Article Title: Guidelines for Cancer-Related Pain: A Systematic Review of Complementary and Alternative Medicine Recommendations

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Abstract

Background and Objective: Although up to 85% of patients with cancer use complementary and alternative medicine (CAM), they commonly do not disclose this information to their healthcare providers. Cancer-related pain (CRP) is one of the most common symptoms among those who may seek CAM. This study was conducted to identify the quantity and assess the quality of CAM recommendations across clinical practice guidelines (CPGs) for the treatment and/or management of CRP, as this has not been explored in the literature.

Methods: A systematic review was conducted to identify cancer pain CPGs. MEDLINE, EMBASE, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) were searched from 2009 to 2020. The Guideline International Network and the National Centre for Complementary and Integrative Health websites were also searched. Eligible CPGs on CRP in adults were assessed using the Appraisal of Guidelines, Research and Evaluation II (AGREE II) instrument.

Results: Of 771 unique search results, 13 mentioned CAM and 11 made CAM recommendations. Eligible CPGs were published in 2009 or later and focused on the treatment/management of CRP. Scaled domain percentages from highest to lowest ranged from (overall, CAM): 88.1%, 88.1% (for scope and purpose) to 21.0%, 8.5% (for applicability). Quality varied within and across CPGs. One CPG was recommended by both appraisers; 6 were recommended as "Yes" or "Yes with modifications."

Conclusions: The present study has identified and summarized a number of CPGs that clinicians may consult to understand what CAMs are recommended in the context of the treatment and/or management of CRP.

Background

Cancer-related pain (CRP) is one of the most common and debilitating symptoms associated with cancer progression and treatment. Affecting approximately half of patients with cancer, CRP has significant implications for the quality of life (QOL), psychosocial well-being, and daily functioning of patients with cancer and cancer survivors [1, 61]. CRP can be caused by a number of factors associated with cancer and, depending on the cause, may manifest in different forms and at varying severities [2]. Appropriate treatment of CRP should be individualized and comprehensive, and should account for patient preferences.3 Frequently explored by patients with CRP [3], complementary and alternative medicine (CAM) serves as a potential option for relief. Complementary medicine is the use of non-mainstream treatments in addition to conventional treatment, while alternative medicine involves the use of non-mainstream treatment instead of conventional treatment [4, 62]. Results of the 2007 National Health Interview Survey indicated that 65% of American respondents who had ever received a cancer diagnosis reported using CAM approaches at some point [5]. In a separate study, CAM use was reported by 40% to 85% of patients with cancer [6]. In a study investigating the prevalence of CAM use by women with breast cancer, 58% of respondents reported having used CAM specifically to relieve symptoms of their cancer or its treatment [7], among the most prevalent of which was CRP [8].

Several CAM therapies have been proposed for the management of symptoms associated with cancer, such as CRP. These therapies include hypnosis, relaxation therapy, acupuncture, massage, and yoga [5, 9]. Evidence suggests that massage in particular can help relieve cancer-related pain [5]. Hypnosis, acupuncture, imagery, and support groups show promising clinical benefits for CRP, though more rigorous trials of these interventions in a CRP context

are lacking [10, 63]. This knowledge gap is further compounded by the fact that clinicians involved in treating CRP rarely receive sufficient training in the use of CAM therapies [11].

Healthcare professionals rely on evidence-based CPGs to make recommendations associated with the management of CRP. Due to a lack of relevant clinician training and knowledge about the use of CAM therapies for CRP [11-13], evidence-based CPGs on CRP treatment are a particularly valuable tool for healthcare professionals involved in CRP treatment. The present study has identified and summarized a number of CPGs that clinicians may consult to understand what CAMs are recommended in the context of the treatment and/or management of CRP. To date, an appraisal of CPGs for CRP including CAM recommendations has not been conducted. As a result, no thorough evaluation of the credibility of CAM recommendations for cancer pain CPGs is available. The purpose of this systematic review was to characterize and define mentions of CAM in cancer pain CPGs, and to assess the quality of CAM recommendations using the Appraisal of Guidelines, Research and Evaluation II (AGREE II) instrument. This review is meant to provide an assessment and summary of existing CPGs for CAM treatment of CRP. These findings may serve to aid clinicians in symptom management and patient counseling during interactions with patients with CRP seeking or using CAM.

Methods

Approach

A systematic review was conducted to identify cancer pain CPGs according to Cochrane's standard methods [14] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria for systematic reviews and meta-analyses [15]. A protocol was registered with PROSPERO, registration number CRD42020182229. Eligible CPGs were

assessed using the AGREE II tool [16, 64], which consists of 23 items in 6 domains: scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability, and editorial independence. CPGs with specific CAM recommendations were assessed a second time by applying the AGREE II items to only the CAM sections of the CPG.

Eligibility Criteria

Eligibility criteria for CRP CPGs were established using the Population, Intervention, Comparison and Outcomes framework for evidence-based practice. The eligible population included adults 19 years of age and older with CRP. Included interventions contributed directly to the treatment or management of CRP and were further examined to determine whether any mention or recommendations of CAM therapies were included. Comparisons referred to the assessed quality of CRP CPGs, and outcomes were AGREE II scores reflecting guideline content and format. The following conditions were also used to characterize eligible CPGs: developed by nonprofit organizations including academic institutions, government agencies, disease-specific foundations, or professional associations or societies; published in 2009 or later; English language; and either publicly available or available for order through our library system. Ineligible publications included those in the form of consensus statements, protocols, abstracts, conference proceedings, letters or editorials, publications based on primary studies that evaluated CRP management or treatment, and those focused on CRP curriculum, education, training, research, professional certification, or performance. It should be noted that only eligible CPGs containing CAM therapy recommendations were assessed using AGREE II to allow for comparison between AGREE II scores for the overall CPG and the CAM sections specifically. Demographic

information is reported for eligible CPGs even if they did not contain CAM therapy recommendations.

