Opioid Conversion in Adults with Cancer

MASCC-ASCO-AAHPM-HPNA-NICSO Guideline

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1 Background & Methodology

Introduction

- Cancer pain and other serious illnesses often require opioid therapy.
- Most patients respond to the first opioid, although a significant number develop dose-limiting side effects or experience suboptimal pain control despite appropriate opioid titration.[1,2]
- Opioid rotation or switching is often done to reduce side effects and/or improve pain control.[2-13]
- Opioid switches or rotations are successful due to inter-individual differences in opioid pharmacodynamics between individuals based on their opioid receptor genetics.[14-17]
- Opioid conversion ratios provide the safe dose between withdrawal and toxicity for a population but should not be referred to as the “equianalgesic” dose.
- Further dose adjustments are likely to be needed in order for patients to experience optimal analgesia and/or reduced side effects.[4,18,19]

Introduction

- A survey of 370 palliative care professionals from 53 countries collected opioid doses and routes used in practice.
- A significant difference in conversion ratios was observed across different clinician groups and geographical regions.[10]
- The present guideline seeks to reduce this variability by providing recommendations regarding opioid conversion in adults with cancer.
- It builds upon a recent ASCO guideline that addressed use of opioids for pain from cancer or cancer treatment.[20]

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
- Due to limitations of the available evidence, recommendations were developed using the ASCO-modified Delphi formal consensus methodology.[21] The 14 members of the Expert Panel were supplemented by 27 additional experts, who were recruited to rate their agreement with the recommendations.
- The full ASCO Guideline methodology manual can be found at: www.asco.org/guideline-methodology

Clinical Questions

This clinical practice guideline addresses three clinical questions:

1. What assessments are important before opioid conversion?
2. How should opioid conversions be conducted?
3. What assessments are important after opioid conversion?

Target Population and Audience

Target Population

- Adults with cancer who are receiving opioids for pain

Target Audience

- Oncologists, palliative care specialists, oncology nurses, oncology pharmacists, hospitalists, primary care clinicians, adults with cancer, and caregivers of adults with cancer

2 Summary of Recommendations

Summary of Recommendations

Clinical Question 1

- What assessments are important before opioid conversion?

Recommendation 1.1

- Recommended pre-conversion assessments include the following:

	n agreed/n voted	% agreement
a. A multidimensional pain assessment, completed at the initial evaluation and periodically based on clinical circumstances, worsening pain severity or distress, or changes in pain characteristics (location, quality, etc.).	38/39	97.4%
b. A thorough review of the pain pathology and other management options (e.g., disease modification, non-opioid analgesics, interventional techniques, and non-pharmacological interventions).	39/39	100%
c. A review of comorbidities, drug-to-drug interactions, and cumulative adverse effects to identify factors that may indicate or contraindicate specific opioid analgesics or routes of administration.	39/39	100%

Summary of Recommendations

Recommendation 1.1 (cont.)

- Recommended pre-conversion assessments include the following:

	n agreed/n voted	% agreement
d. A history of opioid analgesic usage, i.e., adherence, dosage, efficacy, route of administration, and tolerability.	39/39	100%
e. Any history of drug misuse, abuse, addiction, and/or diversion in patients and family members (i.e., alcohol, opioids, and other drugs), or history of adverse childhood events.	38/39	97.4%
f. An evaluation for organ dysfunction (e.g., hepatic or renal).	38/39	97.4%
g. The availability of family members or friends to monitor the patient closely during the first few days after the opioid conversion.	37/39	94.8%
h. A discussion with the patient and their family caregivers about the acceptability of different treatments (i.e., drug, route of administration).	33/39	84.6%

Summary of Recommendations

Recommendation 1.2

- Situations in which opioid conversion may be offered include the following:

	n agreed/n voted	% agreement
a. If pain is uncontrolled despite upward titration of the current opioid analgesic or if the patient cannot tolerate the dose increase of the current opioid.	37/39	94.8%
b. If intolerable adverse effects, such as itching, nausea, etc., persist despite tapering the opioid analgesic, and/or if symptomatic management of adverse effects is ineffective or poorly tolerated and pain is poorly controlled.	38/39	97.4%
c. If signs of opioid-induced neurotoxicity, like allodynia, confusion, excessive drowsiness, hallucination, hyperalgesia, or myoclonus, occur or persist even after the tapering of the current opioid analgesic.	35/39	89.7%
d. If pharmacokinetic factors affect the absorption, metabolism, or excretion of the current opioid analgesic.	39/39	100%
e. If there are availability issues or health economic constraints (drug costs).	37/39	94.8%

Summary of Recommendations

Recommendation 1.3

- If pain is uncontrolled, a change in the opioid route of administration from oral to intravenous or subcutaneous administration (to enable rapid titration) may be appropriate before changing opioids.

n agreed/n voted	% agreement
37/39	94.8%

Note 1.

