Review Article

Pain in Long-Term Survivors of Childhood Cancer: A Systematic Review of the Current State of Knowledge and a Call to Action From the Children's Oncology Group

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Survivors of childhood cancer may be at risk of experiencing pain, and a systematic review would advance our understanding of pain in this population. The objective of this study was to describe: 1) the prevalence of pain in survivors of childhood cancer, 2) methods of pain measurement, 3) associations between pain and biopsychosocial factors, and 4) recommendations for future research. Data sources for the study were articles published from January 1990 to August 2019 identified in the PubMed, PsycINFO, EMBASE, and Web of Science data bases. Eligible studies included: 1) original research, 2) quantitative assessments of pain, 3) articles published in English, 4) cancers diagnosed between birth and age 21 years, 5) survivors at 5 years from diagnosis and/or at 2 years after therapy completion, and 6) a sample size >20. Seventy-three articles were included in the final review. Risk of bias was considered using the Cochrane risk of bias tool. The quality of evidence was evaluated according to Grading of Recommendations Assessment Development and Evaluation (GRADE) criteria. Common measures of pain were items created by the authors for the purpose of the study (45.2%) or health-related quality-of-life/health status questionnaires (42.5%). Pain was present in from 4.3% to 75% of survivors across studies. Three studies investigated chronic pain according the definition in the International Classification of Diseases. The findings indicated that survivors of childhood cancer are at higher risk of experiencing pain compared with controls. Fatigue was consistently associated with pain, females reported more pain than males, and other factors related to pain will require stronger evidence. Theoretically grounded, multidimensional measurements of pain are absent from the literature. ***Cancer* 2020;0:1-10**. © *2020 American Cancer Society*.

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Currently, there are over 500,000 survivors of pediatric cancer in North America alone.[1] Given increasing survival rates for this population, it is imperative that we maximize long-term quality-of-life outcomes. There is emerging research documenting significant pain, including chronic pain (ie, pain lasting >3 months)[2] among survivors of pediatric cancer. It has been noted that pain (eg, musculoskeletal pain, headaches, generalized pain) significantly affects quality of life[3] and psychosocial well-being. Survivors of pediatric cancer may have a unique relationship to pain, given the prominence of pain across multiple points of the cancer journey. In addition, because pain in the general population has been linked to many negative health consequences, including poorer sleep and mental health, it is critical to examine pain among survivors of childhood cancer because their risks for late effects may be compounded by the experience of pain.

Pain among children and adolescents has been conceptualized using a biopsychosocial framework.[4] This framework proposes that there are bidirectional relations among biologic (eg, sex), psychological (eg, anxiety), and social

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(eg, socioeconomic status) factors that contribute to the presence and effect of pain.[5-7] More recently, Alberts and colleagues proposed a model of pain pathways specific to survivors of childhood cancer that considers the influence of a cancer diagnosis, disease-related and treatment-related pain, as well as procedural pain in the development of chronic pain among survivors.[8] Despite the availability of these conceptual models, the literature focused on pain in survivors of pediatric cancer has centered on biomedical risk factors. The research examining the biopsychosocial factors related to pain requires further elucidation.

Therefore, the objective of our study was to evaluate the available evidence of pain in survivors of childhood cancer through a systematic review of the literature. The objectives of this review were: 1) to characterize the prevalence of pain (including chronic pain) in survivors of childhood cancer after completion of treatment, 2) to describe what methods are being used to measure pain, 3) to examine associations between pain and biologic/physical and psychosocial factors, and 4) to make specific recommendations for more rigorous research of pain among long-term survivors of childhood cancer.

METHODS

Cochrane guidelines and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for the completion of systematic reviews were followed.[9,10] In March 2016, the Children's Oncology Group (COG) Guideline Task Force on Neurocognitive and Psychosocial Late Effects performed an extensive review of the literature to identify updates for the COG Long-Term Follow-Up Guidelines (version 5.0). That review was updated for the current report.

