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Use of Opioids for Adults With Pain From Cancer or Cancer Treatment: ASCO Guideline

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abstract

PURPOSE To provide guidance on the use of opioids to manage pain from cancer or cancer treatment in adults.

METHODS A systematic review of the literature identified systematic reviews and randomized controlled trials of the efficacy and safety of opioid analgesics in people with cancer, approaches to opioid initiation and titration, and the prevention and management of opioid adverse events. PubMed and the Cochrane Library were searched from January 1, 2010, to February 17, 2022. American Society of Clinical Oncology convened an Expert Panel to review the evidence and formulate recommendations.

RESULTS The evidence base consisted of 31 systematic reviews and 16 randomized controlled trials. Opioids have primarily been evaluated in patients with moderate-to-severe cancer pain, and they effectively reduce pain in this population, with well-characterized adverse effects. Evidence was limited for several of the questions of interest, and the Expert Panel relied on consensus for these recommendations or noted that no recommendation could be made at this time.

RECOMMENDATIONS Opioids should be offered to patients with moderate-to-severe pain related to cancer or active cancer treatment unless contraindicated. Opioids should be initiated PRN (as needed) at the lowest possible dose to achieve acceptable analgesia and patient goals, with early assessment and frequent titration. For patients with a substance use disorder, clinicians should collaborate with a palliative care, pain, and/or substance use disorder specialist to determine the optimal approach to pain management. Opioid adverse effects should be monitored, and strategies are provided for prevention and management.

Additional information is available at www.asco.org/supportive-care-guidelines.

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INTRODUCTION

Pain remains a common consequence of cancer and its treatment. Approximately 55% of those undergoing active treatment experience pain, while the prevalence is > 66% in people with advanced disease.[1] In most cases, moderate-to-severe cancer pain can be effectively managed with available medications, including opioids. Opioids have long been the foundation of cancer pain management, yet serious challenges to their use exist, including a striking lack of research to guide clinical practice in this population. Compounding an insufficient scientific foundation are interventions designed to combat the current epidemic of opioid misuse and related deaths.[2] Access difficulties include reduced reimbursement, high patient copays, and a lack of availability of opioids at retail pharmacies. As a result of these and other challenges, patients with cancer report stigma and concern related to opioid use.[3,4] Patients express greater fear of addiction along with guilt and a sense of moral failure that they require opioids, causing some to skip a dose or take a lower dose than prescribed.[4-6] All of these barriers place people with cancer at great risk of suffering uncontrolled pain.

Evidence-based information is needed to direct the safe and effective use of opioids and counter misinformation. Clinical practice guidelines informed by systematic reviews of available evidence can provide recommendations to advance the best clinical care. Although guidelines exist for treating cancer-related pain,[7-10] few are focused solely on opioid use in the patient with cancer. Given the current environment of apprehension regarding opioids, specific guidance is warranted to

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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THE BOTTOM LINE

Use of Opioids for Adults With Pain From Cancer or Cancer Treatment: ASCO Guideline

Guideline Question

In what circumstances should opioids be used to manage cancer pain in adults, how should opioids be administered, and how should opioid adverse effects be prevented or managed?

Target Population

Adults with pain from cancer or active cancer treatment.

Target Audience

Clinicians who provide care to adults with cancer (physicians, nurses, advanced practice providers, oncology pharmacists, and others), adults with cancer, and family members and caregivers.

Methods

An Expert Panel was convened to develop clinical practice guideline recommendations on the basis of a systematic review of the medical literature.

Recommendations

Question 1: In what circumstances should opioids be offered?

Recommendation 1.1. Opioids should be offered to patients with moderate-to-severe pain related to cancer or active cancer treatment unless contraindicated (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Recommendation 1.2. Prior to initiating opioid therapy, clinicians, patients, and caregivers should discuss goals regarding functional outcomes, shared expectations, and pain intensity, as well as any concerns about opioids (Type: Informal consensus, benefits outweigh harms; Strength of recommendation: Strong).

Question 2: Which opioids should be offered?

Recommendation 2.1. For patients who are candidates to begin opioid treatment (Recommendation 1.1), clinicians may offer any of the opioids approved by the US Food and Drug Administration or other regulatory agencies for pain treatment (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate to low; Strength of recommendation: Weak).

Qualifying statement. The decision of which opioid is most appropriate should be based on factors such as pharmacokinetic properties, including bioavailability, route of administration, half-life, neurotoxicity, and cost of the differing drugs. Tramadol and codeine have limitations that may make them less desirable than other opioids in this setting. Tramadol is a prodrug, has limitations in dose titration related to a low threshold for neurotoxicity, and has potential interactions with other drugs at the level of cytochrome P450 (CYP) 2D6, 2B6, and 3A4.[11,12] Codeine is a prodrug, requiring CYP2D6 to allow it to be metabolized to morphine to achieve analgesic effects.[12]

Recommendation 2.2. Clinicians with limited experience with methadone prescribing should consult palliative care or pain specialists when initiating or rotating to methadone (Type: Informal consensus, benefits outweigh harms; Strength of recommendation: Strong).

Question 3: How should opioids be initiated and titrated?

Recommendation 3.1. Opioids should be initiated at the lowest possible dose to achieve acceptable analgesia and patient goals (Type: Informal consensus, benefits outweigh harms; Strength of recommendation: Strong).

Recommendation 3.2. Opioids should be initiated as immediate release and PRN (as needed) to establish an effective dose, with early assessment and frequent titration (Type: Informal consensus, benefits outweigh harms; Strength of recommendation: Strong).

Recommendation 3.3. Patients who have been taking other analgesics, such as nonsteroidal anti-inflammatory drugs, may continue these analgesics after opioid initiation if these agents provide additional analgesia and are not contraindicated (Type: Informal consensus, benefits outweigh harms; Strength of recommendation: Weak).

Recommendation 3.4. Evidence remains insufficient to recommend for or against the use of genetic testing, such as for polymorphism of CYP2D6, to guide opioid dosing.

Recommendation 3.5. Evidence remains insufficient to recommend any single set of ranges for dose escalation in opioid titration.

Note: In general, the minimum dose increase is 25%-50%, but patient factors such as frailty, comorbidities, and organ function must be evaluated and considered when changing doses.

