Use of Opioids for Adults with Pain from Cancer or Cancer Treatment:

ASCO Guideline

Paice JA, et al.

Overview

1. Background & Methodology
   - Introduction
   - ASCO Guideline Development Methodology
   - Clinical Questions
   - Target Population and Audience
2. Summary of Recommendations
3. Discussion
   - Patient and Clinician Communication
   - Health Disparities
   - Cost Implications
   - Research Gaps & Future Directions
   - Additional Resources
   - Expert Panel Members

ASCO®
AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

1 Background & Methodology

Introduction

- Approximately 55% of those undergoing active treatment experience pain, while the prevalence is greater than 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 co-pays, and a lack of availability of opioids at retail pharmacies.
- People with cancer report stigma and concern related to opioid use.[3,4]

Introduction

- 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]
- 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 person with cancer.

Introduction

- Given the current environment of apprehension regarding opioids, specific guidance is warranted to 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, the 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.

ASCO Guideline Development Methodology

- The ASCO Evidence Based Medicine Committee (EBMC) guideline process includes:
  - a systematic literature review by ASCO guidelines staff
  - an expert panel provides critical review and evidence interpretation to inform guideline recommendations
  - final guideline approval by ASCO EBMC

- The full ASCO Guideline methodology manual can be found at: www.asco.org/guideline-methodology

Clinical Questions

This clinical practice guideline addresses seven clinical questions:

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)?

Target Population and Audience

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.

ASCO®
AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

2 Summary of Recommendations

Summary of 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.

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Summary of Recommendations

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.

Informal consensus benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
N/A	Strong

Summary of Recommendations

Clinical Question 2

- Which opioids should be offered?

Recommendation 2.1

- For patients who are candidates to begin opioid treatment (Rec 1.1), clinicians may offer any of the opioids approved by the FDA or other regulatory agencies for pain treatment.

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Moderate - Low	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 pro-drug, 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 pro-drug, requiring CYP2D6 to allow it to be metabolized to morphine to achieve analgesic effects.*[12]

Summary of Recommendations

Recommendation 2.2

- Clinicians with limited experience with methadone prescribing should consult palliative care or pain specialists when initiating or rotating to methadone.

Informal consensus benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
N/A	Strong

Summary of Recommendations

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.

Informal consensus benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
N/A	Strong

Summary of Recommendations

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.

Informal consensus benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
N/A	Strong

Recommendation 3.3

- Patients who have been taking other analgesics, such as NSAIDs, may continue these analgesics after opioid initiation if these agents provide additional analgesia and are not contraindicated.

Informal consensus benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
N/A	Weak

Summary of Recommendations

Recommendation 3.4

No recommendation

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

Evidence Quality	Strength of Recommendation
N/A	N/A

Recommendation 3.5

No recommendation

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

Evidence Quality	Strength of Recommendation
N/A	N/A

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.*

Summary of Recommendations

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.

Informal consensus benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
N/A	Strong

Summary of Recommendations

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.

Informal consensus benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
N/A	Strong

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

Summary of Recommendations

Clinical 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.

Informal consensus benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
N/A	Strong

Summary of Recommendations

Recommendation 5.2

- For patients with renal or hepatic impairment who receive opioids, clinicians should perform more frequent clinical observation and opioid dose adjustment.

Informal consensus benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
N/A	Strong

Summary of Recommendations

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.

Informal consensus benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
N/A	Strong for prescribing immediate-release opioids for breakthrough pain
	Weak for dosing

Summary of Recommendations

Recommendation 6.2

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

No recommendation

Evidence Quality	Strength of Recommendation
N/A	N/A

Summary of Recommendations

Clinical Question 7

- When and how should opioids be switched (rotated)?

Recommendation 7.1

- 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.

Evidence based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

ASCO®
AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

3 Discussion

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.
- Patient concerns about opioids include fear of respiratory depression or addiction, along with stigma regarding the use of these drugs.
- Clinicians may assess patient and caregiver knowledge and attitudes regarding pain and the use of opioids.
- Education is needed, as these drugs are often prescribed “as needed,” requiring the patient and their loved ones to decide when and how to take them.
- Web-based applications and electronic pill diaries can help remind patients when to take medications while recording this information to help determine optimal pain treatment strategies.

Patient and Clinician Communication

- 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. The benefits of relief need to be carefully considered while optimizing quality of life.
- Clinicians must educate patients and caregivers about safe storage and disposal of opioids.
- Opioids should be stored in their original packaging in a locked container and not shared.
- Unused opioid medications and other controlled substances should be safely disposed of.

