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RESEARCH

Opioid conversion in adults with cancer: MASCC-ASCO-AAHPM-HPNA-NICSO guideline

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Abstract

Purpose To standardize and improve the safety and efficacy of opioid conversion in people with cancer.

Methods The Multinational Association of Supportive Care in Cancer (MASCC), American Society of Clinical Oncology (ASCO), American Academy of Hospice and Palliative Medicine (AAHPM), Hospice and Palliative Nurses Association (HPNA), and Network Italiano Cure di Supporto in Oncologia (NICSO) convened an Expert Panel to develop recommendations based on a systematic review of the literature and a formal consensus process. The systematic review focused on randomized and non-randomized studies published from database inception to June 2022. A modified Delphi approach was used to develop and finalize recommendations. Recommendations developed by the Expert Panel underwent two rounds of consensus voting before being finalized.

Results The systematic review, published separately, identified 208 eligible studies. These studies provided mixed and inclusive findings regarding optimal approaches to opioid conversion. In consensus voting, 58 of 84 statements met or exceeded the required 75% level of agreement and were accepted. This process demonstrated some consistencies in conversion ratios between particular opioids internationally, but also uncovered variability in opioid conversion ratios among experts, particularly for methadone.

Recommendations The recommendations address three main topics: pre-conversion assessments, strategies for conversion, and post-conversion assessments. The goal is to reduce the relative risk of overdosing or under-dosing opioids when converting from one opioid to another or converting administration routes. The strength of the evidence from the trials is modest, and there are large clinical practice and research gaps. The panel hopes this guideline will establish an international best practice baseline that can be built upon by new research and better-designed trials.

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

Keywords Opioid · Conversion · Guideline · Delphi consensus

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This joint 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.org, is available at www.asco.org/supportive-care-guidelines.

Extended author information available on the last page of the article

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]. It is the exchange of one opioid for another using either the same route or an alternative route, which requires an understanding of conversion ratios. Opioid switches or rotations are successful due to inter-individual differences in opioid pharmacodynamics between individuals based on their opioid receptor genetics [14–17]. It is important to state that 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].

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].

Guideline questions

This clinical practice guideline addresses three overarching clinical questions: (1) What assessments are important before opioid conversion? (2) How should opioid conversions be conducted? and (3) What assessments are important after opioid conversion?

Methods

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

Guideline development process

The guideline was developed by a multidisciplinary Expert Panel, including an ASCO guidelines staff member with expertise in health research methodology (Appendix Table A1, online only). Five full panel meetings and two steering committee meetings were held between 9/23/2022 and 6/1/2023. Members were asked to provide ongoing input on the guideline development protocol, quality, and assessment of the evidence, generation of recommendations, draft content, and review and approve drafts throughout the entire development of the guideline.

Guideline development involved a systematic review of the literature, expert consensus, and clinical experience. Details of the systematic review have been published [21]. In brief, multiple databases were searched from inception until June 2022. Articles were selected for inclusion in the systematic review based on the following criteria:

- Study designs: randomized or non-randomized studies
- Population: people of any age with acute or chronic pain, with or without cancer
- Interventions: opioid conversion
- Outcomes: analgesic outcomes and safety

Studies were excluded if they used indirect comparisons through morphine equivalent daily dose (MEDD) comparisons rather than direct comparisons or did not provide conversion ratios or data from which conversion ratios could be calculated.

Due to limitations of the available evidence, recommendations were developed using the ASCO-modified Delphi formal consensus methodology [22]. This process involved a subgroup of the Expert Panel drafting recommendations using clinical expertise and the available evidence. The Expert Panel reviewed the recommendations and proposed revisions. The 14 members of the Expert Panel were then supplemented by 27 additional experts, who were recruited to rate their agreement with the recommendations. The entire membership of experts is referred to as the Consensus Panel (Appendix Table A2, online only).

A 5-item Likert scale was used to assess agreement. The Likert scale consisted of (1) strongly agree, (2) agree, (3) neither agree nor disagree, (4) disagree, and (5) strongly disagree. Because not all experts had access to all opioids considered, the survey also had an option of "I cannot respond because I am not familiar with the use of this opioid or it is not available in my country." Consensus was defined as at least 75% agreement ("agree" or "strongly agree") among those who responded [23–25]. Those who felt they could not respond to a particular statement were excluded from the consensus for that statement. This approach resulted in a smaller sample size of voters for the less commonly used opioids, and this information is provided along with the recommendations.

Guideline review and approval

Each participating organization reviewed the guidelines before submission for publication. The Expert Panel approved subsequent revisions before submission.

Guideline updating

The Expert Panel and guidelines staff will work with co-chairs to keep abreast of any substantive updates to the guideline. Participating organizations will determine the need to update based on a review of the emerging literature. This is the most recent information as of the publication date.

Results

A total of 140 randomized controlled trials and 68 non-randomized studies were included in the systematic review. Details regarding these studies are provided in a separate publication [21].

Recommendations developed by the Expert Panel underwent two rounds of consensus voting. By the end of the second round of voting, 58 of 84 statements achieved consensus (Tables 1, 2, 3, and 4). The 26 recommendations that failed to reach a consensus are listed in the Supplement. A visual summary of the key recommendations, intended to aid the implementation of the recommendations, is provided in Fig. 1.

