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ASCO SPECIAL ARTICLE

Management of Chronic Pain in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

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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 Data Supplement with additional evidence tables, a Methodology Supplement, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/chronic-pain-guideline and www.asco.org/guidelineswiki.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

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A B S T R A C T

Purpose
To provide evidence-based guidance on the optimum management of chronic pain in adult cancer survivors.

Methods
An ASCO-convened expert panel conducted a systematic literature search of studies investigating chronic pain management in cancer survivors. Outcomes of interest included symptom relief, pain intensity, quality of life, functional outcomes, adverse events, misuse or diversion, and risk assessment or mitigation.

Results
A total of 63 studies met eligibility criteria and compose the evidentiary basis for the recommendations. Studies tended to be heterogeneous in terms of quality, size, and populations. Primary outcomes also varied across the studies, and in most cases, were not directly comparable because of different outcomes, measurements, and instruments used at different time points. Because of a paucity of high-quality evidence, many recommendations are based on expert consensus.

Recommendations
Clinicians should screen for pain at each encounter. Recurrent disease, second malignancy, or late-onset treatment effects in any patient who reports new-onset pain should be evaluated, treated, and monitored. Clinicians should determine the need for other health professionals to provide comprehensive pain management care in patients with complex needs. Systemic nonopioid analgesics and adjuvant analgesics may be prescribed to relieve chronic pain and/or to improve function. Clinicians may prescribe a trial of opioids in carefully selected patients with cancer who do not respond to more conservative management and who continue to experience distress or functional impairment. Risks of adverse effects of opioids should be assessed. Clinicians should clearly understand terminology such as tolerance, dependence, abuse, and addiction as it relates to the use of opioids and should incorporate universal precautions to minimize abuse, addiction, and adverse consequences. Additional information is available at www.asco.org/chronic-pain-guideline and www.asco.org/guidelineswiki.

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INTRODUCTION

As a result of extraordinary advancements in diagnosis and treatment, approximately 14 million individuals with a history of cancer (excluding nonmelanomatous skin cancers) are living in the United States.[1] Two thirds of these individuals are surviving ≥ 5 years after diagnosis.[2] Unfortunately, these impressive outcomes in survival often come with physical, psychosocial, and financial burdens as a result of the tumor, exposure to cancer treatment, or other medical comorbidities. Chronic pain can be a serious, negative consequence of surviving cancer. Although estimates vary, the prevalence of pain in cancer survivors has been reported to be as high as 40%.[3-5] Predictors include the type and invasiveness of the tumor, the treatment regimen used, the time since cancer treatment, and the efficacy of initial pain therapy. Significant pain is associated with impaired quality of life in this population.[6]

Many guidelines and recommendations have been advanced to support the management of

THE BOTTOM LINE

Management of Chronic Pain in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

Guideline Question

How should chronic pain be managed in the adult cancer survivor?

Target Population

Any adult who has been diagnosed with cancer and is experiencing pain that lasts $\geq$ 3 months, irrespective of cause.

Target Audience

Health care practitioners who provide care to cancer survivors.

Methods

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

Key Recommendations

1. SCREENING AND COMPREHENSIVE ASSESSMENT

Recommendation 1.1. Clinicians should screen for pain at each encounter. Screening should be performed and documented using a quantitative or semiquantitative tool. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: strong)

Recommendation 1.2. Clinicians should conduct an initial comprehensive pain assessment. This assessment should include an in-depth interview that explores the multidimensional nature of pain (pain descriptors, associated distress, functional impact, and related physical, psychological, social, and spiritual factors) and captures information about cancer treatment history and comorbid conditions, psychosocial and psychiatric history (including substance use), and prior treatments for the pain. The assessment should characterize the pain, clarify its cause, and make inferences about pathophysiology. A physical examination should accompany the history, and diagnostic testing should be performed when warranted. (Informal consensus; benefits outweigh harms; evidence quality: insufficient strength of recommendation: moderate)

Recommendation 1.3. Clinicians should be aware of chronic pain syndromes resulting from cancer treatments, the prevalence of these syndromes, risk factors for individual patients, and appropriate treatment options. A list of common cancer pain syndromes can be found in Table 3. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)

Recommendation 1.4. Clinicians should evaluate and monitor for recurrent disease, second malignancy, or late-onset treatment effects in any patient who reports new-onset pain. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)

2. TREATMENT AND CARE OPTIONS

Recommendation 2.1. Clinicians should aim to enhance comfort, improve function, limit adverse events, and ensure safety in the management of pain in cancer survivors. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)

Recommendation 2.2. Clinicians should engage patient and family/caregivers in all aspects of pain assessment and management. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)

Recommendation 2.3. Clinicians should determine the need for other health professionals to provide comprehensive pain management care in patients with complex needs. If deemed necessary, the clinician should define who is responsible for each aspect of care and refer patients accordingly. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)

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THE BOTTOM LINE (CONTINUED)

Nonpharmacologic Interventions

Recommendation 2.4. Clinicians may prescribe directly or refer patients to other professionals to provide the interventions outlined in Table 4 to mitigate chronic pain or improve pain-related outcomes in cancer survivors. These interventions must take into consideration pre-existing diagnoses and comorbidities. (Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)

Pharmacologic Interventions

Miscellaneous Analgesics

Recommendation 2.5. Clinicians may prescribe the following systemic nonopioid analgesics and adjuvant analgesics to relieve chronic pain and/or improve function in cancer survivors in whom no contraindications including serious drug–drug interactions exist:

- Nonsteroidal anti-inflammatory drugs
- Acetaminophen (paracetamol)
- Adjuvant analgesics, including selected antidepressants and selected anticonvulsants with evidence of analgesic efficacy (such as the antidepressant duloxetine and the anticonvulsants gabapentin and pregabalin) for neuropathic pain conditions or chronic widespread pain

(Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)

Qualifying statement. The panel acknowledges that many other systemic nonopioids, including many other antidepressants and anticonvulsants, drugs in many other classes (such as the so-called muscle relaxants, benzodiazepines such as clonazepam, N-methyl-D-aspartate receptor blockers such as ketamine, and α-2 agonists such as tizanidine), and varied neutraceutical and botanicals marketed as complementary or alternative medicines, are taken by some cancer survivors with chronic pain and may benefit some of those who receive them. However, the efficacy of these agents and their long-term effectiveness have not been established.

Recommendation 2.6. Clinicians may prescribe topical analgesics (such as commercially available nonsteroidal anti-inflammatory drugs; local anesthetics; or compounded creams/gels containing baclofen, amitriptyline, and ketamine), for the management of chronic pain. (Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)

Recommendation 2.7. Corticosteroids are not recommended for long-term use in cancer survivors solely to relieve chronic pain. (Evidence-based; harms outweigh benefits; evidence quality: intermediate; strength of recommendation: moderate)

Recommendation 2.8. Clinicians should assess the risks of adverse effects of pharmacologic therapies, including nonopioids, adjuvant analgesics, and other agents used for pain management. (Evidence-based and informal consensus; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)

Recommendation 2.9. Clinicians may follow specific state regulations that allow access to medical cannabis or cannabinoids for patients with chronic pain after a consideration of the potential benefits and risks of the available formulations. (Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)

Qualifying statement. As of this writing, 23 states and the District of Columbia allow for medical cannabis,[50] although it is illegal on the federal level. Currently, there is insufficient evidence to recommend medical cannabis for the first-line management of chronic pain in cancer survivors. However, evidence suggests it is worthy of consideration as an adjuvant analgesic or in the management of refractory pain conditions. There is also insufficient evidence to recommend one particular preparation of cannabis over another, and the Food and Drug Administration has not approved any drug product containing or derived from botanical marijuana.

Opioids

Recommendation 2.10. Clinicians may prescribe a trial of opioids in carefully selected cancer survivors with chronic pain who do not respond to more conservative management and who continue to experience pain-related distress or functional impairment. Tables 5 and 6 provide guidelines intended to promote safe and effective prescribing. Nonopioid analgesics and/or adjuvants can be added as clinically necessary. (Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)

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THE BOTTOM LINE (CONTINUED)

Recommendation 2.11. Clinicians should assess risks of adverse effects of opioids used for pain management. Table 7 lists opioid-related long-term adverse effects. (Evidence-based and informal consensus; benefits outweigh harms; evidence quality: intermediate strength of recommendation: moderate)

Qualifying statement. Although there is literature describing dysimmune effects and tumor proliferative effects from opioid drugs (both of which may be of particular concern in the cancer survivor population), there is insufficient evidence to determine whether there are clinically important risks. The expert panel believes that further clinical investigation is required to assess these concerns. In the absence of actionable data, physicians should be made aware of these evolving questions, and patients and their families may be informed about them as part of a discussion of the potential harms of long-term opioid therapy, as described in Table 7.

