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Integrative Medicine for Pain Management in Oncology: Society for Integrative Oncology–ASCO Guideline

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abstract

PURPOSE The aim of this joint guideline is to provide evidence-based recommendations to practicing physicians and other health care providers on integrative approaches to managing pain in patients with cancer.

METHODS The Society for Integrative Oncology and ASCO convened an expert panel of integrative oncology, medical oncology, radiation oncology, surgical oncology, palliative oncology, social sciences, mind-body medicine, nursing, and patient advocacy representatives. The literature search included systematic reviews, meta-analyses, and randomized controlled trials published from 1990 through 2021. Outcomes of interest included pain intensity, symptom relief, and adverse events. Expert panel members used this evidence and informal consensus to develop evidence-based guideline recommendations.

RESULTS The literature search identified 227 relevant studies to inform the evidence base for this guideline.

RECOMMENDATIONS Among adult patients, acupuncture should be recommended for aromatase inhibitor–related joint pain. Acupuncture or reflexology or acupressure may be recommended for general cancer pain or musculoskeletal pain. Hypnosis may be recommended to patients who experience procedural pain. Massage may be recommended to patients experiencing pain during palliative or hospice care. These recommendations are based on an intermediate level of evidence, benefit outweighing risk, and with moderate strength of recommendation. The quality of evidence for other mind-body interventions or natural products for pain is either low or inconclusive. There is insufficient or inconclusive evidence to make recommendations for pediatric patients. More research is needed to better characterize the role of integrative medicine interventions in the care of patients with cancer.

Additional information is available at https://integrativeonc.org/practice-guidelines/guidelines and www.asco.org/survivorship-guidelines.

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ASSOCIATED CONTENT

Listen to the podcast with Dr Mao at guideline.libsyn.com

Appendix

Data Supplement

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

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INTRODUCTION

Pain is one of the most common, disabling, and feared symptoms experienced by patients diagnosed with cancer.[1,2] Among patients with advanced cancer, pain can be a result of tumor burden or invasion of bones, muscles, or nerves. In addition, many conventional cancer treatments such as surgery, chemotherapy, radiotherapy, immunotherapy, or hormonal therapy can result in both acute and chronic pain conditions such as aromatase inhibitor (AI)–induced joint pain or chemotherapy-induced peripheral neuropathy (CIPN) pain.[3,4] With improved oncologic treatment, many patients diagnosed with advanced cancer now live longer with symptomatic illness and ongoing oncologic treatment. Additionally, increasing numbers of patients experience remission and join the 16.9 million cancer survivors in the United States alone.[5] Many survivors, however, continue to experience chronic pain resulting from their cancer treatment that not only negatively affects their quality of life, but also their daily functions.[6] Chronic pain may also lead to nonadherence to oncologic treatment such as hormonal therapies,[7,8] thus, potentially compromising overall survival. Therefore, effective pain management is of critical importance throughout the cancer care trajectory.

As pain in patients and survivors of cancer is complex with different etiologies (eg, tumor burden, treatment-related, and non–cancer-related) and varying presentations (eg, neuropathic and musculoskeletal) and duration (eg, acute and chronic), pain

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THE BOTTOM LINE

Integrative Medicine for Pain Management in Oncology: Society for Integrative Oncology—ASCO Guideline

Guideline Questions

1. What mind-body therapies are recommended for managing pain experienced by adult and pediatric patients diagnosed with cancer?
2. What natural products are recommended for managing pain experienced by adult and pediatric patients diagnosed with cancer?

Target Population

Patients of any age diagnosed with any cancer who are experiencing pain during any stage of their cancer care trajectory.

Target Audience

Clinicians who provide care to patients with cancer, cancer survivors, and family caregivers.

Methods

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

Recommendations

The following recommendations are evidence-based, informed by randomized trials and systematic reviews, and guided by clinical experience. The recommendations were developed by a multidisciplinary group of experts.

NOTE: The following set of recommendations are for adults with cancer. Although many of the recommendations are weak and based on low-quality evidence, the interventions do have clinical relevance, with a favorable benefit-to-harm ratio, and this is the basis for making the recommendations. There is insufficient or inconclusive evidence to make recommendations for pediatric patients with cancer.

Aromatase inhibitor–related joint pain.

Recommendation 1.1. Acupuncture should be offered to patients experiencing AI-related joint pain in breast cancer (Type: Evidence based, benefits outweigh harms; Evidence quality: Intermediate; Strength of recommendation: Moderate).

Recommendation 1.2. Yoga may be offered to patients experiencing AI-related joint pain in breast cancer (Type: Evidence based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

General cancer pain or musculoskeletal pain.

Recommendation 1.3. Acupuncture may be offered to patients experiencing general pain or musculoskeletal pain from cancer (Type: Evidence based, benefits outweigh harms; Evidence quality: Intermediate; Strength of recommendations: Moderate).

Recommendation 1.4. Reflexology or acupressure may be offered to patients experiencing pain during systemic therapy for cancer treatment (Type: Evidence based, benefits outweigh harms; Evidence quality: Intermediate; Strength of recommendation: Moderate).

Recommendation 1.5. Massage may be offered to patients experiencing chronic pain following breast cancer treatment (Type: Evidence based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Moderate).

Recommendation 1.6. Hatha yoga may be offered to patients experiencing pain after treatment for breast or head and neck cancers (Type: Evidence based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Recommendation 1.7. Guided imagery with progressive muscle relaxation may be offered to patients experiencing general pain from cancer treatment (Type: Evidence based, benefits and harms not assessable; Evidence quality: Low; Strength of recommendation: Weak).

Chemotherapy-induced peripheral neuropathy.

Recommendation 1.8. Acupuncture may be offered to patients experiencing chemotherapy-induced peripheral neuropathy from cancer treatment (Type: Evidence based-informal consensus, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

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THE BOTTOM LINE (CONTINUED)

Recommendation 1.9. Reflexology or acupressure may be offered to patients experiencing chemotherapy-induced peripheral neuropathy from cancer treatment (Type: Evidence based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Procedural or surgical pain.

Recommendation 1.10. Hypnosis may be offered to patients experiencing procedural pain in cancer treatment or diagnostic workups (Type: Evidence based, benefits outweigh harms; Evidence quality: Intermediate; Strength of recommendation: Moderate).

Recommendation 1.11. Acupuncture or acupressure may be offered to patients undergoing cancer surgery or other cancer-related procedures such as bone marrow biopsy (Type: Evidence based-informal consensus, benefits outweigh harms; Evidence quality of: Low; Strength of recommendation: Weak).

Recommendation 1.12. Music therapy may be offered to patients experiencing surgical pain from cancer surgery (Type: Evidence based, benefits outweigh harms; Evidence quality of: Low; Strength of recommendation: Weak).

Pain during palliative care.

Recommendation 1.13. Massage may be offered to patients experiencing pain during palliative and hospice care (Type: Evidence based; benefits outweigh harms; Evidence quality: Intermediate; Strength of recommendation: Moderate).

Please refer to the treatment algorithm in Figure 2 for the visual representation of these recommendations.

Additional Resources

Definitions for the quality of the evidence and strength of recommendation ratings are available in Appendix Table A1 (online only). More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at https://integrativeonc.org/practice-guidelines/guidelines and www.asco.org/survivorship-guidelines. The Society for Integrative Oncology Clinical Practice Guidelines Committee's Standard Operating Procedures (available at https://integrativeonc.org/practice-guidelines/guidelines-sops) and the Methodology Manual (available at www.asco.org/guideline-methodology) provide additional information about the methods used to develop this guideline. Patient information is available at https://integrativeonc.org/knowledge-center/patients and www.cancer.net.

Society for Integrative Oncology and ASCO believe that cancer clinical trials are vital to inform clinical decisions and improve cancer care, and that all patients should have the opportunity to participate.

management requires an interdisciplinary approach and should include both pharmacologic and nonpharmacologic treatments, where appropriate.[2] Integrative medicine, defined as the coordinated use of evidence-based complementary practices and conventional care treatments,[9] includes interventions such as acupuncture, massage, meditation, and yoga, which are increasingly available in cancer centers and are recommended for symptom and pain management.[10,11] An estimated 40% of patients with cancer use integrative medicine on an annual basis.[12-14] The key guiding principle of integrative medicine is to use these interventions along with conventional pain management approaches (eg, medications, radiation, injections, and physical therapies) and it is not intended to replace conventional interventions.[9]

Patients often seek integrative medicine because they perceive that conventional medical treatment is not completely meeting their needs, fear side effects from pharmacotherapies, prefer a holistic approach, or because it has been recommended by their family or health care providers.[15-18] A growing number of well-conducted randomized controlled trials (RCTs) have found that interventions such as acupuncture or massage can alleviate pain in patients and survivors of cancer.[19-21] However, for many other interventions, trials are small and are often limited by a lack of methodologic rigor. Ideally studies should not only report the statistical significance of their findings but also the clinically meaningful change in pain severity (a two-point reduction on a 0-10 scale).

To guide a patient-centered and evidence-based approach to pain management incorporating integrative medicine interventions for appropriate indications,[9,22] clinicians and patients need to be equipped with knowledge of the current evidence base of these therapies for pain management in cancer care. The purpose of this guideline is to systematically appraise the evidence from randomized controlled clinical trials, systematic reviews (SRs), and meta-analyses, and to provide guidance to clinicians on the effectiveness of integrative medicine treatment options for pain in adults and children with a cancer diagnosis.

GUIDELINE QUESTIONS

This clinical practice guideline addresses two overarching clinical questions: (1) What mind-body therapies are

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recommended for managing pain experienced by adult and pediatric patients diagnosed with cancer? (2) What natural products are recommended for managing pain experienced by adult and pediatric patients diagnosed with cancer?

