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Symptoms in Children Receiving Treatment for Cancer—Part II: Pain, Sadness, and Symptom Clusters CE

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Abstract

Children and adolescents receiving treatment for cancer experience multiple symptoms as a consequence of their disease and its treatment that interfere with the child's quality of life. Understanding of symptom assessment in children with cancer is foundational to the work of the Children's Oncology Group Nursing Discipline, whose research aims are to address knowledge gaps including understanding illness-related distress. This article is the second of a two-part summary of current evidence addressing the assessment of symptoms frequently reported by children and adolescents receiving treatment for cancer. Studies reporting assessment of pain, sadness, and symptom clusters published between January 2008 and May 2018 were included. Forty-three publications addressed pain. Pain was highly prevalent and distressing, varied in its trajectory across a cycle of chemotherapy and across multiple cycles of treatment, and correlated with biomarkers associated with the pain response. Consequences of pain were poorer functional status and emotional health. Twenty publications addressed sadness. Sadness was the most prevalent psychosocial symptom. Its prevalence decreased over the course of treatment and over a cycle of chemotherapy. Persistent sadness was of greater severity and distress. Eight publications addressed symptom clusters. These studies identified both groups of co-occurring symptoms and groups of patients with common symptom profiles. This two-article series provides evidence for the distressing nature of symptoms among children receiving cancer treatment. Efforts to support clinicians in routine symptom assessment are needed. Additional research directed at alleviating symptoms and building resilience among the child experiencing symptoms is needed.

Keywords

symptoms, childhood cancer, pain, sadness, symptom clusters

Introduction

Children and adolescents receiving treatment for cancer experience multiple symptoms as a consequence of their disease and its treatment. These symptoms interfere with the child's quality of life, including his or her ability to engage in daily, developmentally appropriate activities (Kestler & LoBiondo-Wood, 2012). The distress children and adolescents experience from these symptoms affects not only themselves but extends to their parents and siblings as well (Linder, Bratton, Nguyen, Parker, & Wawrzynski, 2018; Pöder, Ljungman, & von Essen, 2010). As the intensity of treatment for childhood cancer continues to increase, greater attention needs to be placed on alleviating symptoms. The first step in alleviating symptoms is symptom assessment.

An understanding of symptom assessment in children with cancer is foundational to the work of the Children's Oncology Group (COG) Nursing Discipline, which has focused its research aims on key knowledge gaps that include understanding illness-related distress (Landier, Leonard, & Ruccione, 2013). This focus is aligned with the organizing framework for the COG Nursing Discipline (Hooke & Linder, 2019), which aims to appreciate how children and their families sustain or regain optimal health in the context of serious illness, and is based on

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"doing well" concepts, such as resilience, quality of life, courageous coping, and hope (Kelly, Hooke, Ruccione, Landier, & Haase, 2014).

Purpose

This article is the second of a two-part summary (see also, Part I: Hooke & Linder, 2019) of the current evidence addressing the assessment of symptoms frequently reported by children and adolescents receiving treatment for cancer. Data presented in these articles were presented at the COG Nursing Discipline State of the Science Symposium: Symptom Assessment During Childhood Cancer Treatment in October 2018 (R13CA232442). Specifically, this article reports summaries of studies reporting assessment of pain and sadness. The article also includes a presentation of studies meeting inclusion criteria that also reported symptom clusters.

Method

A detailed description of the search strategy has been reported in the first article in this two-part summary of symptoms (Hooke & Linder, 2019). Inclusion criteria were studies and systematic reviews published between January 2008 and May 2018, with a primary focus on symptom assessment among children and adolescents receiving treatment for cancer. Studies with a primary emphasis on instrument development or evaluation of an intervention were excluded, as were those that addressed symptoms at end-of-life or following completion of therapy.

Publications meeting criteria for inclusion for each symptom were further organized based on its emphasis. Categories of emphasis for the purpose of this review were (1) systematic reviews, (2) incidence of the symptom, (3) correlates of the symptom, (4) trajectories of the symptom, (5) biomarkers associated with the symptom, and (6) the experience of the symptom. Publications that reported symptom clusters were organized according to the analytic approach—that is, whether the study sought to identify groups of related symptoms or groups of patients with similar symptom profiles.

Results

Pain

Conceptual Definition. Pain was defined using the International Association for the Study of Pain's (2017) definition, "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." Both acute and chronic sources of pain were considered in relation to the search.

Summary of Studies. After applying the search terms, 88 publications addressing pain and 269 publications addressing multiple symptoms were identified. Forty-three of these publications met criteria for inclusion and are presented in Table 1.

Publications from nine countries: the United States, Australia, Taiwan, Turkey, Thailand, Nigeria, China, Iran, and Canada, were included. Multiple strategies were used to measure pain and its correlates. These included self-report instruments completed by the child and/or parent, drawings, a heuristics-based app, interviews, salivary biomarkers, and medical record documentation.

Prevalence of Pain. Although causes of pain varied across the cancer treatment continuum, pain was consistently among the most prevalent symptoms reported by children, adolescents, and their parents (Baggott et al., 2009; Erickson et al., 2013; Kestler & LoBiondo-Wood, 2012). The prevalence of pain varied from 28% to 62% across studies (Abu-Saad Huijer et al., 2013; Baggott et al., 2012; Linder, Al-Qaaydeh, et al., 2018; Madi & Clinton, 2018; Olagunju et al., 2016; Williams et al., 2014; Williams et al., 2015).

Characteristics of Pain. Pain tended to be of moderate or greater severity and moderate or greater distress when it was reported (Jacob et al., 2008; Linder, Al-Qaaydeh, et al., 2018; Madi & Clinton, 2018; Olagunju et al., 2016; Williams et al., 2015). The most frequent locations of severe pain were the abdomen, lower back, forehead, and upper chest (Jacob et al., 2008; Madi & Clinton, 2018). Of note, approximately half of children who reported severe pain experienced breakthrough pain (Friedrichsdorf et al., 2007). Children often described the pain they experienced during these breakthrough episodes as "sharp" or "shooting." Younger children (7-12 years) were at greater risk for breakthrough pain compared with adolescents (Friedrichsdorf et al., 2007). Adolescent girls reported greater pain intensity compared with boys; however, their parents reported greater pain intensity for boys compared with girls (Hechler et al., 2009).