Searching and Screening

MEDLINE, EMBASE, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) were searched on April 17, 2020, from 2009 to April 15, 2020, inclusive. The search strategy (Table S1) included medical subject headings and keywords that reflect terms commonly used in the literature to refer to CRP [6]. We also searched the Guideline International Network, a repository of CPGs (https://www.g-i-n.net/) using keyword searches restricted based on the eligibility criteria including "cancer pain" and "pain." Lastly, we searched the National Center for Complementary and Integrative Health web site, which contained a single list of CAM CPGs (https://nccih.nih.gov/health/providers/clinicalpractice.htm). A.E.S. and another research assistant screened titles and abstracts from all other sources and then screened full-text items to confirm eligibility. J.Y.N. reviewed the screened titles and abstracts and full-text items to standardize screening, and helped to discuss and resolve selection differences between A.E.S. and the other research assistant.

Data Extraction and Analysis

The following data were extracted from each CPG: publication date, country of first author, type of publishing organization (academic institutions, government agencies, disease-specific foundations, or professional associations or societies), and whether any CAM therapies were mentioned (yes/no). If CAMs were mentioned in a CPG, the types of CAMs mentioned, CAM recommendations made, CAM funding sources, and whether any CAM providers were part of the CPG panel, were also extracted from the data and summarized. Although most

data were available within each CPG, the web site of each developer was browsed for associated knowledge-based resources in support of implementation as part of the CPG applicability assessment.

Guideline Quality Assessment

Data were extracted from eligible CPGs and analyzed according to standardized methods for applying the AGREE II instrument.11 First, A.E.S., J.Y.N., and the other research assistant independently completed a pilot test of the AGREE II instrument by using it to assess 3 separate CPGs. Discrepancies were discussed and resolved. A.E.S. and the other research assistant then independently assessed all eligible CPGs containing CAM therapy recommendations twice (once for the overall CPG, and once for only the CAM sections of the CPG) for each of 23 items included in the 6 domains of the AGREE II instrument. Scoring was conducted using a 7-point Likert scale from strongly disagree (1) to strongly agree (7) that the item is met, and the overall quality of each CPG was scored on the same scale. A.E.S. and the other research assistant then recommended for or against the use of each CPG based on all collected information. The modified AGREE II questions used to guide the scoring of the CAM sections of each CPG are found in Table S2. J.Y.N. served to arbitrate any score differences between A.E.S. and the other research assistant. Average appraisal scores were calculated as the average rating of each individual appraiser for each of the 23 AGREE II items for a single CPG. Average overall assessments were calculated as the average of both appraisers' final "overall quality" scores for each CPG. Scaled domain percentages were calculated by adding both appraisers' ratings of items within each domain, scaling the resulting sums by maximum and minimum possible domain scores, and converting this value to a percentage. These scores were generated for interdomain

comparison within and across CPGs. Average appraisal scores, average overall assessments, and scaled domain percentages for each CPG were tabulated for comparison.

Results

Search Results

Searches retrieved 805 items, and 771 unique items remained after deduplication (Figure 1). Screening eliminated 748 titles and abstracts. Articles that were excluded based on titles and abstracts included those that were not CPGs, were not CRP focused, were not relevant to cancer, or were not in English. This left 23 full-text CPGs to be considered, 1 of which was ineligible because it was irretrievable despite ordering a request from our university library. Of the 22 CPGs eligible for review [17-38], 13 made mention of CAM therapies [17,18,20–26,37,38] and 11 made CAM therapy recommendations [17,18,20–23,25,26,37,38].

Guideline Characteristics

Eligible CPGs were published from 2009 to 2019 in the United States (n = 4), Italy (n = 3), France (n = 3), Spain (n = 2), the United Kingdom (n = 2), China (n = 1), Sweden (n = 1), Japan (n = 1), Germany (n = 1), Belgium (n = 1), Canada (n = 1), Switzerland (n = 1), and Denmark (n = 1). The CPGs were funded and/or developed by professional associations or societies (n = 20), a not-for-profit cancer network, and an international agency. Thirteen CPGs made mention of CAMs. These CAMs included mind-body modalities (n = 8), acupuncture (n = 7), massage (n = 6), application of heat or cold (n = 3), capsaicin (n = 2), herbal remedies (n = 1), coping skills training (n = 1), music (n = 1), exercise (n = 1), yoga (n = 1), aloe vera (n = 1), and breathing exercises (n = 1). Recommendations relating to CAM were made in 11 CPGs for the following therapies: acupuncture (n = 8), mind-body modalities (n = 7), application of heat or cold (n = 6), massage (n = 6), distraction and

relaxation techniques (n = 3), music therapy (n = 3), behavioral and cognitive therapies (n = 3), coping skills training (n = 1), exercise (n = 1), yoga (n = 1), capsaicin (n = 1), emotional counseling (n = 1), and herbal remedies (n = 1); only these CPGs were assessed using the AGREE II tool. CAM funding sources were not identified in any of the CPGs, and no CPGs included CAM providers as part of the guideline development panel. Characteristics of all eligible CPGs are provided in Table 1. We provide a summary of CAM recommendations made across CRP CPGs for the benefit of clinicians and researchers in Figure 2.