METHODS

Guideline Development Process

Both the Society for Integrative Oncology (SIO) and ASCO regularly engage in the development and dissemination of clinical practice guidelines. SIO's mission is to advance evidence-based, comprehensive, integrative health care to improve the lives of people affected by cancer. ASCO's mission is to conquer cancer through research, education, and promotion of the highest-quality, equitable patient care. For this guideline, SIO and ASCO joined efforts to develop a guideline focused on the use of integrative therapies to manage oncology-related pain to provide evidence-based recommendations to patients and clinicians to inform clinical decisions. This guideline builds upon the existing ASCO guidelines on pain management, the growing body of research in this area, and the emphasis from the Centers for Disease Control and Prevention to use nonpharmacologic approaches for pain management.[2,23,24]

This SR-based guideline product was developed by an international multidisciplinary Expert Panel, which included a patient representative and a health research methodologist (Appendix Table A2, online only). The Expert Panel met via video conferences and corresponded through e-mail. Based upon the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were sent for an open comment period of two weeks allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then submitted to the *Journal of Clinical Oncology (JCO)* for editorial review and consideration for publication. All SIO-ASCO guidelines are ultimately reviewed and approved by the Expert Panel, the SIO Clinical Practice Guidelines Committee, and the ASCO Evidence Based Medicine Committee before publication. All funding for the administration of the project was provided by SIO.

The recommendations were developed by using a SR of evidence identified through online searches of PubMed (1990-2021) and Cochrane Library (1990-2021) of RCTs, SRs, and meta-analyses. Articles were selected for inclusion in the SR on the basis of the following criteria:

- Population: Adults and pediatric patients experiencing pain during any stage of their cancer care trajectory
- Interventions: Integrative interventions for pain management, including acupuncture, acupressure, mind-body therapies, and natural products (note: see details in the Data Supplement [online only]; therapies focused on pain prevention were not included)
- Comparisons: No intervention, waitlist, usual care (UC) or standard care, guideline-based care, active control, attention control, placebo, or sham interventions
- Outcomes: Pain intensity, reduction, or change in symptoms reported as the primary outcome in published manuscript
- Sample size: Minimum total sample size of 20

Articles were excluded from the SR if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, and narrative reviews; or (3) published in a non-English language. The guideline recommendations were crafted, in part, using the *Guidelines Into Decision Support* methodology and the accompanying BRIDGE-Wiz software program.[25] 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 type and strength of the recommendation, and evidence quality are provided with each recommendation. The quality of the evidence for each outcome was assessed using the Cochrane Risk-of-Bias tool[26] by the project methodologist in collaboration with the Expert Panel cochairs and reviewed by the full Expert Panel.

The SIO and ASCO Expert Panel and guidelines staff will work with cochairs to keep abreast of any substantive updates to the guideline. On the basis of formal review of the emerging literature, SIO will determine the need to update the guideline. The SIO Guidelines Methodology Manual (available at https://integrativeonc.org/practice-guidelines/sio-guidelines-guidelines-methodology) provides additional information about the guideline process.

Guideline Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by the SIO and the ASCO to assist health care providers in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the

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TABLE 1. Studies on Interventions With Sufficient Evidence to Inform Recommendations

Intervention	Study Type	No.	Pain Symptom Categories
Adult population			
Acupuncture	SRs	17	AI-related joint pain[27-30] CIPN[31,32] Palliative and survivorship care[33-43]
	RCTs	34	AI-related joint pain[19,44-47] General cancer pain[20,48-55] CIPN[56-63] Procedural or surgical pain[64-75]
Yoga	RCTs	4	General cancer pain[76-79]
Guided imagery and PMR	RCTs	2	General cancer pain[80,81]
Hypnosis	SRs	2	Procedural pain[82,83]
	RCTs	8	Procedural pain[84-91]
Reflexology	RCTs	9	General cancer pain[92-98] CIPN[99,100]
Massage	SRs	5[a]	General cancer pain[101,102] Pain during palliative care[33,40,103]
	RCTs	9	General cancer pain[104,105] Pain during palliative care[21,106-111]

Abbreviations: AI, aromatase inhibitor; CIPN, chemotherapy-induced peripheral neuropathy; PMR, progressive muscle relaxation; RCT, randomized controlled trial; SR, systematic review.

[a]Some studies overlap between interventions.

independent professional judgment of the treating clinician, as the information does not account for individual variation among patients. Recommendations specify the level of confidence that the recommendation reflects on the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicate that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating clinician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating clinician in the context of treating the individual patient. Use of the information is voluntary.

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with SIO's and ASCO's shared Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at https://integrativeonc.org/practice-guidelines/guidelines-sops and https://www.asco.org/guideline-methodology). All members of the Expert Panel completed SIO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting, or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

Characteristics of Studies Identified in the Literature Search

A total of 1,346 articles were identified in the literature search. After applying the eligibility criteria, 227 articles remained, forming the evidentiary basis for the guideline recommendations.

The identified trials were published between 1990 and 2021. The trials compared various integrative therapies to standard of care, placebos, sham interventions, other interventions, or active controls. The primary outcome for most of the studies included pain severity, pain reduction, and change in pain symptoms, which were measured with commonly used standardized tools such as the Visual Analog Scale (VAS), Brief Pain Inventory scale (BPI), Numerical Rating Scale

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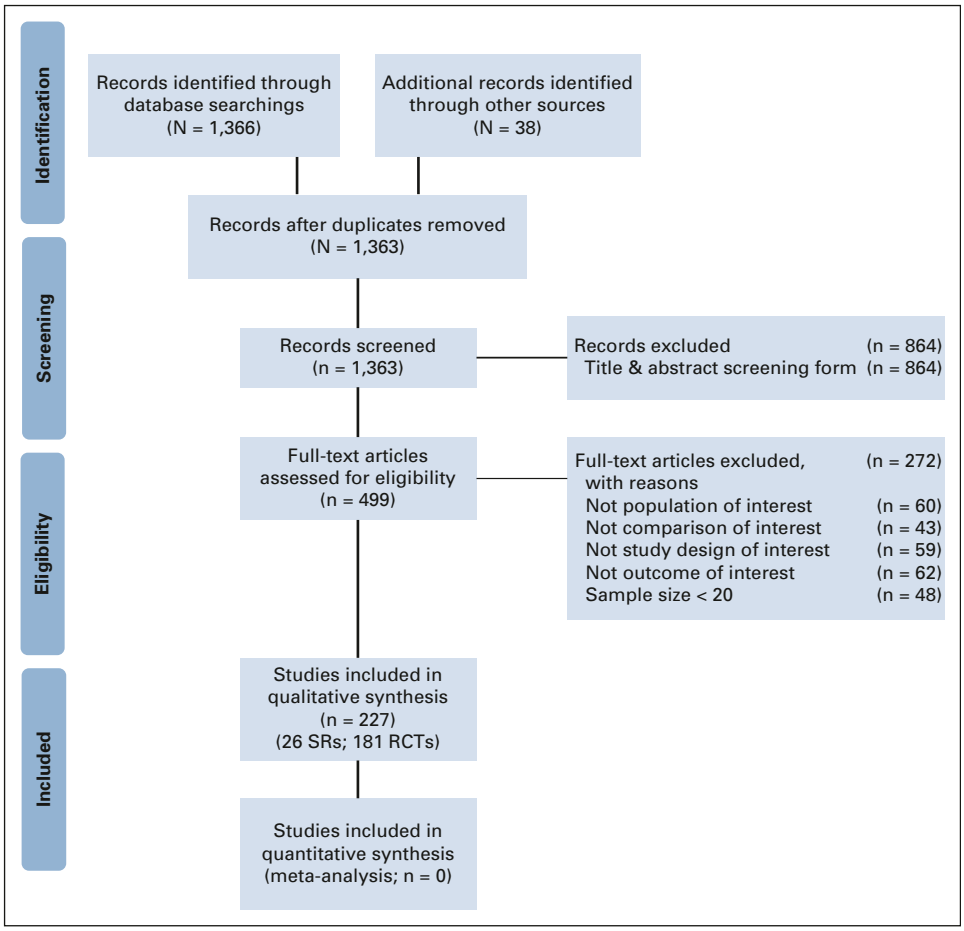

FIG 1. Systematic review flow diagram. RCT, randomized controlled trial; SR, systematic review.

(NRS), etc. Characteristics of the included studies are in the Data Supplement, and Figure 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for the SR. Table 1 includes a breakdown of the included studies by integrative therapies and pain indication, and Table 2 includes studies on interventions with insufficient or inconclusive evidence to inform recommendations.

Study Quality Assessment

Study design aspects related to individual study quality, quality of evidence, strength of recommendations, and risk of bias were assessed for the 227 intervention studies identified. SRs and meta-analyses were assessed for quality using the assessment of multiple systematic reviews (AMSTAR) tool.[252] Design elements, such as blinding, allocation concealment, sufficient sample size, intention-to-treat, and funding sources, were assessed for RCTs using the Cochrane Risk-of-Bias tool.[26] Overall, the included SRs were conducted using established methods; however, many of the primary studies included in these reviews suffered from flaws and/or limitations in study design. Ultimately, we used the SRs as one of the means to identify relevant primary studies. Additional RCTs identified and included in this guideline ranged from low to high overall risk of bias in one or more key domains. Some of the flaws in the study design included lack of blinding; incomparable control arms, small sample sizes and/or high attrition rates; and limited statistical power, all of which lowered the confidence in the findings. The included studies were also heterogeneous with respect to patient populations, sample size, methodologic quality, treatment duration, and outcome measures. The primary outcomes varied across studies and, in most 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 descriptive review was performed. Refer to the Data Supplement for quality rating scores and the Methodology Manual for more information and for definitions of ratings for overall potential risk of bias.

