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## Children's cancer pain in a world of the opioid epidemic: Challenges and opportunities

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### Abstract

The opioid crisis in the United States has grown at an alarming rate. Children with cancer are at high risk for pain, and opioids are a first-line treatment in this population. Accordingly, there is an urgent need to optimize pain management in children with cancer without contributing to the opioid crisis. This report details opportunities for this optimization, including clinical practice guidelines, comprehensive approaches to pain management, mobile health, and telemedicine. It is vital to balance appropriate use of analgesics with efforts to prevent misuse in order to reduce unnecessary suffering and minimize unintended harms.

### Keywords

opioid epidemic; pain guidelines; pediatric oncology; pain management; pain

## 1 | PROBLEM 1: THE OPIOID EPIDEMIC

The opioid crisis in the United States has grown at an alarming rate, with a 200% increase in opioid-related overdose deaths since 2000.<sup>1</sup> The roots of the opioid epidemic in the United States are multifactorial and largely stem from the routine use of opioid medications to treat acute pain starting in the 1980s. This was followed by a shift in the treatment of chronic pain in the 1990s from cognitive-behavioral therapy as the primary intervention to opioids.<sup>2,3</sup> The shift to managing chronic pain with opioids primarily reflects a significant increase in rates

of disabling chronic pain, patient expectations for a “quick fix,” and a medical system that changed reimbursement strategies to prioritize the use of simplistic treatment approaches for complex health problems.<sup>2,4</sup> Moreover, a campaign initiated by the American Pain Society in the 1990s to include pain as the “fifth vital sign” subsequently led to the adoption of routine measurement of pain severity in health settings using a numeric rating scale as well as opioid administration based upon patient pain scores.<sup>5</sup> Accordingly, the United States is in the midst of an epidemic of opioid misuse, addiction, and overdose.<sup>4</sup>

The opioid epidemic extends to the pediatric population, with evidence indicating that deaths from drug overdose in adolescents more than doubled from 1999 to 2007 and have continued to rise, with the majority of deaths due to opioid-related drug overdoses.<sup>6</sup> Most adolescents who abuse opioids began with a prescription opioid<sup>7</sup> and many transitions that occur during adolescence, including neurobiological, behavioral, and psychological changes can leave adolescents vulnerable to both chronic pain and drug use.<sup>8,9</sup> Thus, adolescents are a particularly at-risk population in the context of the opioid epidemic.

There have been many policy changes and trends over the past decade in an effort to combat the opioid crisis. These include guidelines for providers who prescribe opioids, prescription-drug monitoring programs, and investment into prevention and treatment programs.<sup>7</sup> In addition, the National Institutes of Health (NIH) launched a new scientific initiative to fund research to help combat the opioid crisis, focusing on prevention and intervention efforts to reduce mortality, identification of novel interventions to treat opioid addiction, and identification of safe nonaddictive alternatives to the management of chronic pain.<sup>10</sup> However, the overwhelming majority of these programs are focused on adult populations.

## 2 | PROBLEM 2: PAIN IN CHILDREN WITH CANCER

Every year, over 12 000 children will be diagnosed with cancer in the United States<sup>11</sup> and the majority of these children will experience pain, which is one of the most distressing symptoms reported in this population.<sup>12</sup> After diagnosis with leukemia, the most common childhood cancer diagnosis, 100% of children reported pain over the course of the first year.<sup>13</sup> Pain can be related to the underlying disease; however, for most children, the pain they experience is iatrogenic, or caused by the treatment itself.<sup>14,15</sup> Parents have identified pain as the “most problematic” symptom children experience during cancer treatment<sup>16</sup> and children have described pain as the most distressing and frightening aspect of their cancer experience.<sup>17,18</sup> Unfortunately, evidence suggests that cancer pain and symptoms are seriously undertreated in most children, particularly in the home setting.<sup>13,19–23</sup> Pain is not just an issue at diagnosis and during treatment for cancer. Survivors of cancer are also at high risk for the experience of chronic pain given the effects of treatments, which include surgery, radiation, and cytotoxic medications.<sup>24</sup>