CPGs Mentioning CAM Without Recommendations

Of the 13 CPGs that made mention of CAM therapies, 2 did not make CAM recommendations [24, 27]. These CPGs were included in the data extraction process, but were not assessed using the AGREE II instrument. CAM therapies mentioned in these CPGs included massage, application of heat or cold, distraction and relaxation techniques, acupuncture, and aloe vera [24, 27]. Mention of CAM therapies in these CPGs was very brief and lacked adequate detail.

Average Appraisal Scores, Average Overall Assessments, and Recommendations Regarding Use of CPGs: Overall Guideline

Average appraisal scores, average overall assessments, and recommendations for the use for each CPG are shown in Table 2. Average appraisal scores for each of the 11 assessed CPGs ranged from 3.5 to 5.9 on the 7-point Likert scale (where 7 indicates strong agreement that the item criteria are met); 7 CPGs achieved or exceeded an average appraisal score of 4.0, and only 1 CPG achieved or exceeded an average appraisal score of 5.0. Average overall assessments for the 11 CPGs ranged between 3.5 (lowest) and 5.5 (highest). Seven CPGs equalled or exceeded a score of 4.0, and 1 equalled or exceeded 5.0.

Average Appraisal Scores, Average Overall Assessments, and Recommendations Regarding Use of CPGs: CAM Sections

Average appraisal scores, average overall assessments, and recommendation regarding use for each CPG are shown in Table 2. Average appraisal scores for each of the 11 CPGs ranged from 2.8 to 5.1 on the 7-point Likert scale (where 7 indicates strong agreement that the item criteria are met). Three CPGs achieved or exceeded an average appraisal score of 4.0 and 1 CPG achieved or exceeded an average appraisal score of 5.0. Average overall assessments for the 11 CPGs ranged between 3 (lowest) and 5 (highest), including 3 CPGs equalling or exceeding a score of 4.0 and only 1 CPG equalling or exceeding a score of 5.0.

Overall Recommendations: Overall Guideline

Of the 11 CPGs, only 1 was recommended by both appraisers (Table 3). Appraisers agreed in their overall recommendation for 2 of the remaining 10 CPGs, with 1 "No" [18] and 1 "Yes with modifications" [20]. Of the other 8 CPGs, 2 were rated by the two appraisers as "No" and "Yes with modifications", [21, 23] and 6 CPGs were rated as "Yes" and "Yes with modifications" [17, 25, 26, 37, 38].

Overall Recommendations: CAM Sections

None of the 11 CPGs were recommended by both appraisers (see Table 3). Appraisers agreed in their overall recommendation for 2 of 11 CPGs, both of which were rated as "No" [18, 26]. Of the remaining 9 CPGs, 7 were rated by the two appraisers as "No" and "Yes with modifications" [20, 21, 23, 25, 37, 38], and 2 were rated by the 2 appraisers as "Yes" and "Yes with modifications" [17, 22].

Scaled Domain Percentage Quality Assessment

With regard to scaled domain percentages of the overall CPG, scope and purpose scores ranged from 75.0% to 100.0%, stakeholder involvement scores ranged from 25.0% to 69.4%, rigor of development scores ranged from 30.2% to 90.6%, clarity of presentation scores ranged from 47.2% to 83.3%, applicability scores ranged from 0.0% to 39.6%, and editorial independence scores ranged from 0.0% to 75.0% (Table 4). For scaled domain percentages of the CAM sections, scope and purpose scores ranged from 77.8% to 100%, stakeholder involvement scores ranged from 16.7% to 69.4%, rigor of development scores ranged from 22.9% to 80.2%, clarity of presentation scores ranged from 47.2% to 83.3%, applicability scores ranged from 0.0% to 35.4%, and editorial independence scores ranged from 0% to 62.5%.

Scope and Purpose

The overall objectives, health questions, and target population were generally well-defined across all CPGs, and the average score for this domain was higher than that of any other domain. Authors effectively provided the overarching objective(s) of the CPG, described the types of CAM they sought to assess, and outlined the scope of the disease or condition that was the target of CAM therapy or therapies. The population for whom each CPG was developed was also described adequately in all CPGs, although the level of detail varied depending on the purpose and scope of individual CPGs. For instance, the target population description in 2 CPGs was limited to the title “adult cancer pain” [37].

Stakeholder Involvement

Overall, most CPGs adequately characterized the guideline development group, typically providing information including each member’s name, degrees held, geographical location,

and institutional affiliation and, less frequently, describing members' area of expertise and role in the guideline development group [21, 22, 25, 37]. Almost half of the CPGs employed some method of seeking and incorporating the target population's views and preferences into the development process [17, 22, 25, 37], though the slight majority did not [18, 20, 21, 23, 26, 38]. Target users of the CPG were typically defined, though definitions were inconsistent across CPGs. Some CPGs offered clear descriptions, for example, of the type of practitioner that should use the CPG [17, 21, 22], while other CPGs offered much more vague descriptions of target users [18, 20, 23, 26, 37, 38], in some cases completely omitting any explicit mention of the target users [20, 29]. Stakeholder involvement domain scores for the CAM sections of each CPG were generally lower than those for the overall CPGs. Specifically, patient preferences regarding CAM use were sought for only one CPG [17] and only a few CPGs explicitly identified CAM experts as members of the guideline development group [17, 21-23].