Recommendations

Recommendations for pre-conversion assessment, opioid conversion, and post-conversion assessment are available in Tables 1, 2, 3, and 4.

Discussion

This guideline is the first international consensus on the practice of opioid conversion, and it also provided a consensus for certain conversion ratios. The Consensus Panel of experts agreed upon the distinction between conversion ratios and equianalgesic ratios. Conversion ratios are primarily centered on safe practices when converting opioids and/or routes with a secondary goal of analgesia requiring opioid dose adjustments to the individual patient. The guideline established conversion ratios between commonly used first-line opioids (hydromorphone, morphine, oxycodone), which were widely divergent based on country and region in the MASCC survey [10]. The international conversion ratio consensus between multiple opioids summarized in Table 3 is a major accomplishment that will inform future research. This guideline reinforces the practice of using MEDD as an option when direct comparisons between two opioids are not possible. The Expert Panel established an international consensus on the choice of opioids based on clinical circumstances in this guideline. The panel agreed on certain conversion ratios of certain second-line opioids (alfentanil, hydrocodone, oxymorphone, and tapentadol) by experts who had access to these opioids. The panel established that methadone should be prescribed only by experts and that there were added risks to prescribing methadone that were unique to methadone. The panel recognized several different strategies for prescribing methadone and that experts need to be comfortable with these strategies. The guideline contains detailed considerations before and after opioid conversion as a necessity for successful conversions between opioids and/or routes.

For opioid conversion practices that did not reach consensus in this guideline, clinicians will need to depend on published literature, personal practices, or guidance from experts until further research establishes stronger evidence for opioid conversions. Caution is particularly needed when considering route changes or prescribing buprenorphine and fentanyl.

Before converting opioids

Different pain syndromes or phenotypes may have variable and unpredictable responses to pain. Some are more responsive to opioid therapy than others [26, 27]. Certain pain syndromes will be refractory to most opioids, and opioid conversion may not improve analgesia [28, 29]. Pain may "worsen" due to the lack of patient medication adherence due to fear of addiction or as a means of reducing opioid side effects. Lack of adherence may also be due to opioid diversion [30]. Poor dosing strategies like "as needed" immediate-release opioid dosing for continuous cancer pain may lead to suboptimal pain control and are better managed by improving the dosing strategy rather than converting the opioid [5]. An opposite response can occur to exposure to an opioid, which results not only in analgesic tolerance but also can cause opioid-induced hyperalgesia [31]. This may be driven by non-mu receptor and channel activation and neuroinflammation from opioid exposure [32–34]. Dose reduction rather than opioid conversion may paradoxically reduce pain [35, 36]. Opioid-induced hyperalgesia may occur in as many as 18% of patients on long-term opioids and is associated with a change in pain characteristics and a progressive increase in pain severity [37]. Patients with opioid-induced hyperalgesia may have a short-term benefit with a dose increase, but it is later followed by worsening pain. This worsening pain occurs in the absence of cancer progression [38].

Table 1 Recommendations for pre-conversion assessment

Recommendation	*n* agreed/*n* voted, % agreement
1.1. Recommended pre-conversion assessments include the following:	
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%
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%
1.2. Situations in which opioid conversion may be offered include the following:	
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%
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	37/39, 94.8%
Notes:	
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%
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	35/39, 89.7%

It is important to assess factors that will influence opioid choice, dose, and individualization of treatment. Pain severity alone should not be used to consider opioid choices or conversion. The key to managing complex pain in an individual with cancer is an open-minded assessment of the pain experience. Not only should clinicians elicit pain severity, quality, response to treatment, location, and radiating or referring pattern, but they also need to listen to the patient's story and establish rapport to individualize goals to opioid therapy [39]. To many patients, numerical rating scales or visual analog scales for pain severity (though frequently used in pain trials) are abstract. Patients describe their pain in terms of function and interference with daily activities and roles within the family structure [40, 41]. Pain interference with daily activity reasonably separates severe, moderate, and mild pain severity [42]. Some have found a non-linear association between severity and interference [43, 44]. Pain intensity scores may not adequately reflect the patient's desire for opioid analgesics. Expectations of benefits regarding the return of function with pain management may be unrealistic, and the benefits of opioid conversion can be overestimated. The expectations need to be modulated into those that may be achieved and those for which one may hope to achieve. Managing patients expectations is important to avoid being "set up" for failure from the anticipation that the opioid conversion will result in complete pain relief [41]. Patients often use the terms that the pain is "acceptable," "manageable," or "tolerable" for responses to opioid therapy and conversion rather than expressed as a particular number on a severity scale [45].