With changes to the delivery of healthcare that have occurred, the majority of children now receive cancer treatment on an outpatient basis.<sup>25</sup> This phenomenon is not limited to oncology. In fact, the majority of healthcare has transitioned to an ambulatory setting, which has increased patient and family satisfaction,<sup>26,27</sup> but has also shifted healthcare provider responsibility for pain and symptom management to parents and caregivers. Research by our

group and others has shown that parents significantly undertreat children's pain in the home setting,<sup>28</sup> despite raising pain as a major problem during children's cancer treatment.<sup>16</sup> One parent-related factor that has been identified in the literature as a potential barrier to children's pain management at home is parents' attitudes regarding analgesic use for children. For example, parents who endorse concerns about side effects of analgesics and/or report poor understanding of pain management provide less analgesic medication for cancer-related pain that children experience in the home setting.<sup>22</sup> Unfortunately, these misconceptions are prevalent in parents of children with cancer.<sup>29</sup>

Parents are tasked with managing chronic pain in patients with cancer, but are not educated in symptom assessment or use of pharmacological and nonpharmacological interventions. For example, there are very few documented interventions focused on parents and caregivers of patients with cancer.<sup>30</sup> With regard to pharmacologic strategies, the related literature indicates that parents report using "trial and error" to administer analgesics to children following surgery.<sup>31</sup> Considering the myriad tasks related to pharmacologic pain management, including determining what medication may be appropriate, when and how to administer the medication, the appropriate dose to use, determining whether the medication is effective, and monitoring side effects,<sup>32</sup> a "trial and error" approach is particularly concerning. Finally, there are a number of effective nonpharmacological strategies used in pain management, including distraction, mindfulness, or other complementary approaches. However, these strategies are not often introduced to parents,<sup>30</sup> and when they are, they appear to be administered haphazardly and with varying degrees of success.<sup>33</sup>

Unfortunately, data regarding opioid use and adherence in patients with cancer are extremely limited because cancer patients are excluded from almost all guidelines, treatment protocols, and legislation (at both the state and federal levels) focused on the use of opioids. The Centers for Disease Control and Prevention (CDC) released guidelines for opioid prescribing for chronic pain in 2016 that specifically did not include cancer patients due to concerns regarding the complexity of cancer-related pain as well as beliefs that opioid misuse was not an issue in patients with cancer.<sup>24</sup> Moreover, the World Health Organization and other national guidelines have supported the use of opioids in the cancer population.<sup>34,35</sup> The support for opioid use in cancer patients is likely the result of both a perception of the lack of abuse concern and clinical need for opioid use in the treatment of cancer-related pain. Opioids are often considered to be first-line analgesics in the oncology setting due to concerns that the use of over-the-counter pain medications, including acetaminophen and nonsteroidal anti-inflammatory medications (NSAIDs), may mask important clinical symptoms such as fever, which can indicate a medical emergency.<sup>36</sup> In addition, NSAIDs are often contraindicated and potentially dangerous throughout much of cancer treatment due to frequency and severity of thrombocytopenia. In fact, the overwhelming majority of children with cancer referred for neuropathic pain in the outpatient setting were using opioids as either a single agent or in combination with other analgesics.<sup>37</sup> There is also often a need for opioid use and opioid escalation as a part of end-of-life care, particularly considering that a child dying from cancer tends to have significant pain and symptoms, and palliative care is of high priority.<sup>38</sup> Finally, little is known about patterns of opioid use and misuse in the oncology setting because patients with cancer are also excluded from clinical trials that focus on chronic pain and analgesic use. However, given data suggesting potential

for opioid misuse, particularly within the adolescent and young adult (AYA) oncology population,<sup>39</sup> risk factors associated with opioid misuse have begun to be examined. Research in this area suggests that multidisciplinary care of AYA oncology patients is extremely important given the potential for psychiatric distress in this population that may place AYA patients at greater risk for misuse of opioids.<sup>40,41</sup> In addition, history of substance use among patients, peers, and family is a risk factor for opioid misuse.<sup>40</sup>

### **3 | THE CHALLENGE: OPTIMIZING CANCER PAIN MANAGEMENT FOR CHILDREN IN THE CONTEXT OF THE OPIOID CRISIS**

The question, then, arises how can we optimize the management of pain in children with cancer without contributing to the opioid crisis? Given that children with cancer are at high risk for the experience of recurrent pain, both during treatment and throughout survivorship, and that parents are responsible for the majority of children's cancer pain management, it is imperative to equip parents and caregivers with evidence-based strategies to more appropriately manage pain. These strategies should allow for symptom management at home without placing children, particularly adolescents, at risk for opioid misuse. Unfortunately, there is a dearth of research regarding a best practice model in this context.