Rigor of Development

In terms of overall CPGs, only 4 included clear descriptions of the systematic methods used to search for evidence [17, 21, 22, 38]; all others lacked sufficient information surrounding their search strategy. Only 2 CPGs described the criteria for evidence selection in detail [21, 22]. The strengths and limitations of the body of evidence were clearly described in all CPGs. The extent of detail provided regarding methods for formulating the recommendations varied; most CPGs provided detailed descriptions of the recommendation development processes [17, 18, 21, 22, 25, 37, 38], but other CPGs provided minimal information [20, 23, 26]. The health benefits, side effects, and/or risks were considered in the formulation of each CPG's recommendations, with a few exceptions [17, 23, 25]. All CPGs established an explicit link between the recommendations and supporting evidence. All except three CPGs [17, 18, 20]

explicitly stated that they were externally reviewed by experts prior to publication. Of those CPGs that explicitly stated that an external review was conducted, most lacked information about the purpose of the external review and methods by which it was employed [21, 23, 25, 26, 37]. Most CPGs did not include a procedure for updating the CPG [18, 20, 21, 23, 26, 38], and of those that did, only a few provided a detailed methodology [25, 37]. The rigor of development scores for CAM sections of the CPGs were lower in most cases than overall scores for this domain. Descriptions of systematic methods and criteria for evidence selection were lacking in the same CPGs for overall and CAM recommendations, as were identification of strengths and limitations and a description of the recommendation development process. However, the health benefits, side effects, and risks were not considered as frequently for CAM recommendations as in overall CPGs; most CPGs did not adequately consider these factors for CAM recommendations [17, 20, 21, 23, 24, 37, 38]. All CPGs demonstrated a clear link between CAM recommendations and supporting evidence. No CPGs included a CAM expert in the external review.

Clarity of Presentation

With regard to overall CPG scoring, all CPGs contained specific and unambiguous recommendations that included a clear statement of the recommended action. However, most CPGs lacked information on 1 or more of the following components of recommendations: identification of the intent/purpose, relevant population, or caveats. All 11 CPGs presented different options for the management of the condition or health issue, and key recommendations were easily identifiable across all CPGs. High scores for both of these criteria contributed to this domain's relatively high-scaled percentage for overall CPGs. Scores for this domain were slightly lower within CAM sections than overall CPGs, as most

CPGs presented CAM recommendations less clearly and more ambiguously than other recommendations [18, 20-22, 26, 37, 38].

Applicability

Three CPGs discussed facilitators and barriers to implementation of the recommendations [22, 29]. Five CPGs included advice and/or tools to support implementation of the recommendations [21, 22, 25, 29]. No CPGs addressed the resource implications of implementing the recommendations, and only 1 provided monitoring and auditing criteria [22]. The scaled domain percentage for applicability was notably lower for the CAM sections than for the overall CPGs. Some CPGs included less detailed descriptions, if any, of facilitators and barriers to applying CAM recommendations than overall recommendations [22, 29, 38]. Only 5 CPGs included any advice and/or tools for implementing CAM recommendations [18, 21, 22, 29], though the degree of detail in their descriptions varied widely. No CPGs included adequate descriptions of potential resource implications of applying CAM recommendations or monitoring/auditing criteria for CAM recommendations.

Editorial Independence

CPGs varied in methods and level of detail in reporting the influence of the funding source on CPG development and recording competing interests of the members of the guideline development panel. Several CPGs that declared a funding source did not state whether their funding source influenced the content of the CPG [15-19], and no CPGs explicitly stated that no funding supported their development. No CPGs had CAM funding sources. CPGs also varied in reporting of competing interests. Three CPGs did not address competing interests of the guideline development group members [18, 23, 26]. Of the CPGs that did, several did not specify how potential competing interests were identified, sought, or considered, or how they

may have influenced the guideline development process or formation of recommendations [17, 20, 38].

Discussion

The purpose of this research was to identify the quantity and assess the quality of CAM recommendations in CPGs for the treatment and/or management of CRP. In doing so, we identified and summarized a number of CPGs that clinicians may consult to understand what CAMs are recommended in the context of CRP. This study identified 22 CPGs published between 2009 and 2019 that were relevant to the treatment and/or management of CRP, 13 of which made mention of CAM, and 11 of which made CAM therapy recommendations. Quality, as assessed by the 23-item AGREE II tool, varied widely across CPGs overall and by domain. In assessment of overall CPG quality, 1 CPG scored 5.0 or higher in both average appraisal score and average overall assessment [22], and of the remaining 10, five CPGs scored 4.0 or lower in both of these metrics [17, 21, 29, 38]. The rest scored below 4.0 for average appraisal score and average overall assessment. In assessing the quality of the CAM section of each CPG, 2 CPGs scored 4.0 or higher in both average appraisal score and average overall assessment [17, 22], and 1 CPG scored 3.0 or lower in both of these metrics [26] (1 = strongly disagree; 7 = strongly agree that criteria are met).

To our knowledge, no previous studies have identified the quantity nor assessed the quality of CAM therapy recommendations in CRP CPGs, thus, this is the first study to do so. In this study, the scaled domain percentages for the overall CPGs from highest to lowest were, as follows: scope and purpose (88.1%), clarity of presentation (87.6%), rigor of development (52.2%), stakeholder involvement (49.5%), editorial independence (43.8%), and applicability (21.0%). The scaled domain percentages for the CAM section of the CPGs from highest to

lowest were similar, as follows: scope and purpose (88.1%), clarity of presentation (70.0%), rigor of development (45.2%), stakeholder involvement (36.4%), editorial independence (34.5%), and applicability (8.5%). Other studies assessing the quality of CAM recommendations in CPGs for other pain and cancer-related clinical topics that employed the AGREE II tool have reported similar findings [39-42], or no CAM recommendations at all [43, 64]. Although this is the first systematic review of CAM recommendations in CPGs for cancer pain specifically, a past review assessing CPGs for general cancer pain management using the AGREE II tool found significant variability in the quality, content, and evidence level of these CPGs [44]. Therefore, the variable and suboptimal quality of CPGs presented here is not limited to this study.