There are no universally accepted definitions for opioid rotation or opioid switching. One investigator defined "switches" as a change in route of administration and "rotation" as a change in opioid analgesics, while others have

Table 2 Recommendations for opioid conversion

Recommendation	*n* agreed/*n* voted, % agreement
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	37/39, 94.8%
2.2. 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	35/39, 89.7%
2.3. 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	33/39, 84.6%
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	30/38, 78.9%
2.5. Clinicians should know drug interactions when using tramadol and codeine and be aware of medications that block CYP2D6, with tramadol in particular	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	
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	38/38, 100%
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%
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	32/35, 91.4%
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%
2.10. 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	30/38, 78.9%
Note: 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	27/34, 79.4%

Abbreviations: *MEDD*, morphine equivalent daily dose

used the term synonymously [4, 18, 46–48]. The term "opioid conversion" in this guideline encompasses both terms. The primary goal of opioid conversion is to find a safe starting dose, whether by changing route or opioids [6, 7]. The primary reason that changing opioids can be effective is because of non-cross analgesic tolerance between opioids. Non-cross analgesic tolerance is due to differences in mu receptor interactions with receptor subtypes and downstream signaling [15, 49–52].

In retrospective studies of people with cancer or other conditions, 20–44% of patients require opioid conversion, and of those who undergo opioid conversion, 50–90% will be successful in producing acceptable pain control [2, 53–55]. Opioid conversions are usually considered when pain is inadequately controlled and or there are intolerable side effects. In a clinical review of opioid conversions, 39% of patients were converted because they had cognitive side effects, 24% because of hallucinations, 16% for uncontrolled pain, 11% for symptomatic myoclonus, and 9% for intractable nausea [55]. Patients with more difficult pain to manage are usually on higher opioid doses and more frequently require opioid conversion [54]. Opioid conversion should be viewed as one of several ways of addressing unsatisfactory outcomes during opioid therapy. If pain is controlled but side effects are intolerable, 25–30% dose reductions may reduce side effects and maintain analgesia without rotation or conversion. If

Table 3 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

Table 4 Recommendations for post-conversion assessment

Recommendation	*n* agreed/*n* voted, % agreement
4.1. Recommended post-conversion pain assessments include the following:	
a. Pain severity rating using a validated scale. This should include the least and worst pain intensity	33/38, 86.8%
b. Pain severity at rest and with movement using a validated scale	36/38, 94.7%
c. Pain severity rating compared to the patient's personal pain severity goal	35/38, 92.1%
d. Pain-related functional impacts on daily living activities	37/38, 97.3%
e. The average number of daily doses of short-acting opioids used for breakthrough pain	37/38, 97.3%
f. The adverse effects of pain on mood (anxiety, depression) and sleep (e.g., sleep quality and quantity)	38/38, 100%
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%
4.3. Recommended adverse effect monitoring includes the following:	
a. New-onset drowsiness or sedation, the influence of the opioid conversion on the number of hours of sleep for 24 h, 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%
4.4. Dose adjustments should be made based on pain intensity, physical function, and side effects	38/38, 100%
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%
4.6. Assess the affect (mood) of the patient, family, or formal caregivers	29/38, 76.3%
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%
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	38/38, 100%

Abbreviations:*ECG*, electrocardiogram

pain is poorly controlled and side effects are intolerable, converting routes rather than opioids may result in better pain control and fewer side effects. If pain is poorly controlled despite a dose titration, adding an adjuvant analgesic may result in acceptable pain control [6, 18, 56, 57].

There are reasons besides opioid toxicity and uncontrolled pain for opioid conversion. There may need to be a change in route due to dysphagia or nausea, for example [53]. Patients may have preferences, due to family or personal experiences. These preferences may be to avoid certain opioids. Individuals may be on medications that have a drug-drug interaction with particular opioids that either delay or accelerate drug clearance [53]. There may be financial reasons. Certain opioids or the particular pharmaceutical preparation available may be too expensive, or may be denied by insurers, leading to financial toxicity or lack of adherence. Changes in clinical status independent of pain, such as emerging substance use disorder, may be a reason for converting to a different opioid, such as buprenorphine or methadone [58]. Most clinical trials of opioid conversions excluded patients with substance use disorder, psychiatric illnesses, and renal and hepatic comorbidities, which frequently occur in advanced illnesses and are common. Conversion ratios reflect the experience of a healthier patient population. Success in the real world is likely less than what is published, and conversions likely require greater scrutiny and forethought in practice than what is portrayed in published trials [58, 59]. It is important clinicians consider non-pharmacological therapies and not limit themselves to opioids in poorly controlled pain. Acupuncture, cognitive behavioral therapies, kyphoplasty, and palliative