#### **3.1 | Clinical practice guidelines**

As noted above, current guidelines for opioid prescribing for chronic pain exclude cancer patients. Additionally, such guidelines fail to include integrative approaches to pain management, such as complementary and alternative medicine (CAM). Moreover, cancer-specific guidelines, such as those by the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN), focus solely on adults and survivors.<sup>35,42</sup> The lack of guidelines for pediatric patients with cancer should be a call to clinicians, investigators, and professional associations to come together to develop clear guidelines for management of cancer pain in children and adolescents. Opioid stewardship programs that involve a collaborative effort of multidisciplinary stakeholders have shown promise in optimizing pain management.<sup>43</sup> Stewardship programs have been adopted in the hospital setting to ensure appropriate treatment of patients. For example, antibiotic stewardship programs have been implemented in hospitals across the United States to ensure optimal prescribing of antibiotics in an effort to combat antibiotic resistance.<sup>44</sup> These programs require the concerted efforts of a multidisciplinary team, including a commitment by hospital leadership, and the need for an identified leader of the program.<sup>44</sup> Similarly, hospitals are beginning to adopt pain stewardship programs, led by pharmacists, in order to provide oversight for analgesic prescriptions and regimens to optimize pain management and reduce errors.<sup>43</sup> Pharmacists can play a vital role in optimizing pain management and improving medication safety through customizing analgesic medications to the needs of the patient and clinical context and providing necessary patient education.<sup>45</sup> The development and implementation of such stewardship programs generally involve creating a multidisciplinary team to identify barriers to optimal pain management, determine which patients may be at most risk for suboptimal pain management, and enact evidence-based pain management practices that are disseminated through electronic medical record order sets and clinical services.<sup>43,46</sup> Such programs have been shown to improve opioid safety by

reducing reliance on opioids for both acute and chronic pain,<sup>47</sup> and efforts by hospitals to adopt opioid stewardship programs may lead to improved care and safety of pain management in patients with cancer. Opioid stewardship programs may also be viewed as a component of multidisciplinary care for patients in pain.

### 3.2 | The need for a comprehensive approach to pain management

A multidisciplinary approach that incorporates integrative medicine (IM) modalities with conventional strategies is needed to adequately address cancer pain management.<sup>48</sup> IM strategies include evidence-based strategies for pain such as guided imagery, biofeedback, and acupuncture. Although reports suggest the use of these strategies by pediatric oncology patients is high,<sup>49</sup> efficacy data for some IM strategies are lacking, and long-term effectiveness has not been well established, particularly in the pediatric population.<sup>50</sup> This suggests a need for rigorous evaluation of the safety and effectiveness of IM interventions, particularly in the context of pain management for pediatric cancer patients. In order to implement such strategies, pain services must be multidisciplinary and include a range of service providers, such as providers trained in Traditional Chinese Medicine, psychologists with expertise in cognitive and behavioral pain management interventions, and child life specialists who can intervene during painful procedures.

Because pain in patients with cancer can be complex and associated with the cancer itself, the treatment and procedures used to treat the cancer, and/or a secondary diagnosis, interventional pain strategies such as epidural analgesia, peripheral nerve blocks, and celiac plexus blocks are becoming more routine in the oncology setting.<sup>51</sup> Such strategies are considered invasive and thus require understanding of the cancer disease process and prognosis and are generally designed to interrupt nerve conduction to block pain signaling. Nonpermanent interventional procedures largely involve injection of local anesthetic followed by steroids or may involve placement of a catheter for continuous delivery of analgesics.<sup>51</sup> Permanent procedures may involve administration of chemical agents, heat, or cold or surgery to achieve pain control. The use of interventional pain management strategies in oncology is much more specific than analgesic therapies, often used as part of palliative care at end-of-life treatment, but they are becoming an increasing component of multimodal pain management in patients with cancer.<sup>52</sup>

### 3.3 | The role of parents and caregivers

Given the increasing responsibility of parents and caregivers in the role of pain management, efforts targeting appropriate pain assessment are needed. Despite pain as a major concern for children and parents, pain assessment throughout cancer treatment is not performed systematically.<sup>53</sup> Moreover, it has been documented that parents of children with cancer report misconceptions about how children express pain, including beliefs that children will always report when they are in pain and children who are playing or otherwise engaged cannot be in pain.<sup>29</sup> Further, there are no validated parental assessments of children's pain severity in the oncology setting. Thus, efforts are needed to adequately equip parents in understanding proper assessment of children's cancer-related pain as well as development of validated parent-report measures of children's pain in the oncology setting. These efforts may be accomplished by ensuring routine pain assessment at every encounter that goes

beyond simply assessing pain severity and includes functional impairment as a result of pain on physical, emotional, and behavioral functioning. Many “blueprints” for psychosocial assessment in pediatric oncology, that include assessment of pain, have been proposed<sup>54</sup> but are not systemically implemented across hospitals. Given potential risk factors for opioid misuse that may be present among AYA patients in particular, this screening should also include assessment of the potential for substance abuse/opioid misuse.