RECOMMENDATIONS

Aromatase Inhibitor–Related Joint Pain

Recommendation 1.1. Acupuncture should be offered to patients experiencing AI-related joint pain in breast cancer

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TABLE 2. Studies on Interventions With Insufficient or Inconclusive Evidence to Inform Recommendations

Intervention	Study Type	No.	Pain Symptom Categories
Adult population			
Music therapy	RCTs	13	General cancer pain[112-115] Procedural or surgical pain[116-123] Pain during palliative care[124]
Guided imagery and PMR	RCTs	2	Procedural or surgical pain[125] Pain during palliative care[126]
Meditation	RCTs	7	Procedural or surgical pain[127-130] Pain during palliative care[131-133]
Hypnosis	RCTs	4	Pain during palliative care[134-136] Pain during radiation therapy[137]
Reflexology	RCTs	1	Procedural or surgical pain[138]
Massage	RCTs	4[a]	Procedural or surgical pain[69,139-141]
VR therapy	RCTs	2	General cancer pain[142] Surgical pain[143]
Natural products	SRs	4	Oral mucositis[144-147]
Honey	RCTs	19	Oral mucositis[148-166]
Chamomile	RCTs	2	Oral mucositis[167,168]
Propolis	RCTs	3	Oral mucositis[169-171]
Glutamine	RCTs	16	Oral mucositis[172-185] CIPN[186,187]
Curcumin	RCTs	3	Oral mucositis[188-190]
Omega-3 fatty acids	RCTs	4	AI-related joint pain[191-193] CIPN[194]
Teas	RCTs	2	Oral mucositis[195,196]
Mouthwash	RCTs	6	Oral mucositis[197-202]
Others natural products	RCTs	27	AI-related joint pain[203-205] General cancer pain[206-209] CIPN[210] Oral mucositis[211-229]
Vitamin D	RCTs	2	AI-related joint pain[230,231]
Kampo	RCTs	3	General cancer pain[232-234]
Aromatherapy	RCTs	5	General cancer pain[235-237] Procedural or surgical pain[238] Pain during palliative care[239]
Pediatric population			
Hypnosis	RCTs	4	Procedural or surgical pain[240-243]
Meditation	RCTs	1	Procedural or surgical pain[244]
Music therapy	RCTs	1	Procedural or surgical pain[245]
VR therapy	RCTs	2	Procedural or surgical pain[246,247]
Vitamins/natural products	RCTs	5[a]	Oral mucositis[226,248-251]

Abbreviations: AI, aromatase inhibitor; CIPN, chemotherapy-induced peripheral neuropathy; PMR, progressive muscle relaxation; RCT, randomized controlled trial; SR, systematic review; VR, virtual reality.

[a]Some studies overlap between interventions.

(Type: Evidence based, benefits outweigh harms; Evidence quality: Intermediate; Strength of recommendation: Moderate).

Literature review. Four SRs and five RCTs were conducted in the area of acupuncture and AI-related joint and muscle pain.[19,27-30,44-47] The most definitive evidence is from a phase III sham-controlled RCT conducted among 226 patients with moderate to severe AI-related joint pain.[19] After 6 weeks, true acupuncture reduced pain significantly more than sham acupuncture and standard of care (waitlist

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TABLE 3. Summary of Recommendations

Integrative Intervention	Type of Recommendation	Quality of Evidence	Level of Obligation	Benefit/Harm	Strength of Recommendation
AI-related joint muscle pain					
Acupuncture/acutherapy	Evidence based	Intermediate	Should	Benefit outweighs harm	Moderate
Breathing exercises Hatha and restorative yoga postures Meditation	Evidence based	Low	May	Benefit outweighs harm	Weak
General cancer pain/musculoskeletal pain					
Acupuncture/acutherapy	Evidence based	Intermediate	May	Benefit outweighs harm	Moderate
Reflexology	Evidence based	Intermediate	May	Benefit outweighs harm	Moderate
Massage	Evidence based	Low	May	Benefit outweighs harms	Moderate
Yoga	Evidence based	Low	May	Benefit outweighs harm	Weak
Guided imagery + PMR	Evidence based	Low	May	Not assessable	Weak
CIPN					
Acupuncture/acutherapy	Evidence based/informal consensus	Low	May	Not assessable	Weak
Reflexology	Evidence based	Low	May	Benefit outweighs harm	Weak
Procedural pain					
Hypnosis	Evidence based	Intermediate	May	Benefit outweighs harm	Moderate
Surgical pain					
Acupuncture/acutherapy	Evidence based/informal consensus	Low	May	Benefit outweighs harm	Weak
Music therapy	Evidenced based	Low	May	Benefit outweighs harm	Weak
Pain during palliative care					
Massage	Evidence based	Intermediate	May	Benefit outweighs harms	Moderate

Abbreviations: AI, aromatase inhibitor; CIPN, chemotherapy-induced peripheral neuropathy; PMR, progressive muscle relaxation.

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control; 2.05, 1.07, and 0.99 points, respectively, on a 0-10 point NRS). After 6 weeks, there were more responders who had a clinically meaningful change in pain (a two-point reduction on a 0-10 scale)[253] in the true acupuncture group compared with the sham and waitlist control groups (58%, 33%, and 31% respectively).

Recommendation 1.2. Yoga may be offered to patients experiencing AI-related joint pain in breast cancer (Type: Evidence based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Literature review. In one RCT (N = 142),[254] a 4-week yoga intervention was compared with a waitlist control among breast cancer survivors currently receiving hormone therapy (including AIs or tamoxifen) and who reported moderate to severe pain, muscle aches, and body aches (> 2 on 0-4 scale) at baseline. Compared with women randomly assigned to wait-list control, a significantly greater proportion of women randomly assigned to yoga had reductions in total body aches (yoga 88.0% *v* control 56.7%; $P = .02$), while there was a trend for pain (yoga 57.1% *v* control 37.1%; $P = .09$). Limitations of this trial include the analysis of pain as a secondary outcome as the parent trial was powered for insomnia.[254]

Clinical interpretation. Since AI-related joint pain affects up to 50% of women on this class of drugs and negatively affects quality of life and adherence to hormonal treatment, we recommend that acupuncture should be used for management of this painful condition. Our recommendation is based on the available evidence for managing this challenging condition and clinical importance of this issue. Many studies showed joint pain results in nonadherence to AIs[7,8] and such behavior can lead to increased recurrence and mortality for women with breast cancer.[255] Funding to study nonpharmacologic approaches to pain and symptom management is highly limited partly because of the lack of industry support. To date, only acupuncture, duloxetine,[256] and supervised exercise[257] have been found to improve AI-induced pain in large RCTs[258] but only one large definitive trial for each intervention has been conducted. Despite the recommendation, the decision to use acupuncture with other treatments for AI-related pain needs to be based on patient preference, benefit versus risk for each therapy, and availability of and access to the treatment modality. Yoga, other mind-body therapies, and natural products require additional well-conducted RCTs to increase the quality of evidence to inform a change in the level of recommendation, if warranted.

General Cancer Pain or Musculoskeletal Pain

Recommendation 1.3. Acupuncture may be offered to patients experiencing general pain or musculoskeletal pain from cancer (Type: Evidence based, benefits outweigh harms; Evidence quality: Intermediate; Strength of recommendation: Moderate).

Literature review. Eight RCTs investigated the effect of acupuncture on general cancer pain or general musculoskeletal pain among patients with cancer.[20,48-54] Among them, only one RCT had a large sample size,[20] with 360 patients allocated in a 2:1:1 ratio into electroacupuncture (EA), auricular acupuncture (AA), and UC. It showed that EA reduced pain by 1.9 points on a 0-10 NRS, and AA reduced pain by 1.6 points compared with UC at the end of treatment. In addition, the treatment effects were durable at six months from random assignment. Both EA and AA were associated with minimal toxicities, although more patients withdrew early from the AA group because of ear pain.[20] Given the large sample size and large effect size, although there was no blinded sham control, the committee determined that patients may consider using acupuncture to manage chronic musculoskeletal pain.

Recommendation 1.4. Reflexology or acupressure may be offered to patients experiencing pain during systemic therapy for cancer treatment (Type: Evidence based, benefits outweigh harms; Evidence quality: Intermediate; Strength of recommendation: Moderate).

Literature review. There were seven randomized trials, evaluating the effectiveness of reflexology to reduce pain during systemic therapy (chemotherapy, chemoradiotherapy, targeted, and/or hormonal therapy) with six trials showing significantly less pain in the intervention group compared with the controls.[92-96,98] These studies included patients with different cancer types and used different methods to implement the reflexology intervention that was provided (provided by a reflexologist,[92,93,95-97] administered by a trained caregiver[94,98]). Four trials included fewer than 50 patients per arm, but three trials included more than 90 patients per arm.[94,97,98] The type of control varied between trials (attention control,[94,98] usual or standard care,[95-97] and other active treatment such as relaxation) and two trials[94,97] blinded patients to the group assignments.

Recommendation 1.5. Massage may be offered to patients experiencing chronic pain following breast cancer treatment (Type: Evidence based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Moderate).

Literature review. In a SR and meta-analysis,[101] five randomized trials with a total of 127 patients with chronic musculoskeletal pain after breast cancer treatment were included. Three studies were of high methodologic quality and in one study, patients were blinded for the intervention. The trial interventions included myofascial induction, myofascial release, classic massage, ischemic compression of trigger points, and myofascial therapy. Controls used in the trials included an educational session, physical therapy, or sham control. In the massage therapy group, the pain was decreased by a small to moderate effect size (standardized mean difference [SMD] 0.32) compared with the controls. On the basis of

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the available data, massage may be offered to decrease pain intensity in women who have completed surgical treatment, chemotherapy, and/or radiation therapy for breast cancer.