The databases searched included PubMed (web-based), PsycINFO (EBSCO Information Services), EMBASE (Ovid), and Web of Science (Thomson Reuters). Full PubMed search parameters are available in the online material (see Supporting Table 1). Search strategies for PsycINFO, EMBASE, and Web of Science were adjusted for the syntax appropriate for each database using a combination of thesauri and text words. Relevant articles published from January 1990 to August 2019 were included. Narrative and systematic reviews and meta-analyses on this topic were also evaluated to identify relevant original publications, but the reviews themselves were not included in the current analysis. Dissertations, books, book chapters, editorials, letters, case studies, and conference proceedings/abstracts were excluded.

Inclusion and exclusion criteria were determined before article selection. Eligible studies 1) were original research, 2) included quantitative assessment of pain (including chronic pain), 3) were published in English, 4) included children who had been diagnosed with cancer between birth and age 21 years, 5) described survivors of any age who were at least 5 years from diagnosis and/or 2 years from the completion of therapy, and 6) included a sample size >20 (to avoid case studies). Studies that had a wide range of ages and/or intervals from diagnosis and treatment were retained only if the mean age and/or time interval included the aforementioned criteria.

Data extraction was completed according to the Late Effect Evidence Table developed by the COG Late-Effects Guideline Task Force and included study design, median follow-up time, participation rate, and a description of study objectives. The risk of bias was considered for each study using domains adapted from the Cochrane risk of bias tool,[10] including selection/subject bias, attrition bias, instrumentation, and missing data and reporting outcomes. Each category was labeled *low risk of bias*, *high risk of bias*, or *unclear*.[10] The quality of evidence and strength of recommendations according to criteria from the Grading of Recommendations Assessment Development and Evaluation (GRADE) were completed.[11] Specifically, evidence was graded according to 3 categories: 1) level A, high level of evidence; 2) level B, moderate to low level of evidence (eg, risk factor is significant in >50% of studies), and 3) level C, very low level of evidence (eg, risk factor is significant in <50% of studies). Data extraction and quality assessments were completed by 1 independent rater for each published study.

RESULTS

Data Extraction

This review yielded 4302 unique publication titles/abstracts, of which 73 articles were included in the final review (see Supporting Fig. 1). Disagreements were resolved in all cases through consensus. Reasons for further exclusion are presented in Supporting Figure 1.

Quality Assessment

Quality assessment was completed for each study independently and by considering the following 4 key criteria: 1) selection/subject bias, 2) attrition, 3) instrumentation and missing data, and 4) reporting measurement outcomes (see Supporting Table 2).[3,12-83] Of the 73 studies reviewed, 36% reported a low risk of

TABLE 1. Grading of Recommendations Assessment Development and Evaluation (GRADE) Assessment for Factors Related to Pain