Recommendation 3.6. For patients with a substance use disorder, clinicians should collaborate with a palliative care, pain, and/or substance use disorder specialist to determine the optimal approach to pain management (Type: Informal consensus, benefits outweigh harms; Strength of recommendation: Strong).

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THE BOTTOM LINE (CONTINUED)

Question 4: How should opioid-related adverse events be prevented or managed?

Recommendation 4. Clinicians should proactively offer education and strategies to prevent known opioid-related adverse effects, monitor for the development of these adverse effects, and manage these effects when they occur (Type: Informal consensus, benefits outweigh harms; Strength of recommendation: Strong).

Note: Strategies for the prevention and management of common opioid-induced adverse effects are provided in Table 1.

Question 5: How should opioid use be modified in patients with renal or hepatic impairment?

Recommendation 5.1. For patients with renal impairment currently treated with an opioid, clinicians may rotate to methadone, if not contraindicated, as this agent is excreted fecally. Opioids primarily eliminated in urine, such as fentanyl, oxycodone, and hydromorphone, should be carefully titrated and frequently monitored for risk or accumulation of the parent drug or active metabolites. Morphine, meperidine, codeine, and tramadol should be avoided in this population, unless there are no alternatives (Type: Informal consensus, benefits outweigh harms; Strength of recommendation: Strong).

Recommendation 5.2. For patients with renal or hepatic impairment who receive opioids, clinicians should perform more frequent clinical observation and opioid dose adjustment (Type: Informal consensus, benefits outweigh harms; Strength of recommendation: Strong).

Question 6: How should breakthrough pain be managed?

Recommendation 6.1. In patients receiving opioids around the clock, immediate-release opioids at a dose of 5%-20% of the daily regular morphine equivalent daily dose should be prescribed for breakthrough pain (Type: Informal consensus, benefits outweigh harms; Strength of recommendation: Strong for prescribing immediate-release opioids for breakthrough pain, weak for dosing).

Recommendation 6.2. Evidence remains insufficient to recommend a specific, short-acting opioid for breakthrough pain.

Question 7: When and how should opioids be switched (rotated)?

Recommendation 7. Opioid rotation should be offered to patients with pain that is refractory to dose titration of a given opioid, poorly managed side effects, logistical or cost concerns, or trouble with the route of opioid administration or absorption (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Additional Resources

Definitions for the quality of the evidence and strength of recommendation ratings are available in Appendix Table A2 (online only). More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

counteract misinformation while informing clinicians on how to effectively administer these medications, educate patients and loved ones regarding safe use, and advocate for appropriate access. To that end, American Society of Clinical Oncology (ASCO) convened a panel of experts to review the available evidence and develop recommendations to guide best practices regarding the use of opioids to relieve pain from cancer or cancer treatment.

GUIDELINE QUESTIONS

This clinical practice guideline addresses seven clinical questions for adults with pain from cancer or active cancer treatment: (1) In what circumstances should opioids be offered? (2) Which opioids should be offered? (3) How should opioids be initiated and titrated? (4) How should opioid-related adverse events be prevented or managed? (5) How should opioid use be modified in patients with renal or hepatic impairment? (6) How should breakthrough pain be managed? (7) When and how should opioids be switched (rotated)?

METHODS

Guideline Development Process

This systematic review-based guideline was developed by a multidisciplinary Expert Panel, which included patient representatives and an ASCO guidelines staff member with health research methodology expertise (Appendix Table A1). The Expert Panel met via webinar and corresponded through e-mail. Based upon the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were sent for an open comment period of 2 weeks, allowing the

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public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review, and submitted to the *Journal of Clinical Oncology* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Evidence Based Medicine Committee before publication. All funding for the administration of the project was provided by ASCO.

The recommendations were developed using a systematic literature review and clinical experience. The systematic review involved online searches of PubMed and the Cochrane Library for randomized controlled trials (RCTs) and systematic reviews published between January 1, 2010, and February 17, 2022. Articles were selected for inclusion in the systematic review on the basis of the following criteria:

- Population: Adults with pain from cancer or active cancer treatment
- Interventions: Opioid analgesics or interventions to manage opioid side effects
- Comparisons: Placebo, different pharmacologic or nonpharmacologic approaches to pain management, different approaches to the management of opioid side effects
- Outcomes: Pain, quality of life, function, and adverse events
- Sample size: Minimum of 20 patients in total

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, or narrative reviews; or (3) published in a non-English language. The quality of included systematic reviews was assessed using the 11-item AMSTAR tool.[13] Design and analysis elements such as blinding, adequate randomization, sufficient sample size, intention to treat, and funding sources were assessed for RCTs. The guideline recommendations were crafted, in part, using the *Guidelines Into Decision Support* methodology.[14] Ratings for evidence quality and for type and strength of the recommendation are provided with each recommendation. Definitions for these ratings are provided in Appendix Table A2. When evidence was lacking, and the Expert Panel chose to make recommendations based on informal consensus, recommendations felt to be important for patient safety were labeled as strong recommendations.

The ASCO Expert Panel and guidelines staff will work with cochairs to keep abreast of any substantive updates to the guideline. Based on a formal review of the emerging literature, ASCO will determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

Guideline Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by ASCO to assist providers in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations specify the level of confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO does not endorse third party drugs, devices, services, or therapies used to diagnose, treat, monitor, manage, or alleviate health conditions. Any use of a brand or trade name is for identification purposes only. ASCO provides this information on an "as is" basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at https://www.asco.org/guideline-methodology). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory

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role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

Characteristics of Studies Identified in the Literature Search

A total of 820 publications were identified in the literature search. After applying the eligibility criteria, 31 systematic reviews[15-45] and 16 RCTs[46-61] remained, forming the evidentiary basis for the guideline recommendations.

Study Quality Assessment

The quality ratings of included systematic reviews varied greatly, with total AMSTAR scores ranging from 3 to 11 on the 11-item AMSTAR tool. A majority of included RCTs had an intermediate or high risk of bias. Quality results for each publication are provided in the Data Supplement (online only).

RECOMMENDATIONS

Clinical Question 1

In what circumstances should opioids be offered?