Sources of Pain. Studies also addressed distinct sources of pain. Approximately 26% of adolescents receiving chemotherapy reported neuropathic pain—that is, pain occurring as a consequence of damage to the somatosensory nervous system (Acquazzino et al., 2017; International Association for the Study of Pain, 2018). Neuropathic pain was most frequently attributed to treatment (Anghelescu et al., 2014) and was not associated with the cumulative dose of vincristine (Anghelescu et al., 2011). Three fourths of children undergoing amputation reported phantom limb pain—that is, pain perceived as arising in the missing limb (Burgoyne et al.,

Table 1. Studies Reporting Pain.

Title and authors	Sample	Pain measurement	Findings
Systematic reviews (n = 5)			
Multiple symptoms in pediatric oncology patients: A systematic review (Baggott, Dodd, Kennedy, Marina, & Miaskowski, 2009)	9 studies addressing multiple symptoms in children and adolescents with cancer	Varied based on study	Pain recognized as among most prevalent, severe, and distressing symptoms across studies Identified need for studies to examine changes over time, clusters, and relationships.
Symptoms and symptom clusters in adolescents receiving cancer treatment: A review of the literature (Erickson et al., 2013)	11 studies including adolescents with cancer	Varied based on study	Pain more severe at diagnosis; after diagnosis, tends to be of at least moderate intensity when present Causes of pain vary over time; cancer itself most frequent cause at diagnosis; after that, treatment-and procedure-related pain predominate Most frequent sites of pain: head, back, limb, mouth, abdomen Pain greater among hospitalized patients and intensity decreases over the course of the hospitalization Pain intensity persists over a cycle of chemotherapy Strength of evidence for the description of pain was low to moderate
Review of symptom experiences in children and adolescents with cancer (Kestler & LoBiondo-Wood, 2012)	50 studies and 2 dissertations	Varied across studies	Pain was among most often reported and effectively managed symptoms Sources of pain included disease, chemotherapy, procedures, immediate post-op pain, and phantom pain from amputation Treatment or procedure pain reported as most bothersome
Self-reported pain in adolescents with leukemia or a brain tumor: A systematic review (Olson & Amari, 2015)	30 studies including adolescents 10-19 years with leukemia or a brain tumor	Varied across studies	Pain associated with the cancer itself, treatments, and procedures
Pain in children with central nervous system cancer: A review of the literature (Shepherd, Woodgate, & Sawatzky 2014)	34 articles involving children and adolescents with cancer	Varied across studies	Health-related theory of illness provides a framework for interpreting existing literature and investigating responses to pain
Studies of incidence/prevalence of symptom (n = 19)			
Studies with emphasis on pain in general (n = 14)			
Quality of life and symptom prevalence in children with cancer in Lebanon: The perspective of parents. (Abu-Saad Huijer, Sagherian, & Tamim, 2013)	85 children 7-18 years	MSAS 10-18	Pain reported by 28.2% of 7-12 years of age (second most prevalent) Pain reported by 54.3% of 13-18 year-olds (third most prevalent)
Symptom cluster analyses based on symptom occurrence and severity ratings among pediatric oncology patients during myelosuppressive chemotherapy (Baggott, Cooper, Marina, Matthay, & Miaskowski, 2012)	131 children, 10-18 years; about to receive chemotherapy	MSAS 10-18	62.6% reported pain during the week prior to chemotherapy
Breakthrough pain in children with cancer. (Friedrichsdorf, Finney, Bergin, Stevens, & Collins, 2007)	27 inpatients 7-18 years with severe pain	Breakthrough pain questionnaire for children	57% had one or more episodes of breakthrough pain with episodes lasting from seconds to minutes, occurring 3-4 times/day, and characterized as sharp or shooting Younger children (7-12 years) at higher risk of breakthrough pain

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Table 1. (continued)

Title and authors	Sample	Pain measurement	Findings
The symptom experiences of Puerto Rican children undergoing cancer treatments and alleviation practices as reported by their mothers (Gonzalez-Mercado, Williams, Williams, Pedro, & Colon, 2017)	62 children 1-17 years who had received two or more cycles of chemotherapy	Therapy-related symptom checklist for children	57% of mothers reported that their children had experienced pain; Pain was the eighth most frequently reported symptom
Sex differences in pain intensity in adolescents suffering from cancer: Differences in pain memories? (Hechler et al., 2009)	112 adolescents 12-18 years with malignant disease and their parents		Within the past 7 days and the past 4 weeks: Girls reported higher pain intensity than boys; Parents reported higher pain intensity for boys and lower pain intensity for girls
Intensity, location, and quality of pain in Spanish-speaking children with cancer (Jacob, McCarthy, Sambuco, & Hockenberry, 2008)	44 Spanish-speaking children 8-12 years; ambulatory setting	Spanish version of APPT	41% of children experienced pain with mean intensity rating of 5.7 (2.7) on 10-cm scale. If ≥ moderate severity, most frequent locations were abdomen, lower back, and upper chest
Relationships among therapy-related symptoms, depressive symptoms, and quality of life in Chinese children hospitalized with cancer: An exploratory study (Li, Williams, Lopez, Chung, & Chiu, 2013)	135 children and adolescents 9-16 years within 6 months of diagnosis	TRSC-C (children completed)	Pain of ≥ moderate severity 80% of the time it was reported
Symptom characteristics among hospitalized children and adolescents with cancer (Linder, Al-Qaaydeh, & Donaldson, 2018)	50 children and adolescents 7-18 years receiving inpatient chemotherapy	MSAS 7-12 plus item for neuropathy	54% reported pain at least once during the admission; When present, pain of ≥ moderate severity 55% of the time and of ≥ moderate distress 45% of the time.
Pain and its impact on the functional ability in children treated at the Children's Cancer Center of Lebanon (Madi & Clinton, 2018)	62 children 8-17 years	APPT and Functional Disability Inventory	57% reported pain at least "sometimes" with median duration of 2 hours/episode; Mean intensity 5.06 on 10-cm scale; Most frequent locations: forehead, abdomen, and lower back; Children used sensory words to describe pain frequency, duration, location, use of affective descriptors, and treatments predicted pain intensity
Child's symptom burden and depressive symptoms among caregivers of children with cancers: An argument for early integration of pediatric palliative care (Olagunju, Sarimiye, Olagunju, Habeebu, & Aina, 2016)	72 children 7-12 years	MSAS 7-12	62% reported pain; pain positively correlated with maternal depression (0.61; $p < .01$) When present, pain of ≥ moderate severity 58% of the time and ≥ moderate distress 70% of the time.