By describing the quantity and quality of cancer pain CPGs that included CAM recommendations, this study found a moderate number of CPGs that clinicians may consult to understand what CAMs are recommended in the context of the treatment and/or management of CRP. Furthermore, of relevant CPGs on this subject, a number of them are of low quality. This may reflect a limited amount of research conducted on the use of CAM therapies in cancer pain management and treatment. Numerous factors that challenge CAM research have been identified, including negative attitudes toward CAM therapies [66-69], lack of researchers and therapists with appropriate training [45], and a lack of funding [45-48]. Similarly, patients with cancer may hesitate to use CAM due to their fears of impeding conventional cancer treatments and general lack of CAM knowledge [49]. However, this is expected to change as CAM use increases. Despite documented risks [50-53], CAM is currently used by almost 50% of the population in some regions of the world [54-56], and by up to 85% of patients with cancer in some countries [6]. More research is needed to help patients and healthcare professionals understand and navigate the use of CAM therapies. As

this research emerges, so will CPGs that focus on CAM therapies [48]. In turn, higher quality reporting of CAM therapies for CRP may encourage patient disclosure of CAM use, expand healthcare professionals' understanding of associated risks and benefits, and facilitate an improved shared decision-making process for CRP management.

The quality of CRP CPGs varied widely across domains both within and across CPGs. This finding highlights the need for higher quality reporting of CAM recommendations in CPGs. New CPGs and updates on existing CRP CPGs may be conducted according to the AGREE II tool [16], as well as other principles, frameworks, criteria, and checklists available to aid guideline development. The use of these tools can aid guideline developers in generating CPGs, including CRP CPGs, of higher quality [57-60].

Strengths and Limitations

Strengths of this study included the use of a comprehensive systematic review methodology to identify eligible cancer pain treatment and/or management CPGs and the use of the AGREE II instrument, the validated and internationally accepted gold standard for CPG appraisal [35]. One limitation of this study is that CPGs were independently assessed by only 2 appraisers, not 4 as recommended by the AGREE II instrument. To mitigate this and improve reliability and standardization of scores, J.Y.N., A.E.S., and an additional research assistant conducted an initial pilot test, during which they each independently appraised 3 separate CPGs, then discussed the results and achieved consensus on how to apply the AGREE II instrument. Following appraisal of all eligible CPGs, J.Y.N. met with A.E.S. and the additional research assistant to discuss and resolve uncertainties without unintentionally changing legitimate discrepancies.

Conclusions

This study identified 11 cancer pain CPGs published since 2009 making recommendations on the use of CAM therapies including acupuncture, mind-body modalities, herbal remedies, behavioral therapy, counseling, heat/cold application, yoga, massage, and chiropractic manipulation. According to appraisal of these CPGs with the AGREE II instrument, quality varies within and across CPGs. CPGs that achieved higher AGREE II scores and favorable overall recommendations can reliably inform patients and healthcare professionals about CAM therapies. CPGs that achieved variable or relatively low scaled domain percentages and unfavorable overall recommendations for use could be improved in future updates according to criteria listed in the AGREE II instrument and through consultation of various resources meant to support CPG development and implementation. Improvements to existing CPGs that received unfavorable AGREE II scores and continued development of high-quality CRP CPGs will contribute to better understanding of CAM therapies for healthcare providers and will benefit patients with cancer seeking CAM to manage CRP. Further research on the safety and efficacy of CAM therapies is needed to better inform patient-centered practice and to help patients and healthcare professionals make appropriate treatment decisions about CAM therapies. Future research directions should include the identification of CAM therapies other than those that are reviewed here and supported by sufficient evidence. Such research could serve as the basis for the development of CPGs on a wider range of CAM therapies for cancer pain.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

J.Y.N. designed and conceptualized the study, collected and analyzed data, co-drafted the manuscript, and gave final approval of the version to be published. A.E.S. assisted with the collection and analysis of data, co-drafted the manuscript, and gave final approval of the version to be published.

Consent for Publication

All authors consent to this manuscript's publication.

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Ethical Approval and Consent to Participate

This study involved a systematic review of peer-reviewed literature only; it did not require ethics approval or consent to participate.