- The panel recommends that the assessment of “total pain,” defined as emotional, social, and spiritual suffering, isolation, and distress due to financial problems, should be completed because it may influence the patient's perception of pain or self-report and, consequently, the choice of analgesic treatment.

37/39	94.8%

Summary of Recommendations

Note 2.

- The panel defines opioid conversion (also referred to as opioid rotation and/or switching) as either a change of the drug (opioid) or a change of the route of administration or formulation.

n agreed/n voted	% agreement
35/39	89.7%

Summary of Recommendations

Clinical Question 2

- How should opioid conversions be conducted?

Recommendation 2.1

- Opioid doses should be individually adjusted based on patient characteristics, polypharmacy, organ function, and patient-clinician mutually agreed-upon targets for pain intensity and physical function.

n agreed/n voted	% agreement
37/39	94.8%

Summary of Recommendations

Recommendation 2.2

n agreed/n voted	% agreement
35/39	89.7%

- An option for converting from one opioid to another is to use a two-step process. The first step is to calculate the so-called “morphine equivalent daily dose” (MEDD) of the first opioid. The second step uses the calculated morphine equivalent daily dose of the second opioid in conversion.

Recommendation 2.3

33/39	84.6%

- Conversion ratios should not be confused with equianalgesia. Conversion ratios are the doses of an opioid anticipated to prevent withdrawal or overdose when changing opioids or routes of administration. Doses will need to be adjusted to achieve analgesia for the individual patient.

Summary of Recommendations

Recommendation 2.4

- Opioid choices in conversion should consider safety and utility. If patients are at risk for addiction or have a history of addiction or substance use disorder, one should consider buprenorphine or methadone. If the patient has significant renal dysfunction, buprenorphine, fentanyl, or methadone should be considered. If the patient has significant liver disease, hydromorphone, or morphine should be considered.

n agreed/n voted	% agreement
30/38	78.9%

Summary of Recommendations

Recommendation 2.5

- Clinicians should know drug interactions when using tramadol and codeine and be aware of medications that block CYP2D6, with tramadol in particular.

n agreed/n voted	% agreement
37/38	97.3%

Note for Recommendation 2.5

- The analgesia of codeine and tramadol is influenced by CYP2D6 metabolizer status, and drug interactions at CYP2D6 will alter conversion ratios. Ultra-rapid metabolizers with multiple CYP2D6 alleles may have a greater conversion of codeine to morphine, resulting in opioid toxicity if standard conversion ratios are used. Poor metabolizers do not convert tramadol to desmethyl-tramadol and are likely to have a poor analgesic response to tramadol using standard conversion ratios. Medications that block CYP2D6 may do the same.

Summary of Recommendations

Recommendation 2.6

- If converting from another opioid to methadone, a clinician experienced in prescribing methadone as an analgesic, aware of methadone's unique drug interactions, cardiac toxicity, and vast inter-individual differences in pharmacokinetics and pharmacodynamics should be the clinician who manages the conversion to methadone.

n agreed/n voted	% agreement
38/38	100%

Recommendation 2.7

- Multiple strategies can convert a potent opioid to methadone. These strategies include A. “stop-start,” B. an “overlap,” and C. an “as needed” strategy. Clinicians who prescribe methadone should be comfortable with at least one dosing strategy, preferably more than one strategy.

38/38	100%

Summary of Recommendations

Recommendation 2.8

- Though methadone has a long half-life as an analgesic, the daily doses should be divided and given twice or thrice daily if used as an analgesic.

n agreed/n voted	% agreement
32/35	91.4%

Recommendation 2.9

- For breakthrough pain, 10-15% of the MEDD should be used initially to manage breakthrough pain using an immediate-release opioid, preferably the same one used to treat chronic pain. Rapid-acting fentanyl preparations are an alternative. Doses should be adjusted based on the response defined as a 30-50% reduction in pain severity.

30/38	78.9%

Summary of Recommendations

Recommendation 2.10

n agreed/n voted	% agreement
30/38	78.9%

- For breakthrough pain, the rescue dose of either immediate-release opioid or rapid-onset fentanyl needs to be individually titrated, given the poor correlation between the around-the-clock effective dose required to control the background pain and the dose needed to control the breakthrough pain.

Note.

27/34	79.4%

- If converting from a full opioid agonist to buprenorphine, patients may experience opioid withdrawal depending on the dose of the potent opioid and the initial buprenorphine dose in a “stop-start” conversion strategy.