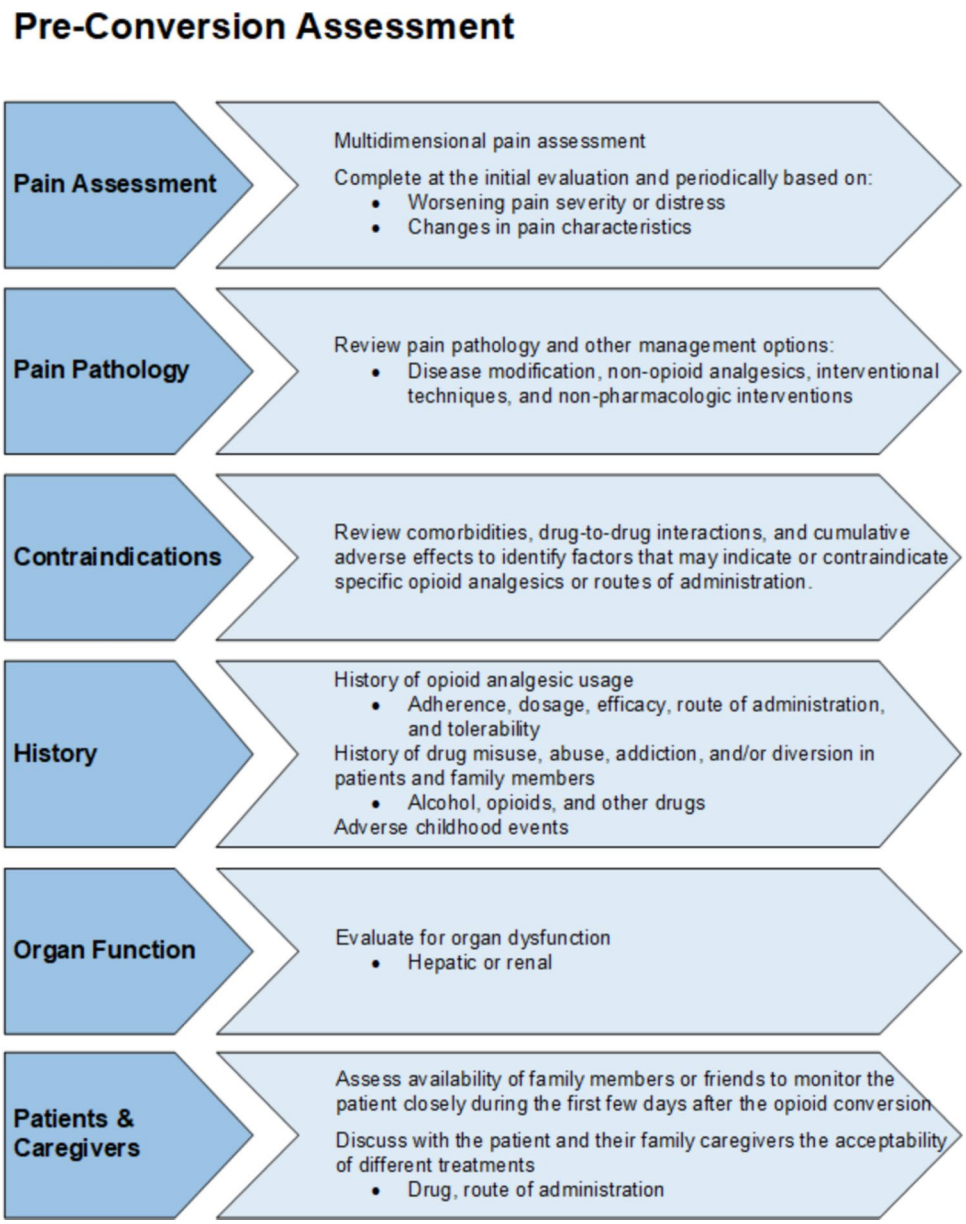
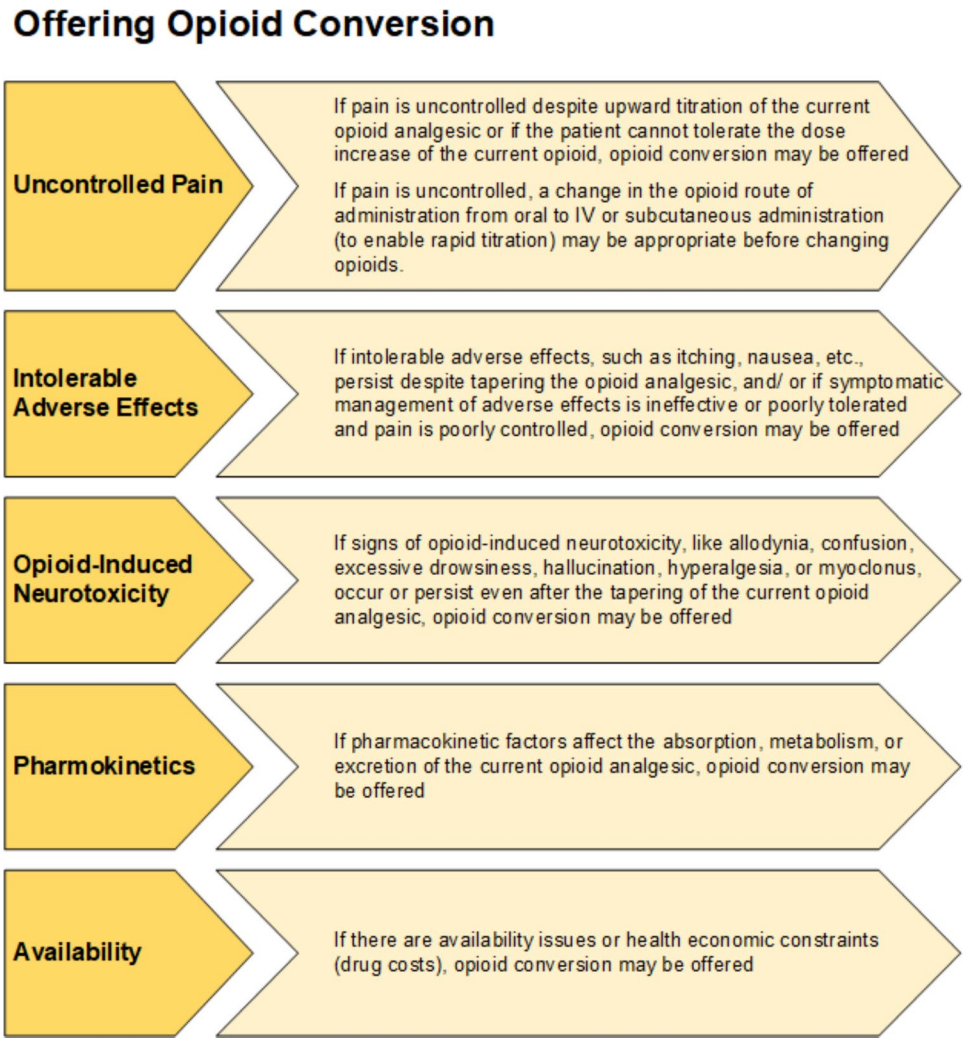