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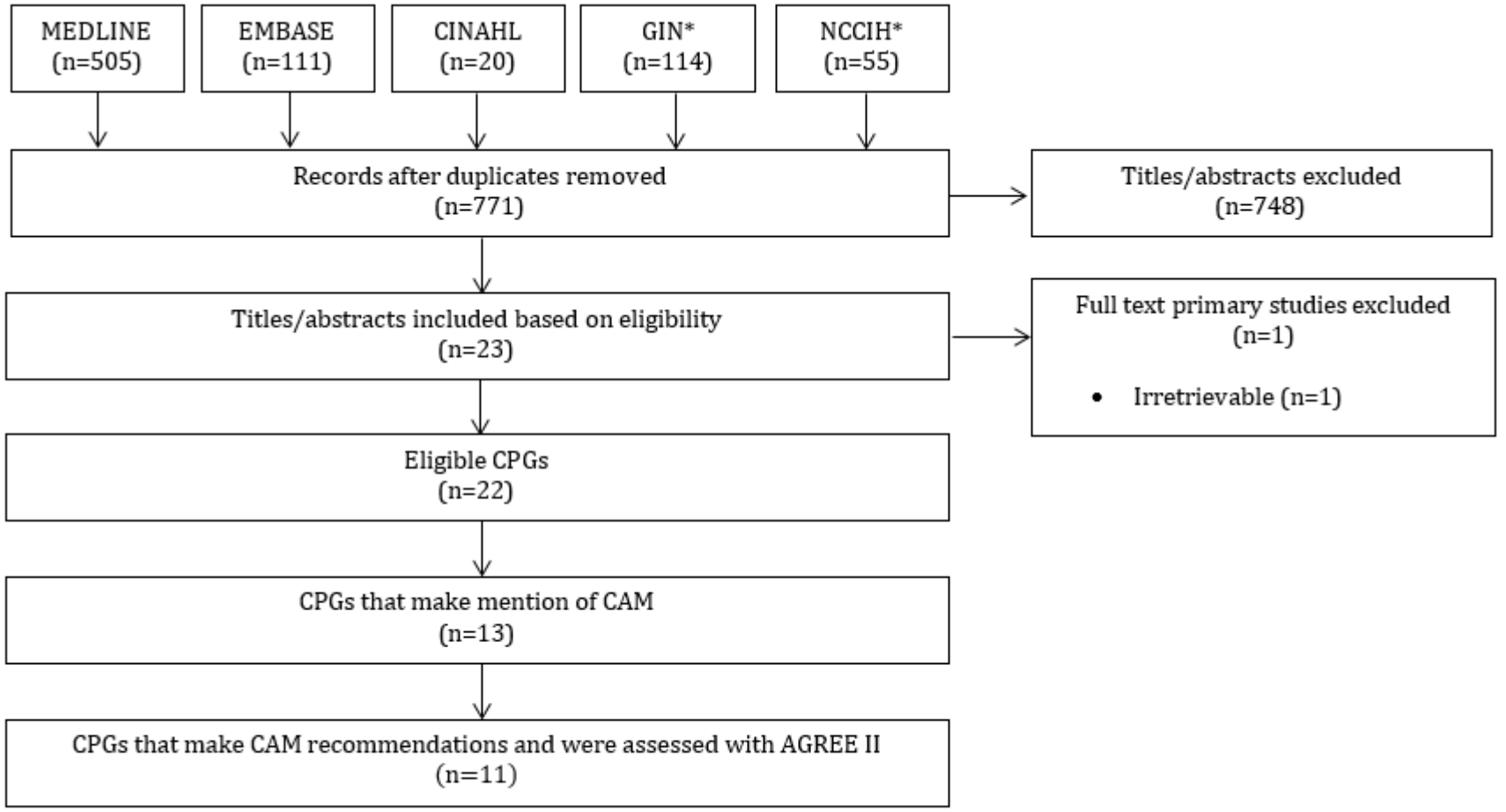
Figures

Figure 1: PRISMA Diagram



*List of Abbreviations: GIN = Guidelines International Network, NCCIH = National Center for Complementary and Integrative Health

Figure 2: Summary of Complementary and Alternative Medicine (CAM) Recommendations in Clinical Practice Guidelines

CAM Therapy							
Guideline	Acupuncture	Behavioural Therapy/ Counselling	Heat/Cold Application	Herbal Therapies	Massage	Mind-Body Modalities	Yoga
Swarm 2010	+	+	+	N/A	+	+	N/A
Swarm 2013	+	+	+	N/A	+	+	N/A
Denlinger 2014	+	+	N/A	+	N/A	+	N/A
Lam 2019	+	+	+	+	N/A	N/A	N/A
Swahney 2017	+	+	N/A	N/A	+	+	N/A
Davies 2009	N/A	N/A	+	N/A	+	+	N/A
Paice 2016	N/A	+	+	N/A	+	N/A	N/A
Binczak 2014	N/A	+	N/A	N/A	N/A	+	N/A
Drewes 2018	N/A	+	N/A	N/A	N/A	+	N/A
Jara 2018	N/A	N/A	N/A	N/A	N/A	+	+
Espitalier 2014	0	N/A	N/A	N/A	N/A	N/A	N/A

Legend:
+/green = recommendation for the therapy's use
-/red = recommendation against the therapy's use
0/yellow = recommendation unclear/uncertain/conflicting
N/A/grey = no recommendation provided

Tables

Table 1. Characteristics of Eligible Clinical Practice Guidelines

Guideline	Country (First Author)	Developer	CAM Category	Guideline Topic
Lam et al., 2019[17]	China	Hong Kong Baptist University	Traditional Chinese medicine	Chinese medicine for cancer palliative care
Drewes et al., 2018[18]	Denmark	International Association of Pancreatology, European Pancreatic Club	Mind-body medicine	Management of pain in pancreatic ductal adenocarcinoma
Fallon et al., 2018[19]	United Kingdom	European Society for Medical Oncology	N/A	Management of cancer pain in adults
Jara et al., 2018[20]	Spain	Spanish Society of Medical Oncology	Mind-body medicine	Clinical treatment of cancer pain
Swahney et al., 2017[21]	Canada	Cancer Care Ontario	Energy medicine, manipulative practices	Pain management in cancer and/or palliative care
Paice et al., 2016[22]	United States	American Society of Clinical Oncology	Energy medicine, body-based practice, natural products	Chronic pain management in adult cancer survivors
Binczak et al., 2014[23]	France	French Society of Otorhinolaryngology	Mind-body medicine	Management of somatic pain induced by