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Table 1. (continued)

Title and authors	Sample	Pain measurement	Findings
Monitoring and alleviation of symptom occurrence and severity among Thai children and adolescents during cancer treatments (Williams, Piamjariyakul, Shanberg, & Williams, 2015)	100 children 0-17 years	TRSC-C (mothers completed)	53% reported pain; 28% reported moderate or greater pain
Symptom occurrence and severity on the therapy-related symptom checklist for children among Hispanic pediatric oncology outpatients (Williams, Robinson, & Williams, 2014)	79 Hispanic children and adolescents 5-17 years; ambulatory setting	TRSC-C (mothers completed)	49% reported pain; 37% reported moderate or greater pain
The mediating role of resilience on quality of life and cancer symptom distress in adolescent patients with cancer (Wu et al., 2015)	40 adolescents 13-20 years	SDS	Mean pain severity 1.88 on a 1-5 scale; 25% reported pain severity scores beyond the midpoint
Assessment of symptoms reported by 10- to 18-year-old cancer patients in Taiwan (Yeh, Wang, Chiang, Lin, & Chien, 2009)	144 children 10-18 years (108 receiving treatment)	MSAS 10-18	41% reported pain; 19% reported quite a bit to very much distress with pain
Studies with emphasis on incidence of specific sources of pain (*n* = 5)			
Patient-reported neuropathic pain in adolescent and young adult cancer patients (Acquazzino et al., 2017)	78 patients 14-39 years; median 18.1 years; 47% female	PainDETECT—screening tool for neuropathic pain	26% of participants receiving therapy and 11% of participants off therapy reported neuropathic pain. Of those reporting neuropathic pain, only 26% had a clinical diagnosis documented.
Neuropathic pain referrals to a multidisciplinary pediatric cancer pain service (Anghelescu et al., 2014)	56 patients 2-28 years; over a 3.5-year period	Medical record review	15% of all referrals were for neuropathic pain Patients with neuropathic pain had a greater mean number of pain visits per consultation than other patients and more days of follow-up Most common cause of neuropathic pain was cancer treatment vs. the malignancy
Neuropathic pain during treatment for childhood acute lymphoblastic leukemia (Anghelescu et al., 2011)	498 patients 1-18 years with ALL	Medical record review	174 of 498 patients had 207 documented episodes of neuropathic pain; 16% (28 of 174) had at least one documented episode of recurrent pain White, non-Hispanic race was the only predictor of neuropathic pain No statistically significant relationship between cumulative dose of vincristine and severity of neuropathic pain
Phantom limb pain in young cancer-related amputees: Recent experience at St Jude children's research hospital (Burgoyne et al., 2012)	25 children, adolescents, and young adults 6-27 years	Medical record documentation	76% had phantom limb pain at some point in time; 64% had pre-amputation pain; 10% (2) still had phantom limb pain at one year postamputation. Phantom limb pain not associated with age or presence of pre-amputation pain.

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Table 1. (continued)

Title and authors	Sample	Pain measurement	Findings
Nonhematologic toxicity of imatinib mesylate in pediatric patients with chronic myelogenous leukemia: A predominance of musculoskeletal pain (Heym, Gressett Ussery, Trinkman, & Philpot, 2015)	9 children 2.8-17.5 years with CML in chronic phase receiving imatinib mesylate	Retrospective chart review covering an 8-year period	8 patients experienced pain and 3 had therapy discontinued because of pain.
Studies of correlation and causes of symptom (n = 6)			
Symptoms and symptom clusters identified by adolescents and young adults with cancer using a symptom heuristics app (Ameringer, Erickson, Macpherson, Stegenga, & Linder, 2015)	72 AYAs 13-29 years receiving chemotherapy	C-SCAT app featuring symptoms from MSAS 10-18	n = 26 (36%) reported pain; perceived causes of pain included chemotherapy, cancer, procedures, treatment, and GCSF injections; also perceived as caused by lack of energy, tingling in hands and feet, nausea, constipation, and worry
Quality of life and chemotherapy-related symptoms of Turkish cancer children undergoing chemotherapy (Arslan, Basbakkal, & Kantar, 2013)	93 children and adolescents 10-18 years receiving chemotherapy	PedsQL and MSAS	37 (40%) reported pain; patients reporting pain had lower emotional scores on the PedsQL subscale (p = .02)
Patterns of symptoms and functional impairments in children with cancer (Buckner et al., 2014)	200 children 8-17 years; receiving treatment or in survivorship	PROMIS Pain interference	Greater pain interference associated with poorer functional status. Those (n = 31) with greatest pain interference also reported other symptoms (anxiety, depression, fatigue) to be of high severity
Social support and symptom distress in adolescents/young adults with cancer (Corey, Haase, Azzouz, & Monahan, 2008)	199 AYA 10-26 years newly diagnosed with cancer	SDS	Social support from friends, family, or health care provider not predictive of distress from pain
The relationship between parent trait anxiety and parent-reported pain, solicitous behaviors, and quality of life impairment in children with cancer (Link & Fortier, 2016)	353 parents of children 0-18 years; children 8-18 years (n = 137) provided own measures of quality of life and pain	Pain VAS and PedsQL	Parent anxiety significantly associated with parent ratings of the child's pain severity and frequency and the parent's solicitous behaviors; Parent anxiety predicted parent's perception of the child's pain frequency and quality of life; No significant relationship between parent anxiety and child-reported pain and quality of life
Physical symptoms, perceived social support, and affect in adolescents with cancer (Wesley, Zelikovsky, & Schwartz, 2013)	102 adolescents 13-19 years	PedsQL Cancer Module Pain Subscale	Pain negatively correlated with negative affect (less pain = better affect); physical symptoms predicted negative affect after controlling for gender, minority status, and life events
Studies of trajectory of symptom (n = 9)			
Identifying symptom clusters in pediatric cancer patients using the Memorial Symptom Assessment Scale (Atay, Conk, & Bahar, 2012)	54 children 10-18 years	MSAS 10-18	Prevalence of pain 59%, 57%, and 37% prevalence at 1, 2, and 3 months postdiagnosis.