Recommendation 1.6. Hatha yoga may be offered to patients experiencing pain after treatment for breast or head and neck cancers (Type: Evidence based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Literature review. Two RCTs evaluated hatha yoga for musculoskeletal pain among patients' postcancer treatment: One RCT for musculoskeletal pain associated with head and neck cancer[76] (N = 40) and the second evaluated hatha yoga for musculoskeletal pain among patients with breast cancer (N = 42).[77] Both trials had small sample sizes, and follow-up assessments were completed at similar intervals (8 weeks, 2.5 months). In one trial, statistically significant differences were observed among patients with head and neck cancer on the BPI (short form), including in patterns of change in pain ($P < .001$, SMD = 0.90), and pain interference with activities of daily living (BPI Interference, $P = .005$, SMD = 0.67). In the second trial among patients with breast cancer, the yoga group demonstrated significant improvement in shoulder and arm pain severity from baseline to post-treatment ($P = .01$ and $P = .01$, respectively). Pain reduction was maintained at 2.5 months post-treatment ($P = .01$ and $P = .01$, respectively). However, the control group demonstrated no significant difference between pretreatment and post-treatment pain levels. These findings provide preliminary evidence supporting the efficacy of hatha yoga for pain after head and neck or breast cancer treatment, although given the small sample sizes and lack of attention controls, the quality of the evidence is low.

Recommendation 1.7. Guided imagery with progressive muscle relaxation (PMR) may be offered to patients experiencing general pain from cancer treatment (Type: Evidence based, benefits and harms not assessable; Evidence quality: Low; Strength of recommendation: Weak).

Literature review. Four RCTs were identified for evaluation of guided imagery and PMR for patients experiencing pain because of a cancer diagnosis.[80,81,125,126] These studies included multiple types of cancers, and two of these studies included intervention arms that included only 20 participants.[81,125] One included an intervention arm of approximately 100 participants.[126] The largest and one of the smaller studies reported decreased pain levels with the intervention compared with the control. One of the studies used audio recorded instruction of PMR and mental imagery as well as live instruction and a control group. Blinding of participants, health professionals, data collectors, and data analysts was inconsistent. These factors adversely affected study quality overall. With only some favorable findings, overall lack of safety data, and quality concerns, guided imagery and PMR may be offered to patients experiencing cancer-related pain, but the strength of the recommendation is weak.

Clinical interpretation. General cancer pain and musculoskeletal pain are common among patients with cancer and can persist even years after cancer treatment. Management of pain requires an interdisciplinary approach that includes pharmacologic treatments (both nonopioid and opioid drugs depending on the severity), physical therapy, and psychotherapy. There is moderate evidence that acupuncture can be used to manage general cancer pain or chronic musculoskeletal pain. In addition, reflexology can be incorporated into systemic cancer treatment. The other integrative medicine interventions, despite some demonstrating promising preliminary results, have low level of evidence because of limited research and methodologic challenges; therefore, more rigorous research is needed.

Chemotherapy-induced Peripheral Neuropathy

Recommendation 1.8. Acupuncture may be offered to patients experiencing CIPN from cancer treatment (Type: Evidence based-informal consensus, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Literature review. There were two SRs[31,32] and seven RCTs[56-62] with small sample sizes investigating the effect of acupuncture on CIPN. No major toxicities were reported in any studies, and most studies showed a benefit of acupuncture for CIPN pain. In a phase II trial (N = 75), acupuncture was associated with significant reduction in CIPN pain, whereas sham acupuncture and UC were not (1.75, 0.91, and 0.19 points, respectively, on a 0-10-point NRS). However, the small sample sizes and high or unclear risk of biases in the studies resulted in low level of evidence.[62]

Recommendation 1.9. Reflexology or acupressure may be offered to patients experiencing CIPN from cancer treatment (Type: Evidence based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Literature review. Two small RCTs with approximately 30 patients per arm evaluated the effectiveness of reflexology for reducing CIPN symptoms, including pain, compared with the control.[99,100] One trial in patients with multiple cancers compared the effects of reflexology foot massage twice a day for 20 minutes over 6 weeks to standard hospital care.[99] This study found improvement in sensory functions in the reflexology group compared with the control group but no group differences for peripheral neuropathy-related pain severity and incidence. The second study was in patients with gynecologic cancers and tested a self-care reflexology approach.[100] Patients in the intervention group were trained to perform aromatherapy self-foot reflexology (three times a week, for 15 minutes on each foot, 18 sessions over a period

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of 6 weeks) and were compared with a waitlist control. The intervention group showed lower levels of peripheral neuropathy symptoms, less interference with daily activities, and higher peripheral skin temperature level. In addition, the self-foot massage seemed to have had a positive effect on mood symptoms. Furthermore, side effects were not reported in either study or, therefore, the potential benefits likely outweigh the potential harms.

Clinical interpretation. CIPN is a highly common, persistent, and debilitating toxicity that not only negatively decreases quality of life but also increases risk for falls.[259] Duloxetine provides modest effect for CIPN pain,[23] but it has side effects poorly tolerated by some patients. On the basis of preliminary efficacy and favorable risk-benefit ratio, acupuncture may be recommended. A phase III acupuncture for CIPN trial is ongoing and will help more definitively clarify the role of acupuncture for this debilitating painful condition (ClinicalTrials.gov identifier: NCT04917796). In addition, albeit with low levels of evidence, aromatherapy self-foot-reflexology may be considered part of self-care for some patients for CIPN pain to improve patients' self-efficacy and to empower them to be more active participants during their cancer care; larger trials would be needed for evidence-based recommendations.

Surgical or Procedural Pain

Recommendation 1.10. Hypnosis may be offered to patients experiencing pain during cancer treatment procedures or diagnostic workups (Type: Evidence based, benefits outweigh harms; Evidence quality: Intermediate; Strength of recommendation: Moderate).

Literature review. Five studies have evaluated the use of hypnosis during procedures,[87-91] including three with methodologic weaknesses and two well-designed studies with an attention control as well as a standard-of-care arm.[88,91] The two most rigorous trials with more than 200 randomly assigned participants each evaluated hypnosis for large core breast biopsies[91] and tumor embolization or radiofrequency ablation.[88] Both studies demonstrated significantly lower pain ratings compared with control arms with a median reduction of ≥ 2 (0-10 point scale) reported during the procedure. On the basis of these two trials, hypnosis may be recommended to help manage pain during procedures. Importantly, both studies involved hypnosis provided throughout the procedure, not just for a short time before the procedure.

Clinical interpretation. Procedures such as biopsy or tumor embolization play an important role in diagnosis and treatment of cancer. However, they are associated with acute pain and frequently require management with intravenous or oral pain medications that have a few side effects. There is moderate evidence for self-hypnosis to be taught and used to prevent treatment procedure-related pain. However, for the other interventions such as mindfulness-based interventions, music therapy, and virtual reality–based imagery interventions, despite their appeal and potential effect, research is very much needed to establish a robust evidence base.

Recommendation 1.11. Acupuncture or acupressure may be offered to patients undergoing cancer surgery or other cancer-related procedures such as bone marrow biopsy (Type: Evidence based-informal consensus, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Literature review. There were 12 RCTs assessing the effect of acupuncture or acupressure in reducing pain associated with surgery or procedure.[64-75] They are all limited by small sample sizes and an unclear or high risk of bias. Among them, two involved acupressure for bone marrow aspiration and biopsy pain,[64,65] one was on acupuncture and mastectomy pain,[66] and nine were on postoperative pain.[67-75] The two acupressure and bone marrow aspiration and biopsy pain RCTs showed that acupressure significantly reduced the proportion of patients who experienced severe pain than sham acupressure (2.7% *v* 20%, $P = .03$),[64] and acupressure resulted in the lowest procedural pain score when compared with sham acupressure or sham ($P = .001$).[65] A trial of acupuncture for mastectomy pain (N = 30) showed that acupuncture significantly reduce pain, nausea, and anxiety in the first 2 postoperative pain days when compared with UC.[66] Among the nine RCTs on acupuncture versus control groups to reduce postoperative pain, six trials showed no statistical difference between the two groups, and three showed acupuncture treatment resulted in lower pain score.[68-70] Adequately powered and well-designed trials are needed to establish the definitive efficacy of acupuncture. Although the quality of evidence was deemed low, the benefit seems to outweigh the risk; therefore, the panel determined that patients may explore use of acupuncture or acupressure to reduce surgical and procedure-related pain.