Guideline	Country (First Author)	Developer	CAM Category	Guideline Topic
				head-and-neck cancer treatment
Blanchard et al., 2014[24]	France	French Society of Otorhinolaryngology	N/A	Management of somatic pain induced by head-and-neck cancer treatment
Denlinger et al., 2014[25]	United States	National Comprehensive Cancer Network	Energy medicine, mind-body medicine, natural products	Managing pain for cancer survivors
Espitalier et al., 2014[26]	France	French Society of Otorhinolaryngology	Energy medicine	Management of somatic pain induced by head-and-neck cancer
Wengström et al., 2014[27]	Sweden	European Oncology Nursing Society	N/A	Breakthrough cancer pain management
Eyssen et al., 2013[58]	Belgium	Belgian Health Care Knowledge Centre	N/A	Supportive treatment for cancer
Swarm et al., 2013[29]	United States	National Comprehensive Cancer Network	Manipulative and body-based practice, mind-body medicine	Adult cancer pain management

Guideline	Country (First Author)	Developer	CAM Category	Guideline Topic
Yamaguchi et al., 2013[30]	Japan	Japanese Society of Palliative Medicine	N/A	Pharmacological management of cancer pain
Bader et al., 2012[31]	Germany	European Association for Urology	N/A	Prostate cancer pain management
Caraceni et al., 2012[32]	Italy	European Association for Palliative Care	N/A	Use of opioid analgesics for cancer pain
Ripamonti et al., 2012[33]	Italy	European Society for Medical Oncology	N/A	Management of cancer pain
Virizuela et al., 2012[34]	Spain	Spanish Society of Medical Oncology	N/A	Treatment of cancer pain
Ripamonti et al., 2011[35]	Italy	European Society for Medical Oncology	N/A	Management of cancer pain
Jost and Roila, 2010[36]	Switzerland	European Society for Medical Oncology	N/A	Management of cancer pain
Swarm et al., 2010[37]	United States	National Comprehensive Cancer Network	Manipulative and body-based practice, mind-body medicine	Adult cancer pain management

Guideline	Country (First Author)	Developer	CAM Category	Guideline Topic
Davies et al., 2009[38]	United Kingdom	Association for Palliative Medicine of Great Britain and Ireland	Manipulative and body-based practice, mind-body medicine	Management of cancer-related breakthrough pain

Table 2. Average Appraisal Scores and Average Overall Assessments of Each Clinical Practice Guideline

Guideline	Metric	Appraiser 1	Appraiser 2	Average	Standard Deviation
Lam et al., 2019[17] (overall)	Appraisal score	4.2	4.6	4.4	0.3
	Overall assessment	4.0	5.0	4.5	0.7
Lam et al., 2019[17] (CAM section)	Appraisal score	4.2	4.7	4.4	0.4
	Overall assessment	4.0	5.0	4.5	0.7
Drewes et al., 2018[18] (overall)	Appraisal score	3.5	3.9	3.7	0.3
	Overall assessment	3.0	4.0	3.5	0.7
Drewes et al., 2018[18] (CAM section)	Appraisal score	3.0	3.3	3.2	0.2
	Overall assessment	3.0	3.0	3.0	0.0
Jara et al., 2018[20] (overall)	Appraisal score	3.3	3.9	3.6	0.4
	Overall assessment	3.0	4.0	3.5	0.7

Guideline	Metric	Appraiser 1	Appraiser 2	Average	Standard Deviation
Jara et al., 2018[20] (CAM section)	Appraisal score	2.9	3.4	3.2	0.3
	Overall assessment	3.0	3.0	3.0	0.0
Swahney et al., 2017[21] (overall)	Appraisal score	4.6	4.8	4.7	0.2
	Overall assessment	4.0	4.0	4.0	0.0
Swahney et al., 2017[21] (CAM section)	Appraisal score	4.5	4.4	4.4	0.0
	Overall assessment	4.0	3.0	3.5	0.7
Paice et al., 2016[22] (overall)	Appraisal score	5.8	6.0	5.9	0.1
	Overall assessment	6.0	5.0	5.5	0.7
Paice et al., 2016[22] (CAM section)	Appraisal score	5.0	5.1	5.0	0.0
	Overall assessment	6.0	5.0	5.5	0.7

Guideline	Metric	Appraiser 1	Appraiser 2	Average	Standard Deviation
Denlinger et al., 2014[25] (overall)	Appraisal score	4.4	4.4	4.4	0.0
	Overall assessment	4.0	3.0	3.5	0.7
Denlinger et al., 2014[25] (CAM section)	Appraisal score	4.0	3.8	3.9	0.1
	Overall assessment	4.0	3.0	3.5	0.7
Espitalier et al., 2014[26] (overall)	Appraisal score	3.3	3.6	3.4	0.2
	Overall assessment	3.0	5.0	4.5	1.4
Espitalier et al., 2014[26] (CAM section)	Appraisal score	2.9	2.8	2.9	0.0
	Overall assessment	3.0	3.0	3.0	0.0
Binczak et al., 2014[23] (overall)	Appraisal score	3.5	3.6	3.6	0.0
	Overall assessment	3.0	4.0	3.5	0.7