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Table 1. (continued)

Title and authors	Sample	Pain measurement	Findings
Changes in children's reports of symptom occurrence and severity during a course of myelosuppressive chemotherapy (Baggott et al., 2010)	66 children and adolescents 10-18 years	MSAS 10-18	Prevalence of pain did not decrease over a cycle of myelosuppressive chemotherapy. 75% of occasions pain was reported, it was of ≥ moderate severity
Anxiety, pain, and nausea during the treatment of standard-risk childhood acute lymphoblastic leukemia: A prospective, longitudinal study from the Children's Oncology Group (Dupuis et al., 2016)	160 children 2-9 years with standard risk ALL	PedsQL 3.0 proxy version	Pain decreased over the first year of treatment among children receiving treatment at 31 COG sites per parent report
Symptom trajectories in children receiving treatment for leukemia: A latent class growth analysis with multitrajectory modeling (Hockenberry et al., 2017)	236 children and adolescents 3-18 years receiving treatment for ALL	6-point scale (0-2-4-6-8-10)	Pain severity decreased over three post-induction time points
The influence of oxidative stress on symptom occurrence, severity, and distress during childhood leukemia treatment. (Hockenberry et al., 2014)	36 children 3-14 years receiving treatment for ALL	MSAS 10-18; parents completed for children ≤ 7 years of age	Prevalence of pain decreased over six time points during treatment for ALL 32.1% of participants reported pain at T6 (during continuation therapy)
Variations in pain, sleep, and activity during hospitalization in children with cancer (Jacob, Hesselgrave, Sambuco, & Hockenberry, 2007)	49 children and adolescents 8-17 years in the inpatient setting	MSAS 10-18	27 of 49 reported pain at time of enrollment; 16 with ≥ moderate pain; Pain intensity greatest on hospital day 1 and decreased over the course of hospitalization
Nausea, pain, fatigue, and multiple symptoms in hospitalized children with cancer (Miller, Jacob, & Hockenberry, 2011)	39 children and adolescents 10-17 years in an inpatient setting	MSAS 10-18	Prevalence of pain decreased over the 5-day period Overall symptom burden greater if pain, nausea, or fatigue present
Symptom prevalence and physiologic biomarkers among adolescents using a mobile phone intervention following hematopoietic stem cell transplantation (Rodgers, Krance, Street, & Hockenberry, 2014)	16 adolescents 11-17 years	Symptoms included in EAT! (derived from MSAS)	Pain persisted at 60 days following discharge for HSCT Distress from pain greater at 40 and 60 days postdischarge
Differences in symptom occurrence, frequency, intensity, and distress in adolescents prior to and one week after the administration of chemotherapy (Walker, Gedaly-Duff, Miaskowski, & Nail, 2010)	51 children 10-18 years receiving chemotherapy	MSAS 7-12 plus item for neuropathy	Pain reported by approximately half of participants prior to and 1 week following receipt of ambulatory chemotherapy Intensity, frequency, and distress did not differ at each time point

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Table 1. (continued)

Title and authors	Sample	Pain measurement	Findings
Studies of biomarkers of the symptom (*n* = 2)			
A pilot exploration of symptom trajectories in adolescents with cancer during chemotherapy (Ameringer, Elswick, Schockey, & Dillon, 2013)	9 adolescents 13-18 years within 6 months of diagnosis	Pain VAS; salivary alpha amylase	Pain positively correlated with biologic markers of stress Trajectory of pain severity not significant
Sensitivity to pain in children with acute lymphoblastic leukemia (ALL) (Firoozi & Rostami, 2012)	78 children 3-12 years	Morning salivary cortisol; BSSPC; PL-BPRS	High significant correlation between cortisol levels and pain sensitivity Gender- and age-moderated relationship between sensitivity to pain and cortisol level
Studies of Experience of Symptom (*n* = 2)			
Symptoms and self-management strategies identified by children with cancer using draw-and-tell interviews (Linder, Bratton, et al., 2018)	27 children 6-12 years receiving cancer treatment	Draw-and-tell interviews	44% reported some type of pain whether as part of their sick day experience Sources of pain included general pain (30% reporting) that was distinct from headache (19% reporting).
Feeling states: A new approach to understanding how children and adolescents with cancer experience symptoms (Woodgate, 2008)	13 children and adolescents 9-17 years	Open-ended interviews	Pain a component of feeling state "I feel sore/hurting"—reflecting pain as an extension of the child; defining who she or he is

Note. ALL = acute lymphoblastic leukemia; AYAs = adolescents and young adults; CML = chronic myeloid leukemia; COG = Children's Oncology Group; EAT! = Eating After Transplant app; GCSF = granulocyte colony stimulating factor; HSCT = hematopoietic stem cell transplant. *Pain instruments*: APPT = Adolescent and Pediatric Pain Tool; BSSPC = Behavioral Scales of Sensitivity to Pain for Children; C-SCAT = Computerized Symptom Capture Tool; MSAS = Memorial Symptom Assessment Scale; PedsQL = Pediatric Quality of Life; PL-BPRS = Pre-Linguistic Behavioral Pain Reactivity Scale; PROMIS = Patient-Reported Outcomes Measurement Information System; SDS = Symptom Distress Scale; TRSC-C = Therapy-Related Symptom Checklist—Children; VAS = Visual Analog Scale.

2012; International Association for the Study of Pain, 2014). This pain was not associated with the child's age or presence of pre-amputation pain. Children's pain experiences also influenced the treatment they received. Eight of nine children receiving imatinib for chronic myelogenous leukemia reported pain, and three of these children had this medication discontinued because of their pain (Heym et al., 2015).

Correlates and Perceived Causes of Pain. Pain was associated with poorer emotional well-being and functional status. The presence of pain was correlated with lower emotional scores (Arslan et al., 2013) and less positive affect (Wesley et al., 2013). Children who experienced greater interference from their pain also experienced poorer functional status (Buckner et al., 2014). The child's experience of pain also extended to others. Parental anxiety was positively correlated with their perception of the child's pain (Link & Fortier, 2016).

Adolescents and young adults (AYA) reported multiple and varied perceived causes of their pain using a symptom heuristics app. These perceived sources of pain included chemotherapy, cancer, procedures, treatment, GCSF (granulocyte colony stimulating factor) injections, lack of energy, tingling in hands and feet, nausea, constipation, and worry (Ameringer et al., 2015).

Pain Trajectory. Studies provided perspectives on the trajectory of pain at different aspects of the treatment continuum. Children's self-reported and parent-reported pain decreased during the first year following initiation of therapy for acute lymphoblastic leukemia (ALL) (Dupuis et al., 2016; Hockenberry et al., 2017). The prevalence and severity of pain decreased during a hospitalization (Jacob et al., 2007; Miller et al., 2011), suggesting that pain among hospitalized children may be more episodic in nature. In contrast, however, the prevalence and severity of pain persisted over the course of a cycle of chemotherapy (Baggott et al., 2010; Walker et al., 2010). Adolescents reporting pain following hematopoietic stem cell transplant (HSCT) also experienced persistence of pain at 60 days posttransplant (Rodgers et al., 2014).