### 3.4 | mHealth

Mobile devices have become ubiquitous in the United States, and nearly 80% of Americans own smartphones.<sup>55</sup> Patients and caregivers routinely search for health-related information using their mobile devices, and mobile apps are particularly engaging for pediatric patients living in the current technology-rich environment.<sup>56,57</sup> Accordingly, globally, there has been an explosion in mobile health (mHealth)—the use of mobile devices to assess, monitor, and impact health outcomes. Although the field of mHealth is not without its challenges,<sup>58</sup> it does provide a potential avenue to deliver pain management to populations more broadly.

In recent years, investigators have harnessed mHealth technology to attempt to bridge gaps in pain management in pediatric oncology. Our own group has developed Pain Buddy, an animated, interactive web-based pain and symptom assessment and management program for children and adolescents aged 8 to 18 years undergoing treatment for cancer. Pain Buddy is composed of a validated pain and symptom assessment component, an electronic communication component that provides symptom data to healthcare providers in real time, and cognitive and behavioral skills training for children (e.g., guided imagery, mindfulness, diaphragmatic breathing) for pain management.<sup>59</sup> Pain Buddy has been shown to be well accepted and feasible to use by patients and healthcare providers<sup>59</sup> and is currently undergoing efficacy testing. Pain Squad is another app that is used on smartphones for children and adolescents with cancer that assesses pain severity and characteristics and strategies used to manage pain.<sup>60</sup> Pain Squad+ is a newer iteration of the program that focuses on self-management of cancer-related pain in adolescents that uses algorithms to provide adolescents with both pharmacological and nonpharmacological pain management strategies.<sup>61</sup> Pain Squad+ has improved pain-related outcomes for children and adolescents with cancer.<sup>62,63</sup> Despite evidence supporting the efficacy and acceptability of these apps, broader dissemination efforts have been limited; thus, efforts focused on implementation of such programs are necessary in order to have a substantive impact on pediatric cancer-related pain. Moreover, in the adult arena, there are many commercially available applications targeting healthcare in patients with cancer (e.g., <https://www.mobihealthnews.com/content/mobile-app-launches-better-connect-cancer-patients-appropriate-care-clinical-trials>; <https://www.cancer.net/navigating-cancer-care/managing-your-care/mobile-applications>). One such app known as Driver functions to connect patients to appropriate treatment and providers, including options for evidence-based care and clinical trials, and allows for communication between patients and providers. [Cancer.Net Mobile](#) assists patients in navigating their medical care and can create a “network” of providers involved in a patient’s care in order to better integrate healthcare treatments and services. Efforts to develop similar resources for the pediatric population *and* include a focus on pain management may be an avenue to bridge the gap in cancer pain management.

### 3.5 | Telemedicine

Telemedicine has been defined as “technology-enabled health and care management and delivery systems that extend capacity and access.”<sup>64</sup> More recently, the benefits of telemedicine have been recognized by the healthcare community and have been increasingly used to enhance the accessibility of tertiary care for children, particularly in rural and underserved areas.<sup>65,66</sup> In the adult arena, telemedicine has been shown to be effective for the management of multiple cancer-related symptoms, including pain.<sup>67</sup> In pediatric oncology, telemedicine has been utilized to improve access to care and has been effective in improving cancer-related outcomes.<sup>68</sup> Telepharmacy, a more specific application of telemedicine, involves pharmacist-related services such as medication management, chronic disease management, care transition, pharmacogenomics, and remote dispensing and ambulatory care. In the ambulatory setting, telepharmacy interventions have improved disease outcomes, patient self-management, and treatment adherence; however, such interventions have not been assessed in pediatric oncology patients.<sup>69</sup> Utilizing advanced technologies with better decision support and real-time reporting capabilities, healthcare providers can effectively manage a patient’s symptoms in a timely manner. For pediatric patients with cancer, telemedicine may provide a cost-effective approach to optimize pain management in the home setting. Given trends for more comprehensive coverage for telemedicine services and the feasibility and cost-effectiveness of these approaches, hospitals, and clinics would benefit from adopting telemedicine for pain management.<sup>70</sup>