3. RISK ASSESSMENT, MITIGATION, AND UNIVERSAL PRECAUTIONS WITH OPIOID USE

Recommendation 3.1. Clinicians should assess the potential risks and benefits when initiating treatment that will incorporate long-term use of opioids. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)

Recommendation 3.2. Clinicians should clearly understand terminology such as tolerance, dependence, abuse, and addiction as it relates to the use of opioids for pain control. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)

Recommendation 3.3. Clinicians should incorporate a universal precautions approach to minimize abuse, addiction, and adverse consequences of opioid use such as opioid-related deaths. Clinicians should be cautious in coprescribing other centrally acting drugs, particularly benzodiazepines (Table 7). (Evidence-based and informal consensus; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)

Recommendation 3.4. Clinicians should understand pertinent laws and regulations regarding the prescribing of controlled substances. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)

Recommendation 3.5. Clinicians should educate patients and family members regarding the risks and benefits of long-term opioid therapy and the safe storage, use, and disposal of controlled substances. Clinicians are encouraged to address possible myths and misconceptions about medication use and should educate patients about the need to be cautious when using alcohol or sedating over-the-counter medications or in receiving centrally acting medications from other physicians. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)

Qualifying statement. Education and information about treatment should ideally take into account the patient's literacy level and the need for interpreters and should be provided in a culturally congruent manner.

Recommendation 3.6. If opioids are no longer warranted, clinicians should taper the dose to avoid abstinence syndrome. The rate of tapering and the use of cotherapies to reduce adverse effects should be individualized for each patient. (Evidence-based and informal consensus; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)

Additional Resources: More information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/chronic-pain-guideline and www.asco.org/guidelineswiki. 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

cancer pain, yet the focus of these documents has been primarily on relieving acute pain or pain associated with advanced disease.[7,8] Few evidence-based cancer pain guidelines address the more nuanced care required when pain persists for months or years. This situation is in part caused by the relative absence of studies exploring the experiences of chronic pain in cancer survivors, or the long-term safety and effectiveness of analgesic interventions.

Whereas opioid-based pharmacotherapy is widely accepted as the foundation of care for acute pain or pain associated with advanced cancer, the management of patients who are free of

cancer after treatment, or who are living with cancer as a chronic illness, is not grounded in broad consensus. The management of these populations with chronic cancer pain requires greater consideration of a multimodality plan of care that balances pharmacologic and nonpharmacologic techniques and may necessitate the involvement of an interdisciplinary team; the goals of treatment in these populations may focus on improving function and limiting the long-term adverse effects of pain and of its treatment, as much or more as they do on improving comfort.[9,10]

As the population of cancer survivors expands, all clinicians, including oncologists, advanced practice providers, and primary care physicians who interact with these individuals, will require the knowledge and skills to implement best practices in the management of chronic pain. When analgesic drugs are used, the imperative to prescribe safely must expand beyond immediate adverse effects, such as the resulting respiratory depression or constipation associated with opioids, to incorporate awareness and mitigation of the long-term consequences of these and other analgesic agents. The purposes of this systematic review and evidence-based guideline are to evaluate randomized controlled trials (RCTs) and other fundamental studies regarding chronic pain in cancer survivors reported in the literature, to compare outcomes among trials, and to provide guidance to clinicians on the effectiveness of treatment options for pain in adults with a history of cancer.

Guideline Question

This clinical practice guideline addresses how chronic pain in survivors of adult cancers should be managed.

METHODS

Guideline Development Process

The expert panel met in person and via teleconference and corresponded through e-mail. On the basis of the consideration of the evidence, the authors were asked to contribute to the development of the guideline, to provide critical review, and to finalize the guideline 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 *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 Clinical Practice Guideline Committee prior to publication (Appendix Table A1, online only).

The recommendations were developed by an expert panel with multidisciplinary representation, who used a systematic review (1996 to 2015) of RCTs, observational studies, and clinical experience. In some selected cases in which evidence was lacking, but where there was a high level of agreement among the members of the panel and where the benefits clearly outweighed the harms, informal consensus was used (as noted in Recommendations).

Articles were selected for inclusion in the systematic review of the evidence if they:

- Included adult cancer survivors at risk of or with chronic pain, although literature on chronic pain in other adult populations was also considered because of the paucity of evidence in cancer survivors
- Considered either cancer pain or noncancer pain
- Investigated the efficacy or harms of pharmacologic or nonpharmacologic interventions for pain management
- Reported results on any of the following outcomes: symptom relief; patient-reported pain intensity (pain rating scale); participant-reported global impression of clinical change; quality of life (measured by a validated, reliable instrument (eg, the Functional Assessment of Cancer Therapy–Endocrine Symptoms and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire); disability measure; pain interference; functional outcomes; caregiver end points such as distress or decision burden; adverse events, including misuse or diversion; barriers; or risk assessment or mitigation
- Were fully published, English-language reports of systematic reviews, meta-analyses, RCTs, or comparative observational studies

Articles that considered acute pain were not included. Studies were also excluded from the systematic review if they were meeting abstracts that were not published subsequently in peer-reviewed journals, or were editorials, commentaries, letters, news articles, case reports, or narrative reviews. The guideline recommendations are crafted, in part, using the GuideLines Into Decision Support methodology.[11] In addition, a guideline implementability review was conducted. On the basis of the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation (see Methodology Supplement for more detail).

Detailed information about the methods used to develop this guideline, including an overview (eg, panel composition, development process, and revision dates); literature search and data extraction; the recommendation development process; and quality assessment, is available in the Methodology Supplement and Data Supplement at www.asco.org/chronic-pain-guideline.

The ASCO panel and guidelines staff will work with co-chairs to keep abreast of any substantive updates to the guideline. On the basis of formal review of the emerging literature, ASCO will determine the need to update. The Methodology Supplement (available at www.asco.org/chronic-pain-guideline) provides additional information.

This is the most recent information as of the publication date. For updates and the most recent information or to submit new evidence, please visit www.asco.org/chronic-pain-guideline and the ASCO Guidelines Wiki (www.asco.org/guidelineswiki).

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 on 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. Furthermore, the information is not intended to substitute for the independent professional judgment of the treating provider, because the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of such words as "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 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

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Guideline and Conflicts of Interest

The expert panel was assembled in accordance with ASCO's Conflict of Interest Management Procedures for Clinical Practice Guidelines (Procedures, summarized at http://www.asco.org/rwc). Members of the panel completed ASCO's disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience a 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 role; speakers' bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the procedures, the majority of the members of the Panel did not disclose any such relationships.

RESULTS

Characteristics of Studies Identified in the Literature Search

A total of 35 systematic reviews, nine RCTs, and 19 comparative studies met the eligibility criteria and form the evidentiary basis for the guideline recommendations. Two existing clinical practice guidelines were also identified to help inform the discontinuation of long-term opioid therapy. The included studies are heterogeneous with respect to patient populations, sample size, methodologic quality, treatment duration, and outcome measures. The primary outcomes varied across studies and, in the majority of cases, were not directly comparable because of different outcomes, measurements, and instruments used at different time points. This diversity precluded a quantitative analysis, and, as such, only a qualitative review was performed. Table 1 outlines the studies that were particularly pertinent to the development of the recommendations.

Table 1. Included Studies

Topic	No. Studies	Summary of Results*
Screening and comprehensive assessment	Informal consensus used	—
Nonpharmacologic treatment		
Physical medicine and rehabilitation	Two systematic reviews, three RCTs	Table 8
Integrative and neurostimulatory therapies	Six systematic reviews	Table 9
Interventional therapies	One systematic review, three RCTs, two observational studies	Table 10
Psychological approaches	Seven systematic reviews	Table 11
Pharmacologic treatment		
Adjuvant analgesics	10 systematic reviews, one RCT	Table 12
Cannabinoids	Five systematic reviews, one RCT, one observational study	Table 13
Opioids	Six systematic reviews, one RCT	Table 14
Risk assessment, mitigation, and universal precautions	Two guidelines, one systematic review, 16 comparative studies	—

Abbreviation: RCT, randomized clinical trial.
*Available in Data Supplement.

Study Quality Assessment

An assessment of study quality was performed for all the included evidence by one methodologist. Systematic reviews and meta-analyses were assessed for quality using A Measurement Tool to Assess Systematic Reviews (AMSTAR).[12]

Design elements such as blinding, allocation concealment, placebo control, intention to treat, funding sources, and so forth, were assessed for RCTs. Methodologic criteria assessed for other study designs included type of data collection, sampling method, and conflicts of interest. In general, most of the identified studies exhibited a low to intermediate potential risk of bias. AMSTAR scores ranged from 3 to 11 out of a possible 11 points. Overall, the included systematic reviews were conducted in a rigorous fashion; however, many of the primary studies included in these reviews, and other primary RCTs identified for inclusion in this analysis, suffered from industry sponsorship, short follow-up, lack of blinding, and lack of reporting of intention-to-treat analyses. Moreover, outcomes varied greatly across studies and were often assessed by different methods or measurement scales. Refer to the Data Supplement for ratings of overall potential risk of bias.

Key Outcomes of Interest

Data on key outcomes of interest are summarized in Table 2 and are reported in detail in Tables 8 to 14 in the Data Supplement. Because all outcomes are described in detail in the Data Supplement, only studies that detected a significant difference for any of the outcomes of interest are discussed here.

Pain Measures

Measures of pain intensity and relief were considered in the vast majority of studies. Pain outcomes were measured in many ways, including pain ratings on a visual analog scale (VAS) and proportion of patients achieving a 30% or a 50% reduction in pain. Statistically significant results were seen for both nonpharmacologic and pharmacologic interventions.