Biomarkers. Two studies provided insights into biomarkers associated with the pain experience. Morning salivary cortisol levels were positively correlated with greater sensitivity to pain among 78 Iranian children with ALL (Firoozi & Rostami, 2012). Gender and age moderated the relationship with girls and younger children demonstrating a higher pain sensitivity.

Salivary alpha amylase levels were positively correlated with pain severity among nine adolescents receiving chemotherapy during the initial 6 months following diagnosis (Ameringer et al., 2013). The trajectory of pain across four time points during a cycle of chemotherapy was not significant, suggesting a varied individual experience of this symptom.

Experience of Pain. Two studies provided qualitative perspectives of children's experiences of pain. Interviews with 13 children and adolescents indicated that children frequently described symptoms as feeling states, such as "I feel sore and hurting." Children also related how pain became an extension of themselves, defining who they are, taking over their lives, was associated with feelings of unfairness; and felt like pincushion, bruised, and wounded (Woodgate, 2008).

Pain was represented in 12 of 27 drawings of "sick day" experiences by 6- to 12-year-old children (Linder, Bratton et al., 2018). Sources of pain included general pain, headaches, and procedural pain. Children's drawings also included the self-management strategies they initiated in response to pain such as to "stay in bed" or "lie down on the couch with a blanket."

Sadness

Conceptual Definition. Sadness was defined as an emotion that can be regarded as a natural response to physical or psychological pain. For the purpose of this review, sadness was regarded as distinct from clinically diagnosed mood disorders, such as depression.

Summary of Studies. After applying the search terms, 25 publications addressing sadness and 269 publications addressing multiple symptoms were identified. Nineteen publications met criteria for inclusion and are presented in Table 2.

Publications from seven countries—the United States, Nigeria, Pakistan, Taiwan, Turkey, China, and Lebanon—were included. Multiple strategies were used to measure sadness and its correlates. These included self-report instruments completed by the child and/or parent, drawings, a heuristics-based app, interviews, and investigator observation.

Prevalence and Characteristics of Sadness. Sadness was the most prevalent psychosocial symptom and was among the five most prevalent symptoms across studies reporting multiple symptoms (Abu-Saad Huijer et al., 2013; Linder, Al-Qaaydeh, et al., 2018). Nearly all children experienced at least some degree of sadness (Li et al., 2010), and the prevalence at any given point in time ranged from 15% to 61%. Sadness was also prevalent across the cancer treatment continuum, both prior to and following receipt of chemotherapy (Baggott et al., 2012; Walker et al., 2010; Yeh et al., 2009). When present, sadness was of moderate or greater severity $\geq$ 50% of the time and of moderate or

Table 2. Studies Reporting Sadness.

Title and authors	Sample	Sadness measurement	Findings
Studies of incidence/prevalence of symptom ($n = 9$)			
Quality of life and symptom prevalence as reported by children with cancer in Lebanon (Abu-Saad Huijer et al., 2013)	85 children 7-18 years	MSAS 10-18	Sadness fourth most prevalent symptom in children 7-12 years old and seventh most prevalent in 13- to 18-year-olds; in both groups, the mean sadness score was greater than the mean pain score
Identifying symptom clusters in pediatric cancer patients using the Memorial Symptom Assessment Scale (Atay et al., 2012)	54 children 10-18 years newly diagnosed with cancer	MSAS 10-18	Sadness most prevalent psychosocial symptom and among the 5 most common symptoms overall following a new diagnosis of cancer. Sadness persists during the first 3 months following diagnosis
Symptom cluster analyses based on symptom occurrence and severity ratings among pediatric oncology patients during myelosuppressive chemotherapy (Baggott et al., 2012)	131 children 10-18 years about to start a new cycle of chemotherapy	MSAS 10-18	46% reported feeling sad during the week prior to chemotherapy Sadness part of a mood disturbance cluster
Assessment of psychological distress among Asian adolescents and young adults (AYA) cancer patients using the distress thermometer: A prospective study (Chan et al., 2016)	65 AYAs 15-39 years	Rotterdam Symptom Checklist Distress thermometer	Sadness was one of the top 5 problems for AYAs $>$ 24 years of age but not those $\leq$ 24 years Distress thermometer scores significantly associated with depressed mood
The impact of cancer on children's physical, emotional, and psychosocial well-being (Li, Chung, & Chiu, 2010)	95 children 7-15 years receiving chemotherapy	Semistructured interviews	Nearly all participants experienced some degree of sadness or worry
Symptom characteristics among hospitalized children and adolescents with cancer (Linder, Al-Qaaydeh, et al., 2018)	50 children and adolescents 7-18 years receiving inpatient chemotherapy	MSAS 7-12	Sadness fourth most prevalent symptom; 44% reported at least once during the admit. If present, sadness was of moderate to severe severity 58% of the time and was of moderate to severe distress 30% of the time.
Child's symptom burden and depressive symptoms among caregivers of children with cancers: An argument for early integration of pediatric palliative care (Olagunju et al., 2016)	72 children 7-12 years	MSAS 7-12	47% reported sadness. If present, sadness was of moderate to severe severity 56% of the time and was of moderate to severe distress 60% of the time.
Differences in symptom occurrence, frequency, intensity, and distress in adolescents prior to and one week after the administration of chemotherapy (Walker et al., 2010)	51 children and adolescents 10-18 years receiving chemotherapy	MSAS 7-12 plus item for neuropathy	Sadness reported by 32.6% of participants at T1 and T2 The frequency, intensity, and distress if sadness did not differ from T1 to T2
Assessment of symptoms reported by 10- to 18-year-old cancer patients in Taiwan (Yeh et al., 2009)	144 children 10-18 years; 108 were still receiving treatment	MSAS 10-18	22% reported sadness; 10% reported quite a bit to very much distress with sadness Sadness in a *cluster* that included difficulty concentrating, difficulty sleeping, lack of energy, feeling drowsy, worrying, feeling irritable, and sweating "fatigue, sleep disturbance, and depression"
Studies of correlation and causes of symptom ($n = 3$)			
Symptoms and symptom clusters identified by adolescents and young adults with cancer using a symptom heuristics app (Ameringer, et al., 2015)	72 AYAs 13-29 years receiving chemotherapy	C-SCAT app featuring symptoms from MSAS 10-18	$n = 14$ (19.4%) reported feeling sad Perceived causes of sadness included cancer experience, uncertainty, hair loss, and "a lot going on"; sadness also perceived as caused by feeling irritable and lack of energy