Fig. 1 Visual summary of key recommendations

Fig. 1 (continued)



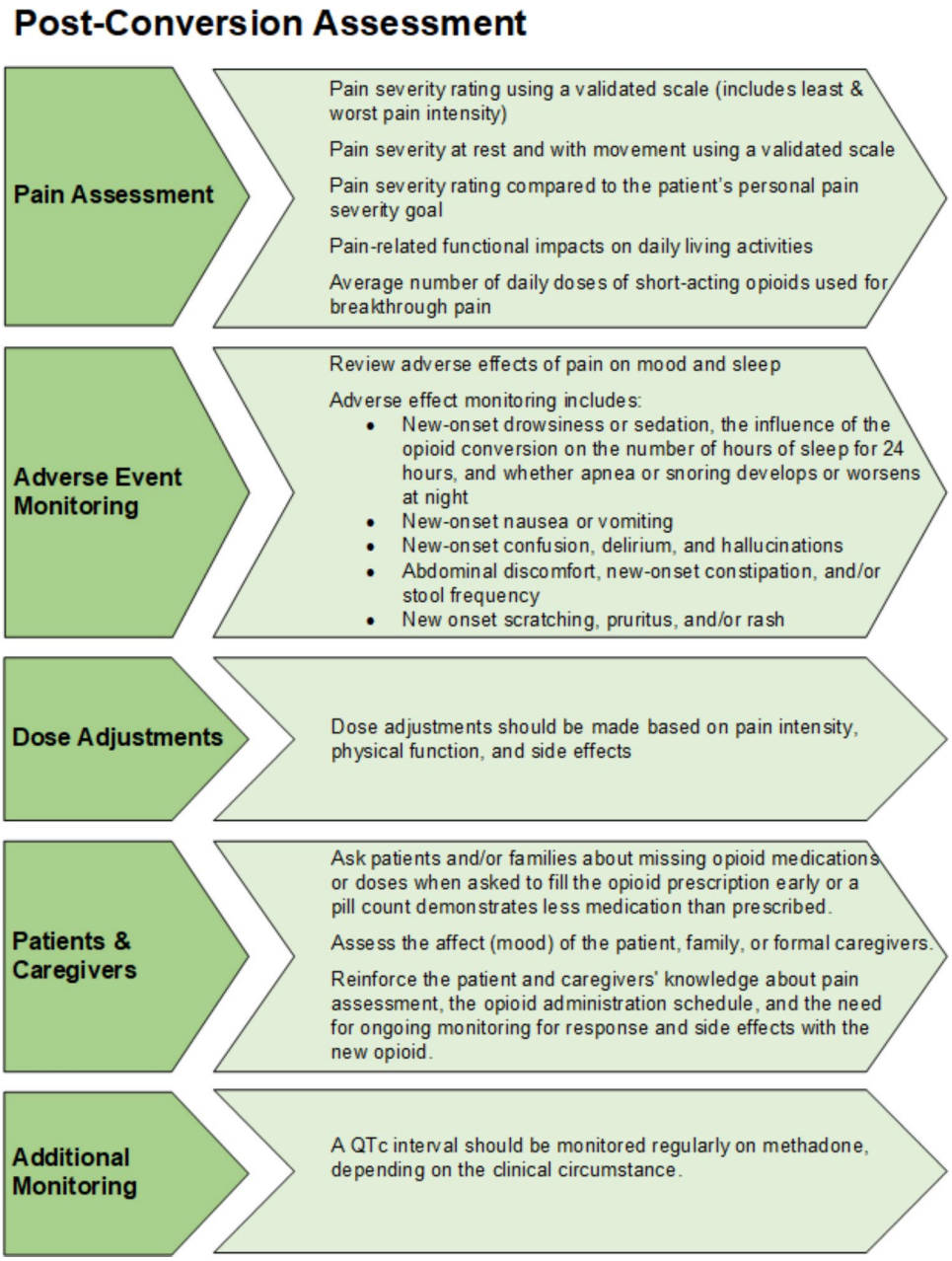
radiation may be better choices or welcome additions to pain management in certain clinical situations rather than converting opioids [56].