Recommendation 1.1. Opioids should be offered to patients with moderate-to-severe pain related to cancer or active cancer treatment unless contraindicated (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Recommendation 1.2. Prior to initiating opioid therapy, clinicians, patients, and caregivers should discuss goals regarding functional outcomes, shared expectations, and pain intensity, as well as any concerns about opioids (Type: Informal consensus, benefits outweigh harms; Strength of recommendation: Strong).

Literature review and analysis. RCTs of opioids for cancer pain have focused primarily on patients with moderate-to-severe cancer pain, and most used an active comparator (eg, another formulation, dose, or type of opioid).[42] In a 2016 review of oral morphine, the results from 17 studies indicated that 96% of morphine-treated patients (362 of 377) achieved the outcome of no worse than mild pain.[43] Several systematic reviews have focused on the relative efficacy of different opioids, with few reported differences but low to very low certainty of evidence.[19,23,27,33,38,41] Opioid adverse events have been well characterized, including constipation, nausea, vomiting, drowsiness, and respiratory depression.[42] A 2016 review of oral morphine for cancer pain reported that 7% of patients discontinued morphine due to adverse events.[43]

Clinical interpretation. Opioids should be offered to patients with moderate-to-severe pain related to the primary or metastatic tumor, or acute painful treatment complications such as mucositis.[62-65] Before prescribing opioids, it is useful to assess the mechanism for the pain syndrome (imaging may be required if unclear), the response to nonopioid analgesics (eg, acetaminophen or nonsteroidal anti-inflammatory drugs), and the presence of risk factors for nonmedical opioid use such as a history of misuse of alcohol, recreational substances, or prescription drugs. This can be done using simple tools such as the Cut down, Annoyed, Guilty, Eye-Opener Adapted to Include Drugs,[66] the Opioid Risk Tool,[67] or the Screener and Opioid Assessment for Patients in Pain.[66] Approximately 15% of patients with cancer will score positive in these simple risk screening tools, and they should receive opioids in the same way as those who score negative, but will need closer follow-up and regular monitoring of behaviors related to nonmedical opioid use and the Prescription Drug Monitoring Program (PDMP) database[64-66,68] (in some states, monitoring of PDMP each time before opioid prescription is mandatory). Random urinary drug tests can be positive in more than 20% of patients with cancer receiving opioids.[69] There is no consensus regarding the usefulness of regularly monitoring urinary drug tests before or during opioid treatment among patients with cancer receiving opioids. For those patients who are no longer receiving active cancer treatment and do not have pain related to ongoing tumor burden, the authors refer readers to the ASCO Management of Chronic Pain in Survivors of Adult Cancer[9] for guidance related to the use of opioids in this population.

When opioids are no longer indicated, they should be weaned or tapered. Patients with cancer and their caregivers can be reassured that this is feasible at the initiation of opioid therapy. For example, acute syndromes such as mucositis will resolve, and anticancer therapies or interventional treatments may lead to significant pain relief. Additionally, there may be situations when it is not safe to continue prolonged opioid therapy, usually in the setting of long-term cancer survivorship.[9] Although there is little evidence regarding strategies for opioid tapering in the oncology population, clinical experience can be guided by tapering in those with persistent noncancer pain. Opioid doses can be reduced more rapidly for those on lower doses for short periods without precipitating abstinence syndrome. For patients on higher doses of opioids for longer periods, dose reduction must be conducted slowly (5%-20% per month) to avoid abstinence syndrome while optimizing nonopioid and nonpharmacologic pain interventions.[70]

Clinical Question 2

Which opioids should be offered?

Recommendation 2.1. For patients who are candidates to begin opioid treatment (Recommendation 1.1), clinicians may offer any of the opioids approved by the US Food and

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Drug Administration or other regulatory agencies for pain treatment (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate to low; Strength of recommendation: Weak).

Qualifying statement. The decision of which opioid is most appropriate should be based on factors such as pharmacokinetic properties, including bioavailability, route of administration, half-life, neurotoxicity, and cost of the differing drugs. Tramadol and codeine have limitations that may make them less desirable than other opioids in this setting. Tramadol is a prodrug, has limitations in dose titration related to a low threshold for neurotoxicity, and has potential interactions with other drugs at the level of cytochrome P450 (CYP) 2D6, 2B6, and 3A4.[11,12] Codeine is a prodrug, requiring CYP2D6 to allow it to be metabolized to morphine to achieve analgesic effects.[12]

Recommendation 2.2. Clinicians with limited experience with methadone prescribing should consult palliative care or pain specialists when initiating or rotating to methadone (Type: Informal consensus, benefits outweigh harms; Strength of recommendation: Strong).

Literature review and analysis. As noted previously, systematic reviews have identified few differences in analgesic efficacy across opioids used for cancer pain. Comparisons have included hydromorphone in relation to oxycodone, morphine, and fentanyl[23]; methadone in relation to morphine[27]; transdermal fentanyl in relation to oral morphine or other active agents[19,38]; oxycodone in relation to morphine and other opioids[33]; oral tapentadol in relation to oxycodone and morphine[41]; and buprenorphine in relation to various active comparators.[34] A 2017 systematic review of tramadol reported that it may be less effective than morphine, on the basis of very low certainty of evidence.[40] This was based largely on a 2016 trial by Bandieri et al,[71] which compared weak opioids (tramadol with or without acetaminophen or codeine with acetaminophen) to low-dose morphine in 240 patients with moderate cancer pain. A $\geq$ 20% reduction in pain intensity occurred in 88% of patients treated with low-dose morphine and 58% of patients treated with a weak opioid.

Systematic reviews have also compared adverse events across opioids.[19,23,33,38] Some differences were reported in individual adverse events, but none of the investigated agents offered a clear advantage over others in terms of adverse event profiles.

Clinical interpretation. Most patients who report unrelieved pain with nonopioids initially receive as-needed, immediate-release opioid agonists such as codeine, hydrocodone, or oxycodone combined with acetaminophen.[62-65] These drugs were considered step 2 in the three-step opioid analgesic ladder by the WHO and a step required before starting strong immediate-release and extended-release opioids (step 3). A number of studies found no major advantage in using the step 2 drugs,[71] and the most recent WHO guideline dropped the analgesic ladder as universally required for opioid initiation.[63] However, these drugs are usually well tolerated and inexpensive. Moreover, it is possible to determine in just a few days if they will be able to control pain or if a strong regularly dosed opioid without acetaminophen will be needed.