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Table 2. (continued)

Title and authors	Sample	Sadness measurement	Findings
Quality of life and chemotherapy-related symptoms of Turkish cancer children undergoing chemotherapy (Arslan et al., 2013)	93 children and adolescents 10-18 years receiving chemotherapy	PedsQL and MSAS	62% reported sadness; patients reporting sadness had lower emotional scores on the PedsQL subscale ($p = .00$) and total PedsQL scores ($p = .03$). Frequency of sadness greater among children receiving corticosteroids ($p = .009$)
Resilience in adolescents with cancer: Association of coping with positive and negative affect (Murphy et al., 2017)	39 children and adolescents 10-15 years	Self-report and video recording	Use of secondary coping predicted higher positive affect
Studies of trajectory of symptom ($n = 3$)			
Changes in children's reports of symptom occurrence and severity during a course of myelosuppressive chemotherapy (Baggott et al., 2010)	66 children and adolescents 10-18 years	MSAS 10-18	Overall prevalence of sadness decreased over a cycle of chemotherapy ($p = .008$). If sadness was present, its severity increased over a cycle of chemotherapy.
The influence of oxidative stress on symptom occurrence, severity, and distress during childhood leukemia treatment. (Hockenberry et al., 2014)	36 children 3-14 years receiving treatment for ALL	MSAS 10-18; parents completed for children ≤ 7 years of age	Prevalence of sadness decreased over six time points during treatment for ALL
Symptom prevalence and physiologic biomarkers among adolescents using a mobile phone intervention following hematopoietic stem cell transplantation (Rodgers, Krance, Street, & Hockenberry, 2014)	16 adolescents 11-17 years	Symptoms included in EAT! (derived from MSAS)	Sadness persisted at 60 days following discharge for HSCT
Studies of experience of symptom ($n = 4$)			
A content analysis of emotional concerns expressed at the time of receiving a cancer diagnosis: An observational study of consultations with adolescent and young adult patients and their family members (Korsvold, Mellblom, Finset, Ruud, & Lie, 2017)	9 AYAs 12-25 years	Audio-recorded consultations during which AYAs learned of their diagnosis	Sadness and fear were key concerns related to the cancer experience. Health care providers less responsive to affective aspects of concerns.
Symptoms and self-management strategies identified by children with cancer using draw-and-tell interviews (Linder, Bratton, et al., 2018)	27 children 6-12 years receiving cancer treatment	Draw-and-tell interviews	Sadness associated with separation from siblings, grief, and extending to other family members; predominant emotion on sick days
Understanding the perceptions of children battling cancer about self and others through drawing (Sadruddin & Hameed-ur-Rehman, 2013)	78 children 7-12 years receiving cancer treatment	Drawings of self and others	Sadness most common emotion; associated with social isolation
Experience and nursing needs of school-age children undergoing lumbar puncture during the treatment of acute lymphoblastic leukaemia: A descriptive and qualitative study (Xie, Shan, Niu, Chen, & Wang, 2017)	21 children 7-12 years receiving treatment for ALL	Semistructured interviews; qualitative content analysis	Sadness part of the psychosocial response to undergoing lumbar puncture as part of ALL treatment

Note. ALL = acute lymphoblastic leukemia; AYAs = adolescents and young adults; HSCT = hematopoietic stem cell transplant; PRO = patient reported outcome. *Sadness instruments*: C-SCAT = Computerized Symptom Capture Tool; EAT! = Eating After Transplant app; MSAS = Memorial Symptom Assessment Scale; PedsQL = Pediatric Quality of Life; QLIC-ON PROfile = Quality of Life in Childhood Oncology Patient-Reported Outcome Questionnaire.

greater distress 30% to 60% of the time (Linder, Al-Qaaydeh, et al., 2018; Olagunju et al., 2016).

Correlates and Perceived Causes of Sadness. The presence of self-reported sadness was correlated with lower quality of life scores among 93 Turkish children and adolescents receiving chemotherapy (Arslan et al., 2013). Adolescents' use of secondary coping skills such as cognitive reappraisal and the use of distraction techniques predicted a higher positive affect during the initial 6 months following diagnosis (Murphy et al., 2017). Seventy-two AYAs reported their perceived causes of sadness using a symptom heuristics app delivered via a tablet computer. These included their cancer experience, uncertainty, hair loss, "a lot going on," feeling irritable, and lack of energy (Ameringer et al., 2015).

Sadness Trajectory. The prevalence and characteristics of sadness varied over time. Although the overall prevalence of sadness decreased over a cycle of chemotherapy, its severity increased among those children and adolescents reporting the symptom (Baggott et al., 2010). The prevalence of sadness decreased over six time points during the first year of treatment for ALL (Hockenberry et al., 2014). Its prevalence persisted, however, among adolescents during the initial 60 days following discharge for HSCT (Rodgers et al., 2014).

Experience of Sadness. Drawings by American and Pakistani elementary school–age children emphasized the pervasiveness of sadness as an emotional response to the cancer experience. Children's drawings depict sadness as associated with social isolation, separation from siblings, grief, and extending to other family members (Linder, Bratton et al., 2018; Sadruddin & Hameed-ur-Rehman, 2013). School-age children receiving treatment for ALL also experienced sadness in response to lumbar punctures (Xie et al., 2017). Sadness was a prevalent theme of concern among AYAs at the time of diagnosis (Korsvold et al., 2017). Review of audio-recorded interviews indicated that health care providers were less responsive to AYAs' emotional concerns and responses compared with requests for information.

Symptom Clusters

Conceptual Definition. Although the exact definition of a symptom cluster remains "elusive" (Barsevick, 2007), a cluster is generally regarded as two or more co-occurring symptoms that are related to one another (Kim, McGuire, Tulman, & Barsevick, 2005). Clusters are regarded as being independent of one another; however, the symptoms within a given cluster may or may not share a common etiology.

Summary of Studies. After applying the search terms across the individual symptoms that were included in this review and the 269 publications addressing multiple symptoms, eight publications met criteria for inclusion and are presented in Table 3. Publications from three countries—the United States, Taiwan, and Turkey—were included. Strategies for evaluating clusters varied across studies and included identification of groups of related symptoms as well as groups of children and adolescents with similar symptom profiles.