## 4 | SUMMARY

The opioid epidemic is a national health concern that is not specific to the adult population. Misuse of opioids extends to the pediatric setting and has particular importance with regard to pediatric oncology, where pain is prevalent and opioids are often the first-line analgesic used to manage cancer-related pain. Despite the high rates of pain in pediatric oncology patients and potential benefits of opioid use, there is little clinical and policy guidance on opioid use in this setting. Further, the shift in pain management to the home setting has complicated appropriate opioid use as parents and caregivers often are not well equipped to assess and manage children’s pain. To make progress in this area, multidisciplinary researchers, healthcare providers, and policy makers need to pave the way in optimizing pain management. Fruitful advancement can come from creating clinical practice guidelines, testing and implementing integrative approaches to care, developing systematic pain measurement methods for parents and caregivers to use, and providing parents and caregivers with best practices in the area of pain management. Capitalizing on mHealth, telemedicine, and telepharmacy could be useful to achieve these goals and allow for the safe and appropriate use of opioids to treat cancer-related pain in pediatric patients and increase their quality of life. A vital aspect of this effort is that fear of opioids does not lead to the significant undertreatment of children’s cancer pain. Rather, it is critical to implement practices, guidelines, and clinical services that can provide evidence-based, multimodal interventions for the management of cancer-related pain in children that reduce unnecessary suffering and minimize unintended harms.



## Abbreviations:

<b>ASCO</b>	American Society of Clinical Oncology
<b>AYA</b>	adolescent and young adult
<b>CAM</b>	complementary and alternative medicine
<b>CDC</b>	Centers for Disease Control and Prevention
<b>IM</b>	integrative medicine
<b>mHealth</b>	mobile health
<b>NCCN</b>	National Comprehensive Cancer Network
<b>NIH</b>	National Institutes of Health
<b>NSAIDS</b>	nonsteroidal anti-inflammatory medications

## REFERENCES

- Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in drug and opioid overdose deaths—United States, 2000–2014. *MMWR Morb Mortal Wkly Rep.* 2016;64(50–51):1378–1382. [PubMed: 26720857]
- Dasgupta N, Beletsky L, Ciccarone D. Opioid crisis: no easy fix to its social and economic determinants. *Am J Public Health.* 2018;108(2):182–186. [PubMed: 29267060]
- Kolodny A, Courtwright DT, Hwang CS, et al. The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. *Annu Rev Public Health.* 2015;36(1):559–574. [PubMed: 25581144]
- Volkow ND, McLellan AT. Opioid abuse in chronic pain—misconceptions and mitigation strategies. *N Engl J Med.* 2016;374(13): 1253–1263. [PubMed: 27028915]
- Levy N, Sturgess J, Mills P. ‘Pain as the fifth vital sign’ and dependence on the ‘numerical pain scale’ is being abandoned in the US: why? *Br J Anaesth.* 2018;120(3):435–438. [PubMed: 29452798]
- Curtin SC, Tejada-Vera B, Warner M. Drug overdose deaths among adolescents aged 15–19 in the United States: 1999–2015. *NCHS Data Brief.* 2017(282):1–8.
- Vadivelu N, Kai AM, Kodumudi V, Sramcik J, Kaye AD. The opioid crisis: a comprehensive overview. *Curr Pain Headache Rep.* 2018;22(3): 16. [PubMed: 29476358]
- Cicchetti D, Rogosch FA. A developmental psychopathology perspective on adolescence. *J Consult Clin Psychol.* 2002;70(1):6–20. [PubMed: 11860057]
- Rosenbloom BN, Rabbitts JA, Palermo TM. A developmental perspective on the impact of chronic pain in late adolescence and early adulthood: implications for assessment and intervention. *Pain.* 2017;158(9):1629–1632. [PubMed: 28267063]
- Volkow ND, Collins FS. The role of science in addressing the opioid crisis. *N Engl J Med.* 2017;377(4):391–394. [PubMed: 28564549]
- American Cancer Society. *Cancer in Children.* Atlanta, GA: ACS; 2013.
- Miller E, Jacob E, Hockenberry MJ. Nausea, pain, fatigue, and multiple symptoms in hospitalized children with cancer. *Oncol Nurs Forum.* 2011;38(5):E382–393. [PubMed: 21875835]
- Van Cleve L, Bossert E, Beecroft P, Adlard K, Alvarez O, Savedra MC. The pain experience of children with leukemia during the first year after diagnosis. *Nurs Res.* 2004;53(1):1–10. [PubMed: 14726771]
- Ljungman G, Gordh T, Sorensen S, Kreuger A. Pain variations during cancer treatment in children: a descriptive survey. *Pediatr Hem Onc.* 2000;17(3):211–221.