Factor Assessed	GRADE[a]	Reference(s)
Disease-related factors		
Diagnosis		
Neuroblastoma	Level C (1 of 1 study)	Portwine 2016[64]
Brain tumor	Level C (1 of 1 study)	Hsiao 2016[40]
High-risk acute lymphoblastic leukemia	Level C (1 of 1 study)	Hsiao 2016[40]
Hodgkin lymphoma	Level C (2 of 2 studies)	Barr 2001,[15] Shimoda 2008[75]
Germ cell tumor	Level C (1 of 1 study)	Shimoda 2008[75]
Wilms tumor	Level C (2 of 2 studies)	Barr 2001,[15] Crom 1999[29]
Osteosarcoma	Level C (2 of 2 studies)	Crom 1999,[29] Kelada 2019[45]
Soft-tissue sarcoma	Level C (1 of 1 study)	Kelada 2019[45]
Development of post-treatment meningioma	Level C (1 of 1 study)	Bowers 2017[22]
History of disease recurrence or progression	Level C (1 of 1 study)	Recklitis 2019[69]
Treatment-related factors		
Treatment		
Hemiabdominal radiation in children with Wilms tumor	Level C (1 of 1 study)	Crom 1999[29]
Hematopoietic stem cell transplantation in children with neuroblastoma	Level C (1 of 1 study)	Portwine 2016[64]
Lower extremity amputation in children with osteosarcoma	Level C (1 of 1 study)	Crom 1999[29]
Abdominal radiation in children with soft-tissue sarcomas	Level C (1 of 1 study)	Marina 2013[52]
Total knee replacement	Level C (1 of 1 study)	Katsumoto 2019[44]
Radiation	Level C (3 of 3 studies)	Crom 1999,[29] Odame 2006,[61] Recklitis 2019[69]
Biologic factors		
Age		
Some evidence suggests that younger age at diagnosis is associated with increased pain	Level C (3 of 4 studies)	Cox 2009,[28] Lu 2011,[51] Meeske 2005,[53] van Dijk 2008[78]
Some evidence suggests that younger age at diagnosis is associated with increased pain in females but not in males	Level C (1 of 1 study)	Cox 2009[28]
Some evidence suggests that age at the time of study is associated with pain	Level C (4 of 5 studies)	Boman 2009,[20] Hudson 2003,[39] Marina 2013,[52] Meeske 2005,[53] Recklitis 2019[69]
Sex		
There is evidence to suggest that females report more pain than males	Level A (9 of 9 studies)	Alessi 2007,[12] Arpaci 2016,[13] Hudson 2003,[39] Bowers 2012,[21] Lu 2011,[51] Marina 2013,[52] Pogany 2006,[63] Recklitis 2019,[69] Sadighi 2014[72]
Psychological factors		
Sleep		
Some evidence suggests that pain is associated with excessive daytime sleepiness	Level C (1 of 1 study)	Rach 2017[66]
Some evidence suggests that pain is associated with sleep difficulties	Level C (2 of 2 studies)	Rach 2017,[66] Berg & Hayashi 2012[18]
Fatigue		
There is evidence to suggest that pain is associated with increased fatigue	Level A (6 of 6 studies)	Kelada 2019,[45] Meeske 2005,[53] Rach 2017,[66] Rueegg 2013,[71] Sadighi 2014,[72] Zeller 2014[82]
Psychological distress		
Some evidence suggests that pain is associated with increased psychological distress	Level C (3 of 3 studies)	Brinkman 2013,[26] D'Agostino 2016,[31] Oancea 2014[60]
Body image		
Some evidence suggests that pain is associated with poorer body image	Level C (1 of 1 study)	Boman 2013[19]
Sports/physical activity-related self-confidence		
Some evidence suggests that pain is associated with decreased sports/physical activity-related self-confidence	Level C (1 of 1 study)	Boman 2013[19]
Anxiety		
Some evidence suggests that pain is associated with increased anxiety	Level C (2 of 2 studies)	Cox 2009,[28] Oancea 2014[60]
Depression		
Some evidence suggests that pain is associated with increased depression	Level C (3 of 3 studies)	Brinkman 2013,[26] Meeske 2005,[53] Oancea 2014[60]
Suicidal ideation		
Some evidence suggests that pain is associated with suicidal ideation	Level C (2 of 2 studies)	Recklitis 2006,[67] 2010[68]
Quality of life		
Evidence suggests that pain is associated with reduced quality of life	Level B (3 of 3 studies)	Finnegan 2009,[33] Schultz, 2014[73] Recklitis 2019[69]
Social factors		
Socioeconomic status		
Some evidence suggests lower socioeconomic status is associated with increased pain	Level C (3 of 3 studies)	Crom 1999,[29] Hudson 2003,[39] Oancea 2014[60]
Ethnic background		

TABLE 1. *Continued*

Factor Assessed	GRADE[a]	Reference(s)
Some evidence suggests that individuals of Hispanic or African American background are associated with increased pain	Level C (1 of 1 study)	Lu 2011[51]
Educational level		
Some evidence suggests lower educational level and not completing high school are associated with increased pain	Level C (3 of 3 studies)	Langeveld 2005,[49] Lu 2011,[51] Punyko 2007[65]
Employment status		
Some evidence suggests that current employment status is related to pain	Level C (1 of 1 study)	Alessi 2007[12]
Relationship status		
Some evidence suggests that single status is associated with increased pain	Level C (2 of 2 studies)	Alessi 2007,[12] Punyko 2007[65]