Studies Reporting Clusters of Symptoms. Six publications reported groups of related symptoms. Among 67 children and adolescents receiving highly emetogenic chemotherapy, a linear mixed model using principal component analysis identified greater depressive symptoms among adolescents with a cluster of sleep disturbance and fatigue (Hockenberry et al., 2011).

Ten cluster categories were identified using qualitative content analysis procedures of clusters that were self-reported by 72 AYAs receiving myelosuppressive chemotherapy (Ameringer et al., 2015). The most frequently named clusters included nausea/eating problems/appetite problems, treatment and chemotherapy-related, irritating symptoms, and sleep/sleeping.

Exploratory factor analysis identified three symptom clusters among children and adolescents receiving myelosuppressive chemotherapy (Baggott et al., 2012). These clusters included mood disturbance, neuropsychological discomfort, and chemotherapy sequelae, and remained stable whether using the occurrence of a symptom or its severity as the basis for analysis. Of note, fatigue was included in the chemotherapy sequelae cluster when analyses were based on occurrence and in the neuropsychological discomfort clusters when analyses were based on severity.

Three publications reported clusters identified using cluster analysis procedures. Among 54 Turkish children newly diagnosed with cancer, the number and composition of clusters varied across the first 3 months of treatment. Eight symptoms—changes in the way food tastes, dizziness, feeling irritable, lack of energy, nausea, sadness, vomiting, and worry—were present in clusters at each of the three time points (Atay et al., 2012).

Among 67 children and adolescents receiving highly emetogenic chemotherapy, hierarchical agglomerative cluster analysis identified two clusters, an emotional cluster that included fatigue and sadness and a physical cluster that included vomiting, nausea, physical performance, and disrupted sleep (Hockenberry et al., 2011). A cross-sectional study that included 144 children and adolescents who were receiving therapy ($n = 108$) and who had completed therapy ($n = 36$) identified five clusters. These clusters included sensory discomfort/body image,

Table 3. Studies Reporting Clusters.

Title and authors	Sample	Analytic approach	Findings
Studies identifying clusters of symptoms (n = 6)			
A priori identified cluster (n = 1)			
Symptom clusters in children and adolescents receiving cisplatin, doxorubicin, or ifosfamide (Hockenberry et al., 2010)	67 children and adolescents 7-18 years	Linear mixed model; principal component analysis	Depressive symptoms greater among adolescents with cluster of sleep disturbance and fatigue
Patient-reported clusters (n = 1)			
Symptoms and symptom clusters identified by AYAs with cancer using a symptom heuristics app (Ameringer et al., 2015)	72 AYAs 15-29 years	Content analysis of patient-identified clusters	10 cluster categories identified Most frequent included nausea/eating problems/appetite problems, treatment and chemotherapy-related, irritating symptoms, and sleep/sleeping.
Statistically identified clusters (n = 4)			
Identifying symptom clusters in paediatric cancer patients using the Memorial Symptom Assessment Scale (Atay et al., 2012)	54 children 10-18 years newly diagnosed with cancer	Cluster analysis with Pearson correlation as distance measure	Clusters varied in composition across the first 3 months after diagnosis. Eight symptoms—changes in the way food tasted, dizziness, feeling irritable, lack of energy, nausea, sadness, vomiting, and worry —present in clusters at each of the first 3 months.
Symptom cluster analyses based on symptom occurrence and severity ratings among pediatric oncology patients during myelosuppressive chemotherapy (Baggott, et al., 2012)	131 children 10-18 years about to receive chemotherapy	Exploratory factor analysis	Three clusters: Mood disturbance, neuropsychological discomfort, and chemotherapy sequelae identified whether using symptom occurrence or severity for analysis
Sickness behavior clustering in children with cancer (Hockenberry, Hooke, McCarthy, & Gregurich, 2011)	67 children and adolescents 7-18 years	Hierarchical agglomerative cluster analysis	Two clusters: Emotional, including fatigue and sadness; Physical, including vomiting, nausea, physical performance, and sleep
Symptom clustering in older Taiwanese children with cancer (Yeh et al., 2008)	144 children 10-18 years	Hierarchical agglomerative cluster analysis	Five clusters: sensory discomfort/body image, circulatory/respiratory system, fatigue/sleep disturbance/depression, body image, gstrointestinal/pain
Studies identifying patients with similar symptom profiles (n = 2)			
Symptom trajectories in children receiving treatment for leukemia: A latent class growth analysis with multitrajectory modeling (Hockenberry et al., 2017)	236 children with leukemia 3-18 years	Latent class growth analysis	Three latent classes of symptom trajectories identified over the first 18 months of treatment: mild, moderate, and severe symptom trajectories Race/ethnicity only demographic variable significantly related to group membership.
Physical activity, the childhood cancer symptom cluster-leukemia, and cognitive function: A longitudinal mediation analysis (Hooke et al., 2018)	327 children 3-18 years	Longitudinal parallel process	When physical activity levels were high at the first of 4 time points during the first year of ALL treatment, children had a decrease in the severity of the symptom cluster of fatigue, sleep disturbances, pain, nausea, and depression.

Note. ALL = acute lymphoblastic leukemia; AYAs = adolescents and young adults.

circulatory/respiratory system, fatigue/sleep disturbance/depression, body image, and gastrointestinal pain (Yeh et al., 2008).

Studies Reporting Symptom Profiles. Two publications reported symptom profiles among children receiving treatment for ALL. Three latent classes of trajectories for the symptoms of fatigue, sleep disturbance, pain, nausea, and depression—mild, moderate, and severe—were identified among 236 children and adolescents during the first 18 months of therapy (Hockenberry et al., 2017). Race/ethnicity was the only demographic variable significantly related to group membership. Hispanic children and adolescents were less likely than non-Hispanic participants to experience more severe symptoms over time.

The role of the symptom cluster of fatigue, sleep disturbances, pain, nausea, and depression was further analyzed as a mediator between physical activity and cognitive function among 327 children and adolescents during the first year of treatment for ALL (Hooke et al., 2018). When physical activity was high at the first of four time points during the first year of treatment, children had a decrease in the severity of the symptom cluster. Children with a greater severity of the symptom cluster at the first time point also had poorer cognitive function, and their cognitive function declined over time.

Discussion

The reviews presented in this two-part series provide evidence for the high prevalence and persistence of distressing symptoms across treatment for childhood and adolescent cancer. These symptoms are a disruptive presence in the lives of children and their families. Whether experienced in the hospital or at home, symptoms interfere with children's ability to participate in age-appropriate activities and negatively influence their quality of life.