There is robust evidence that placebo and nocebo (negative expectations of treatment or prognosis) responses influence patient experiences with opioid therapy. How clinicians guide patients through opioid therapy and the compassionate manner in which it is delivered is as important as the drug [60, 61]. Placebo and nocebo responses substantially modulate the efficacy and tolerability of active treatments [62]. One can enhance placebo responses through attention to patient concerns and goals, modulating expectations that may be overly negative or positive, and expressing empathy in patient-clinician encounters. This communication should be a regular part of opioid therapy, whether initiating opioid therapy or converting opioids [63]. How patients are informed about risks and side effects influences the likelihood of side effects. Ethically, clinicians need to weigh honesty and transparency and minimize harm in discussing the risks and benefits of opioid conversions [63].

Morphine equivalent daily dose

An aspect of opioid conversion that may require explanation is the use of MEDD as a basis for opioid conversion. MEDD is based on the premise that distinct doses of different opioids that vary in analgesic potency produce similar analgesia. Therefore, if an opioid has been compared with morphine and dose ratios established for which conversions were safe, then the MEDD for that particular opioid is used to convert to another opioid, absent of a direct comparison between the two. The indirect conversion ratio is through the third opioid, morphine, in MEDDs [64–66]. The use of MEDDs has been helpful in opioid conversions when two opioids have not been directly compared. There are two drawbacks to MEDDs. MEDDs are used for analgesia but do not apply to opioid-unique toxicities [67]. When MEDDs have been compared to direct conversion ratios, the MEDD is significantly more likely to be inaccurate, particularly at high doses [68].

Fig. 1 (continued)



Methadone

Only clinicians experienced with methadone should be prescribing methadone since there is a morphine dose-dependent change in the conversion ratio. At higher morphine doses, methadone appears to have a greater analgesic potency when converting from morphine to methadone. Therefore, conversion ratios are likely to be different when converting at high doses of potent opioids, particularly when converting from morphine to methadone. The relative potency of methadone is dependent on the morphine dose [4, 69, 70]. The conversion ratio increases and becomes less predictable at higher morphine doses. Small variations in conversion ratios will lead to larger differences in the calculated dose of the second opioid when converting from high doses, particularly with methadone [71]. Methadone oral bioavailability is both higher and more predictable than morphine, and methadone has an unpredictably long half-life, both of which contribute to the complexity of the conversion [72, 73]. As a result, *only* clinicians experienced with methadone should prescribe it, particularly when converting to methadone. Multiple strategies are used to convert from morphine to methadone, and experienced prescribers should be able to utilize multiple conversion strategies depending on the clinical situation. As an aside, patients converted to methadone for pain and a substance use disorder should have methadone doses divided into 2 or 3 doses per day rather than once daily as maintenance therapy [74]. Some patients may experience

withdrawal and pain if a large single dose of methadone is used to manage cancer pain [75].

Breakthrough pain

The consensus group adopted two recommendations regarding breakthrough pain. The first recommendation states that clinicians should begin at a safe dose but adjust the doses according to the severity of the breakthrough pain. The second recommendation is that the dose to treat breakthrough pain will need to be adjusted independent of the baseline pain severity since there is a poor or weak concordance between the baseline pain severity and the breakthrough pain severity.

There is no universal definition of breakthrough pain. In a systematic review of breakthrough pain, most experts proposed that breakthrough pain is sudden and severe (greater than 7 out of 10 on a numerical rating scale, 0 as no pain and 10 as severe pain). The pain is usually brief and usually crescendos to a peak severity within 10 min. Most definitions require the baseline pain to be adequately controlled and in the mild to moderate severity range [76]. Pain may be predictable with voluntary or involuntary movement or spontaneous. In general, end-of-dose failure pain is considered inadequately treated chronic pain. A reasonable starting dose is 10–15% of the MEDD [77]. Clinical experience and multiple research studies have found that the final dose needed to control breakthrough pain is widely different between individuals (and often has little association with the opioid doses required to control the background pain) [78]. The breakthrough dose must be titrated separately according to breakthrough pain severity.

Buprenorphine

Buprenorphine was developed as an analgesic in the 1970s and is increasingly being considered an important analgesic to treat pain largely due to its safety as a Schedule III rather than a Schedule II opioid [79–83]. One of the difficulties with buprenorphine as a second or third-line opioid is the risk of precipitating withdrawal using a "stop-start" (or direct conversion where the potent opioid is stopped and buprenorphine is immediately started) in patients on high-dose potent opioids [84, 85]. A gap between stopping the potent opioid and starting buprenorphine or weaning the potent opioid before starting full dose buprenorphine was initially recommended to avoid buprenorphine-induced withdrawal symptoms. Microdosing is now done, which maintains the potent opioid while incrementally increasing buprenorphine doses. The potent opioid may be maintained or gradually lowered in an overlap dosing strategy [86–90]. Access to buprenorphine may also be a challenge due to limitations in insurance coverage and availability at retail pharmacies.

Comments concerning draft recommendations not achieving consensus

Draft recommendations that did not reach consensus included conversion ratios involving fentanyl, automatic reductions in opioid doses [11], and bidirectional differences in opioid conversion ratios [91, 92]. Statements failing to reach a consensus are provided in the Supplement.