As noted, tramadol and codeine have limitations in dose titration and drug interactions. Patients with genetic polymorphism of CYP2D6 (more common among Asians[72]) may have less response to codeine. Although tests for CYP2D6 polymorphism are available, there is insufficient evidence to recommend for or against their use in guiding opioid selection or dosing. In addition, drugs that inhibit or compete for CYP2D6 might reduce the analgesic effects of codeine.

Methadone has some potential clinical advantages, including potency, efficacy in neuropathic pain, use as a long-acting agent after crushing (for enteral feeding tube delivery), relative safety in those with renal impairment, and very low cost. However, because of very unique pharmacokinetic and pharmacodynamic properties, it should only be prescribed as a first- or second-line opioid by experienced clinicians.[24]

Clinical Question 3

How should opioids be initiated and titrated?

Recommendation 3.1. Opioids should be initiated at the lowest possible dose to achieve acceptable analgesia and patient goals (Type: Informal consensus, benefits outweigh harms; Strength of recommendation: Strong).

Recommendation 3.2. Opioids should be initiated as immediate release and PRN (as needed) to establish an effective dose, with early assessment and frequent titration (Type: Informal consensus, benefits outweigh harms; Strength of recommendation: Strong).

Recommendation 3.3. Patients who have been taking other analgesics, such as nonsteroidal anti-inflammatory drugs, may continue these analgesics after opioid initiation if these agents provide additional analgesia and are not contraindicated (Type: Informal consensus, benefits outweigh harms; Strength of recommendation: Weak).

Recommendation 3.4. Evidence remains insufficient to recommend for or against the use of genetic testing, such as for polymorphism of CYP2D6, to guide opioid dosing.

Recommendation 3.5. Evidence remains insufficient to recommend any single set of ranges for dose escalation in opioid titration.

Note: In general, the minimum dose increase is 25%-50%, but patient factors such as frailty, comorbidities, and organ function must be evaluated and considered when changing doses.

Recommendation 3.6. For patients with a substance use disorder, clinicians should collaborate with a palliative care, pain, and/or substance use disorder specialist to determine the optimal approach to pain management (Type: Informal

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consensus, benefits outweigh harms; Strength of recommendation: Strong).

Literature review and analysis. Few included publications directly addressed these questions. Varying approaches to dose titration were evaluated.[21,52,56] Genetic variation may contribute to opioid response and dosing requirements,[44] but evidence remains insufficient for a recommendation.

Clinical interpretation. The initial opioid dose is dictated by safety considerations rather than pain type or intensity, and it is a dose of approximately 30 mg of morphine equivalent (MME) per day.[73-75] Opioids are usually initiated during a short course of an immediate-release formulation as needed to establish the effective dose. In the setting of stable pain, the effective dose can often be determined within a few days. The US Food and Drug Administration also recommends this practice of as-needed immediate-release opioids before starting regularly scheduled opioids.[76] Once the effective dose has been determined, extended-release opioids are considered. Extended-release opioids can be administered by mouth every 12 or 24 hours, or transdermal every 72 hours (fentanyl) or every 7 days (buprenorphine). The main advantage of these formulations is the need for much less frequent administration compared with immediate-release opioids, while their main disadvantage is higher cost and frequent insurance company denials or elevated copayments. Immediate-release opioids are inexpensive but they need to be administered every 4 hours to maintain stable blood levels and analgesia. This requires patients to wake up in the middle of the night to take an opioid dose.[77]

Dose titration can be done a few days after each dose increase or reduction. Because of the wide variation in individual opioid dose response, the increase or decrease in opioid daily dose is calculated as a percentage of the total daily dose (usually approximately 25%-50%). A dose increase should occur when the patient reports persistent pain after being on a certain dose of a regular opioid for a few days, or when the pain is low but the patient needs to take multiple doses of a breakthrough opioid per day. A simple way to determine the new dose of an opioid administered around the clock is to add the total daily dose of the regular plus breakthrough opioids and increase this number by 20%-30%. It is also useful to update the dose of the breakthrough opioid to keep each dose at about 10% (5%-20%) of the regular daily opioid dose.

Clinical Question 4

How should opioid-related adverse events be prevented or managed?

Recommendation 4. Clinicians should proactively offer education and strategies to prevent known opioid-related adverse effects, monitor for the development of these adverse effects, and manage these effects when they occur (Type: Informal consensus, benefits outweigh harms; Strength of recommendation: Strong).

Note: Strategies for the prevention and management of common opioid-induced adverse effects are provided in Table 1.

Literature review and analysis. Studies designed to explore strategies to prevent opioid-induced constipation suggest that the stimulant laxative senna provides effective control without the addition of the softener docusate.[61] Although prevention is crucial, at times, constipation as a result of opioid intake may occur. A 2018 systematic review by Candy et al[16] addressed the efficacy and safety of mu-opioid antagonists for opioid-induced bowel dysfunction in patients with cancer and patients in palliative care (a majority of whom had cancer). There was moderate-quality evidence that naldemedine improved bowel function over 2 weeks in adults with cancer, with an increased risk of adverse events such as diarrhea compared with placebo. In patients receiving palliative care, methylnaltrexone was associated with more laxations in 24 hours than placebo, with moderate-quality evidence for efficacy and low-quality evidence of no increase in side effects.

A 2019 systematic review[32] evaluated the management of opioid-induced nausea and vomiting in patients with cancer. Eight of the included RCTs reported on opioid switching, with no clear conclusions because of limitations of the evidence: nausea and vomiting was a secondary or tertiary outcome, interventions and comparison arms varied across the trials, and sample sizes tended to be small. Evidence regarding antiemetics or different routes of opioid administration was also limited. In a 2018 RCT not included in the 2019 review, 120 patients with cancer without prior opioid use who started to receive oral oxycodone were randomly assigned to prophylactic prochlorperazine (5 mg) or placebo, three times daily for 5 days. Complete response (no emetic episode and no rescue medication) occurred in 69.5% of patients in the prochlorperazine arm and 63.3% of patients in the placebo arm ($P = .47$).