[a]Level A indicates a high level of evidence; level B, moderate-to-low level of evidence (eg, risk factor is significant in >50% of studies); level C, very low level of evidence (eg, risk factor is significant in <50% of studies).

bias with respect to selection/subject bias (n = 26 of 73), 1% reported a low risk of bias for attrition (n = 1 of 73), 19% reported a low risk of bias for instrumentation and missing outcomes (n = 14 of 73), and 7% reported a low risk of bias for reporting outcomes (n = 5 of 73). GRADE assessments are provided in Table1.[12,13,15,16,18-22,24-26,28,29,31-34,36,38-41,44,45,49-53,60,61,63-69,71-73,75,76,78,80,82-89]

DATA SYNTHESIS

Descriptive Characteristics of Included Studies

Supporting Table 2 provides descriptive characteristics of the studies included. Studies were largely observational, cross-sectional study designs (46.6%; n = 34); and the remaining studies were categorized as observational, cohort studies (41.1%; n = 30); observational, case control studies (11%; n = 8); and nonexperimental studies (1.3%; n = 1). Three studies evaluated pain longitudinally (4.1%). Of all the studies reviewed, 24 (32.9%) included a comparison group of healthy or population controls (n = 10), siblings (n = 13), and other cancer survivors (eg, a comparison of survivors with vs without meningioma, survivors with vs without chronic fatigue, and various diagnoses; n = 3). The remaining 67.1% of studies did not include any comparison sample. The sample size of studies ranged from 25 to 20,051 participants. The length of follow-up ranged from an average of 5.4 to 32 years after diagnosis. Among the current sample of studies reporting pain in their results, only 13 (17.8%) identified pain in their specific study objectives. Of those 13 studies, 3 used a comparison group in their analyses.

Objective 1: What Is the Prevalence of Pain?

Only 3 studies investigated chronic pain according to a definition of pain lasting >3 months. The prevalence of chronic pain was identified in 11% to 43.9% of survivors.[21,41,72] These 3 studies focused specifically on survivors of acute lymphoblastic leukemia (ALL) and lymphoma, particularly chronic headache,[80] chronic hip pain, and/or chronic back pain in ALL survivors,[65] or any type of chronic pain in lymphoma survivors.[20] The study reporting on any type of chronic pain reported the highest prevalence. Only 1 of these studies included a control group.[21] The overall occurrence of any pain reported across studies was between 4.3% and 75%.[16,32]

Twenty-four studies included control groups. Of these, evidence suggested that survivors of childhood cancer are at higher risk of experiencing any occurrence of pain (GRADE level B, 21 of 25 studies). Evidence from these studies generally suggests that survivors reported more pain compared with controls and population norms,[21,16,34,36,51,64,65,80] with the exception of 5 studies.[20,38,49,63,76]

Of those 5 studies, 1 found that survivors reported significantly less bodily pain than their healthy peers,[49] whereas the other 4 studies demonstrated that survivors had no significant differences in pain compared with controls.[20,38,63,76] Importantly, the 1 study that showed less bodily pain in cancer survivors compared with healthy peers was a sample comprised of 45% females in the cancer survivor sample versus 55% females in the healthy peers.

Objective 2: Methods for Measuring Pain

Specific measures for measuring pain varied, and most were self-reports or parent-proxy reports (see Table 2). The most commonly used measures of pain were items created by the authors for the purpose of the study (45.2%) or items derived from health-related quality-of-life or health status questionnaires (42.5%). Most author-created measures were limited to only 1 or2 items. Examples of items created by authors include,

TABLE 2. Frequency of Measures of Pain Included in Studies

Measure	No. of Studies Using Measure (%)
Author-created measures	33 (45.2)
Health-related quality-of-life or health status measures	31 (42.5)
Disease-specific measures	9 (12.3)
Valid pain measures	7 (9.6)
Chart review	2 (2.7)
Unclear	2 (2.7)

"Does your child currently have pain as a result of his/her cancer, leukemia, tumor, or similar illness or its treatment?"[24,25] Only a small minority of studies (9%) used independent pain measures that have been validated in other populations. One study[82] used an algometer, a validated measurement of pain tolerance and pain sensitivity. However, that study only used the algometer to measure pain sensitivity.