Guideline	Metric	Appraiser 1	Appraiser 2	Average	Standard Deviation
Binczak et al., 2014[23] (CAM section)	Appraisal score	3.3	3.3	3.3	0
	Overall assessment	3.0	4.0	3.5	0.7
Swarm et al., 2013[29] (overall)	Appraisal score	4.6	4.7	4.7	0.0
	Overall assessment	4.0	4.0	4.0	0.0
Swarm et al., 2013[29] (CAM section)	Appraisal score	4.0	3.6	3.8	0.3
	Overall assessment	4.0	3.0	3.5	0.7
Swarm et al., 2010[37] (overall)	Appraisal score	4.6	4.6	4.6	0.0
	Overall assessment	4.0	4.0	4.0	0.0
Swarm et al., 2010[37] (CAM section)	Appraisal score	3.6	3.3	3.4	0.2
	Overall assessment	4.0	3.0	3.5	0.7

Guideline	Metric	Appraiser 1	Appraiser 2	Average	Standard Deviation
Davies et al., 2009[38] (overall)	Appraisal score	4.0	4.6	4.3	0.4
	Overall assessment	4.0	5.0	4.5	0.7
Davies et al., 2009[38] (CAM section)	Appraisal score	3.3	3.7	3.5	0.3
	Overall assessment	4.0	3.0	3.5	0.7

Table 3. Overall Recommendations for Use of Appraised Clinical Practice Guidelines

Guideline	Overall Guideline		CAM Section	
	Appraiser 1	Appraiser 2	Appraiser 1	Appraiser 2
Lam et al., 2019[17]	Yes with modifications	Yes	Yes with modifications	Yes
Drewes et al., 2018[18]	No	No	No	No
Jara et al., 2018[20]	Yes with modifications	Yes with modifications	Yes with modifications	No
Swahney et al., 2017[21]	Yes with modifications	No	Yes with modifications	No
Paice et al., 2016[22]	Yes	Yes	Yes	Yes with modifications
Binczak et al., 2014[23]	No	Yes with modifications	No	Yes with modifications
Denlinger et al., 2014[25]	Yes	Yes with modifications	Yes with modifications	No
Espitalier et al., 2014[26]	Yes with modifications	Yes	No	No
Swarm et al., 2013[29]	Yes	Yes with modifications	Yes with modifications	No

Guideline	Overall Guideline		CAM Section	
	Appraiser 1	Appraiser 2	Appraiser 1	Appraiser 2
Swarm et al., 2010[37]	Yes	Yes with modifications	Yes	No
Davies et al., 2009[38]	Yes with modifications	Yes	Yes with modifications	No

Table 4. Scaled Domain Percentages for Appraisers of Each Clinical Practice Guideline

Guideline	Domain Score (%)					
	Scope and Purpose	**Stakeholder Involvement**	**Rigor of Development**	**Clarity of Presentation**	**Applicability**	**Editorial Independence**
Lam et al., 2019[17]						
Overall guideline	88.9	66.7	55.2	88.9	0	66.7
CAM section	88.9	63.9	59.4	88.9	0	62.5
Drewes et al., 2018[18]						
Overall guideline	88.9	36.1	37.5	91.7	20.8	0.0
CAM section	86.1	27.8	36.5	61.1	4.2	0.0
Jara et al., 2018[20]						

Guideline	Domain Score (%)					
	Scope and Purpose	**Stakeholder Involvement**	**Rigor of Development**	**Clarity of Presentation**	**Applicability**	**Editorial Independence**
Overall guideline	86.1	25.0	36.5	83.3	12.5	29.2
CAM section	88.9	30.6	28.1	47.2	8.3	29.2
Swahney et al., 2017[21]						
Overall guideline	97.2	69.4	70.0	72.2	14.6	45.8
CAM section	97.2	69.4	63.5	63.9	8.3	45.8
Paice et al., 2016[22]						
Overall guideline	100.0	75.0	90.6	97.2	58.3	45.8

Guideline	Domain Score (%)					
	Scope and Purpose	**Stakeholder Involvement**	**Rigor of Development**	**Clarity of Presentation**	**Applicability**	**Editorial Independence**
CAM section	100.0	50.0	80.2	83.3	35.4	37.5
Binczak et al., 2014[23]						
Overall guideline	91.7	47.2	30.2	86.1	14.6	0.0
CAM section	97.2	41.7	25.0	83.3	6.2	0.0
Denlinger et al., 2014[25]						
Overall guideline	86.1	47.2	51.0	88.9	22.9	75.0
CAM section	86.1	27.8	50.0	72.2	6.2	58.3
Espitalier et al., 2014[26]						

Guideline	Domain Score (%)					
	Scope and Purpose	**Stakeholder Involvement**	**Rigor of Development**	**Clarity of Presentation**	**Applicability**	**Editorial Independence**
Overall guideline	88.9	36.1	35.4	91.7	0.0	0.0
CAM section	80.6	16.7	22.9	77.8	0.0	0.0
Swarm et al., 2013[29]						
Overall guideline	77.8	55.6	51.0	97.2	39.6	75
CAM section	77.8	27.8	40.6	83.3	16.7	58.3
Swarm et al., 2010[27]						
Overall guideline	75.0	47.2	54.2	94.4	37.5	75.0

Guideline	Domain Score (%)					
	Scope and Purpose	**Stakeholder Involvement**	**Rigor of Development**	**Clarity of Presentation**	**Applicability**	**Editorial Independence**
CAM section	86.1	22.2	40.6	58.3	6.2	45.8
Davies et al., 2009[38]						
Overall guideline	88.9	38.9	62.5	72.2	10.4	62.5
CAM section	80.6	22.2	50.0	50.0	2.1	41.7