There is also very little evidence to guide the management of other opioid side effects, such as cognitive impairment and sedation.[36]

Clinical interpretation. Relatively little research has been conducted to explore the prevention and management of opioid-induced adverse effects. Guidelines exist for opioid-induced constipation and for constipation related to cancer, yet none specifically address opioid-induced constipation in the oncology population.[78-80] As a result, clinicians must rely upon expert guidance on the basis of clinical experience. In Table 1, the ASCO Expert Panel provides consensus-based strategies for preventing and managing common opioid-induced adverse effects.

Clinical Question 5

How should opioid use be modified in patients with renal or hepatic impairment?

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TABLE 1. Prevention and Management of Opioid-Induced Adverse Effects in People With Cancer

Adverse Effect	Description	Prevention and Treatment
Constipation[78-80,126,127]	• Continues throughout the course of opioid therapy	• Rule out other causes (often multifactorial, including medications) • Rule out potentially emergent conditions such as bowel obstruction • Goal: Soft, formed bowel movements every 1-2 days without straining or pain • Always begin a prophylactic bowel regimen when starting opioid therapy • Prevention: Senna with or without docusate daily, titrated as needed to meet goal • Treatment: Once constipation occurs, magnesium-based products and laxatives such as bisacodyl. Agents used for prevention and treatment of constipation are over the counter and rarely covered by insurance • PAMORAs—peripherally acting mu-opioid receptor antagonists (eg, methylnaltrexone, naldemedine, and naloxegol)—are effective if primary cause of constipation is an opioid. Access to these agents is frequently limited by insurance denials • If patient feels nauseated as a result of constipation, consider suppositories or enemas (contraindicated in thrombocytopenia or neutropenia)
Delirium and neurotoxicity[62]	• Reported with all opioids • Can include myoclonus, hyperalgesia, and cognitive effects (eg, attentional deficits) • More common in higher opioid dose, prolonged treatment, concomitant psychoactive agents, and in reduced renal function	• Assess carefully as hypoactive delirium is often missed; hyperactive delirium more readily identified • Rule out other causes. Assess urinary function given that opioids are primarily eliminated through kidneys (except methadone); accumulation of the opioid or its metabolites can contribute to delirium and neurotoxicity • Strong suspicion and early intervention when rapid opioid dose escalation occurs • Eliminate other medications when feasible • Rotate to another opioid • Neuroleptics such as haloperidol may be beneficial • Consider a short course of hydration to assist in clearance of metabolites
Endocrinopathy[128,129]	• Opioids disrupt hypothalamic-pituitary-gonadal axis • Erectile dysfunction, reduced libido, infertility, fatigue, depression, hot flushes, lowered bone density, and increased fracture risk	• Educate patients about role of opioids in endocrinopathy • Consider other, potentially treatable, causes • Consider alternate pain therapies if feasible • Initiate testosterone replacement if benefits outweigh risks
Nausea and vomiting[130]	• Seen in as many as 50% when opioids are initiated or when the dose is increased greatly • Tolerance develops in most cases with reduction in few days • Can be related to central effects and reduced gastric motility	• Rule out other causes (constipation, other medications) • Metoclopramide has both central and peripheral effects and is recommended as first line for the management of chronic nausea, including opioid-related • For patients reporting previous episodes of nausea during past exposure to opioids, prevention may include pretreatment with metoclopramide or prochlorperazine around the clock for the first few days of opioid therapy, with gradual weaning of the antiemetic
Pruritus[131,132]	• Early response to treatment • More frequent after neuraxial delivery • May be more common with opiates (eg, morphine and codeine) than synthetic agents	• Rule out other causes (uremia, cholestasis, some malignancies, HIV, and medications) • Rotate to synthetic opioid (eg, fentanyl) • Nonsedating antihistamines before opioid administration if feasible • Sedating antihistamines such as hydroxyzine or diphenhydramine if no excessive sedation • 5-HT3 receptor antagonists such as ondansetron (although conflicting data) • Mixed agonist/antagonists such as nalbuphine alone or in combination with existing opioid (caution is advised in patients who are opioid-tolerant as this may reduce analgesic effect or cause abstinence) • Low-dose naloxone (0.25 μg/kg/h) infusion may be considered

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TABLE 1. Prevention and Management of Opioid-Induced Adverse Effects in People With Cancer (continued)

Adverse Effect	Description	Prevention and Treatment
Sedation and respiratory depression[91,133-136]	• Some degree of sedation is common during initiation of an opioid or during dose escalation • Tolerance usually develops after a few days • Respiratory depression is typically preceded by sedation and is uncommon during chronic opioid administration	• Rule out other causes (often new medications such as benzodiazepines and gabapentinoids; organ system failure) • Educate patients regarding expected degree of sedation during early therapy to improve adherence to the opioid treatment plan • Limit polypharmacy if feasible • Review potential drug-drug interactions that may be affecting opioid metabolism • Methylphenidate and other psychostimulants can decrease sedation without affecting analgesia • New-onset sedation with stable opioid dosing is generally related to the addition of other sedating agents; discontinue these drugs or greatly reduce the dose • Consider prescribing naloxone to those receiving ≥ 50 morphine milligram equivalents as a rescue resource if there is concern for unintended access of the opioid by children or vulnerable family members (eg, cognitively impaired persons). Consider naloxone also for patients receiving opioids with benzodiazepines, gabapentinoids, or other sedating agents. Educate patients and caregivers on the use of this antagonist in the case of overdose and respiratory depression, including its relatively short half-life and need for continued therapy and monitoring. Intranasal naloxone and intramuscular naloxone are both currently available in the United States. Ensure that naloxone administration is consistent with patient's goals of care at the end of life
Urinary retention[137]	• More common in early course of treatment • Occurs in 25% of postoperative patients • More frequent after neuraxial delivery • Can be acute or chronic • Higher prevalence in elderly (because of benign prostatic hyperplasia or polypharmacy)	• Rule out other causes, especially spinal cord compression • Review medications and modify regimen if feasible • Catheterization in acute cases • Tamsulosin reported to be beneficial in postoperative opioid use • Rotate to synthetic opioid (eg, fentanyl) • Consider methylnaltrexone or low-dose naloxone (0.25 μg/kg/h) infusion

Recommendation 5.1. For patients with renal impairment currently treated with an opioid, clinicians may rotate to methadone, if not contraindicated, as this agent is excreted fecally. Opioids primarily eliminated in urine, such as fentanyl, oxycodone, and hydromorphone, should be carefully titrated and frequently monitored for risk or accumulation of the parent drug or active metabolites. Morphine, meperidine, codeine, and tramadol should be avoided in this population, unless there are no alternatives (Type: Informal consensus, benefits outweigh harms; Strength of recommendation: Strong).