15. McGuire DB. Occurrence of cancer pain. *J Natl Cancer Inst.* 2004;32:51–56.
16. Pöder U, Ljungman G, von Essen L. Parents' perceptions of their children's cancer-related symptoms during treatment: a prospective, longitudinal study. *J Pain Symptom Manage.* 2010;40(5):661–670. [PubMed: 20678894]
17. Hedstrom M, Haglund K, Skolin I, von Essen L. Distressing events for children and adolescents with cancer: child, parent, and nurse perceptions. *J Pediatr Oncol Nurs.* 2003;20(3):120–132. [PubMed: 12776260]
18. Jacob E, McCarthy KS, Sambuco G, Hockenberry M. Intensity, location, and quality of pain in Spanish-speaking children with cancer. *Pediatr Nurs.* 2008;34(1):45–52. [PubMed: 18361086]
19. Gordon DB, Dahl JL, Miaskowski C, et al. American pain society recommendations for improving the quality of acute and cancer pain management: American Pain Society Quality of Care Task Force. *ArchIntern Med.* 2005;165(14):1574–1580.
20. Mercadante S. Cancer pain management in children. *Palliat Med.* 2004;18(7):654–662. [PubMed: 15540676]
21. Hockenberry M. Symptom management research in children with cancer. *J Pediatr Oncol Nurs.* 2004;21(3):132–136. [PubMed: 15296040]
22. Fortier MA, Wahi A, Bruce C, Maurer EL, Stevenson R. Pain management at home in children with cancer: a daily diary study. *Pediatr Blood Cancer.* 2014;61(6):1029–1033. [PubMed: 24376073]
23. Wolfe J, Orellana L, Ullrich C, et al. Symptoms and distress in children with advanced cancer: prospective patient-reported outcomes from the PediQUEST study. *J Clin Oncol.* 2015;33(17):1928–1935. [PubMed: 25918277]
24. Manchikanti L, Manchikanti KN, Kaye AD, Kaye AM, Hirsch JA. Challenges and concerns of persistent opioid use in cancer patients. *Expert Rev Anticancer Ther.* 2018;18(7):705–718. [PubMed: 29739242]
25. Flury M, Caflisch U, Ullmann-Bremi A, Spichiger E. Experiences of parents with caring for their child after a cancer diagnosis. *J Pediatr Oncol Nurs.* 2011;28(3):143–153. [PubMed: 21490277]
26. Rubenstein EB. Costs and benefits of outpatient therapy. *Support Care Cancer.* 1994;2(5):307–311. [PubMed: 8000729]
27. Hendershot E, Murphy C, Doyle S, Van-Cleaf J, Lowry J, Honeyford L. Outpatient chemotherapy administration: decreasing wait times for patients and families. *J Pediatr Oncol Nurs.* 2005;22(1):31–37. [PubMed: 15574724]
28. Fortier MA, MacLaren JE, Martin SR, Perret D, Kain ZN. Pediatric pain after ambulatory surgery: where's the medication? *Pediatrics.* 2009;124(4):e588–e595. [PubMed: 19736260]
29. Fortier MA, Wahi A, Maurer EL, Tan ET, Sender LS, Kain ZN. Attitudes regarding analgesic use and pain expression in parents of children with cancer. *J Pediatr Hematol Oncol.* 2012;34(4):257–262. [PubMed: 22322939]
30. Given BA, Given CW, Kozachik S. Family support in advanced cancer. *CA Cancer J Clin.* 2001;51(4):213–231. [PubMed: 11577488]
31. Howard RF. Current status of pain management in children. *JAMA.* 2003;290(18):2464–2469. [PubMed: 14612483]
32. Ferrell BR, Ferrell BA, Rhiner M, Grant MM. Family factors influencing cancer pain. *Post Gr Med J.* 1991;67(Suppl 2):S64–S69.
33. Ferrell BR, Cohen M, Rhiner M, Rozek A. Pain as a metaphor for illness. Part II: family caregivers' management of pain. *Oncol Nurs Forum.* 1991;18:1315–1321. [PubMed: 1762972]
34. Wiffen PJ, Wee B, Derry S, Bell RF, Moore RA. Opioids for cancer pain – an overview of Cochrane reviews. *Cochrane Database Syst Rev.* 2017;7:CD012592.
35. Paice JA, Portenoy R, Lacchetti C, et al. Management of chronic pain in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol.* 2016;34(27):3325–3345. [PubMed: 27458286]
36. American Cancer Society. American Cancer Society's Guide to Controlling Cancer Pain. Atlanta, GA: ACS; 2018.