Health Disparities

- In the case of opioids, prescribing in the US varies by age, sex, gender, race, and ethnicity.[13-16]
- A 2020 analysis of linked SEER-Medicare data assessed opioid prescriptions among opioid-naïve, older patients with nonmetastatic cancer.[14]
  - Compared with non-Hispanic white patients, the likelihood of a new opioid prescription was lower in non-Hispanic black patients (OR 0.75; 95% CI 0.67 to 0.84), non-significantly 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).
- Awareness of disparities in access to care should be considered in the context of this guideline, and clinicians should strive to deliver the highest level of cancer care to these vulnerable populations.
- Stakeholders should work towards achieving health equity by ensuring equitable access to high-quality cancer care and research and addressing the structural barriers that preserve health inequities.[17]

Cost Implications

- Discussion of cost can be an important part of shared decision-making.[18]
- 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 insurance plan, and the price may vary between different pharmacies.
- When discussing financial issues and concerns, patients should be informed of any financial counseling services available.[18]

Research Gaps & 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?

Research Gaps & Future Directions

- What are the conversion factors for different opioids and routes, and do these vary based upon dose (low dose versus 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 non-medical opioid use?

Additional Resources

- More information, including a supplement and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines

- Patient information is available at www.cancer.net

Expert Panel Members

Name	Affiliation/Institution	Role/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	Brookline, MA	Patient/family representative
Joanna Stimmel, PhD	Los Angeles, CA	Patient/family representative
Kari Bohlke, ScD	American Society of Clinical Oncology, Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)

Abbreviations

- ASCO, American Society of Clinical Oncology
- CI, confidence interval
- CYP2, cytochrome P450
- EBMC, Evidence Based Medicine Committee
- FDA, United States Food and Drug Administration
- N/A, not applicable
- NSAIDs, non-steroidal anti-inflammatory drugs
- OR, odds ratio
- PRN, as needed
- SEER, Surveillance, Epidemiology, and End Results
- US, United States

References

1. van den Beuken-van Everdingen MH, Hochstenbach LM, Joosten EA, et al: Update on Prevalence of Pain in Patients With Cancer: Systematic Review and Meta-Analysis. J Pain Symptom Manage 51:1070-1090.e9, 2016
2. Paice JA: Cancer pain management and the opioid crisis in America: How to preserve hard-earned gains in improving the quality of cancer pain management. Cancer, 2018
3. Bulls HW, Chu E, Goodin BR, et al: Framework for opioid stigma in cancer pain. Pain 163:e182-e189, 2022
4. Schenker Y, Hamm M, Bulls HW, et al: This Is a Different Patient Population: Opioid Prescribing Challenges for Patients With Cancer-Related Pain. JCO Oncol Pract 17:e1030-e1037, 2021
5. Wright EM, El-Jawahri A, Temel JS, et al: Patient Patterns and Perspectives on Using Opioid Regimens for Chronic Cancer Pain. J Pain Symptom Manage 57:1062-1070, 2019
6. Azizoddin DR, Knoerl R, Adam R, et al: Cancer pain self-management in the context of a national opioid epidemic: Experiences of patients with advanced cancer using opioids. Cancer, 2021
7. World Health Organization: WHO Guidelines for the Pharmacological and Radiotherapeutic Management of Cancer Pain in Adults and Adolescents, World Health Organization. https://apps.who.int/iris/handle/10665/279700. License: CC BY-NC-SA 3.0 IGO, 2018
8. Swarm RA, Paice JA, Anghelescu DL, et al: Adult cancer pain, version 3.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 17:977-1007, 2019
9. Paice JA, Portenoy R, Lacchetti C, et al: Management of Chronic Pain in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 34:3325-45, 2016
10. Fallon M, Giusti R, Aielli F, et al: Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines. Ann Oncol 29 Suppl 4:iv166-iv191, 2018
11. Grond S, Sablotzki A: Clinical pharmacology of tramadol. Clin Pharmacokinet 43:879-923, 2004
12. Crews KR, Monte AA, Huddart R, et al: Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy. Clin Pharmacol Ther 110:888-896, 2021
13. Enzinger AC, Ghosh K, Keating NL, et al: US Trends in Opioid Access Among Patients With Poor Prognosis Cancer Near the End-of-Life. J Clin Oncol:JCO2100476, 2021
14. Vitzthum LK, Nalawade V, Riviere P, et al: Racial, Ethnic, and Socioeconomic Discrepancies in Opioid Prescriptions Among Older Patients With Cancer. JCO Oncol Pract 17:e703-e713, 2021
15. Morden NE, Chyn D, Wood A, et al: Racial Inequality in Prescription Opioid Receipt - Role of Individual Health Systems. N Engl J Med 385:342-351, 2021
16. Fisch MJ, Lee JW, Weiss M, et al: Prospective, observational study of pain and analgesic prescribing in medical oncology outpatients with breast, colorectal, lung, or prostate cancer. J Clin Oncol 30:1980-8, 2012
17. Patel MI, Lopez AM, Blackstock W, et al: Cancer Disparities and Health Equity: A Policy Statement From the American Society of Clinical Oncology. J Clin Oncol:Jco2000642, 2020
18. Meropol NJ, Schrag D, Smith TJ, et al: American Society of Clinical Oncology guidance statement: the cost of cancer care. J Clin Oncol 27:3868-74, 2009

Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by the American Society of Clinical Oncology, Inc. (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.