Recommendation 5.2. For patients with renal or hepatic impairment who receive opioids, clinicians should perform more frequent clinical observation and opioid dose adjustment (Type: Informal consensus, benefits outweigh harms; Strength of recommendation: Strong).

Literature review and analysis. A 2021 systematic review of opioids for patients with cancer-related pain and hepatic impairment identified no RCTs and three prospective observational studies.[20] The authors noted that no recommendations could be made regarding the preferred opioid in patients with hepatic impairment. A 2017 systematic review evaluated opioid side effects in patients with cancer pain and renal impairment.[31] The review included 18 studies (no RCTs), with no clear evidence to identify a preferred opioid in the setting of renal impairment.

Clinical interpretation. In patients with significant renal function impairment, morphine use may result in the accumulation of neurotoxic metabolites such as morphine-3-glucuronide and normorphine, and opioid-induced neurotoxicity.[81-83] Other opioids such as hydromorphone or fentanyl are less likely to result in accumulation of active metabolites in renal failure. Methadone can also be a good alternative since it is primarily metabolized in the liver, but as previously mentioned, it should only be used by experienced clinicians.

Clinical Question 6

How should breakthrough pain be managed?

Recommendation 6.1. In patients receiving opioids around the clock, immediate-release opioids at a dose of 5%-20% of the daily regular morphine equivalent daily dose should be prescribed for breakthrough pain (Type: Informal consensus, benefits outweigh harms; Strength of recommendation: Strong for prescribing immediate-release opioids for breakthrough pain, weak for dosing).

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Recommendation 6.2. Evidence remains insufficient to recommend a specific, short-acting opioid for breakthrough pain.

Literature review and analysis. A 2015 systematic review focused on oral or nasal fentanyl for breakthrough pain.[30] The review included 11 RCTs with a total of 1,121 patients. No meta-analysis was possible. Fentanyl was reported to be effective compared with placebo, but evidence was limited regarding efficacy relative to other opioids. In a more recent, 2017 noninferiority trial of fentanyl sublingual tablet versus subcutaneous morphine in 114 patients, fentanyl was *not* noninferior to morphine at 30 minutes.[60] By contrast, a 2015 crossover trial of fentanyl buccal tablet versus oral morphine in 68 patients favored fentanyl for pain reduction at 30 minutes.[53]

Clinical interpretation. For many patients, the ideal prescription consists of an immediate-release or extended-release opioid administered regularly around the clock, plus an immediate-release opioid at a dose of approximately 10% (ranging from 5% to 20%) of the daily MME dose to be taken if there are episodes of breakthrough pain. Most people with cancer report good pain control with this combined approach.[84]

Clinical Question 7

When and how should opioids be switched (rotated)?

Recommendation 7. Opioid rotation should be offered to patients with pain that is refractory to dose titration of a given opioid, poorly managed side effects, logistical or cost concerns, or trouble with the route of opioid administration or absorption (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Literature review and analysis. Opioid rotation was evaluated in a 2018 systematic review among adults with chronic, cancer-related pain and regular use of oral or transdermal opioids.[35] The review included three systematic reviews, four RCTs, and five prospective observational studies. The authors concluded that opioid rotation can improve pain relief and patient satisfaction. Dose escalation after rotation was necessary to achieve adequate pain relief in a majority of studies evaluated, with the exception of rotation to methadone.

Clinical interpretation. Opioid rotation is common in the management of cancer pain, with one study demonstrating a frequency of close to one third of patients requiring a change.[85] The goal of opioid rotation is to safely switch from one opioid, or one route, to an alternate agent. Unfortunately, there are few studies comparing the potency of one opioid or route to another, including in models of different types of pain (eg, acute *v* chronic, neuropathic *v* nociceptive). One exception is the work conducted by Reddy et al exploring conversion factors between a variety of opioids in clinical settings.[86-88] Vigorous debate currently centers around the use of equianalgesic tables or conversion factors.[89] Widely divergent information is available in the very large number of existing tools and online applications. Current equianalgesic tables assume fixed and bidirectional values and require more complicated mathematical formulas that may be prone to error. Yet, a very large number of conversion factors would be required to address all the potential permutations for rotating from one opioid to another or from one route to another. Additionally, none of these tools consider the clinical context that is crucial when converting opioids and/or routes. To address these concerns, ASCO has partnered with the Multinational Association of Supportive Care in Cancer and other organizations to develop an international opioid conversion guideline. Until there is greater evidence and consensus within the field, clinicians and teams should select one method to calculate a safe dose and use this consistently when switching from one opioid to another or from one route to another.

Regardless of the methodology used, opioid rotation should be personalized on the basis of the underlying reason to change the medication. The dose might be more conservative in those individuals experiencing significant adverse effects, particularly sedation or a history of falls. This is also true when rotating to a parenteral route of administration if there is any question about absorption of the drug when taken enterally (eg, possible loss through vomiting or rapid motility). Conversely, when patients are in severe pain, doses may be more liberal. Close monitoring and frequent follow-up with necessary dose titration are warranted.