Opioid Conversion Ratios that Reached Consensus

Converting from	Converting to	Recommended conversion ratios*	n agreed/n voted, % agreement
Oral morphine	Oral oxycodone	1.5:1	34/38, 89.4%
Oral morphine	Oral hydromorphone	5:1	33/37, 89.1%
Oral morphine	Oral oxymorphone	3:1	16/20, 80%
Parenteral morphine	Parenteral alfentanil	10:1	15/18, 83.3%
Oral oxycodone	Oral morphine	Between 1:1 and 1:2*	32/38, 84.2%
Oral oxycodone	Oral oxymorphone	2:1	17/19, 89.4%
Oral oxycodone	Oral tapentadol	1:5	20/24, 83.3%
Oral oxycodone	Intravenous oxycodone	2:1	22/25, 88%
Oral hydrocodone	Oral morphine	1:1	23/26, 88.4%
Oral hydrocodone	Oral oxycodone	1.5:1	21/26, 80.7%
Oral tramadol	Oral morphine	10:1	29/36, 80.5%
Oral codeine	Oral hydrocodone	8:1	18/22, 81.8%
Oral tapentadol	Oral morphine	3:1	21/25, 84%
Subcutaneous administration (any opioid)	Intravenous administration (any opioid)	1:1	33/36, 91.6%

*A range was provided because of variability between the study conversion ratios

Summary of Recommendations

Clinical Question 3

- What assessments are important after opioid conversion?

Recommendation 4.1

- Recommended post-conversion assessments include the following:
  a. Pain severity rating using a validated scale. This should include the least and worst pain intensity.
  b. Pain severity at rest and with movement using a validated scale.
  c. Pain severity rating compared to the patient's personal pain severity goal.
  d. Pain-related functional impacts on daily living activities.

n agreed/n voted	% agreement
33/38	86.8%
36/38	94.7%
35/38	92.1%
37/38	97.3%

Summary of Recommendations

Recommendation 4.1 (cont.)

	n agreed/n voted	% agreement
• Recommended post-conversion assessments include the following:	37/38	97.3%
e. The average number of daily doses of short-acting opioids used for breakthrough pain.		
f. The adverse effects of pain on mood (anxiety, depression) and sleep (e.g., sleep quality and quantity).	38/38	100%

Recommendation 4.2

• Pain behaviors (such as agitation, facial expressions, etc.) should be evaluated regularly if patients cannot complete a pain intensity scale.	38/38	100%

Summary of Recommendations

Recommendation 4.3

- Recommended adverse effect monitoring includes the following:

	n agreed/n voted	% agreement
a. New-onset drowsiness or sedation, the influence of the opioid conversion on the number of hours of sleep for 24 hours, and whether apnea or snoring develops or worsens at night.	36/38	94.7%
b. New-onset nausea or vomiting.	37/38	97.3%
c. New onset confusion, delirium, and hallucinations.	38/38	100%
d. Abdominal discomfort, new-onset constipation, and/or stool frequency.	37/38	97.3%
e. New onset itching, scratching, pruritus, and/or rash.	34/38	89.4%

Summary of Recommendations

Recommendation 4.4

- Dose adjustments should be made based on pain intensity, physical function, and side effects.

n agreed/n voted	% agreement
38/38	100%

Recommendation 4.5

- After opioid conversion, ask patients and/or caregivers about missing opioid medications or doses when asked to fill the opioid prescription early or if a pill count demonstrates less medication than prescribed.

31/38	81.5%

Summary of Recommendations

Recommendation 4.6

- Assess the affect (mood) of the patient, family, or formal caregivers.

n agreed/n voted	% agreement
29/38	76.3%

Recommendation 4.7

- A QTc interval should be monitored regularly on methadone, depending on the clinical circumstance. For example, a patient with cancer receiving curative treatment may require routine ECG (electrocardiogram) monitoring. In contrast, a patient with advanced cancer or those approaching the end of life will not require the same degree of monitoring.

31/37	83.7%

Summary of Recommendations

Recommendation 4.8

- Reinforce the patient and caregivers' knowledge about pain assessment, the opioid administration schedule, and the need for ongoing monitoring for response and side effects with the new opioid.

n agreed/n voted	% agreement
38/38	100%

3 Discussion

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.org

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Abbreviations

- AAHPM, American Academy of Hospice and Palliative Medicine
- ASCO, American Society of Clinical Oncology
- EBMC, Evidence Based Medicine Committee
- ECG, electrocardiogram
- HPNA, Hospice and Palliative Nurses Association
- MASCC, Multinational Association of Supportive Care in Cancer
- MEDD, morphine equivalent daily dose
- NICSO, Network Italiano Cure di Supporto in Oncologia

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