Although pain has long been identified as a highly prevalent and distressing symptom resulting from the child's cancer, its treatment, and procedures, current literature provides evidence of its persistence. Studies included in this review provided evidence of the prevalence and distressing nature of pain across the childhood cancer treatment continuum and across international settings.

Studies provided evidence for the varying trajectory of children's pain experience across multiple cycles of chemotherapy as well as within a given cycle. From a larger scale perspective, the prevalence of pain decreased over the course of treatment for ALL (Dupuis et al., 2016; Hockenberry et al., 2014; Hockenberry et al., 2017). Those children and adolescents who reported pain at the start of a cycle of myelosuppressive chemotherapy, however, tended to experience persistent pain across that cycle (Baggott et al., 2010; Walker et al., 2010).

Studies also provided evidence of biologic correlates of pain and specific sources of pain, including neuropathic pain, phantom limb pain, and procedural pain. Neuropathic pain, specifically, may be underrecognized and, therefore, undermanaged (Acquazzino et al., 2017).

Consequences of pain, particularly persistent pain, included poorer emotional health and decreased functional status (Arslan et al., 2013; Buckner et al., 2014; Wesley et al., 2013). Persistent pain also had consequences affecting the child's treatment, including discontinuation of disease-directed therapy (Heym et al., 2015).

Sadness was a typical emotional response, and the most prevalent psychosocial symptom associated with the cancer experience. The experience of sadness was common across age-groups and across countries. Children experienced multiple sources of sadness, including treatment-related procedures as well as a sense of isolation and grief (Linder, Bratton, et al., 2018; Sadruddin & Hameed-ur-Rehman, 2013; Xie et al., 2017). Although the prevalence of sadness decreases over the course of treatment and over a cycle of chemotherapy (Hockenberry et al., 2014), persistent sadness, when it occurred, was of greater severity and associated distress (Baggott et al., 2010).

Of note, the experience of sadness, in and of itself, is not abnormal and should be anticipated as part of the child or adolescent's response to cancer and its diagnosis (Korsvold et al., 2017). Sadness that persists or is of high severity may warrant additional attention and intervention. Efforts to build capacity in the child or adolescent, such as the use of secondary coping mechanisms, may serve to build resilience and help alleviate a more severe experience (Murphy et al., 2017).

Although studies investigating symptom clusters were heterogeneous with regard to their methods, study sample characteristics, and definitions of variables, they provide important insights into the patient experience, as well as potential etiologies for individual symptoms. As an example, depending on the analytic approach, fatigue could be included as either a physical or emotional symptom within a cluster (Baggott et al., 2012; Hockenberry et al., 2011). The clusters identified within these studies, regardless of analytic approach, also reflected the prevalence, severity, and distress of the symptoms included as part of this review. Publications identifying latent classes, or groups of patients, based on a common symptom experience also provide evidence for varied individual trajectories of symptoms over time.

Limitations

The scope of the review presented in this two-part article series was limited to a 10-year period and was also limited to studies including children receiving treatment with curative intent. The exclusion of intervention studies limited

the ability to address the efficacy, or lack thereof, of interventions targeted at the symptoms included in this review.

The heterogeneity with regard to study methods, approaches to symptom measurement, and study samples across studies are additional limitations. Most studies were cross-sectional and some included children who had completed therapy. These factors limited the ability to make inferences about the course or characteristics of a symptom during treatment as well as to distinguish between symptom reports of children who were receiving therapy compared with those who had completed treatment. Different measures were used across studies. These measures may or may not have had the same sensitivity to capturing change over time.

Among those studies that included a single diagnostic group, ALL was the predominant diagnosis. As a result, the symptom experiences of children and adolescents with other distinct diagnoses is not clearly known.

Clinical Implications

Results of this review provide support for the need for symptom assessment in the clinical setting. Because the patient's self-report is the gold standard for determining the presence of a symptom (Cleeland & Mendoza, 2011; Humphreys et al., 2008), approaches to symptom assessment need to incorporate the child's perspective with the understanding that even children as young as 4 years of age have the capacity to provide self-report (Woodgate, Degner, & Yanofsky, 2003).

A comprehensive approach to symptom assessment in the clinical setting is needed.

Although pediatric oncology clinicians have a broad awareness of children's symptoms, routine symptom assessment is often guided by regulatory criteria such as Joint Commission expectations for pain assessment (Linder & Wawrzynski, 2018). Resources to support children's self-report of symptoms in the clinical setting are emerging and are being developed for children as young as 4 years of age (Dupuis et al., 2018; Tomlinson et al., 2014; Tomlinson et al., 2019).

Clinician education also needs to address the changing nature of symptoms on a daily basis and even within the course of a day. Guidance on reassessment, particularly during inpatient admissions in which patients may be experiencing acute exacerbations of a given symptom, is needed. Clinicians also need to be aware that persistent symptoms are more likely to be of greater severity and distress.

Future Directions

The COG framework for nursing research provides guidance for future directions targeted at alleviating symptoms and their associated distress (Landier et al., 2013). Interventions targeted at both the symptoms themselves as well as supporting the child's coping with symptoms and fostering resilience have the potential to enhance the child's well-being. Interventions have the potential not only to provide relief of the symptom itself but also may extend to other aspects of the child's development, including cognitive function (Hooke et al., 2018).

Although evidence is emerging about the trajectories of symptoms over time, whether across a cycle of chemotherapy or multiple cycles of treatment, more research is needed. For some children, the experience of symptoms may become their "new normal." Future research could investigate the extent to which, for some children, symptoms truly improve over time, or whether the child becomes used to the experience of chronic symptoms.

Recommendations for symptom assessment across the treatment continuum and in different settings such as inpatient versus ambulatory and during chemotherapy versus between treatments are needed. Opportunities for future recommendations include frequencies for assessment as well as measurement approaches to support exploration of trajectories and evaluation of interventions in clinical and research contexts.

A better understanding of latent classes, that is, groups of patients with similar symptom profiles, is needed. Such research would include a better understanding of children's individual biologic variables as well as the contributions of the child's disease and treatment and sociocultural factors that may influence the experience of a symptom.

Conclusion

This two-article series presents evidence for the prevalence and persistence of distressing symptoms among children and adolescents receiving treatment for cancer. As ongoing advancements in treatment lead to intensified therapies, the need to assess and respond to symptoms is crucial. Pediatric oncology nurses are in a key role to facilitate timely interventions to alleviate symptoms. These efforts will alleviate suffering in the child or adolescent and have the potential to benefit the well-being of the family.

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