Recommendation 1.12. Music therapy may be offered to patients experiencing surgical pain from cancer surgery (Type: Evidence based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Literature review. Although all the three studies in this section demonstrated a significant effect of music therapy to improve surgical pain scores more than UC, quality of evidence is low as two trials showed high risk of bias[117,118] and one was a small study to test the hypothesis.[116] A trial of 60 patients undergoing lung cancer resection indicated potential association between music therapy and the need for less analgesic medication, including opioid drugs.[118] The smallest study of 30 mastectomy patients used a high-dose (4 hours of recorded music) music therapy intervention and found the music therapy group experienced a 41.4% less increase in pain from time 1 (preoperative) to time 2 (postoperative) compared with women in the control.[116] Similarly, a trial of 120 women with breast cancer undergoing radical mastectomy surgery in China

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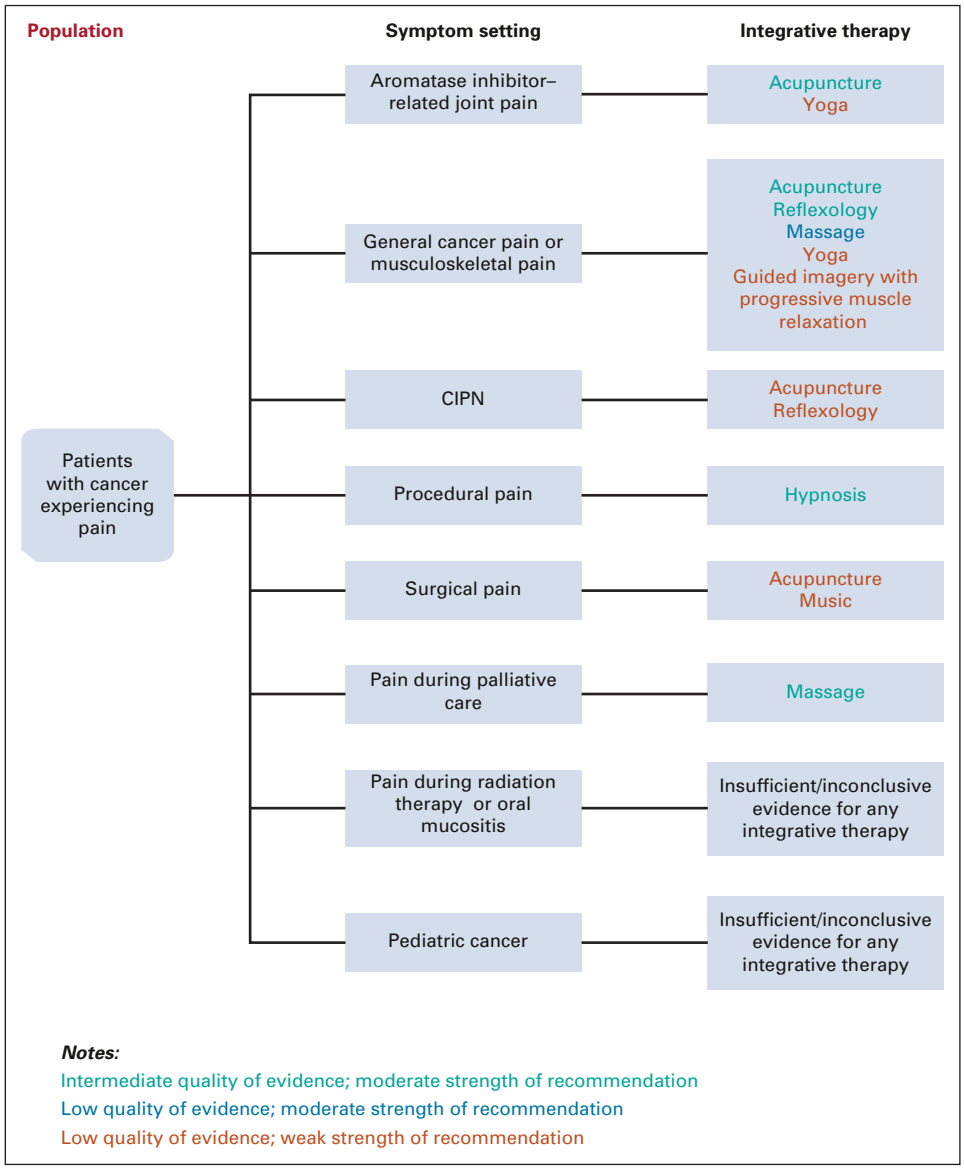

FIG 2. Treatment algorithm. CIPN, chemotherapy-induced peripheral neuropathy.

found a statistically significant improvement in the primary end point (change in Pain Rating Index scores from baseline [the first day after radical mastectomy (pretest)]) for the music therapy group compared with the control group (–2.38 (95% CI, –2.80 to –1.95), $P < .001$) at the first post-test (evaluation on the day before discharge from hospital). This improvement remained significant, although the difference narrowed, at the third post-test (evaluation on the day of admission for second chemotherapy session).

Clinical interpretation. Cancer surgery is associated with acute pain and can also lead to chronic pain. The primary mode of pain management during the perioperative or postoperative periods involves anesthesia, opioid, and nonopioid drugs. Despite the preliminary evidence and potential value of several integrative medicine interventions such as acupuncture, music therapy, or massage, the quality of research evidence is low and insufficient. Adequately powered clinical trials evaluating the effectiveness of these interventions in the perioperative or postoperative settings are needed to guide further recommendations.

Pain During Palliative Care

Recommendation 1.13. Massage may be offered to patients experiencing pain during palliative and hospice care (Type: Evidence based, benefits outweigh harms; Evidence quality: Intermediate; Strength of recommendation: Moderate).

Literature review. A SR from 2009 assessing 14 low-quality trials concluded (on the basis of four trials) that there is encouraging evidence that massage can alleviate pain in

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palliative cancer patients with various types of cancers.[103] A more recent SR from 2020 included three RCTs evaluating the effectiveness of massage for pain in patients receiving palliative treatment, all of them showing favorable results for massage.[40] Although two studies included smaller samples (10-20 patients per arm), the third trial was a high-quality large multicenter trial[21] that was also included in the previous SR. A total of 380 adults with various types of advanced cancers who were experiencing moderate-to-severe pain were included (90% were enrolled in hospice) and randomly assigned to massage or simple touch sessions (six 30-minute sessions over 2 weeks). The intervention included gentle gliding stroke; squeezing, rolling, and kneading the muscles; and trigger point release, while the control group received simple touch. Immediate outcomes were obtained just before and after each treatment session on a 0- to 10-point scale (Memorial Pain Assessment Card), and sustained outcomes (including BPI) were obtained at baseline and weekly for 2 weeks. Massage seems to have an immediate beneficial effect on pain reduction (mean difference, 0.90; $P < .001$), and no side effects were observed. No between-group mean differences occurred over time in the sustained measurements of pain. On the basis of the available favorable data from multiple trials, massage may be offered to patients experiencing pain during palliative and hospice care.

Clinical interpretation. Effective pain management is a central component in providing high-quality palliative care. On the basis of moderate evidence, massage can be incorporated into palliative and hospice setting to provide short-term pain relief and enhance coping for patients living with advanced cancer. The research is very limited in both quantity and quality for other interventions to make sound recommendations for pain management in this population. Chronic pain management in cancer survivorship is also essential for improving quality of life and functional recovery. With the ongoing opioid epidemic in the United States, Canada, and other countries, rigorous research and appropriate implementation and integration of nonpharmacologic interventions (eg, acupuncture, yoga, and massage) even as first-line pain management is needed for the growing population of cancer survivors.

Figure 2 provides a visual representation of these recommendations in the treatment algorithm. Table 3 shows the breakdown of the summary of recommendations.

EVIDENCE SUMMARY OF INTERVENTIONS WITH INSUFFICIENT OR INCONCLUSIVE EVIDENCE TO INFORM AN ACTIONABLE RECOMMENDATION

Adult Population

Natural products for AI-related joint pain. There is insufficient evidence to recommend for or against use of omega-3 fatty acids, Yi Shen Jian Gu granules, or topical pure emu oil to manage AI-related pain. Four trials tested the effects of natural products on the treatment of AI-induced pain in patients with breast cancer. Two randomized, placebo-controlled trials tested the effects of omega-3 fatty acids on the prevention and treatment of AI-induced musculoskeletal pain.[191,192] The first trial was a large multisite trial that tested the effects of omega-3 fatty acids on reducing AI-induced musculoskeletal pain in women with a history of breast cancer (N = 262).[192] In this trial, improvements were observed in both the omega-3 fatty acid and placebo (soybean or corn oil) arms with no differences between groups. The second trial was a smaller pilot and feasibility trial, again testing the effects of omega-3 fatty acids on preventing AI-induced arthralgias in patients with breast cancer (N = 44) and found no differences in pain severity between groups.[191] One trial tested the effects of a combination of Chinese herbal formulation Yi Shen Jian Gu granules,[203] while another tested topical pure emu oil.[204] The emu oil did not yield differences compared with the placebo. However, the women who received Yi Shen Jian Gu (n = 40) appeared to have improved pain at 12 and 24 weeks. Given that there was only one trial of each treatment intervention with relatively small sample sizes, there are insufficient data to make a clinical recommendation.

General cancer pain.

Music therapy. There is insufficient evidence to recommend for or against the use of music therapy for patients experiencing general cancer pain. Of the three studies identified, only two trials specified pain as a primary outcome and were, therefore, reviewed.[114,115] These two trials did not contribute evidence of music therapy as effective for generalized oncology pain because of methodologic flaws. One RCT compared one-time 30-minute sedative music therapy, instrumental intervention versus UC for 126 inpatient oncology patients experiencing levels of pain rated three and greater on a 0-10 numerical rating scale.[114] The music therapy intervention included self-selected music styles intended for relaxation or distraction. The other study compared music therapy (passive listening to instrumental music) to poetry (listening to spoken-word poetry) in a three-arm trial with the control group receiving usual inpatient care.[115] Use of opioid analgesics and nonsteroidal anti-inflammatory drugs were reported for both groups, with no significant difference of use between groups. Primary outcomes were changes in daily pain levels over the 3 days during which music or poetry was offered. Both intervention groups showed statistically significant improvements in perceptions of pain, which may indicate that it was the distraction provided by the interventions that was sufficient to decrease perception of pain, and not effects specific to music therapy.