Objective 3: Factors Related to Pain

To conceptualize the factors related to pain, we considered an adapted theoretical model that incorporates the conceptual model of pain among survivors of childhood cancer developed by Alberts et al[8] as well as the biopsychosocial model of pain (see Fig. 1). The available literature according to these factors is summarized below. The evidence related to these factors, as evaluated using the GRADE criteria, can be found in Table 1.

Disease-related pain

Disease-related pain factors explored in the literature included diagnosis, treatment, and age at diagnosis. Six studies reported on diagnosis, in which survivors of germ cell tumor, high-risk ALL, neuroblastoma, Hodgkin lymphoma, Wilms tumor, and osteosarcoma reported more pain compared with population norms, as did survivors who developed subsequent meningioma compared with those who did not.[15,22,29,40,64,75]

Survivors of bone and soft-tissue sarcomas were almost 5 times more likely to report cancer-related pain compared with survivors of leukemia in 1 study.[45] Another study found that brain tumor survivors reported experiencing more pain than those diagnosed with ALL treated on a standard-risk or high-risk protocol as well as those diagnosed with a solid tumor.[40] Finally, 1 study indicated that a history of disease recurrence or progression was significantly related to pain.[69]

There was conflicting evidence that age at diagnosis was related to pain, with 3 studies indicating that younger age was significantly related to increased reports of pain,[28,51,78] and 1 study demonstrating no association between age at diagnosis and pain.[53]

Treatment-related pain

Children diagnosed with Wilms tumor who received hemiabdominal radiation, children with neuroblastoma who underwent hematopoietic stem cell transplantation, children with osteosarcoma who underwent lower extremity amputation, and children diagnosed with soft-tissue sarcomas who received abdominal radiation all were more likely to report more pain during survivorship compared with their survivor peers who did not receive these therapies.[21,16,64]

Hsiao and colleagues[40] observed that ALL survivors who were treated on a high-risk protocol reported experiencing significantly greater pain than survivors treated on a standard-risk protocol,[40] whereas Meeske and colleagues found no associations between pain with treatment in survivors of ALL.[53] Survivors who had undergone total knee replacement surgery were also more likely to report pain in their limbs than those who had undergone other surgical procedures.[44] In addition, it was observed that radiation therapy put survivors at increased risk for pain.[69] Another study explored small-fiber toxicity and pain sensitization in survivors of ALL and discovered that survivors with increased pain sensitization suffered from at least 2 or 3 losses of quantitative sensory testing parameters.[50]

Biologic factors

Biologic factors explored in relation to pain included age and sex. There was robust evidence in the current literature to support the finding that females report significantly more pain than males.[12,13,21,39,51,52,63,69,72] Data supporting age at the time of study were inconsistent: 1 study indicated that pain was negatively associated with age,[20] and other studies indicated that pain was positively associated with age.[39,52,53] Recklitis and colleagues[69] separated survivors into 3 different age groups and found that survivors who were currently ages 13 to 17 years had a higher frequency of pain than those ages 18 to 22 years, but not those ages 23 to 31 years.[69] Interestingly, Cox et al[28] found that younger age at diagnosis was associated with pain in male survivors, but not in female survivors.[28]

Psychological factors

Psychological factors examined in the literature included sleep, fatigue, emotional distress, and quality of life. Fatigue and daytime sleepiness were consistently positively related to pain.[45,53,66,71,72,82] Sleep difficulties also were associated with increased reports of pain.[18,66] With