37. Angheliescu DL, Faughnan LG, Popenhagen MP, Oakes LL, Pei D, Burgoyne LL. Neuropathic pain referrals to a multidisciplinary pediatric cancer pain service. *Pain Manag Nurs*. 2014;15(1):126–131. [PubMed: 24602431]
38. Friedrichsdorf SJ. Pain management in children with advanced cancer and during end-of-life care. *Pediatr Hematol Oncol*. 2010;27(4):257–261. [PubMed: 20426516]
39. Ehrentraut JH, Kern KD, Long SA, Qi An A, Faughnan LG, Angheliescu DL. Opioid misuse behaviors in adolescents and young adults in a hematology/oncology setting. *J Pediatr Psychol*. 2014;39(10):1149–1160. [PubMed: 25225182]
40. Peck KR, Harman JL, Angheliescu DL. Family and peer-group substance abuse as a risk-factor for opioid misuse behaviors for a young adult with cancer-related pain—a case study. *J Adolesc Young Adult Oncol*. 2018;7(1):137–140. [PubMed: 28910174]
41. Peck KR, Harman JL, Angheliescu DL. Provision of adequate pain management to a young adult oncology patient presenting with aberrant opioid-associated behavior: a case study. *J Adolesc Young Adult Oncol*. 2019;8(2):221–224. [PubMed: 30335554]
42. Swarm R, Abernethy AP, Angheliescu DL, et al. Adult cancer pain. *J Natl Compr Canc Netw*. 2010;8(9):1046–1086. [PubMed: 20876544]
43. Brenn BR, Choudhry DK, Sacks K, Como-Fluehr S, Strain R. Toward better pain management: the development of a ‘pain stewardship program’ in a tertiary children’s hospital. *Hosp Pediatr*. 2016;6(9):520–528. [PubMed: 27493066]
44. Pollack LA, van Santen KL, Weiner LM, Dudeck MA, Edwards JR, Srinivasan A. Antibiotic stewardship programs in U.S. acute care hospitals: findings from the 2014 national healthcare safety network annual hospital survey. *Clin Infect Dis*. 2016;63(4):443–449. [PubMed: 27199462]
45. Matson KL, Johnson PN, Tran V, Horton ER, Sterner-Allison J. Group for the AC on behalf of PPA. Opioid use in children. *J Pediatr Pharmacol Ther*. 2019;24(1):72–75. [PubMed: 30837819]
46. Ghafoor VL, Phelps P, Pastor J. Implementation of a pain medication stewardship program. *Am J Heal Pharm*. 2013;70(23):2070.
47. Sandbrink F, Uppal R. The time for opioid stewardship is now. *Jt Comm J Qual Patient Saf*. 2019;45(1):1–2. [PubMed: 30522832]
48. Misra SM, Monico E, Kao G, et al. Addressing pain with inpatient integrative medicine at a large children’s hospital. *Clin Pediatr (Phila)*. 2019;58(7):738–745. [PubMed: 30931605]
49. Bishop FL, Prescott P, Chan YK, Saville J, von Elm E, Lewith GT. Prevalence of complementary medicine use in pediatric cancer: a systematic review. *Pediatrics*. 2010;125(4):768–776. [PubMed: 20308209]
50. Zia FZ, Olaku O, Bao T, et al. The National Cancer Institute’s conference on acupuncture for symptom management in oncology: state of the science, evidence, and research gaps. *J Natl Cancer Inst Monogr*. 2017;2017(52). 10.1093/jncimonographs/lgx005
51. Raphael J, Hester J, Ahmedzai S, et al. Cancer pain: part 2: physical, interventional and complimentary therapies; management in the community; acute, treatment-related and complex cancer pain: a perspective from the British Pain Society Endorsed by the UK Association of Palliative Medicine and the Royal College of General Practitioners. *Pain Med*. 2010;11(6):872–896. [PubMed: 20456069]
52. Eidelman A, White T, Swarm RA. Interventional therapies for cancer pain management: important adjuvants to systemic analgesics. *J Natl Compr Cancer Netw*. 2007;5(8):851–858.
53. Dupuis LL, Ethier M-C, Tomlinson D, Hesser T, Sung L. A systematic review of symptom assessment scales in children with cancer. *BMC Cancer*. 2012;12(1):430. [PubMed: 23009053]
54. Kazak AE, Rourke MT, Alderfer MA, Pai A, Reilly AF, Meadows AT. Evidence-based assessment, intervention and psychosocial care in pediatric oncology: a blueprint for comprehensive services across treatment. *J Pediatr Psychol*. 2007;32(9):1099–1110. [PubMed: 17626069]
55. Pew Research Center. Mobile Fact Sheet; 2018.
56. Pandey A, Hasan S, Dubey D, Sarangi S. Smartphone apps as a source of cancer information: changing trends in health information-seeking behavior. *J Cancer Educ*. 2013;28(1):138–142. [PubMed: 23275239]