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Herbal products. There is insufficient evidence to recommend for or against the use of Xiao Zheng Zhitong paste, Jinlongshe granule, Shuangbai San paste, or Xiao-Ai-Tong decoction for general cancer pain. Four trials tested the effects of Chinese herbal preparations on treating general cancer pain, including Xiao Zheng Zhitong paste in patients with a range of different cancer types,[207] Jinlongshe granules in patients with gastric cancer,[208] Shuangbai San paste in patients with liver cancer,[209] and Xiao-Ai-Ton decoction with and without morphine in patients with a range of different cancer types.[206] Given that there was only one trial of each treatment intervention, variability in quality of the trials, there are insufficient data to make a clinical recommendation.

Chemotherapy-induced peripheral neuropathy.

Natural products. There is insufficient evidence to recommend for or against the use of omega-3 fatty acids, and glutamine to patients experiencing CIPN from cancer treatment. A single moderate-size randomized, double-blind, placebo-controlled trial (N = 69) tested the effects of omega-3 fatty acid on reducing the incidence and severity of peripheral neuropathy in patients with breast cancer receiving paclitaxel chemotherapy.[194] Trial results showed that patients receiving the omega-3 fatty acids were less likely to develop peripheral neuropathy, but there were no differences in severity of neuropathy and motor nerve conduction measurements. Although the trial results are intriguing, subsequent trials need to replicate and confirm these findings before a clinical recommendation can be made.

Two RCTs tested the effects of glutamine on the incidence and severity of peripheral neuropathy.[186,187] The first trial was a moderate-size (N = 86) trial comparing oral levo-glutamine compared with no intervention in patients with colorectal cancer receiving oxaliplatin.[186] Patients who received levo-glutamine had lower incidence and severity of peripheral neuropathy symptoms; however, the trial did not control for placebo effects. The second smaller trial (N = 43) compared oral glutamate to placebo in women with ovarian cancer receiving paclitaxel.[187] There were no differences between groups in incidence of peripheral neuropathy; patients who received glutamate reported lower pain severity. No clinical recommendations can be made on the basis of these results because of low study quality and/or small sample size.

Surgical or procedural pain.

Meditation-based interventions. There is inconclusive evidence to recommend for or against the use of meditation-based interventions to patients with breast cancer experiencing procedural pain. Four RCTs evaluated meditation or mindfulness-based interventions for patients experiencing procedural pain for breast cancers.[127-130] Two studies examined loving-kindness meditation versus music intervention versus UC, and showed loving-kindness meditation's superiority to UC, but not to music.[129,130] The third study examined guided meditation plus massage versus massage alone, and showed no significant difference between study arms.[128] The fourth study was composed of three arms comparing guided mindfulness-based meditation to guided focused breathing and standard of care in women scheduled for stereotactic breast biopsy.[127] The result of this study was also negative. All four studies were relatively small in size ($n < 50$ per arm). The mixed findings suggest that meditation-based therapies are not superior to active control conditions, but it is likely that these studies were underpowered. In the absence of fully powered trials, there are no clear indications for meditation-based therapies for patients experiencing procedural pain for breast cancers.

Music therapy. There is inconclusive evidence to recommend for or against the use of music therapy to patients experiencing procedural pain. The five trials reviewed[119-123] showed either no effect[119,123] or suffered from various methodologic flaws, including weak music therapy interventions,[122] high risk of bias in trial methodology,[121] inadequate assessment and reporting of pain scores,[121,122] and inconsistent tracking of analgesic or anxiolytic medication provided during the intervention period.[120,121] These studies, therefore, yielded results insufficient to determine the effect of music therapy on procedural pain.

Reflexology. There is insufficient evidence to recommend for or against the use of reflexology for pain associated with surgery or procedure. There is only one small, randomized trial[138] (n = 31 patients per arm) in patients with gastric or liver cancer who received major abdominal surgery evaluating the effectiveness of foot reflexology compared with a control. The foot reflexology was provided at least 24 hours after surgery by a trained reflexologist (10 minutes on each foot for 3 consecutive days). The control group received routine care. The results were inconclusive; although there was no significant group difference for the McGill Pain Questionnaire, the VAS showed a difference in favor of the intervention group. The present data are insufficient to recommend the use of reflexology for pain associated with cancer-related surgery or procedures.

Hypnosis. There is inconclusive evidence to recommend for or against the use of hypnosis in treating surgical pain in patients with cancer. Two studies evaluated hypnosis for surgical pain with inconsistent results.[84,85] Montgomery et al[85] randomly assigned 200 patients with breast cancer scheduled for excisional biopsy or lumpectomy to 15-minute hypnosis intervention before surgery versus an attention control. Subjects in the hypnosis group reported less pain intensity (means = 22.43 *v* 47.83; difference = 25.40; 95% CI, 17.56 to 33.25) and pain unpleasantness

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(means = 21.19 *v* 39.05; difference = 17.86; 95% CI, 9.92 to 25.80). Hypnosis also led to decreased utilization of propofol and lidocaine compared with controls. The second study allocated 150 patients with breast cancer scheduled for minor breast surgery to hypnosis (≤ 15 minutes) versus UC control.[84] The study found increased mean pain in the hypnosis arm (2.63, standard deviation 1.62) versus control (1.75, standard deviation 1.59; $P = .004$) on a pain VAS (0-10). Despite the large and well-designed clinical trials, the inconsistent results make any conclusions impossible at this time.

Massage. There is inconclusive evidence to recommend for or against the use of massage for peri-postoperative pain from major surgical procedures in breast and gynecologic cancer. There were two RCTs evaluating the effectiveness of massage for pain reduction after major surgical procedures in patients with breast cancer. A small trial with 19 patients per arm undergoing autologous tissue reconstruction showed no extra benefits in the massage group compared with controls.[128] Another trial with 30 patients per arm undergoing lymph node dissection evaluated the effectiveness of postsurgical arm massage provided by the patient's significant other.[139] The intervention group reported less pain in the immediate postoperative period than the control group that received no massage. A three-armed trial analyzed 35 women per arm with gynecologic cancers and compared Swedish massage with vibration and UC as additional treatment to postoperative pain medication.[141] The interventions were applied for 3 consecutive days after surgery. Massage showed only minor effects on short-term sensory and affective pain. On this basis, the data are inconclusive to recommend massage for peri-postoperative pain following major surgical procedures in patients with breast and gynecologic cancer.

There is also insufficient evidence to recommend for or against the use of massage for pain from minor surgical procedures. There are very little data evaluating the effectiveness of massage to improve pain from minor surgical procedures. In a pilot trial with 2:1 random assignment, 40 patients received a 20-minute massage before and after the surgical placement of a vascular access device (port) and 20 patients received attention control.[140] No relevant differences in postsurgical pain were observed between both groups. The available data are insufficient to recommend massage for pain following minor surgical procedures.

Pain from survivorship and palliative care.

Meditation-based interventions. There is inconclusive evidence to recommend for or against the use of meditation-based interventions to patients experiencing pain after treatment or survivorship for breast cancers. Three RCTs evaluated meditation-based interventions for patients experiencing pain after treatment or survivorship for breast cancer or bone cancer.[131-133] One study was relatively small (n < 50 per arm),[133] reporting superiority of Mindfulness-Based Stress Reduction (MBSR) plus music therapy over a waitlist control for reducing pain intensity in osteosarcoma. The other two studies were moderately large (n > 50 per arm),[131,132] with one study demonstrating the superiority of Mindfulness-Based Cognitive Therapy over a waitlist control for reducing late post-treatment pain intensity in women with breast cancer.[132] By contrast, the other trial (the largest meditation-based intervention trial evaluated in this review, N = 322) showed no effect of MBSR over a waitlist control for chronic pain in breast cancer survivors who completed treatment.[131] The null effect in this trial may be associated with low baseline pain or the high heterogeneity of the sample (women had completed treatment between 2 weeks to 2 years before study enrollment). Adverse events were not reported for all four studies. Given these mixed findings, and the lack of safety data, there are no clear indications for meditation-based intervention for patients experiencing pain following treatment or survivorship for breast or bone cancers.

Hypnosis. There is inconclusive evidence to recommend for or against the use of hypnosis in treating pain in cancer survivors (active treatment and post-treatment survivors). Studies of hypnosis during cancer survivorship were limited because of significant methodologic issues. Two studies combined hypnosis with another intervention—support group[135] or cognitive behavioral therapy.[134] These studies generally reported positive benefits; however, interpretation is limited because of the combination approach. A study randomly assigned patients receiving a bone marrow transplant to hypnosis training, cognitive behavioral coping, therapist contact, and UC.[136] The patients in the hypnosis arm attended two prehospital sessions and then received taped recordings for daily practice while in the hospital. Descriptive results showed lower oral pain in the hypnosis group but were limited by the small numbers in each group (10-12 in each arm). Therefore, this area could benefit from more research with large sample sizes.

Music therapy. There is insufficient evidence to recommend for or against the use of music therapy in treating palliative or chronic pain in patients with cancer. There was only one study reviewed for music therapy for pain in patients receiving palliative care.[124] This trial was conducted as an RCT, but the group designated as control received an effective intervention (MBSR involving deep breathing, visual imagery, and muscle relaxation). Although the study was well designed and blinded, pain scores did not change significantly and both groups improved in relaxation and well-being scores. The dose for the music therapy intervention was low, consisting of the availability of 45 minutes of prerecorded music on a cassette tape player, which most participants in the music therapy group reported listening to only 2-4 times per week. The music therapist met once with each intervention group participant

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to choose the type of music they preferred. The study, therefore, does not support the use of this music therapy intervention for pain during palliative care.