In one meta-analysis[36] and three RCTs,[38-40] exercise and physical therapy had a small but significant impact on pain. Three systematic reviews,[42-44] two with meta-analyses,[43,44] confirmed that acupuncture and massage were effective in improving pain. Furthermore, psychological-based interventions showed promise, with moderate and significant effects on pain reported in six systematic reviews that considered acceptance-based interventions, patient education, relaxation, guided imagery, meditation, hypnosis, and music interventions.[45,52-55] Finally, interventional therapies had demonstrable effects on pain improvement. Evidence exists for celiac plexus block (CPB),[46] implantable intrathecal drug delivery systems (IDDs),[51] percutaneous vertebroplasty, and kyphoplasty.[49]

The effectiveness of adjuvant analgesics in pain outcomes was also evident. Six systematic reviews on antidepressants[13,23] and anticonvulsants[13,20-22] showed significant and clinically relevant effects on pain. Statistical and clinically meaningful improvements in pain were reported in four systematic reviews of opioid therapy.[13-15,18] Similarly, cannabinoids were reported to provide statistically significant analgesic effect in four systematic reviews,[29-32] one RCT,[34] and one observational study.[35]

Table 2. Summary of Findings

First Author	Study Design: Systematic Review ± Meta-analysis	Study Design: RCT	Study Design: Observational Study	Primary Intervention	Significant Differences in Outcomes Reported With Intervention Agent Compared With Control Agent: Pain Rating (Intensity/Relief)	QOL	Level of Function	Opioid or Additional Analgesic Consumption	Adverse Events
Pharmacologic management									
Opioids									
Jongen[13]	√	—	—	Various opioids	↑	—	—	—	↑
Koyyalagunta[14]	√	—	—	Various opioids	↑	—	—	—	↑
Riemsma[15]	√	—	—	Tapentadol	↑	—	—	—	↑
Pigni[16]	√	—	—	Hydromorphone	—	—	—	—	↑
King[17]	√	—	—	Oxycodone	↑-	—	—	—	—
Mayyas[18]	√	—	—	Oxymorphone	↑	—	—	—	↑
Ahmedzai[19]	—	√	—	Oxycodone-naloxone	↑	—	—	—	—
Miscellaneous analgesics									
Jongen[13]	√	—	—	Antidepressants Anticonvulsants	↑	—	—	—	↑
Moore[20]	√	—	—	Gabapentin	↑	—	—	—	↑
Bennett[21]	√	—	—	Antidepressants	↑-	—	—	—	↑
Finnerup[22]	√	—	—	Anticonvulsants Antidepressants Anticonvulsants	↑	—	—	—	↑
Saarto[23]	√	—	—	Antidepressants	↑	—	—	—	↑
Bredlau[24]	√	—	—	Ketamine	—	—	—	—	↑
Bell[25]	√	—	—	Ketamine	—	—	—	—	↑
Paulsen[26]	√	—	—	Corticosteroid	—	—	—	—	↑
Nabal[27]	√	—	—	NSAID	↑	—	—	↑	—
Nabal[27]	√	—	—	Paracetamol	—	—	—	—	—
Derry[28]	√	—	—	Topical therapy	—	—	—	—	↑
Cannabinoids									
Lynch[29]	√	—	—	Cannabinoids	↑	—	—	—	↑
Whiting[30]	√	—	—	Cannabinoids	↑	—	—	—	—
Andreae[31]	√	—	—	Inhaled cannabis	↑	—	—	—	↑
Lynch[32]	√	—	—	Cannabinoids	↑	—	↑	—	↑
Campbell[33]	√	—	—	Cannabinoids	↑	—	—	—	↑
Johnson[34]	—	√		Sativex	↑	—	—	—	↑
Ware[35]	—	—	√	Cannabis	↑	—	—	—	↑
Nonpharmacologic management									
Physical medicine and rehabilitation									
Mishra[36]	√	—	—	Exercise	↑	—	—	—	↑
Fong[37]	√	—	—	Physical activity		—	↑	—	
Cantarero-Villanueva[38]	—	√	—	Water exercise	↑	—	—	—	↑
Fernández-Lao[39]	—	√	—	PT program	↑	—	—	—	—
May[40]	—	√	—	Training program *v* CBT	↑	—	—	—	—
Integrative therapies									
Paley[41]	√	—	—	Acupuncture	—	—	—	—	—
Garcia[42]	√	—	—	Acupuncture	↑	—	—	—	—
Choi[43]	√	—	—	Acupuncture	↑	—	—	—	—
Lee[44]	√	—	—	Massage	↑	—	—	—	—
Kwekkeboom[45]	√	—	—	Music therapy	↑-	—	—	—	—

(continued on following page)

Table 2. Summary of Findings (continued)

First Author	Study Design: Systematic Review ± Meta-analysis	Study Design: RCT	Study Design: Observational Study	Primary Intervention	Significant Differences in Outcomes Reported With Intervention Agent Compared With Control Agent: Pain Rating (Intensity/Relief)	QOL	Level of Function	Opioid or Additional Analgesic Consumption	Adverse Events
Interventional therapies									
Arcidiacono[46]	√	—	—	CPB	↑	—	—	↑	—
Karmakar[47]	—	√	—	TPVB	↑	↑	—	—	—
Berenson[48]	—	√	—	Kyphoplasty	↑	—	↑	—	—
Fourney[49]	—	—	√	Vertebro- & kyphoplasty	↑	—	—	↑	—
Thimineur[50]	—	—	√	IDDS	↑	—	↑	—	—
Smith[51]	—	√	—	IDDS	↑	—	—	—	↓
Psychological approaches									
Johannsen[52]	√	—	—	Psychosocial interventions	↑	—	—	—	—
Sheinfeld Gorin[53]	√	—	—	Psychosocial interventions	↑	—	—	—	—
Veehof[54]	√	—	—	Acceptance-based intervention	↑	↑	—	—	—
Cramer[55]	√	—	—	Hypnosis	↑	—	—	—	—
Kwekkeboom[45]	√	—	—	Relaxation	↑	—	—	—	—
Matchim[56]	√	—	—	Mindfulness	—	↑	—	—	—
Neurostimulatory approaches									
Hurlow[57]	√	—	—	TENS	—	—	—	—	—

NOTE. Boldface denotes statistically significant differences between treatment groups; ↑, difference in outcomes favoring the intervention arm; ↓, difference in outcomes not favoring the intervention arm; ↑-, differences favoring the intervention in some studies in a systematic review and not favoring in others; —, no meaningful differences reported between groups or data were not reported.

Abbreviations: CBT, cognitive-behavioral therapy; CPB, celiac plexus block; IDD, intrathecal drug delivery system; NSAID, nonsteroidal anti-inflammatory drug; PT, physical therapy; QOL, quality of life; RCT, randomized clinical trial; TENS, transcutaneous electrical nerve stimulation; TPVB, thoracic paravertebral block.

Quality of Life

A systematic review of mindfulness-based stress reduction (MBSR)[56] found MBSR to be effective in improving and sustaining quality of life in breast cancer survivors. Thoracic paravertebral block (TPVB) was also reported to result in better physical and mental health-related quality of life in randomly assigned patients.[47]

Level of Function

Improvement in function was reported in four studies. Physical activity was one intervention shown to improve physical function, as measured by the 36-Item Short Form Health Survey in an RCT, although the effect was modest.[37] Implanted drug delivery systems, kyphoplasty, and vertebroplasty significantly improved physical function and disability for patients with chronic pain.[48,50] One systematic review reported that, of five trials considering level of function, two found a statistically significant improvement in function as assess by the Pain Disability Index and Fibromyalgia Impact Questionnaire in patients who used cannabis-based medicines compared with placebo.[32]

Opioid or Analgesic Consumption

A number of adjuvant analgesic studies considered opioid consumption as an outcome, but most failed to show a statistically significant difference. However, in one systematic review, the addition of nonsteroidal anti-inflammatory drugs (NSAIDS) to opioids was reported to result in a reduction of opioid consumption.[27] In an observational study, interventional procedures such as percutaneous vertebro- and kyphoplasty led to a reduction in analgesic consumption.[49]

RECOMMENDATIONS

Clinical Question

How should chronic pain be managed in the adult cancer survivor?

1. SCREENING AND COMPREHENSIVE ASSESSMENT

Recommendation 1.1. Clinicians should screen for pain at each encounter. Screening should be performed and documented using a quantitative or semiquantitative tool. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: strong)

Qualifying statement. Screening may be as simple as a two-question verbal screen (eg, "Have you had frequent or persistent pain since the last time you were seen?" and if the answer is yes, "How severe has this pain been, on average, during the past week?") A simple screen of this type, which quantitates the response to the second question using a verbal rating scale or a numeric scale, can identify patients who should undergo an initial comprehensive pain assessment designed to determine cause and to develop a treatment plan.

