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Opioid use and misuse in children, adolescents, and young adults with cancer: a systematic review of the literature

Melissa Beauchemin^{1,2}, Richard Dorritie³, Dawn L. Hershman^{1,2}

¹Mailman School of Public Health, Department of Epidemiology, Columbia University, 722 W. 168th Street Room 719, NY 10032 New York, USA

²Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY 10032, USA

³Helene Fuld College of Nursing, New York, NY 10035, USA

Abstract

Adolescents and young adults (AYAs) are at increased risk for negative opioid-related outcomes, including misuse and overdose. High-quality cancer care requires adequate pain management and often includes opioids for tumor- and/or treatment-related pain. Little is known about opioid use and misuse in children and AYAs with cancer, and we therefore conducted a systematic review of the literature using PRISMA guidelines to identify all relevant studies that evaluated opioid use and/or misuse among this population. Eleven studies were identified that met our inclusion criteria. The range of opioid use among the studies was 12–97%, and among the five studies that reported opioid misuse or aberrant behaviors, 7–90% of patients met criteria. Few studies reported factors associated with opioid misuse but included prior mental health and/or substance use disorders, and prior opioid use. In summary, opioid use is highly variable among children and AYAs with cancer; however, the range of use varies widely depending on the study population, such as survivors or end-of-life cancer patients. Few studies have examined opioid misuse and/or aberrant behaviors, and future research is needed to better understand opioid use and misuse among children and AYAs with cancer, specifically those who will be cured of their cancer and may subsequently experience adverse opioid-related outcomes.

Keywords

Opioid misuse; Opioid prescribing; Adolescent and young adults; AYAs

Melissa Beauchemin mmp2123@cumc.columbia.edu.

Authors' contributions MB conceptualized the study. MB and RD contributed in data abstraction, quality appraisal, and analysis. DH provided input at the study development, search strategy, and assisted in manuscript preparation.

Data availability N/A

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethics approval N/A

Consent to participate N/A

Consent for publication N/A

Code availability The search strategy is included in Appendix.

Background

During the 1990s, the USA entered what the Department of Human and Health Services would later declare an opioid epidemic and public health emergency in 2017 [1], and in 2018, 2 million Americans misused prescription opioids for the first time [2]. Adolescents and young adults (AYAs) are more likely to misuse and overdose on opioids compared with other age groups [3–6], and although rates of opioid use across all age groups have started to decrease, likely due to increased awareness and efforts to address the opioid epidemic, the negative downstream effects of opioid use such as hospitalization, heroin use, and overdose have not improved among AYAs. In fact, the rate of fatal opioid overdose in AYAs has increased over the past 10 years [7], with half of overdose deaths in this age group attributed to opioid misuse. Factors associated with overdose in AYAs include prescription of both more tablets and higher doses of opioids [8, 9], whereas known risk factors for opioid misuse include acute and chronic pain, history of mental illness or substance use, and witnessing others' misuse/overdose [10, 11]. Strategies to reduce opioid misuse and overdose include a focus on safe prescribing practices, such as reducing or limiting opioid prescriptions [12, 13].

For AYAs with cancer, defined broadly by the National Cancer Institute as ages 15–39 years old, pain is a common symptom and may be post-surgical, cancer-related, and/or treatment-related [14]. Appropriate high-quality pain management often includes opioids, putting AYAs with cancer at risk for negative opioid-related outcomes. Although younger children are not commonly included in opioid-related initiatives, children with cancer, similar to adolescents and young adults, commonly receive opioids for pain management during and after treatment for cancer. They may therefore have a similar risk for opioid misuse and negative outcomes, particularly among those who survive their cancer. In addition, the healthcare providers who treat children are often the same as those treating adolescents, and future strategies would be directed toward these providers. It therefore is prudent to include children in investigations about opioid use and misuse. Opioid misuse in adult cancer patients has been reported in the literature; however, little is known about opioid use and misuse among younger cancer patients. We therefore conducted a systematic review of the literature to describe opioid use and misuse in children and AYAs with cancer.