BARRIERS TO OPIOID ACCESS

Complicating the limited research related to opioid use in those with cancer are serious challenges in accessing these medications. Barriers include regulations that burden prescribers, such as frequent, mandatory review of the PDMP database. Additionally, limits on the daily dose of an opioid or the number of doses that can be dispensed greatly hinder availability.[90] The 2016 Centers for Disease Control and Prevention Guideline for Prescribing Opioids for Chronic Pain[91] suggested maximum daily doses that explicitly excluded those with active cancer or those approaching the end of life, yet oncologists report that the guidelines are widely misinterpreted to include those with cancer.[4] Compounding this misinterpretation, state laws often exempt cancer-related pain, yet are insufficiently clear to guide prescribers as they address the needs of diverse cancer populations.[92]

These regulations and other measures designed to mitigate the opioid misuse epidemic have been associated with decreased opioid prescribing in cancer and noncancer pain and have even been noted in those patients entering hospice.[93-98] One study observed a correlation between decreased opioid prescribing and an increase in cancer pain–related emergency department visits.[96] The most

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vulnerable patients remain the most affected, with reduced rates of opioid prescribing, along with lower doses, reported in people of color.[99,100]

When provided a prescription for an opioid, patients with cancer consistently recount problems obtaining the medication, with one quarter describing perceived difficulties during interactions with pharmacy staff.[101] Some of these problems arise because of the complexities of medication dispensing in our current health care system. Is the drug available at the pharmacy, and if so, will insurance pay? Shortages of opioids have been noted as the US Drug Enforcement Administration has repeatedly reduced production quotas. Pharmacies are often unwilling to carry these crucial medications. Delays in access can occur because of increasing requirements by payors for prior authorizations, a cumbersome process that can take 3-7 business days. Many payors require step therapy, where a patient must undergo unnecessary trials of medications to demonstrate the failure of an agent, before obtaining approval for a requested opioid. As discussed previously, the WHO no longer supports a step-wise analgesic ladder for opioid initiation.[63] Furthermore, although a prior authorization may eventually be approved, patients are frequently charged higher, onerous copays.[102]

The consequences of these burdensome regulatory and payment requirements include stigma and fear. People with cancer report stigma related to opioid use generated by their interactions with clinicians, pharmacists, and society.[3,4] Patients express greater fear of addiction, along with guilt and a sense of moral failure that they require the use of opioids, causing some to skip a dose or take a lower dose than prescribed.[4-6] Another broader consequence of these many obstacles is the pharmaceutical industry's disinterest in investment in research and development of new opioids, harboring little hope for future effective treatments for cancer pain.

The increasing number of substance-related deaths, including opioids, is a serious public health emergency that has only escalated during the COVID-19 pandemic.[103,104] Because those with cancer are not exempt from substance use disorder and/or nonmedical opioid use, a thorough proactive assessment of pain, function, and risk is required, along with strategies to balance risk mitigation with effective pain control.[105-107] It is imperative that we do not compound this crisis by undertreating cancer pain.

PATIENT AND CLINICIAN COMMUNICATION

Safe and effective use of opioids requires clear communication among patients, caregivers, and clinicians. Clinicians can help patients and caregivers understand that early and effective pain management improves quality of life and is a key component of cancer care. Common patient concerns about opioids include fear of respiratory depression or addiction, along with stigma regarding the use of these drugs. To address these concerns, clinicians may assess patient and caregiver knowledge and attitudes regarding pain and the use of opioids. Education is needed, particularly as these drugs are often prescribed as needed, requiring the patient and their loved ones to decide when and how to take them. Additionally, web-based applications and electronic pill diaries can help remind patients when to take medications while recording this information to help clinicians determine optimal pain treatment strategies. Regular follow-up of patients is important to monitor opioid efficacy and safety, and to make timely changes to the treatment regimen when needed. Patients should be informed that inadequate pain relief or bothersome opioid side effects can be managed and should be reported. Especially in advanced disease, patients and caregivers should be aware that some symptoms, such as confusion or loss of mental clarity, may occur in part due to opioids, but also as a result of organ dysfunction and disease progression. In those circumstances, the benefits of relief need to be carefully considered while optimizing quality of life.

When opioids are prescribed, clinicians must educate patients and their caregivers about safe storage and disposal. Opioids should be stored in their original packaging in a locked container and not shared with others. Unused opioid medications and other controlled substances such as benzodiazepines should be safely disposed of, ideally through take-back programs or medication drop boxes.

For general recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.[108]

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care or receive fragmented care. Factors such as race and ethnicity, age, socioeconomic status, sexual orientation and gender identity, geographic location, and insurance access are known to affect cancer care outcomes.[109] Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial or ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving fragmented or poor-quality care than other Americans.[110,111] In the case of opioids, prescribing in the United States varies by age, sex, gender,

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race, and ethnicity.[96,99,100,112] A 2020 analysis of linked Surveillance, Epidemiology, and End Results-Medicare data assessed opioid prescriptions among opioid-naive, older patients with nonmetastatic cancer.[99] Compared with non-Hispanic White patients, the likelihood of a new opioid prescription was lower in non-Hispanic Black patients (odds ratio [OR], 0.75; 95% CI, 0.67 to 0.84), nonsignificantly higher in Hispanic patients (OR, 1.14; 95% CI, 0.99 to 1.30), and higher in Asian-Pacific Islander patients (OR, 2.15; 95% CI, 1.85 to 2.50). In addition, many patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and clinicians should strive to deliver the highest level of cancer care to these vulnerable populations. Additionally, stakeholders should work toward achieving health equity by ensuring equitable access to high-quality cancer care and research, and addressing the structural barriers that preserve health inequities.[109]

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform the treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCC)—is challenging. Patients with MCC are a complex and heterogeneous population, making it difficult to account for all possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients to avoid potential interaction effects or confounding of results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

A particularly challenging chronic condition in the oncology setting is persistent noncancer pain.[113] Patients with noncancer pain who are now diagnosed with cancer after being treated with opioids for many years frequently experience difficulty obtaining relief. These obstacles are greatly exacerbated in these patients who also suffer from comorbid substance use disorder or mental health conditions. Primary care clinicians may be unwilling to continue prescribing these medications, deferring to the oncology team.[114] If there is an additive effect of new cancer pain on top of persistent noncancer pain, dose escalation in the face of already high doses of opioids may be restricted by tolerance and toxicity along with access obstacles such as reduced reimbursement or limited availability of these medications at retail pharmacies. For cancer survivors, long-term opioid therapy may be detrimental,[9] yet few oncology clinicians have been trained in tapering high-dose opioid therapy.