Recommendation 1.2. Clinicians should conduct an initial comprehensive pain assessment. This assessment should include an in-depth interview that explores the multidimensional nature of the pain (pain descriptors, associated distress, functional impact, and related physical, psychological, social, and spiritual factors) and captures information about cancer treatment history and comorbid conditions, psychosocial and psychiatric history (including substance use), and prior treatments for the pain. The assessment should characterize the pain, clarify its cause, and make inferences about pathophysiology. A physical examination should accompany the history, and diagnostic testing should be performed when warranted. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)

Recommendation 1.3. Clinicians should be aware of chronic pain syndromes resulting from cancer treatments, the prevalence of these pain syndromes, risk factors for individual patients, and appropriate treatment options. A list of common cancer pain syndromes can be found in Table 3. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)

Recommendation 1.4. Clinicians should evaluate and monitor for recurrent disease, second malignancy, or late-onset treatment effects in any patient who reports new-onset pain. (Informal

Table 3. Chronic Pain Syndromes Associated With Cancer Treatment

Chemotherapy-related pain syndromes
Bony complications of long-term corticosteroids
Avascular necrosis
Vertebral compression fractures
Carpal tunnel syndrome
Chemotherapy-induced peripheral neuropathy
Raynaud's syndrome
Hormonal therapy–related pain syndromes
Arthralgias
Dyspareunia
Gynecomastia
Myalgias
Osteoporotic compression fractures
Radiation-related pain syndromes
Chest wall syndrome
Cystitis
Enteritis and proctitis
Fistula formation
Lymphedema
Myelopathy
Osteoporosis
Osteoradionecrosis and fractures
Painful secondary malignancies
Peripheral mononeuropathies
Plexopathies: brachial, sacral
Stem-cell transplantation–mediated graft-versus-host disease
Arthralgias/myalgias
Dyspareunia, vaginal pain
Dysuria
Eye pain
Oral pain and reduced jaw motion
Paresthesias
Scleroderma-like skin changes
Surgical pain syndromes
Lymphedema
Postamputation phantom pain
Postmastectomy pain
Postradical neck dissection pain
Postsurgery pelvic floor pain
Post-thoractomy pain/frozen shoulder
Postsurgery extremity pain (eg, sarcoma)

consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)

Literature review, analysis, and clinical interpretation. These recommendations were developed through informal consensus of the expert panel. Although there are few trials investigating optimal evaluation of pain in cancer survivors, screening and multidimensional assessment of pain provide data to inform clinical practice. Awareness of the array of potential pain syndromes will guide the treatment plan. Because of the risk of recurrence or secondary malignancy, these must also be considered when conducting this evaluation. Clinicians should also be aware that many patients with a history of cancer may also report chronic pain unrelated to the cancer, such as arthritis, degenerative disk disease, or diabetic neuropathy

2. TREATMENT AND CARE OPTIONS

Recommendation 2.1. Clinicians should aim to enhance comfort, improve function, limit adverse events, and ensure safety in the management of pain in cancer survivors. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)

Recommendation 2.2. Clinicians should engage patient and family/caregivers in all aspects of pain assessment and management. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)

Recommendation 2.3. Clinicians should determine the need for other health professionals to provide comprehensive pain management care in patients with complex needs. If deemed necessary, the clinician should define who is responsible for each aspect of care and refer patients accordingly. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)

Nonpharmacologic Interventions

Recommendation 2.4. Clinicians may prescribe directly or refer patients to other professionals to provide the interventions outlined in Table 4 to mitigate chronic pain or improve pain-related outcomes in cancer survivors. These interventions must take into consideration pre-existing diagnoses and comorbidities and should include an assessment for adverse events. (Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)

Literature review, analysis, and clinical interpretation. A number of randomized trials investigated the use of nonpharmacologic therapies in the management of chronic pain. The evidence to support their use is modest at best. Many of the studies had small sample sizes, were of short durations, and had methodologic limitations that increased their risk of bias. However, there was some consistency in the findings and most often those therapies had minimal adverse effects. In areas where the evidence was weak or unavailable, informal consensus of the expert panel was used to develop the recommendations on nonpharmacologic interventions. There were no compelling data to recommend one of these therapies over another. In fact, a variety of these interventions may be selected on the basis of patient/family goals, potential toxicities, ability to participate, and cost.

Physical medicine and rehabilitation.

- A Cochrane review[36] of seven RCTs evaluated the effectiveness of exercise on pain in adult cancer survivors who had completed active treatment. Modes of exercise included strength training, resistance training, walking, cycling, yoga, qigong, or tai chi. As measured on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-30, a significant reduction in pain was reported at 12 weeks (standardized mean difference [SMD], −0.29; 95% CI, −0.55 to −0.04) in patients in the exercise intervention groups compared with those randomly assigned to usual care or other nonexercise interventions. However, no difference was seen in longer follow-up periods.
- A statistically significant improvement in physical function (pooled difference 3.0 [95% CI, 0.7 to 5.3), $P = .01$), as measured by the 36-Item Short Form Health Survey, was reported in cancer survivors who were randomly assigned to physical activity that included aerobic, resistance, or weight training in 34 RCTs included in a systematic review with meta-analysis.[37] Because the minimal clinically important

Table 4. Disciplines and Interventions for Chronic Pain

Disciplines	Examples of Possible Interventions	Strength of Evidence and Recommendation
Physical medicine and rehabilitation	Physical therapy, occupational therapy, recreational therapy, individualized exercise program, orthotics, ultrasound, heat/cold	Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate
Integrative therapies	Massage, acupuncture, music	Evidence-based; benefits outweigh harms; evidence quality: low; strength of recommendation: weak
Interventional therapies	Nerve blocks, neuraxial infusion (epidural/intrathecal), vertebroplasty/kyphoplasty	Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate
Psychological approaches	Cognitive behavioral therapy, distraction, mindfulness, relaxation, guided imagery	Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate
Neurostimulatory therapies	TENS, spinal cord stimulation, peripheral nerve stimulation, transcranial stimulation	Evidence-based; benefits outweigh harms; evidence quality: low; strength of recommendation: weak

Abbreviation: TENS, transcutaneous electrical nerve stimulation.

difference for this subscale is 3, the effect of physical activity on physical function compared with a control group is small at best.

- Three RCTs not included in the Cochrane[36] and Fong et al[37] systematic reviews also considered physical training programs in adult cancer survivors. Cantarero-Villanueva et al[38] found that an 8-week water physical therapy program improved cervical and shoulder pain in 66 breast cancer survivors. The increase in edema and fatigue experienced by some survivors in the trial was transient. Fernández-Lao et al[39] reported that a multidimensional physical therapy program including aerobic and strengthening exercises also decreased neck pain (effect size, 2.72) and shoulder pain (effect size, 2.45) in 44 breast cancer survivors. The addition of once-per-week cognitive-behavioral therapy to a 12-week physical training program did not enhance the already beneficial effect of physical training on the quality of life of cancer survivors over a 1-year period.[40]

Integrative therapies.

- A recent Cochrane review[41] examining the effectiveness of acupuncture in reducing cancer-related pain in five RCTs concluded that there was insufficient evidence to judge its effectiveness. In another systematic review of 11 RCTs, effect size estimates for significant pain studies ranged from 1.11 to 2.10 for true acupuncture and from −0.45 to 0.45 for sham.[42] A third meta-analysis[43] of 437 patients with cancer reported that acupuncture plus drug therapy significantly improved pain (risk ratio, 1.36; 95% CI, 1.13 to 1.64; $P = .003$) compared with drug therapy alone.
- Meta-analytic results of massage therapy compared with no massage or conventional care in patients with cancer[44] revealed a significant reduction in pain with massage (SMD, −1.25; 95% CI, −1.63 to −0.87; $P < .001$) when data from nine RCTs and three nonrandomized controlled clinical trials were pooled. In a subgroup analysis that was based on different time periods of measurement, massage had a significant effect in reducing cancer pain (SMD, −0.70; 95% CI, −0.99 to −0.41; $P < .001$) in two studies.
- Four studies evaluating the effectiveness of music interventions on pain were reported in a systematic review.[45] Significant pre- to post-treatment reductions in pain were observed in two studies of hospitalized patients with cancer pain, but no difference in pain was found the other two studies.

Interventional therapies.

- A Cochrane review[46] of CPB trials in patients with pancreatic cancer found improved pain, as measured on a VAS, at 4 weeks in patients receiving CPB over those in the control groups. Moreover, opioid consumption was significantly lower in patients receiving CPB, and its safety profile makes this a viable option in indicated patients.
- Although TPVB did not reduce the incidence of chronic pain at 3 and 6 months in 180 women undergoing radical mastectomy, patients randomly assigned to TPVB did report less severe chronic pain, exhibited fewer signs and symptoms of chronic pain, and experienced better physical and mental health-related quality of life compared with patients randomly assigned to general anesthesia only.[47]
- A prospective study reported improvements in pain and function from baseline to 36 months in participants with chronic non-malignant pain who were implanted with a drug delivery system. In contrast, participants who were not treated via an intrathecal device showed a considerable decline in physical function.[50]
- In an RCT of patients with cancer and painful vertebral compression fractures, kyphoplasty was reported to be an effective and safe treatment that improved scores on the Roland-Morris disability questionnaire.[48] Both percutaneous vertebro- and kyphoplasty performed for vertebral body fractures in a consecutive group of patients with cancer also provided a significant reduction in VAS pain scores, which were sustained for up to 1 year.[49] Moreover, analgesic consumption was reduced at 1 month.[49]
- One of the first trials[51] investigating implantable IDDSs found that 84.5% of patients with IDDS achieved clinical success compared with 70.8% of patients receiving comprehensive medical management (CMM) ($P = .05$). Patients with IDDS also achieved a ≥ 20% reduction in both pain VAS and toxicity (57.7% *v* 37.5%, $P = .02$). The mean CMM VAS score showed a 39% reduction compared with a 52% reduction for the IDDS group ($P = .055$). Moreover, mean toxicity scores fell by 17% for the CMM group versus 50% for the IDDS group ($P = .004$).

Psychological approaches.