Fentanyl

The panel did not reach a consensus regarding the conversion ratio between transdermal (TD) fentanyl and oral morphine. In randomized trials in the systematic review, there was a wide difference in ratios between TD fentanyl and oral morphine. The absorption of TD fentanyl is highly variable between individuals [93, 94]. Secondly, particularly in patients with advanced cancer and cachexia, transdermal fentanyl absorption is decreased, which alters expected responses if conversion ratios are based on healthier populations [95–98]. Cancer cachexia is also associated with a reduction in the mixed-function oxidase CYP3A4, responsible for metabolizing fentanyl to the inactive metabolite norfentanyl. Paradoxically, cachexia is associated with delayed clearance of parenteral fentanyl [99]. As a result, there is likely to be wide interindividual differences in conversion ratios between oral morphine and fentanyl in general.

Automatic adjustments in opioid doses

Several guidelines have recommended automatically reducing the calculated conversion ratio dose by 25–50% because of non-cross analgesic tolerance [6, 9]. The panel did not reach a consensus on this practice. Adjusted doses do not represent published conversion ratios for which there is clinical experience [18]. Furthermore, while it is assumed to be safer, it does increase the risk of opioid withdrawal symptoms. Importantly, patients may experience atypical withdrawal, such as dysphoria, fatigue, insomnia, and irritability [18]. Recommendations are "expert opinion" only due to the lack of randomized trials supporting the practice [6].

Bidirectional differences in opioid conversion ratios

Certain studies indicate potential bidirectional differences in opioid conversion ratios [92]. Bidirectional differences in opioid conversion ratios remain unproven, and the experts did not reach a consensus. Because opioid conversion ratios are imprecise due to the high degree of interindividual variability, studies investigating bidirectional differences involve small numbers of patients and were underpowered for the

outcome [13, 91, 100]. Investigators who suggested that there might be directional differences have also stated that they are not proven and require further investigation [92].

Post opioid conversion

Opioid doses derived from any conversion ratio must be adjusted based on clinical circumstances. Adjustments are recommended based on age (adjusting the dose down in older adults) and for organ dysfunction and potential drug-drug interactions [18, 101–103]. Vigilance is needed, and close follow-up after converting opioids. Overdoses may still occur even when the conversion dose is appropriately calculated [4]. A 5-step process has been recommended with close follow-up after conversion [104].

After converting opioids, clinicians must follow patients closely. Most believe that opioids produce analgesia in a graded, incremental, predictable manner [105–107]. However, based on randomized trials, opioid responses are quantal, i.e., analgesia appears abruptly when the threshold dose for an individual is reached [108]. This pattern of response means that conversion ratios are safe doses, unlikely to produce withdrawal or opioid toxicity in the majority. Nevertheless, close observation and dose adjustments will be needed after opioid conversion.

Patients should be followed closely for the first 24–48 h after opioid conversion. Usually, immediate-release opioids are used, and a steady state is reached at 48 h. Dose adjustments should only be made once reaching a steady state, which may be 5–6 days after initiating methadone [109]. Further dose adjustments will need to be made based on the number of "rescue" opioid doses. Patients should be further followed closely for an additional 7–14 days [6]. Clinicians should assess pain intensity, function, and side effects after opioid conversion. Methadone has a unique cardiac toxicity, which results in QTc interval prolongation from interference with cardiac repolarization. This effect may lead to Torsades de Pointe. If patients are still receiving anticancer therapy, ECG monitoring should be done. Patients transitioned to hospice do not require ECG monitoring [110].

Health equity considerations

Factors such as race and ethnicity, age, socioeconomic status, sexual orientation and gender identity, geographic location, and insurance access are known to impact cancer care outcomes [111]. Racial and ethnic disparities in health care contribute significantly to this problem in the USA. 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 [112, 113]. In the case of opioids, prescribing in the USA varies by age, sex, gender, race, and ethnicity [114–117]. 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.

Opioid stigma

Opioids, in general, have a stigma in the general population. For example, many lay persons believe that morphine is used only in those who are dying. Certain opioids such as methadone and buprenorphine, both developed as analgesics, have particularly been used as maintenance therapy for opioid use disorders and thus have a greater stigma. Offering methadone or buprenorphine in opioid conversions may be very appropriate. Still, patients and caregivers may fear that the patient is being treated for addiction or that methadone and buprenorphine are only used for addiction therapy. It will be very important that clinicians who use opioids in opioid conversion to educate the patient and caregivers on the reasons for and benefits of the selected opioid to reduce the stigma [118].

Pharmacogenetics

Pharmacogenetics influence opioid responses and individual conversion ratios. Genotype-guided therapy using CYP2D6, the MOR OPRMI, and catechol-O-methyl transferase genotypes in choosing opioids leads to fewer adverse effects and improved pain at lower morphine equivalent doses at 3 months [119]. Although genotype testing is not routinely done in clinical practice, and access to testing remains limited, choices guided by pharmacogenomics have the potential to alter conversion ratios and improve the therapeutic index of opioids. There are population frequency differences in CYP2D6 genotype frequency in the Chinese, African, Swedish, and Spanish populations. Therefore, population differences in opioid conversions likely exist depending on the particular opioid and cytochrome responsible for metabolizing the particular opioid [120]. Ethnic differences in conversion ratios have not yet been established, and this should be a focus for future research.