57. Majeed-Ariss R, Baildam E, Campbell M, et al. Apps and adolescents: a systematic review of adolescents' use of mobile phone and tablet apps that support personal management of their chronic or long-term physical conditions. *J Med Internet Res*. 2015;17(12):e287.
58. Kumar S, Nilsen WJ, Abernethy A, et al. Mobile health technology evaluation. *Am J Prev Med*. 2013;45(2):228–236. [PubMed: 23867031]
59. Fortier MA, Chung WW, Martinez A, Gago-Masague S, Sender L. Pain buddy: a novel use of m-health in the management of children's cancer pain. *Comput Biol Med*. 2016;76:202–214. [PubMed: 27479493]
60. Stinson JN, Jibb LA, Nguyen C, et al. Development and testing of a multidimensional iPhone pain assessment application for adolescents with cancer. *J Med Internet Res*. 2013;15(3):e51. [PubMed: 23475457]
61. Jibb LA, Cafazzo JA, Nathan PC, et al. Development of a mHealth real-time pain self-management app for adolescents with cancer: an iterative usability testing study. *J Pediatr Oncol Nurs*. 2017;34(4):283–294. [PubMed: 28376666]
62. Jibb LA, Stevens BJ, Nathan PC, et al. Implementation and preliminary effectiveness of a real-time pain management smartphone app for adolescents with cancer: a multicenter pilot clinical study. *Pediatr Blood Cancer*. 2017;64(10):e26554.
63. Stinson JN, Jibb LA, Nguyen C, et al. Construct validity and reliability of a real-time multidimensional smartphone app to assess pain in children and adolescents with cancer. *Pain*. 2015;156(12):2607–2615. [PubMed: 26580680]
64. Hall RW, Dehnel PJ, Alexander JJ, et al. Telemedicine: pediatric applications. *Pediatrics*. 2015;136(1):e293–e308. [PubMed: 26122813]
65. Yang CP, Hunt EA, Shilkofski N, Dudas R, Egbuta C, Schwartz JM. Can telemedicine improve adherence to resuscitation guidelines for critically ill Children at Community Hospitals? A randomized controlled trial using high-fidelity simulation. *Pediatr Emerg Care*. 2017;33(7):474–479. [PubMed: 26945195]
66. Kohler JE, Falcone RA, Fallat ME. Rural health, telemedicine and access for pediatric surgery. *Curr Opin Pediatr*. 2019;31(3):391–398. [PubMed: 31090582]
67. Sikorskii A, Given CW, Given B, et al. Symptom management for cancer patients: a trial comparing two multimodal interventions. *J Pain Symptom Manage*. 2007;34(3):253–264. [PubMed: 17618080]
68. White Y, Castle VP, Haig A. Pediatric oncology in developing countries: challenges and solutions. *J Pediatr*. 2013;162(6):1090–1091. [PubMed: 23708414]
69. Niznik JD, He H, Kane-Gill SL. Impact of clinical pharmacist services delivered via telemedicine in the outpatient or ambulatory care setting: a systematic review. *Res Soc Adm Pharm*. 2018;14(8):707–717.
70. Van Allen J, Davis AMG, Lassen S. The use of telemedicine in pediatric psychology: research review and current applications. *Child Adolesc Psychiatr Clin N Am*. 2011;20(1):55–66. [PubMed: 21092912]