive Care
Robert A. Swarm, MD	None	None	None	Anesthesiology, and Supportive Care
Susan G. Urba, MD	None	Heron Therapeutics, Inc.	None	Medical Oncology, and Supportive Care
Jeanie M. Youngwerth, MD	None	None	None	Internal Medicine, and Supportive Care

The NCCN Guidelines Staff have no conflicts to disclose.

[a]The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty:
Arif H. Kamal, MD, MBA, MHS: Prepped Health LLC