Older adults and methadone

Older individuals have an increasing frequency of chronic pain but respond well to opioids [121, 122]. Older adults often require lower doses and may even respond better than younger patients [123]. Aging is associated with increased adipose tissue, reduced body mass, reduced body water, reduced gastrointestinal blood flow, increased gastric pH,

reduced hepatic blood flow, and reduced glomerular filtration rate, all of which may influence opioid pharmacokinetics [103]. Additionally, polypharmacy and drug-drug interactions are common in older individuals. The risk of adverse effects increases with the number of medications [124]. Undertreatment of pain in older adults has adverse effects: increased fall risk, reduced mobility, increased functional dependence, and increased risk of delirium leading to more frequent and longer hospital stays [125, 126].

Conversion to methadone in older adults has been reported to be quite successful. The advantages of methadone are it is safer in renal impairment and lacks active metabolites as opposed to oxycodone and morphine. On the other hand, drug-drug interactions are greater due to methadone's metabolism through multiple cytochromes. In a case series, analgesia in older adults may occur at extremely low doses, which may be lower than anticipated based on conversion ratios [127, 128]. There is insufficient high-quality evidence to guide clinicians in converting methadone in older adults, requiring future studies to address this gap in our understanding.

Older individuals with cognitive deficits and dementia are less likely to be treated with opioids, which may, in part, be related to the difficulty in assessing pain and a greater reliance on behaviors associated with pain [129]. Opioid conversions are less likely to occur in those individuals with cognitive deficits or dementia, and this is an opportunity for further investigation.

Limitations

The Delphi technique has limitations. Surveys and expert consensus are considered subordinate to evidence-based guidelines. Such expert consensus does not directly account for reliable findings on observed cause-effect, though many have scoping reviews as part of the process. Delphi techniques are usually used when cause-effect evidence in quality randomized trials is poor or lacking [130]. The composition of experts and handling of divergent judgments may influence the final consensus. Different experts and the number of experts may have altered the final consensus guideline. For draft recommendations on certain opioids, like buprenorphine, hydrocodone, oxymorphone, and tapentadol, a significant number of experts abstained, and thus, recommendations on these particular opioids met consensus through fewer experts. There are no universal quality standards for the Delphi technique [131].

Conclusions

The purpose of this guideline is to reduce the relative risk of overdosing or under-dosing opioids when converting from one opioid to another and/or converting routes. An inaccurate ratio can lead to potentially life-threatening toxicity or uncontrolled pain. The evidence from trials is modest, and there are large clinical practice and research gaps. Our findings highlight the need for personalized titration and very frequent follow-up during the first week of an opioid rotation for all opioids, to prevent severe toxicity or uncontrolled pain. The panel hopes this guideline is a beginning that establishes an international baseline for practice that can be built upon by new research and better designed trials.

Guideline implementation

These guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers and also to provide adequate services in the face of limited resources. The guideline recommendations table and accompanying tools (available at www.asco.org/supportive-care-guidelines) were designed to facilitate implementation of recommendations. This guideline will be distributed widely.

Additional resources

For current information, including selected updates, supplements, slide sets, and clinical tools and resources, visit www.asco.org/supportive-care-guidelines. The Data Supplement for this guideline includes statements that did not reach consensus and the disclosures of potential conflicts of interest for the Consensus Panel. Guideline recommendations and algorithms are also available in the free ASCO Guidelines app (available for download in the Apple App Store and Google Play Store). Listen to key recommendations and insights from panel members on the ASCO Guidelines podcast. 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.org.

We welcome your comments on this guideline, including implementation challenges, new evidence, and how this guideline impacts you. To provide feedback, contact us at guidelines@asco.org. Comments may be incorporated into a future guideline update. To submit new evidence or suggest a topic for guideline development, complete the form available at www.asco.org/guidelines.

Related guidelines (text box to appear on last page of content)

- Palliative care for patients with cancer [132]
https://ascopubs.org/doi/full/https://doi.org/10.1200/JCO.24.00542

Related guidelines (text box to appear on last page of content)

• Use of opioids for adults with pain from cancer or cancer treatment https://ascopubs.org/doi/full/https://doi.org/10.1200/JCO.22.02198 [20]

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Author contribution AUTHOR CONTRIBUTIONS All authors participated in the panel, research plan, Delphi consensus and editing the guideline and reviewed the manuscript MPD wrote the manuscript and provided the systematic review for the panel and consensus group CR provided the systematic review and edited the manuscript MPD, MLM, AD, JP, AR and KB participated in the steering group to construct the Delphi Consensus statements KB edited the manuscript and directed the guideline through ASCO and MASCC guideline committees MLM directed the guidelines through the AAHPM CR directed the guidelines through NICSO All authors reviewed the final version and agreed to submission.

Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval Not applicable.

Competing interests RA, SM, AK, ED, MPD are on the editorial board of the JSCC.

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