- A systematic review and meta-analysis of acceptance-based interventions for the treatment of chronic pain[54] reported that, in 10 studies, a moderate and significant effect on pain (pooled SMD, 0.37), physical well-being (pooled SMD, 0.35), and quality of life (pooled SMD, 0.41) was revealed.
- Two systematic reviews with meta-analyses evaluating the effectiveness of psychosocial interventions including patient education, relaxation, guided imagery, meditation or hypnosis, and supportive group therapy on pain in patients with cancer and cancer survivors[52,53] found a statistically significant overall effect for the interventions.
- A systematic review investigating the effectiveness of hypnosis on pain in 1,357 women with breast cancer reported that hypnosis had a positive influence on pain and distress in seven trials.[55]
- Four studies evaluating the effectiveness of relaxation interventions on pain were reported in a systematic review.[45] Significantly greater pain relief was seen in three of these trials that included hospitalized patients with cancer pain, outpatients with chronic cancer pain, and women with early-stage breast cancer.
- A systematic review considering MBSR found that MBSR was effective in improving quality of life in breast cancer survivors.[56] These effects were maintained at 6- and 12-month follow-ups.

Neurostimulatory therapies.

- A Cochrane review[57] of three RCTs investigating the effectiveness of transcutaneous electrical nerve stimulation (TENS)

in a total of 88 patients with cancer-related pain found that the studies differed in methodologic quality, mode of TENS used, treatment duration, and outcomes measured. Only one study, designed as a feasibility study and not measuring true effect, suggested that TENS may improve bone pain in patients with cancer. The other two studies did not find significant differences between TENS and a control group, although one of these studies was underpowered. Few adverse effects were reported. The authors concluded that there was insufficient evidence to indicate whether TENS should be used in pain management.

Pharmacologic Interventions

Miscellaneous Analgesics

Recommendation 2.5. Clinicians may prescribe the following systemic nonopioid analgesics and adjuvant analgesics to relieve chronic pain and/or improve function in cancer survivors in whom no contraindications, including serious drug–drug interactions exist:

- NSAIDS
- Acetaminophen (paracetamol)
- Adjuvant analgesics, including selected antidepressants and selected anticonvulsants with evidence of analgesic efficacy (such as the antidepressant duloxetine and the anticonvulsants gabapentin and pregabalin) for neuropathic pain conditions or chronic widespread pain

(Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)

Qualifying statement. The panel acknowledges that many other systemic nonopioids, including many other antidepressants and anticonvulsants, drugs in many other classes (such as the so-called muscle relaxants, benzodiazepines such as clonazepam, N-methyl-D-aspartate receptor blockers such as ketamine, and α-2 agonists such as tizanidine), and varied neutraceutical and botanicals marketed as complementary or alternative medicines, are taken by some cancer survivors with chronic pain and may benefit some of those who receive them. However, the efficacy of these agents and their long-term effectiveness have not been established.

Recommendation 2.6. Clinicians may prescribe topical analgesics (such as commercially available NSAIDS; local anesthetics; or compounded creams/gels containing baclofen, amitriptyline, and ketamine) for the management of chronic pain. (Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)

Recommendation 2.7. Corticosteroids are not recommended for long-term use in cancer survivors solely to relieve chronic pain. (Evidence-based; harms outweigh benefits; evidence quality: intermediate; strength of recommendation: moderate)

Recommendation 2.8. Clinicians should assess the risks of adverse effects of pharmacologic therapies, including nonopioids, adjuvant analgesics, and other agents used for pain management. (Evidence-based and informal consensus; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)

Recommendation 2.9. Clinicians may follow specific state regulations that allow access to medical cannabis or cannabinoids for patients with chronic pain after a consideration of the potential benefits and risks of the available formulations. (Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)

Qualifying statement. As of this writing, 23 states and the District of Columbia allow for medical cannabis,[58] although it is illegal on the federal level. Currently, there is insufficient evidence to recommend medical cannabis for first-line management of chronic pain in cancer survivors. However, evidence suggests it is worthy of consideration as an adjuvant analgesic or in the management of refractory pain conditions. There is also insufficient evidence to recommend one particular preparation of cannabis over another, and the Food and Drug Administration has not approved any drug product containing or derived from botanical marijuana.

Literature review, analysis, and clinical interpretation.

- A systematic review considering the addition of NSAIDS to opioids found improved analgesia and a reduction of opioid consumption in patients with cancer pain.[27]
- Nabal et al[27] considered the addition of paracetamol to step 3 opioid treatment and found only marginal effectiveness reported in one of five trials included in their review.
- Two systematic reviews found that antidepressants such as venlafaxine can be effective for at least moderate pain relief in patients with neuropathic pain conditions.[13,23]
- Anticonvulsants were reported to have a clinically relevant effect on neuropathic pain conditions in four systematic reviews.[13,20-22] The best evidence supports gabapentin and pregabalin.
- Current evidence on the effectiveness of ketamine is insufficient to make a recommendation for routine clinical use. Two systematic reviews[24,25] considering ketamine as an adjuvant to opioids reported that ketamine can reduce opioid requirement in patients with chronic pain that is refractory to opioids. However, its effectiveness in pain control remains unclear. Increased adverse events are also a concern.
- A Cochrane review[28] that included six studies and 2,073 patients found evidence that high-concentration (8%) topical capsaicin worked in only two types of neuropathic pain: pain after shingles and nerve-injury pain resulting from HIV infection. Evidence of effectiveness in other types of neuropathy is limited. Localized skin reactions are common.
- The analgesic effect of corticosteroids in cancer pain was assessed in a systematic review of four studies. Effectiveness results were inconsistent; however, toxicity associated with corticosteroids, particularly over 8 weeks, was a serious concern.[26]

Several recent systematic reviews[29-33] on the use of cannabis in the treatment of chronic pain found that cannabis offered modest analgesia with minimal mild adverse effects. Lynch and Ware[29] updated and extended earlier work[32] that, when taken together, demonstrates that 22 of 29 RCTs reported effectiveness in the management of chronic pain. A statistically significant improvement in pain was reported for nabilone, oral mucosal cannabis spray and extract, and smoked or vaporized cannabis, compared with placebo.[29,33,34] An individual patient data meta-analysis[39] found a statistically significant proportion of patients experienced a $>$ 30% clinical improvement in chronic neuropathic pain with inhaled cannabis versus placebo (OR, 3.2; 95% CI, 1.6 to 7.2). This translates into a high likelihood that inhaled cannabis is effective in the short term for one in five or six patients with

Table 5. Universal Precautions in Chronic Cancer Pain Management

Steps	Strategies	Comment
1. Assess and stratify risk of opioid misuse	Assess Review of medical records including diagnosis Interview (consider risk factors such as age, personal or family history of alcohol or drug abuse, major psychiatric disorder, history of sexual abuse) Examination Screening questionnaires Review of prescription drug monitoring program data Urine drug screening	All patients should undergo risk assessment Although many questionnaires have been developed to predict aberrant behavior or addiction, the clinical assessment is generally used in practice Risk stratification and adherence monitoring are illustrated in Table 6
2. Decide whether or not to prescribe	Risk of diversion: Low → prescribe High and the controlled drug is preferred but not a standard of care → do not prescribe High and the controlled drug is the standard of care and no reasonable alternatives exist → proceed only if controls and adherence monitoring can be established to ensure that diversion is not occurring Risk of drug abuse: Low → prescribe Moderate or high: decision to prescribe requires a critical analysis of: whether the severity of the pain is meaningfully compromising physical or mental well-being, whether there are reasonable alternatives that may ameliorate pain with manageable risk, and whether the nature of the drug abuse risk is more (eg, relapse of heroin abuse) or less (eg, pattern of early refills) serious	Proceed only if: Prescribing protocol and adherence monitoring commensurate with the risk can be put in place, and The patient is educated about the purpose of these strategies and the plan to modify prescribing or discontinue the drug if abuse occurs Do not prescribe unless warranted by the severity of the pain experience, there are no reasonable alternatives, and the risk of abuse or diversion is manageable
3. Minimize risk	Structure treatment in a manner that: establishes an appropriate level of adherence monitoring and helps patients avoid nonadherence Always optimize adjuvant analgesics, nonpharmacologic and interventional approaches; psychological support for treatment of psychiatric illness, anxiety, depression, sleep disorders	Adherence monitoring is illustrated in Table 6
4. Monitor drug-related behaviors	Effectiveness (pain is described as less intense, with a relationship to dose and dosing that is expected, and the pain reduction is associated with the ability to sustain or improve physical or psychological functioning Adverse effects Adherence monitoring, including compliance with current analgesic and nonopioid analgesic treatments, on the basis of risk assessment	Monitoring of outcomes is consistent with integration of pain management into a palliative care model
5. Respond to aberrant behaviors	A. Reassess and diagnose Realize that aberrant drug-related behaviors have a differential diagnosis and that an assessment must be performed to clarify whether behavior indicates addiction, other psychiatric condition associated with impulsive drug use, family issues, desperation or impulsivity driven by uncontrolled pain, or some combination of these factors. Also recognize that diversion is possible and assess for this behavior. B. Consider whether to continue prescribing If diversion is occurring or risks now exceed benefit, taper and discontinue C. If diversion is not occurring and the assessment suggests that the benefits of therapy will continue to outweigh the risk if the aberrant behaviors are stopped, restructure prescribing to increase control and adherence monitoring Avoid agents with higher abuse liability Prescribe small amounts at short intervals Review prescription drug monitoring data routinely Use pill counts Monitor use of substances through urine/other toxicology screening Require use of one pharmacy Use written agreement Obtain consultation from psychiatry/addiction specialists	Advanced illness does not free the clinician from the requirement of compliance with laws and regulations