Virtual reality. There is insufficient evidence to recommend for or against the use of virtual reality imagery and relaxation in treating palliative or chronic pain in patients with cancer. Only two studies were identified for the use of virtual reality imagery and relaxation interventions in adults, both for pain during palliative care.[142,143] The first study investigated female patients with breast cancer experiencing pain and receiving analgesic painkillers (intravenous or oral) in a palliative care setting.[142] This trial did not specify the primary outcome, and although both pain and anxiety were assessed, conclusions were that an immersive virtual reality imagery and relaxation intervention is acceptable in an Arab culture (study is from Jordan), and that virtual reality holds promise as an effective distraction intervention for managing pain and anxiety among this study population.[142] The second trial also only studied female patients with breast cancer who had undergone breast cancer surgery.[143] Both intervention and control groups received upper-extremity physiotherapy, with the intervention group adding an Xbox 360 Kinect technology-based gamification of physiotherapy for weeks 2 through 5 in addition to some additional physiotherapy exercises. Both groups experienced statistically significant improvement over time with no differences between groups.

Pain during radiation therapy and/or oral mucositis.

Hypnosis. There is inconclusive evidence to recommend for or against the use of hypnosis in treating radiotherapy-induced pain in patients with cancer. For radiotherapy, only one study has been published.[137] This study randomly assigned 68 patients with head and neck cancer receiving radiotherapy to a single 20-minute session of hypnosis or UC. The hypnosis treatment demonstrated significantly lower pain scores –1.966 (95% CI, –2.260 to –1.673; $P < .001$) compared with controls. This study should be considered hypothesis-generating.

Honey. There is inconclusive evidence to recommend for or against the clinical use of honey for oral mucositis. Nineteen trials tested the effects of honey on the prevention and/or treatment of oral mucositis.[148-166] The results across trials are inconsistent and, thus, it is not possible to make a conclusive recommendation. Study populations included patients with head and neck cancer receiving radiation (some of whom also received chemotherapy),[149-159,165] patients with acute myeloid leukemia receiving chemotherapy,[160] patients with chemotherapy-induced oral mucositis,[163] patients with radiation therapy-induced oral mucositis,[164] and patients with lung cancer receiving chemotherapy and radiation therapy.[166] No two trials used the same honey preparation, dose, mode, and/or timing of delivery. Some studies did suggest that the studied honey preparation did provide some benefit, although the size and quality of the studies limit the ability to draw definitive conclusions. The largest and most rigorously designed trial was a three-arm trial conducted within the National Clinical Trials Network NRG Oncology clinical trial network that tested the effects of standard supportive care, liquid manuka honey, and manuka honey lozenges in preventing radiation esophagitis in patients with lung cancer. Neither honey arm was superior to supportive care in preventing radiation esophagitis; however, the honey preparation in this trial was irradiated, which may have inhibited the beneficial effect of bacteria within the honey. Because of the heterogeneity of interventions and outcomes, the data are inconclusive on the use of honey to prevent or treat oral mucositis.

Other natural products. There is insufficient evidence to recommend for or against the clinical use of chamomile, propolis, glutamine, curcumin, teas, mouthwashes, and other herbal combinations. Multiple trials tested a variety of botanical and natural products to prevent and/or treat mucositis in a range of different cancer types receiving different chemotherapy and/or radiation therapy treatments.[167-174,188,189,195-202,211-229] Interventions included chamomile,[167,168] propolis,[169-171] glutamine,[172-185] curcumin,[188-190] botanical teas,[195,196] mouthwashes,[197-202] and other natural products (Data Supplement).[211-229] No two trials used the same formulation. Although some trials suggested that there might be some benefit, most trials did not have clearly defined end points and were not clearly powered to detect differences. Thus, there are insufficient data to make clinical recommendations on the use of these natural products for the prevention and/or treatment of oral mucositis.

Oral mucositis pain represents a challenging toxicity associated with radiation and some chemotherapy agents. The current management often involves topical local anesthetics, opioids, and liquid diets, and in many cases, patients require a gastric tube for adequate nutrition. Despite tremendous unmet needs, the research evidence for integrative medicine (both mind-body and natural products) is low and requires thoughtful investigation to make evidence-informed recommendations.

Pediatric Population

Although we sought out to evaluate the evidence of integrative medicine for pain in pediatric population, there were very few trials in this population. Several small RCTs focused on procedural pain: hypnosis,[240-243] music therapy,[245] and virtual reality[246,247] were conducted. Despite showing acceptability, feasibility, and promising effect in some trials, these studies had substantial methodologic flaws such as lack of appropriate control groups and small sample size; therefore, there is insufficient evidence to support the use of hypnosis, music therapy, and virtual reality in treating procedural pain in pediatric patients with cancer. A number of RCTs evaluated various natural products for oral mucositis pain with honey.[148,161,162] The study populations included pediatric patients receiving methotrexate,[162] and other children receiving chemotherapy and/or radiation therapy.[148,161] The

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results from these studies were inconsistent. Natural products (eg, vitamin E, Traumeel S, pine bark extract, andiroba gel, and propolis) were evaluated in clinical trials as treatment of chemotherapy-induced oral mucositis in children with cancer[226,248-251]; however, these trials were early phase and had limited sample size and poor control groups; therefore, the risk of bias was high; the evidence for these therapies were insufficient or inconclusive.

Pain in children or infants with cancer is common during medical or surgical treatment; however, because of the limited research in this area, no recommendations can be made to incorporate integrative medicine intervention for pain management. Research in alleviating pediatric pain and other symptoms is particularly challenging because of the difficulty in assessing and measuring children's pain, the involvement of parents, which adds complexity, and small sample sizes. However, to provide evidence-informed integrative treatment for children with cancer, novel research methods, carefully developed interventions, and rigorous study design and conduct are needed for children with cancer and their parents.

DISCUSSION

Pain remains a challenging clinical issue for both patients with cancer and health care providers. Effective pain management requires careful consideration of the research evidence for both pharmacologic and nonpharmacologic interventions. On the basis of reviewing 198 RCTs and 26 SRs and meta-analyses, several integrative medicine interventions can be considered for management of pain in oncology settings, using rigorous criteria for the basis of recommendations. Acupuncture should be recommended to manage AI-related joint pain. Acupuncture and reflexology or acupressure may be recommended for general cancer pain and musculoskeletal pain. Hypnosis may be recommended for patients undergoing painful procedures, and massage may be recommended for patients receiving palliative or hospice care. These recommendations were based on at least intermediate quality of evidence and overall appraisal of benefits outweighing potential harms. The use of other integrative medicine interventions for other types of pain currently has low quality of evidence. This guideline provides the evidence base for integrating selected integrative medicine approaches into a comprehensive pain management strategy to improve symptom control and quality of life for patients with cancer and survivors. In addition, the review highlights the gaps in evidence that should inspire future research.

PATIENT AND CLINICIAN COMMUNICATION

Effective communication between health care providers and their patients is essential for patient-centered pain management. It is well documented that physicians rarely inquire about the use of integrative medicine, and patients often do not disclose such use.[260] Health care providers need to have a knowledge base to engage in meaningful communication with their patients about integrative medicine use and provide answers to their questions.[261] The results of a large survey suggest that lack of knowledge about integrative medicine is often the biggest barrier to use by patients, particularly among racial and ethnic minorities and among those with less education.[262,263] Patients with positive beliefs about natural health approaches, higher treatment expectancy, lower barriers, and with family endorsement are likely to prefer integrative medicine over pharmacology to manage pain.[17,263] Facilitating open communication and acknowledging patient values and preferences will enable shared decision making about selecting the most appropriate pain management approach to ensure high-quality care. For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.[264]

HEALTH DISPARITIES

Although SIO-ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care or receive fragmented care. Demographic factors such as race and ethnicity, age, socioeconomic status, sexual orientation and gender identity, geographic location of residence, immigrant status, insurance access, and other social determinants are known to affect cancer care outcomes.[265] The impact of intersectionality is often cumulative and more than simply additive,[17] resulting in knowledge gaps, limited availability to high-quality primary and specialty care, and transportation barriers. These demographic elements are bolstered by structural factors that maintain health inequities in marginalized communities in the United States and other countries. In countries without universal health care, for many patients, the quintessential barrier to health care is access to health insurance, whether uninsured or underinsured. Since integrative medical care generally is not covered by health insurance, and many countries with universal health care do not provide routine integrative medical care, its access is often limited to those who can pay the out-of-pocket costs.

This clinical practice guideline should be considered in the context of existing health inequities and structural barriers to access to care. Health care professionals should strive to deliver the highest level of cancer care to all populations including those who have traditionally been marginalized and underserved. Future trials should critically evaluate inclusion and exclusion criteria to avoid, when possible, excluding patients with comorbid conditions, usually more prevalent among minority patients, to avoid systematically excluding patients traditionally under-represented in

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clinical trials.[266] Thoughtful design with regard to inclusion and exclusion criteria and recruitment procedures will enhance sample representativeness and maximize generalizability to diverse and under-represented patients. Moreover, trial participation often systematically disadvantages marginalized individuals as participation often requires frequent clinic visits, only offers interventions during work hours, and does not provide funding for transportation, parking, and/or childcare. Additionally, stakeholders should work toward achieving health equity by ensuring equitable access to both high-quality cancer care and research and addressing the structural barriers that uphold inequities in health and health care.[265]

GUIDELINE IMPLEMENTATION AND POTENTIAL BARRIERS

SIO-ASCO guidelines are developed for implementation across oncology care settings. Patient, provider, and health system barriers exist for the implementation of this guideline. First, patients and health care providers often lack the knowledge and awareness of the evidence base of integrative medicine for pain. Second, despite the recent growth of integrative medicine programs in comprehensive cancer centers,[11] these clinical services may not be as available in community hospitals, especially hospitals serving low income, racial, or ethnic minority populations.[267] Third, oncology patients often have medical complexity (such as neutropenia, thrombocytopenia, or presence of tumor or surgical wound), which community integrative health providers (eg, acupuncturists and massage therapists) may not have the necessary knowledge of or competency to ensure safe and effective care.[268] Finally, although many nonpharmacologic integrative medicine interventions have relatively low cost, they generally are not covered by health insurance.[269]

The 2012 National Health Interview Survey in the United States found that most adults who saw a practitioner for acupuncture or massage therapy did not have health insurance coverage for these interventions, and those with coverage were more likely to have costs only partly covered.[270] Given the financial toxicity experienced by many patients with cancer,[271] additional out-of-pocket expenses represent significant barriers to implementation of these recommendations. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the SIO and ASCO guideline information networks. Joint SIO and ASCO guidelines are posted on the SIO and ASCO websites and are published in the Journal of Clinical Oncology.