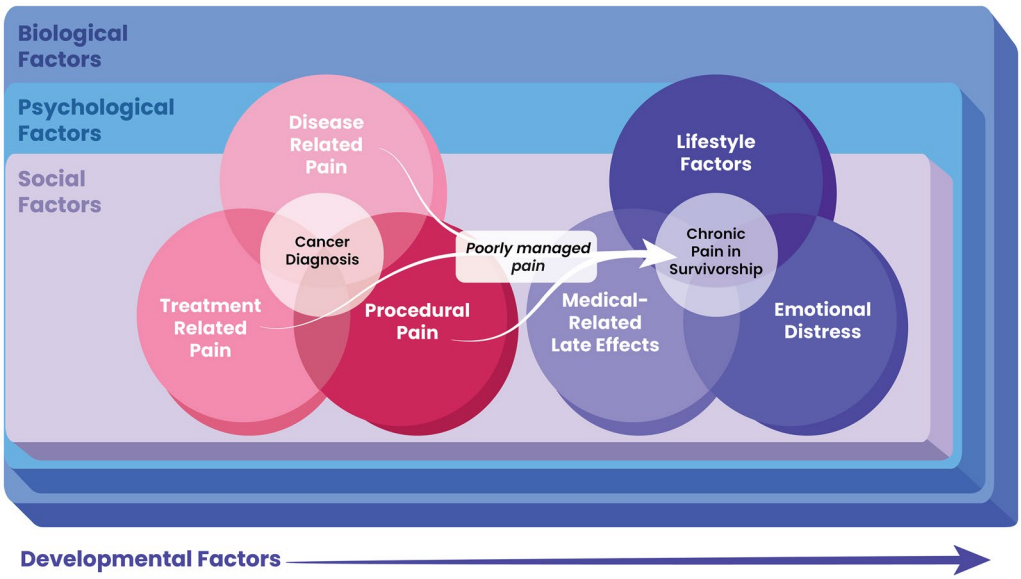

Figure 1. A conceptual model of the factors associated with pain in survivors of childhood cancer.

respect to emotional distress, 1 study found that pain was associated with poorer body image and sports/physical activity-related self-confidence,[19] and another found that headaches were associated with emotional symptoms affecting daily activities and work.[72] Pain was positively associated with global emotional distress,[26,31,60] anxiety,[28,60] depression,[53,26,60] and suicidal ideation.[67,68] Finally, it was generally observed that more pain was significantly related to decreased health-related quality of life.[33,73] Importantly, survivors who reported experiencing cancer-related pain were also more likely to report unmet information needs for managing pain as well as fear of cancer recurrence.[45]

Social factors

Only 5 studies examined social factors related to pain in the current sample. Survivors with lower socioeconomic status had increased reports of pain[29,39,60] as well as survivors with lower educational attainment[49] and those who did not complete high school.[51,65] Other social factors related to increased pain included identifying as Hispanic or African American,[51] single relationship status,[51,65] and being unemployed.[51]

Objective 4: Recommendations for Future Research in Pain Among Survivors of Childhood Cancer

Based on the existing literature and, more specifically, the gaps in the existing literature, we have also considered areas for future research in pain among survivors of childhood cancer. These recommendations are summarized in Table 3.

DISCUSSION

The objectives of the current review were to characterize the prevalence of pain (including chronic pain) in survivors of childhood cancer, describe the measurement of pain, examine factors associated with pain, and provide recommendations for future work in this field. The results of this study revealed significant gaps in the assessment of pain among survivors of childhood cancer, leading to a wide range of prevalence rates reported among the literature and limiting our understanding of pain in this vulnerable population. The majority of the included studies reported pain outcomes based on a single item or very few items and did not use theoretically grounded, multidimensional measurements of pain. In addition, rigorous, high-quality studies assessing pain among this population are limited.

Importantly, we have proposed a conceptual model that amalgamates 2 existing pain frameworks[7,8] in an attempt to capture the complex contributions to pain among this unique population. Based on our review, with respect to the factors found to be related to pain, only a few factors emerged consistently in their relation to pain. Females were more likely to report pain than males, which is consistent with chronic noncancer pain populations. Fatigue was also a prominent comorbid concern alongside pain in survivors of childhood cancer. These findings