NOTE. Definitions of abuse, addiction, and diversion are listed in the Appendix (online only). Adapted from Portenoy and colleagues.[10,60]

Table 6. Risk Stratification and Adherence Monitoring

Action	Low Risk	Moderate Risk	High Risk
Risk stratification*	No history of alcohol abuse or drug abuse, no family history of alcohol or drug abuse No history of a major psychiatric disorder Older age No smoking Stable social support	Remote history of alcohol or drug abuse History of addiction with a sustained period of recovery and a strong system to help sustain recovery Questionable family history of alcohol or drug abuse History of major psychiatric disorder that has been managed effectively Younger age Smoking History of physical or sexual abuse Lack of social support Involvement with others engaging in drug abuse	Recent history, or multiple episodes, of alcohol or drug abuse History of addiction with limited or no system to sustain recovery Strong family history of alcohol or drug abuse History of major psychiatric disorder
Adherence monitoring and mitigation	At least annual adherence monitoring Monitoring should usually include: detailed interviewing about drug-related behavior questioning of family member and record review from other treating physicians check of prescription monitoring program urine drug screen	At least semiannual adherence monitoring (more frequent at higher levels of assessed risk) Monitoring should usually include: detailed interviewing about drug-related behavior questioning of family member and record review from other treating physicians check of prescription monitoring program urine drug screen	Adherence monitoring at least every 2-3 months and more frequent visits Monitoring should usually include: detailed interviewing about drug-related behavior questioning of family member and record review from other treating physicians check of prescription monitoring program urine drug screen pill counts
Respond to aberrant behaviors	Reconsideration of treatment to determine whether nonopioid therapies can be better used	Reconsideration of treatment to determine whether nonopioid therapies can be better	Reconsideration of treatment to determine whether nonopioid therapies can be better used Refills limited or not permitted Small frequent prescriptions No concurrent use of more than one opioid (eg, no prescription of a second short-acting drug for breakthrough pain in those prescribed a long-acting drug for daily use) Mandated consultation with addiction specialists/psychiatrist

*The level of risk conferred is indicated by the presence of one or more factors itemized in the corresponding risk categories.

chronic neuropathic pain.[31] Whiting[30] et al reported a pooled pain reduction > 30% (OR, 1.41; 95% CI, 0.99 to 2.00) with smoked tetrahydrocannabinol (THC) or nabiximols compared with placebo, although this did not reach statistical significance. Both oral THC and an oral synthetic analog of THC were found to be as effective as codeine.[33] Drug-related adverse effects were reported to be well tolerated and transient. Overall, the formulations, doses, and routes of administration in the included studies vary considerably, making such decisions by clinicians and patients difficult. Additional high-quality studies of cannabis and cannabinoids that demonstrate the clinical benefits of the various strains and the bioactive compounds found within them, together with routes of administration, are warranted.[59]

Opioids

Recommendation 2.10. Clinicians may prescribe a trial of opioids in carefully selected cancer survivors with chronic pain who do not respond to more conservative management and who continue to experience pain-related distress or functional impairment. Tables 5 and 6 provide guidelines intended to promote safe and effective prescribing. Nonopioid analgesics and/or adjuvants can be added as clinically necessary. (Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)

Recommendation 2.11. Clinicians should assess the risks of adverse effects of opioids used for pain management. Table 7 lists opioid-related long-term adverse effects. (Evidence-based and informal consensus; benefits outweigh harms; evidence quality: intermediate strength of recommendation: moderate)

Qualifying statement. Although there is literature describing dysimmune effects[64,65] and tumor proliferative effects[1,66-69] from opioid drugs (both of which may be of particular concern in the cancer survivor population), there is insufficient evidence to determine whether there are clinically important risks. The expert panel believes that further clinical investigation is required to assess these concerns. In the absence of actionable data, physicians should be made aware of these evolving questions, and patients and their families may be informed about them as part of a discussion of the potential harms of long-term opioid therapy, as described in Table 7.

Literature review, analysis, and clinical interpretation.

- Six systematic reviews[13-18] evaluated the effectiveness of opioids in patients who suffered from either cancer or non–cancer-related chronic pain. Each systematic review received a high quality rating, although the quality of the primary studies included in these reviews did vary

Table 7. Adverse Effects Associated With Long-Term Opioid Use

Persistent common adverse effects
Constipation
Mental clouding
Upper GI symptoms (pyrosis, nausea, bloating)
Endocrinopathy (hypogonadism/hyperprolactinemia)
Fatigue
Infertility
Osteoporosis/osteopenia
Reduced libido
Reduced frequency/duration or absence of menses
Neurotoxicity
Myoclonus
Other changes in mental status (including mood effects, memory problems, increased risk of falls in the elderly)
Risk of opioid-induced hyperalgesia (incidence and phenomenology uncertain, but escalating pain in tandem with dose escalation raises concern)
Sleep-disordered breathing
Increased risk of concurrent benzodiazepine in patients predisposed to sleep apnea
New-onset sleep apnea
Worsening of sleep apnea syndromes

NOTE. Data adapted.[61-63]

considerably. Of particular note, the follow-up periods in the primary studies ranged from < 7 days only to 24 months. Long-term effectiveness was considered in the 2012 American Society of Interventional Pain Physicians' Guideline for Responsible Opioid Prescribing in Chronic Non-Cancer Pain,[70] but the lower-quality evidence available for long-term treatment periods precluded clear results. Studies used to inform the recommendations are discussed below and in Table 13 in the Data Supplement.

- The proportion of patients who reported a clinically meaningful improvement in neuropathic cancer pain while receiving opioids was 0.95 (95% CI, 0.93 to 0.96) in a systematic review of four studies.[13] Mean pain reduction was reported to be 82%, whereas mean absolute risk of harm in patients receiving active treatment was 0.06 (95% CI, 0.02 to 0.18).
- Considering pain relief as the primary outcome, a systematic review of nine RCTs[14] reported that, although transdermal fentanyl was superior to oral codeine/acetaminophen, it had efficacy equal to that of other opioids. Similarly, morphine, methadone, and oxycodone all had comparable efficacy.
- A systematic review[15] of adults suffering from chronic pain reported that in three trials, tapentadol showed a 30% improvement in pain relief (relative effectiveness, 0.68) and a 50% improvement in pain relief (relative effectiveness, 0.75) compared with oxycodone in patients with severe chronic pain. Similar results were seen in patients with moderate chronic pain on the basis of four trials. Tapentadol did have significantly more treatment discontinuation because of adverse effects than did placebo (OR, 0.33; 95% CI, 0.27 to 0.40) but it had fewer discontinuations than did morphine (OR, 2.03), oxycodone (OR, 2.31), transdermal fentanyl (OR, 1.82), oxymorphone, (OR, 4.27) and hydromorphone (OR, 2.38). The beneficial effects of tapentadol reported in this review may be attributed in part to the improved tolerability and fewer drop-outs in tapentadol-treated patients.[20] Moreover, the vast majority of the included trials in this systematic review had questionable potential sources of bias, and the systematic review itself was industry sponsored.
- In adult patients with moderate to severe chronic cancer pain never treated with strong opioids, hydromorphone showed no evidence of superior effectiveness over morphine or oxycodone in a systematic review of nine RCTs,[16] yet adverse effects such as diarrhea and sedation were more common.
- The systematic review by King et al,[17] including 14 RCTs and one meta-analysis, found that mean pain scores were no different in patients with moderate to severe cancer-related pain who received oxycodone and those who received morphine and hydromorphone (pooled standardized mean difference, 0.04; $P = .8$). Considering the opioids separately, pain scores were reported to be higher for oxycodone compared with morphine and lower for oxycodone compared with hydromorphone. However, the authors questioned the clinical significance of these differences.[17]
- A meta-analysis[18] of five RCTs found that the pooled mean difference in pain intensity as measured on a VAS for 40 to 100 mg of oxymorphone was −13 (95% CI, −17 to −9) compared with placebo ($P < .001$). Opioid-related adverse effects included nausea, vomiting, dizziness, headache, constipation, sedation, somnolence, and itching.
- Although opioids are the foundation of cancer pain management in moderate to severe acute pain as well as in pain caused by advanced disease, the efficacy of long-term use in survivors has not been well established. The balance between potential risks and benefits must be weighed when considering the long-term use of these agents in people who are surviving cancer. Benefits are no longer simply evaluated on the basis of pain relief but must also include improvements in function, tailored to the abilities of the individual.

3. RISK ASSESSMENT AND MITIGATION AND UNIVERSAL PRECAUTIONS WITH OPIOID USE

Recommendation 3.1. Clinicians should assess the potential risks and benefits when initiating treatment that will incorporate long-term use of opioids. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)

Recommendation 3.2. Clinicians should clearly understand terminology such as tolerance, dependence, abuse, and addiction as it relates to the use of opioids for pain control. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)

Recommendation 3.3. Clinicians should incorporate a universal precautions approach to minimize abuse, addiction, and adverse consequences of opioid use such as opioid-related deaths. Clinicians should be cautious in coprescribing other centrally acting drugs, particularly benzodiazepines (Table 7). (Evidence-based and informal consensus; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)

Recommendation 3.4. Clinicians should understand pertinent laws and regulations regarding the prescribing of controlled substances. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)

Recommendation 3.5. Clinicians should educate patients and family members regarding the risks and benefits of long-term opioid therapy and the safe storage, use, and disposal of controlled substances. Clinicians are encouraged to address possible myths and misconceptions about medication use and should educate patients about the need to be cautious when using alcohol or sedating over-the-counter medications, or in receiving centrally acting medications from other physicians. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)

Qualifying statement. Education and information about treatment should ideally take into account the patient's literacy level and the need for interpreters and should be provided in a culturally congruent manner.