OPEN COMMENT REVIEW

The draft recommendations were released to the public for open comment from November 10 through November 23, 2021, with invitations sent out to 24 organizations. There were eight respondents in total representing medical oncology (3), integrative oncology (2), surgical oncology (1), family medicine (1), and nursing (1). Response categories of "Agree as written," "Agree with suggested modifications" and "Disagree. Listen comments" were captured for every proposed recommendation with 42 written comments received. A total of 80%-91% of the responses either agreed or agreed with slight modifications to the recommendations, while 9% of responses disagreed. Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. All changes were incorporated before the SIO Clinical Practice Guidelines Committee and ASCO Evidence Based Medicine Committee review and approval.

LIMITATIONS OF THE RESEARCH

The methodologic rigor is limited in some of the studies included. For mind-body interventions, adequate blinding is often difficult, if not impossible. In addition, the interventions often vary in dosing and format, and fidelity of the interventions is not always monitored. For natural product interventions, the quality of products is often not well characterized, and the dosing is rarely standardized. The methods used to assess pain are often inconsistent among trials, which created difficulties in interpreting the data.[269] Because many integrative medicine intervention studies do not receive funding from industry, a large RCT of a specific intervention (eg, acupuncture) for a specific outcome (eg, AI-related joint pain, or massage for pain in palliative care setting) is often limited to one large trial, which does not allow for adequate replication of data. Additionally, most of the studies failed to report any adverse events from these interventions. Furthermore, our guideline methodology excluded nonrandomized pragmatic studies, which may be more reflective of real-life integrative oncology practice.[272]

FUTURE DIRECTIONS

SIO and ASCO believe that cancer clinical trials are vital to inform clinical decisions and improve cancer care, and that all patients should have the opportunity to participate in these trials. As this guideline has identified scientific gaps in a number of mind-body interventions (eg, meditation, yoga, and music) for pain management in specific populations (eg, postsurgical, radiation, and pediatric), careful intervention development, testing, and well-designed and executed RCTs are needed to increase the evidence base. Where the results were mixed (eg, meditation for post-treatment survivorship pain), additional large-scale trials and meta-analyses are needed to resolve ambiguity stemming from the presence of both positive and negative trials. Despite tremendous patient interest, no herbs or natural supplements can currently be recommended for treatment of pain; thus, well-designed, placebo-controlled

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phase I-III trials are needed to establish the safety and efficacy of high-quality natural products for pain.

For treatments such as acupuncture, massage, or reflexology where there is an existing evidence base, there is a need for hybrid trials using appropriate implementation research frameworks and measures to determine optimal implementation and integration of these interventions into community oncology practices. It is particularly important to conduct trials that address the needs of underserved patients with cancer and survivors (eg, racial and/or ethnic minority, rural, older, pediatric, adolescent, and young adult). Patient-centered outcomes research, comparative effectiveness trials, and real-world trials are especially beneficial for comparing the relative benefits and harms of different integrative medicine treatments and other appropriate pharmacologic, behavioral, or rehabilitative treatments, so patients and clinicians can choose among evidence-based approaches to manage pain.

Finally, with advances in omics technology, wearable sensors, behavioral and neuroscience, big data, and novel trial designs, research needs to guide precision integrative pain management so that the right patient receives the right treatment to improve their pain and related outcomes.

Society for Integrative Oncology and ASCO believe that cancer clinical trials are vital to inform clinical decisions and improve cancer care, and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/survivorship-guidelines and https://integrativeonc.org/practice-guidelines/guidelines.

Patient information is available at www.cancer.net and https://integrativeonc.org/knowledge-center/patients.

RELATED SOCIETY FOR INTEGRATIVE ONCOLOGY AND ASCO GUIDELINES

- Clinical practice guidelines on the evidence-based use of integrative therapies during and after breast cancer treatment[273] (https://acsjournals.onlinelibrary.wiley.com/doi/full/10.3322/caac.21397)
- Complementary therapies and integrative medicine in lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines[274] (https://pubmed.ncbi.nlm.nih.gov/23649450/)
- Evidence-Based Clinical Practice Guidelines for Integrative Oncology: Complementary Therapies and Botanicals[275] (https://integrativeonc.org/docman-library/docs/65-sio-guidelines-2009/file)
- Patient-Clinician Communication[264] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Integrative Therapies During and After Breast Cancer Treatment[276] (https://ascopubs.org/doi/10.1200/JCO.2018.79.2721)
- Management of Chronic Pain in Survivors of Adult Cancers[2] (https://ascopubs.org/doi/10.1200/JCO.2016.68.5206)
- Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers[23] (https://ascopubs.org/doi/10.1200/JCO.20.01399)

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EDITOR'S NOTE

This joint Society for Integrative Oncology (SIO) and ASCO Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information, is available at https://integrativeonc.org/knowledge-center/patients and www.cancer.net, https://integrativeonc.org/practice-guidelines/guidelines and www.asco.org/survivorship-guidelines.

EQUAL CONTRIBUTION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Conception and design: All authors
Collection and assembly of data: All authors
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Manuscript writing: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Integrative Medicine for Pain Management in Oncology: Society for Integrative Oncology–ASCO Guideline

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APPENDIX

TABLE A1. Recommendation Rating Definitions

Term	Definitions
Quality of evidence	
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (eg, balance of benefits *v* harms) and further research is very unlikely to change either the magnitude or direction of this net effect
Intermediate	Intermediate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change the magnitude and/or direction of this net effect
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. Reliance on consensus opinion of experts may be reasonable to provide guidance on the topic until better evidence is available
Strength of recommendation	
Strong	There is high confidence that the recommendation reflects best practice. This is based on
	Strong evidence for a true net effect (eg, benefits exceed harms)
	Consistent results, with no or minor exceptions
	Minor or no concerns about study quality; and/or
	The extent of panelists' agreement
	Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on
	Good evidence for a true net effect (eg, benefits exceed harms)
	Consistent results with minor and/or few exceptions
	Minor and/or few concerns about study quality; and/or
	The extent of panelists' agreement
	Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on
	Limited evidence for a true net effect (eg, benefits exceed harms)
	Consistent results, but with important exceptions
	Concerns about study quality; and/or
	The extent of panelists' agreement
	Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation

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TABLE A2. Society for Integrative Oncology–ASCO Integrative Medicine for Pain Management in Oncology Guideline Expert Panel Membership

Name	Affiliation	Role or Area of Expertise
Eduardo Bruera, MD (ASCO Cochair)	MD Anderson Cancer Center, Houston, TX	Palliative and Medical Oncology
Jun J. Mao, MD (SIO Cochair)	Memorial Sloan Kettering Cancer Center, New York, NY	Integrative Oncology (Acupuncture)
Heather Greenlee, ND, PhD	Fred Hutchinson Cancer Research Center, Seattle, WA	Integrative Oncology (Naturopathic Medicine)
Richard T. Lee, MD	City of Hope Comprehensive Cancer Center, Duarte, CA	Medical Oncology and Palliative Oncology
Ting Bao, MD	Memorial Sloan Kettering Cancer Center, New York, NY	Integrative and Medical Oncology (Acupuncture)
Eran Ben-Arye, MD	Lin & Carmel Medical Centers, Clalit Health Services; Technion Faculty of Medicine Haifa, Israel	Integrative Oncology
Claudia M. Witt, MD, MBA	University Hospital Zurich, Zurich, Switzerland	Integrative Oncology
Gary H. Lyman, MD, MPH	Fred Hutchinson Cancer Research Center, Seattle, WA	Medical Oncology
Charles Loprinzi, MD	Mayo Clinic, Rochester, MN	Medical Oncology
Ana Maria Lopez, MD	Thomas Jefferson, Sidney Kimmel Cancer Center, Philadelphia, PA	Medical Oncology
Eleanor M. Walker, MD	Henry Ford Hospital Detroit, MI	Radiation Oncology
Kavitha Ramchandran, MD	Stanford Healthcare, Palo Alto, CA	Palliative Oncology
Thomas Leblanc, MD	Duke University School of Medicine, Durham, NC	Palliative Oncology
Viraj A. Master, MD, PhD	Winship Cancer Institute of Emory University, Atlanta, GA	Surgical Oncology and Integrative Oncology
Eric Garland, PhD	College of Social Work, University of Utah, Salt Lake City, UT	Mind-Body Medicine
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Debra Barton, PhD, RN	University of Michigan School of Nursing, Ann Arbor, MI	Nursing
Deborah Watkins Bruner, RN, PhD	Winship Cancer Institute of Emory University, Atlanta, GA	Nursing
Jodi MacLeod	Philadelphia, PA	Patient Representative
Nofisat Ismaila, MD, MSc	ASCO, Alexandria, VA	Guideline Methodologist

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