Oncology clinicians can collaborate with primary care clinicians and geriatricians so that once cancer treatment is completed, patients will resume pain care through these clinicians. During cancer treatment, complex pain may require referral to pain management, palliative care, mental health, and substance use experts. Abruptly discontinuing opioids after long-term use has been shown to increase illicit substance use, emergency department visits, and deaths from overdose or suicide.[115-117] As a result, tapering opioid therapy must be conducted slowly, engaging patients throughout the process.[118]

As many patients for whom guideline recommendations apply present with MCC, any treatment plan needs to account for the complexity and uncertainty created by the presence of MCC and highlight the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

COST IMPLICATIONS

Increasingly, patients with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[119,120] Higher patient out-of-pocket costs are a barrier to initiating and adhering to recommended cancer treatments.[121,122]

Discussion of cost can be an important part of shared decision making.[123] Clinicians should discuss with patients the use of less-expensive alternatives when it is practical and feasible for the treatment of the patient's disease and there are two or more treatment options that are comparable in terms of benefits and harms.[123] Opioid costs can vary markedly by agent: morphine, methadone, and immediate-release hydrocodone tend to be the least expensive, while the cost for more recently introduced agents for which there is no available generic equivalent is typically higher. Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be informed of any financial counseling services available to address this complex, heterogeneous, and ever-changing landscape.[123]

EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment from July 8 through July 22, 2022. Response categories of "Agree as written," "Agree with

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suggested modifications," and "Disagree. See comments" were captured for every proposed recommendation, with 34 written comments received. For each recommendation, the proportion of respondents who agreed or agreed with slight modifications ranged from 88% to 100%. Expert Panel members reviewed the comments and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. All changes were incorporated before Evidence Based Medicine Committee review and approval.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO's Practice Guideline Implementation Network (PGIN) on the panel. The additional role of this PGIN representative on the guideline panel is to assess the suitability of the recommendations for implementation in the community setting, but also to identify any other barrier to implementation of which a reader should be aware. Barriers to implementation include the need to increase awareness of the guideline recommendations among frontline practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate the implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. ASCO guidelines are posted on the ASCO website and most often published in the Journal of Clinical Oncology.

RESEARCH GAPS AND FUTURE DIRECTIONS

Despite the prevalence and impact of cancer pain, many questions remain about the optimal use of opioids in this setting. Priorities for future research include the following:

- What are the clinically meaningful differences between opioids in patients with cancer?
- What are the clinically meaningful differences between scheduling an immediate-release opioid with as-needed opioid dosing versus extended-release opioid administration with as-needed immediate-release opioids for breakthrough pain?
- Which is the preferred opioid for breakthrough pain?
- What is the optimal increase or decrease when modifying the opioid dose in response to changes in pain?
- What is the clinical impact of renal dysfunction on the absorption, distribution, metabolism, and excretion of each opioid?
- What is the clinical impact of hepatic dysfunction on the absorption, distribution, metabolism, and excretion of each opioid?
- What are the conversion factors for different opioids and routes, and do these vary based upon dose (low dose *v* high dose)?
- What is the optimal strategy for opioid switching?
- What are the most effective strategies for preventing and managing opioid-induced adverse effects?
- What is the real-world role of genetic testing in guiding opioid dosing?
- What are the safest and most effective strategies for treating cancer pain in patients with opioid use disorders or nonmedical opioid use?

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Management of Chronic Pain in Survivors of Adult Cancers[9] (https://ascopubs.org/doi/pdf/10.1200/JCO.2016.68.5206)
- Integration of Palliative Care Into Standard Oncology Care[124] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[108] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Integrative Medicine for Pain Management in Oncology: SIO-ASCO Guideline[125] (https://ascopubs.org/doi/10.1200/JCO.22.01357)

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DISCLAIMER

J.A.P. and E.B. were Expert Panel co-chairs.

EDITOR'S NOTE

This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/supportive-care-guidelines.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Conception and design: All authors
Administrative support: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Use of Opioids for Adults With Pain From Cancer or Cancer Treatment: ASCO Guideline

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APPENDIX

TABLE A1. Use of Opioids for Adults With Pain From Cancer or Cancer Treatment Expert Panel Membership

Name	Affiliation	Role or Area of Expertise
Judith A. Paice, PhD, RN (Co-Chair)	Northwestern University Feinberg School of Medicine, Chicago, IL	Cancer pain management, palliative care
Eduardo Bruera, MD (Co-Chair)	The University of Texas MD Anderson Cancer Center, Houston, TX	Medical oncology, hospice and palliative medicine
Debra Barton, PhD, RN	University of Michigan School of Nursing, Ann Arbor, MI	Oncology nursing, oncology symptom management
David S. Craig, PharmD	H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL	Pharmacy, pain and symptom management
Areej El-Jawahri, MD	Massachusetts General Hospital, Boston, MA	Hematology/oncology, bone marrow transplantation
Dawn L. Hershman, MD, MS	Mailman School of Public Health and Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, New York, NY	Medical oncology, cancer prevention and survivorship
Lynn R. Kong, MD	Ventura County Hematology Oncology Specialists, Oxnard, CA	Medical oncology, PGIN representative
Geana P. Kurita, PhD, MNSc	Rigshospitalet Copenhagen University Hospital, University of Copenhagen, Copenhagen, Denmark	Adult health nursing, pain relief, palliative care
Thomas W. LeBlanc, MD, MA, MHS	Duke University School of Medicine, Durham, NC	Medical oncology (hematologic malignancies), palliative care
Sebastiano Mercadante, MD	La Maddalena Cancer Center, Palermo, Italy	Anesthesiology, pain relief, palliative care
Kristina L. M. Novick, MD, MS	Penn Radiation Oncology Chester County, Chester County Hospital, West Chester, PA	Radiation oncology, palliative care
Ramy Sedhom, MD	Penn Center for Cancer Care Innovation, Abramson Cancer Center, Penn Medicine, Philadelphia, PA	Medical oncology, hospice and palliative medicine
Carole Seigel, MBA	Patient/Family Representative, Brookline, MA	Patient/family representative
Joanna Stimmel, PhD	Patient/Family Representative, Los Angeles, CA	Patient/family representative
Kari Bohlke, ScD	American Society of Clinical Oncology, Alexandria, VA	ASCO practice guideline staff (health research methods)

Abbreviation: PGIN, Practice Guideline Implementation Network.

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TABLE A2. Recommendation Rating Definitions

Term	Definitions
Quality of evidence	
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Strength of recommendation	
Strong	In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects All or almost all informed people would make the recommended choice for or against an intervention
Weak	In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists Most informed people would choose the recommended course of action, but a substantial number would not

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