Recommendation 3.6. If opioids are no longer warranted, clinicians should taper the dose to avoid abstinence syndrome. The rate of tapering and the use of cotherapies to reduce adverse effects should be individualized for each patient. (Evidence-based and informal consensus; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)

Literature review, analysis, and clinical interpretation. Chronic pain management using the universal precaution approach to assess and manage patients happens in a multistep process.[71] The rationale for adopting a universal precautions approach is a reduction in stigma, an improvement in patient care, and a containment of overall risk.[72] Evidence supporting various aspects of these steps is presented below. Where evidence is sparse, weak, or absent, recommendations were developed through consensus.

- A number of validated risk-assessment instruments and screening questionnaires are available to help identify patients prone to misuse or those currently misusing prescribed opioids. Some of the tools include the Screener and Opioid Assessment for Patients in Pain[72] and its revision,[73] the Current Opioid Misuse Measure,[74] the Opioid Risk Tool,[75] and the Brief Risk Interview[76] and Questionnaire.[77] These tools vary in how they are conducted, but all offer clinicians resources for conducting risk stratification.
- Boscarino and colleagues[78] found that dependence was associated with age $<$ 65 years (OR, 2.33; $P = .001$), opioid abuse history (OR,3.81; $P < .001$), high dependence severity (OR, 1.85; $P = .001$), major depression (OR, 1.29; $P = .022$), and psychotropic medication use (OR, 1.73; $P = .006$). A combination of four variables (age, depression, psychotropic medications, and pain impairment) predicted increased risk of current dependence (OR, 8.01; $P < .001$). Furthermore, patient history of severe dependence and opioid abuse increased this risk substantially (OR, 56.36; $P < .001$). Similar results were reported in a cross-sectional study of 597 primary care patients with chronic pain.[79] Prescription drug use disorder was found to be concentrated among those with a family history of substance use disorders, those who had spent time in jail, current cigarette smokers, male sex, white ethnicity, those with pain-related functional limitations, and those with post-traumatic stress disorder (PTSD). White et al[80] used data from medical and prescription drug claims to develop models that identify patients at risk of prescription opioid abuse or misuse. As in other studies, factors associated with a risk of prescription opioid abuse or misuse included age 18 to 24 years, male sex, $\geq$ 12 opioid prescriptions, opioid prescriptions from three or more pharmacies, early prescription opioid refills, escalating morphine dosages, psychiatric outpatient visits, hospital visits, diagnoses of nonopioid substance abuse, depression, PTSD, and hepatitis.
- Prospective studies have shown that adherence monitoring with a controlled substance agreement, periodic monitoring, periodic drug testing, pill counts, and education when necessary served to reduce controlled substance abuse and increase compliance.[81-86] A systematic review investigating the effectiveness of opioid treatment agreements and urine drug testing in reducing opioid misuse among patients with chronic noncancer pain found a decrease in opioid misuse with the use of treatment agreements as part of the opioid management strategy.[87] Absolute risk reductions ranged from 6.5% (95%, CI 1.3% to 11.7%) to 22.9% (95% CI, 17.3% to 28.7%) in four controlled studies.
- Existing guidelines[88,89] and systematic reviews[90] offer recommendations for practitioners aiming to discontinue long-term opioid therapy.
- Most of the studies evaluating risk factors associated with misuse have been conducted in people diagnosed with noncancer pain syndromes. There is no evidence to suggest that people surviving cancer, who might also have PTSD-like symptoms, would be at reduced risk. In fact, some populations may be at more risk of misuse in concert with lifestyle choices that may have contributed to the development of cancer (eg, smoking, excess alcohol intake, obesity). Tools such as agreements, urine drug testing, and use of drug monitoring programs that may mitigate risk are available, although more information is needed to determine which are most effective in the setting of cancer survivorship.

DISCUSSION

Chronic pain can be a serious negative consequence of surviving cancer, yet the magnitude of the problem is poorly understood. One challenge faced by the committee is the divergence in the definitions of survivors. Although the committee upholds the definition advanced by the National Coalition for Cancer Survivorship, which considers anyone to be a survivor from the moment of diagnosis through the rest of their life, this would have diluted the primary aim of this guideline, which is to explore pain as a later phenomenon of cancer and its treatment. Therefore, we used the National Cancer Institute's Office of Cancer Survivorship characterization of a survivor as a person with a history of cancer who is beyond the acute diagnosis and treatment phase. The number of these survivors is greatly increasing, nearing 14 million in the United States. Two thirds of these individuals are surviving $\geq$ 5 years after diagnosis, supporting the need to study pain in this growing population.[2] Estimates of the prevalence of pain in cancer survivors vary widely and have been reported to be as high as 40%.[3-5] Much of the variability in prevalence is a result of the

heterogeneity of the populations studied. Risk factors for chronic pain in survivors include the type and invasiveness of the tumor, the treatment regimen used, the time since cancer treatment, and the efficacy of initial pain therapy.

Because significant pain is associated with impaired quality of life in this population,[6] there is an urgent need to better characterize pain syndromes specific to the survivor. This information will allow greater understanding of underlying mechanisms, potential therapies, and optimally, preventive measures. However, even with a fairly well-characterized pain syndrome that seems to be more homogenous in origin and presentation, guideline development for painful cancer conditions can be challenging. The ASCO guideline, Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy (CIPN) in Survivors of Adult Cancers,[91] found few high-quality, consistent trials and was unable to make a recommendation regarding any agent for prevention of CIPN. In addition, duloxetine was the only agent recommended by the guideline panel for the treatment of CIPN. Other therapies, although anecdotally beneficial or supported for their use in other neuropathic conditions, could not be recommended, although the guideline committee suggested that it might be reasonable to try these agents in selected patients. Available CIPN studies enrolled people who may have been exposed to different neurotoxic agents, may have received a variety of agents, and may have had comorbid conditions creating greater risk of neuropathy. This experience illustrates the complexity underlying guideline development in this nascent field of understanding painful syndromes in cancer survivors. Our committee faced these same challenges in exploring the broader context of pain and its treatment in cancer survivors.

CIPN is one of many well-recognized pain disorders, together with other treatment-related pain syndromes, such as postsurgical and postradiation pain. Hormonal therapies, such as aromatase inhibitors, can produce arthralgias. As the use of hematopoietic stem-cell transplantation expands, graft-versus-host disease (GVHD) is seen with greater frequency, leading to pain syndromes that can affect almost any organ system. In addition, immunosuppressive agents used to treat GVHD can lead to painful complications (eg, corticosteroids and avascular necrosis). Vigilance is warranted as novel treatments are being introduced that may lead to new pain syndromes. For example, muscle cramping, a debilitating painful condition that often interrupts sleep, is known to occur with polyneuropathies (including CIPN),[92] and with GVHD,[93] and has been reported as an adverse effect of newer inhibitors of the Hedgehog pathway, such as vismodegib.[94] The recent validation of a tool specific to musculoskeletal symptoms in hematopoietic stem-cell transplantation will allow better characterization of this painful phenomenon.[95]

The committee considered numerous pharmacologic and nonpharmacologic treatments to relieve pain, yet recommendations regarding specific interventions were difficult to make because of the limited number of studies, heterogeneity in populations and types of pain, disparity in outcomes selected, and other limitations of existing studies. Even therapies long considered foundational to the management of acute cancer pain or to relief of pain at end of life were supported by little high-quality evidence in the survivor population. Clinicians are challenged in making practice decisions in the absence of strong data.

An additional consideration when designing an analgesic regimen, particularly in the absence of strong supporting data, is the potential for harm. The ratio of benefit to harm of therapy and goals of care are different when comparing the person at the end of life with the long-term survivor. In an attempt to reduce harm, drug–drug interactions with cancer therapies or other treatments should be considered. Cytochrome P450 CYP 3A and CYP2D6 inhibitors can increase concentrations of opioids, such as codeine, oxycodone, hydrocodone, fentanyl, tramadol, and methadone, metabolized by this system.[96-99] Methadone and buprenorphine can prolong the QT interval, an effect that can be potentiated by many other drugs, notably doxorubicin, nilotinib, pazopanib, sorafenib, and other chemotherapeutic agents.[100]

If pain is severe and disabling, and long-term opioid therapy is being considered, the potential for opioid-related harm over time must also be evaluated. Again, the data are sparse. Persistent adverse effects such as constipation are well recognized, and evolving information about persistent endocrinopathy and risk of sleep-disordered breathing suggests that these conditions must be considered when opioid therapy is initiated and later during the course of treatment. The potential for neurotoxicities, such as persistent mental clouding, increased risk of falls in the elderly, and other phenomena may occur. Opioid-induced hyperalgesia is well described in preclinical models but has uncertain clinical importance; the potential is considered when a patient reports escalating pain in tandem with opioid dose escalation in the absence of identifiable worsening of a pain cause. A more recent line of inquiry is the effect of opioids on immune function and tumor progression, and ultimately, survival. Preclinical studies implicate μ opioids in tumor progression,[101] although studies in humans are lacking. Clearly, there is an urgent need for additional research.