TABLE 3. Directions for Future Research

Background	1. Adapt current models of pain to unique characteristics of cancer survivors
	2. Reach consensus on a consistent definition of pain to be applied to survivors of childhood cancer
Measurement	1. Identify theoretically grounded, multidimensional measurements of pain for use as assessment, including intensity, duration, frequency, location, affect, chronicity, and interference
	2. Determine reliability and validity of identified measures when applied among survivors of childhood cancer
	3. Identify potential screening tools that might be used in the context of clinical assessment
Research design	1. Conduct epidemiological studies to clarify prevalence, severity, duration, location, and interference of pain
	2. Conduct longitudinal studies to identify potential directionality of relations among factors
Factors related to pain	1. Identify specific diagnoses (eg, osteosarcoma, leukemia) and treatment exposures (eg, vincristine, steroid use) related to the experience of pain
	2. Broaden exploration of psychological factors that might be related to pain, including pain catastrophizing, intolerance of uncertainty, fear of cancer recurrence
	3. Consider social factors (eg, SES) and cultural factors (eg, ethnicity) related to the experience of pain
	4. Consider factors that may be comorbid with pain, including fatigue and sleep
Intervention	1. Assess the strength of evidence regarding pain management strategies among survivors of childhood cancer
	2. Develop and/or adapt interventions that may target pain in survivors of childhood cancer considering the possibility of multipronged approaches based on findings related to factors related to pain
	3. Test interventions for feasibility and acceptability among survivors of childhood cancer
	4. Conduct randomized controlled trials of interventions deemed to be feasible among this population
Clinical care	1. Develop care coordination and communication methods, implementation standards, and evaluation measures among multidisciplinary teams for surveillance and potential interventions for prevention and/or treatment

have important implications for developing interventions that target pain and fatigue concurrently, which may also include components of sleep as well. The chronic noncancer pain literature has demonstrated that pain may disrupt sleep and, subsequently, lack of sleep may exacerbate pain, leading to a cycle that is hard to overcome.[84] The only other factor that demonstrated a moderate level of evidence in its relation to pain was quality of life. The finding that quality of life is related to pain highlights that, perhaps regardless of prevalence rates, pain among survivors of childhood cancer negatively affects the quality of survivorship, thereby warranting intervention.

Strong evidence supports the use of behavioral interventions for the management of procedural pain[85] in pediatric patients with cancer, and generally the most effective pain management approaches combine pharmacologic approaches with psychosocial procedural preparation and intervention.[86-88] Little research has been conducted with respect to interventions for chronic pain among survivors of childhood cancer; however, considerable evidence also supports the use of behavioral interventions for the management of chronic pain among noncancer populations.[89] Certainly, given increasing concerns regarding the use of opioids to manage pain, attention must now turn to research focused on behavioral interventions specific to survivors of childhood cancer.

The remaining factors reported in the literature reviewed were considered to have very low evidence for their relation to pain, reinforcing our call to action for more work in this field. Certainly, based on the current review, pain has not been a priority in the pediatric cancer survivor literature, as evidenced by the absence of pain as a primary outcome in the majority of studies and the use of 1 or 2 items driving analyses around pain outcomes. Accordingly, we advocate for a commitment to future research in this field within the domains of our background theoretical understanding of pain, improved measurement, enhanced research design, factors related to pain, intervention, and clinical care.

This review was not without limitations. To begin, we intentionally left our definition of pain broad to capture the broad range of studies that have assessed pain among survivors; however, this limited our ability to be more specific in describing outcomes. In addition, as part of our search, we excluded qualitative publications. Despite this, we acknowledge the strength of qualitative research to better capture the context of one's experiences and provide greater perspective to quantitative findings. Finally, we acknowledge that, within our review, we did not take into account the era of treatment for studies reviewed. We are aware that treatment protocols have shifted significantly over the last several decades in favor of less toxic therapies; therefore, we might expect differing prevalence rates of pain over time.

Conclusions

In summary, although many studies have reported on pain in survivors of childhood cancer, the quality of pain assessment across these studies is quite poor, as evidenced by inconsistent findings and a large range of reported pain prevalence. Based on the results, it is important that future research on this topic use more comprehensive

measures of pain as well as longitudinal designs to disentangle this complex, multidimensional construct. Deeper understanding of pain experienced by this population will inform future research into tailored interventions that address the complex and unique histories of survivors of childhood cancer. Clinically, greater attention to the experience of pain is warranted during regular follow-up appointments.

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CONFLICT OF INTEREST DISCLOSURES

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