Opioid-related harm may also result from misuse or abuse, the development of opioid addiction, or the occurrence of drug diversion within the community. The problem of prescription drug abuse is serious,[102] leading to an increase in opioid-related deaths, but mitigation efforts designed to assess, stratify, and limit risk can enhance safety for patients, prescribers, and the community. These efforts must be coupled with the education of professionals, patients, and their family members. together with the public, about safe storage (eg, locked boxes for medications) and safe disposal (eg, take-back programs).[103] Balance in policies and regulations regarding opioids is needed to ensure appropriate access to prescription opioids for those in pain.[104]

The issues described throughout this guideline are complex. The question arises regarding who should provide pain management for the cancer survivor: the oncologist and his or her team, the patient's primary care provider, a multidisciplinary pain service, or another professional? The answer may be dictated, in part, by the resources available within each community. Oncology teams providing ongoing care for cancer survivors may be the optimal group to address pain, because they routinely manage a complex regimen of cancer therapies and related symptoms. If other professionals are managing the cancer survivor's pain, clear, early, and ongoing communication should occur to delineate each team's role and responsibilities. Because knowledge deficits and inadequate training in cancer pain assessment and management have been well documented,

education for all clinicians caring for these survivors is needed. Resources for education are available through ASCO and other organizations.

Patient and Clinician Communication

As therapeutic treatment options and outcomes improve, patients with cancer are living longer. Of course, this is good news, but it sometimes comes at a cost. Put simply, chronic pain from treatment-related adverse effects can significantly affect the quality of life of many cancer survivors for years after initial treatment stops. Chronic pain can develop from a variety of sources: peripheral neuropathy, muscle or bone pain, surgery, radiation, and other conditions. Comorbidity with other conditions or syndromes can make assessing chronic pain more difficult. Because post-treatment pain is so complicated, good communication between patients and their medical providers is essential. Cancer survivors are more than their cancer history or their pain; they are individuals with unique needs. They may have varying capacities to deal with a great deal of information that can sometimes be overwhelming. Just as no two cancers are alike, patients experience pain differently. Some patients may even be reluctant to discuss their pain, seeing it as a sign of weakness or fearing a recurrence; some may see it an expected and untreatable complication of their cancer treatment. That is why a pain assessment is recommended at every visit. In teasing out how they are coping, clinicians need to ask patients how chronic pain is affecting them and suggest how they can work together to better manage their symptoms and improve their quality of life. Survivors who understand all aspects of their pain treatment plan (and their role in it) may have a better overall outcome.

Health Disparities

Although ASCO clinical practice guidelines represent expert recommendations on 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 health care. Lack of access because of geographic location and distance from appropriate treatment facilities is an ongoing concern for many patients. Racial and ethnic disparities in health care also contribute significantly to this problem in the United States. Patients with cancer who are members of racial/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 care of poor quality than are other Americans.[1,105] Considering pain management, the literature suggests that the sources of pain disparities among racial and ethnic minorities are complex, involving patient, health care provider, and health care system factors.[106] A systematic review of pain management confirmed that racial/ethnic minorities consistently receive less adequate treatment of acute and chronic pain than do non-Hispanic whites, even after controlling for age, sex, and pain intensity.[107] Although opioid-prescribing patterns can be complex, multiple studies report that black patients are less likely to be prescribed opioids for pain than are whites.[108-110] Individuals of minority groups also seem to underreport pain intensity, contributing in part to pain-management disparities.[107] Physicians' own cultural beliefs and stereotypes regarding pain, minority individuals, and use of narcotic analgesics also play a role.[107] Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

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, is challenging. Patients with multiple chronic conditions are a complex and heterogeneous population and are frequently excluded from clinical trials, making it difficult to account for all the possible permutations to develop specific recommendations for care. Insomnia and psychological distress are common conditions in patients with chronic pain, present in 17% and 90% of adult suffers, respectively.[111] The most common psychiatric disorders comorbid with chronic pain include depression, anxiety, personality disorders, and PTSD.[111,112] Prospective studies have provided important information about the impact of comorbidity. Patients with chronic pain with these comorbidities have significantly greater functional limitations and pain intensity.[111] Moreover, evidence suggests that patients with comorbid conditions are less likely to improve with standard chronic pain treatment.[113] The optimal approach to incorporating comorbidity information in chronic pain management continues to be explored, but screening and diagnosis are key.

External Review

The draft was submitted to two external reviewers with content expertise. It was rated as high quality, and it was agreed it would be useful in practice. Specific feedback on Table 5 suggested that oncologists would find the information, as presented, overwhelming. As such, the table was revised and broken into two separate tables in an attempt to make the presentation less complicated. Other comments, such as acknowledging the paucity of evidence in the abstract and highlighting the fact that many recommendations are based on expert consensus, and the inclusion of a strong statement on the need for research in this area, were reviewed by the expert panel and integrated into the final manuscript before approval by the Clinical Practice Guideline Committee.

Guideline Implementation

ASCO guidelines are developed for implementation across health care settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and their caregivers and to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the

ASCO Web site and most often published in *Journal of Clinical Oncology* and *Journal of Oncology Practice*.

Limitation of the Research

Limitations in methodologic rigor are evident in some of the included studies. Conflict of interest is one potential source of bias. Industry-sponsored research in the area of pain medicine is a reality. As government research funding has diminished over the years, industry has stepped in, funding a greater proportion of medical research.[114] However, this funding is important for the advancement of the science.[114] Several studies included in the evidentiary base were industry funded, and their conclusions should be interpreted cautiously. Moreover, the inclusion of some observational evidence was believed to be warranted, because it allowed for long-term follow-up of patients. However, observational studies are considered to be of lower quality and, as such, the inherent limitations of such designs should be taken into consideration. In the case of evidence for risk assessment, mitigation, and universal precautions with opioid use, the inconsistency in definitions was problematic. Nonetheless, the panel reviewed the current available evidence and through consensus and clinical experience developed the recommendations.

Future Directions

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. The identification of chronic pain syndromes in people surviving cancer is evolving as new treatments are introduced. However, numerous gaps in existing evidence have been identified and highlighted in this guideline. The expert panel believes that there is both a need and an opportunity to advance the pace and quality of clinical pain research. Comprehensive assessment, including the impact of pain on function and quality of life, is warranted for all survivors. Long-term assessment is also needed after clinical trials to better recognize novel or previously unrecognized painful consequences of treatment, including those syndromes that may occur after treatment is completed. Carefully designed, extended studies of pharmacologic and nonpharmacologic interventions to relieve pain and improve function are indicated in this population. An especially relevant and urgent need is research identifying those cancer survivors who respond optimally to opioid therapy and those at greatest risk of adverse effects. Also essential is the elucidation of opioid effects on basic systems, such as immune function and inflammatory markers, and the possible interplay with tumor growth. This will better inform patients and clinicians about the ultimate effect of opioids on survival. This call to action can set the stage for the next generation of studies to improve the evidence base of chronic pain in cancer survivors.

Additional Resources

More information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/chronic-pain-guideline and www.asco.org/guidelineswiki. Patient information is available at www.cancer.net. Visit www.asco.org/guidelineswiki to provide comments on the guideline or to submit new evidence.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

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Appendix

Definitions Used in Tables 5 and 6

Abuse. Substance-use disorder is a diagnostic term in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) referring to recurrent use of alcohol or other drugs that causes clinically and functionally significant impairment, such as health problems, disability, and failure to meet major responsibilities at work, school, or home. Depending on the level of severity, this disorder is classified as mild, moderate, or severe.[1]

Addiction. Addiction is a term used to indicate the most severe, chronic stage of substance-use disorder, in which there is a substantial loss of self-control, as indicated by compulsive drug taking despite the desire to stop taking the drug. In the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition), the term addiction is synonymous with the classification of severe substance-use disorder (Volkow ND, et al: N Engl J Med 374:363-371, 2016).

Drug Diversion. Drug diversion is best defined as the diversion of licit drugs for illicit purposes. It involves the diversion of drugs from legal and medically necessary uses towards uses that are illegal and typically not medically authorized or necessary (http://www.drugwarfacts.org/cms/Diversion#sthash.2XMd9w6p.dpuf).

Standard of Care

1. A diagnostic and treatment process that a clinician should follow for a certain type of patient, illness, or clinical circumstance. Adjuvant chemotherapy for lung cancer is "a new standard of care, but not necessarily the only standard of care." (Volkow ND et al: N Engl J Med 374:363-371, 2016).
2. In legal terms, the level at which the average, prudent provider in a given community would practice. It is how similarly qualified practitioners would have managed the patient's care under the same or similar circumstances. The medical malpractice plaintiff must establish the appropriate standard of care and demonstrate that the standard of care has been breached (http://www.medicinenet.com/script/main/art.asp?articlekey=33263).

Table A1. Management of Chronic Pain in Adult Cancer Survivors Expert Panel Membership

Name and Designation	Affiliation/Institution	Area of Expertise
Judith A. Paice, PhD/RN*	Northwestern University Feinberg School of Medicine	Hematology/oncology, pain, palliative care, hospice
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Andrea Cheville, MD	Mayo Clinic	Rehabilitation
Paul Glare, MD	University of Sydney	Palliative care
Frank Keefe, PhD	Duke University	Psychology
Lakshmi Koyyalagunta, MD	MD Anderson Cancer Center	Pain medicine
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Andrea Cooper		Patient representative

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