Methods

We conducted a review of the literature using PubMed database to identify studies where opioid use and/or misuse were reported in children and AYAs with cancer. Key words included cancer, children, or adolescents or young adults, and opioid prescription (see Appendix for search strategy). The population of interest was children and AYAs with cancer, the exposure was opioids for pain management, and outcomes included opioid use, misuse, overdose, or opioid-aberrant behaviors. Our search included studies from database inception through February 20, 2020; another confirmation search was run on December 3, 2020. We included studies (1) if they included cancer patients, at least a subset; (2) if they included children, adolescent, and/or young adults up to age 39 years, at least as a subset; (3) separate analyses were conducted by disease and/or age if the study population was broader; and (4) if opioid prescriptions, opioid use, and/or opioid misuse were reported. Regarding

treatment setting, we included studies of opioid use during any treatment period, such as outpatient, inpatient, end-of-life/palliative care settings, and survivorship. Studies that were original research and where full text was available were included. Case studies were excluded. Reference lists in the full-text reviewed articles were examined, and relevant articles were included for review. The review was registered with PROSPERO International prospective register of systematic reviews (ID 196360) [15].

All eligible studies were entered into an EndNote database and then de-duplicated using the Bramer Method [16]. All citations were then independently screened by two reviewers (MB, RD) by title and abstract using Covidence [17, 18], and reasons for exclusion were documented. Any potentially relevant citations were then included in the full-text review, and the same procedures were repeated. Discrepancies were reviewed, and final consensus was achieved with a third reviewer, if necessary.

After full-text review, variables of interest for the data synthesis were extracted from each included article by one reviewer. These included (1) population and study sample, (2) the opioid-specific outcome of interest, (3) geographic location of study and year(s) study was conducted, (4) the study design, and (5) the study intervention or exposure. The Joanna Briggs Institute Critical Appraisal Checklist for Quasi-experimental Studies was used to determine the study quality of the included articles [19, 20]. Studies received 1 point for every component met with a possible total of 8 points. One reviewer completed the checklist for each of the included studies; all appraisals were reviewed by two reviewers to ensure agreement. All studies were described qualitatively by study objective, study design, time period, study setting, and sample, including whether the focus was patients on active therapy, palliative or end-of-life settings, or survivorship. Opioid-specific outcomes and associated factors with the outcome were described and synthesized. Due to the anticipated dearth of literature in this area, meta-analysis was not conducted.

Results

Search results

Our initial literature search retrieved 181 citations, and we identified an additional 2 studies through reference searching. All 183 were included in title and abstract screening, and 110 were removed, mostly due to an outcome inclusion criteria mismatch, not including opioid prescribing or misuse. We reviewed 73 full-text studies, and 61 studies were excluded (Fig. 1). The main reasons for exclusion were not including cancer patients and not including or separately analyzing adolescents or adults younger than 39 years old in a study of adults. Twelve unique, original studies met our inclusion criteria.

Description of studies

Table 1 summarizes the characteristics of the 12 included studies. Seven of the studies were retrospective (five cohort, two case-control), two were cross-sectional survey studies, and three were prospective, non-interventional studies. Nine studies were conducted in the USA, two in Europe, and one in South America. Overall, the quality of the studies was high, with studies scoring between 5 and 8. Of the 12 studies, two were studies of adult cancer patients

that included an analysis by age, specifically including age 39 as a cut-point in the analysis [21, 22]. Eight studies focused specifically on children, adolescents, and young adults with cancer [12, 23–29], and the remaining two included survivors of childhood cancer [21, 22].

The opioid-specific outcomes varied across studies (Table 1). All studies reported the proportion of participants who used or received opioids, ranging from 6 to 97%. Among studies that focused on patients receiving active therapy or palliative care/end-of-life, the proportion ranged from 24 to 97%; among survivors, the proportion ranged from 6 to 46%. The study populations varied widely from hospitalized patients at the end-of-life to survivors of childhood cancer.

Five studies reported opioid aberrant behaviors, such as misuse, and four examined factors associated with opioid misuse. Misuse behaviors were identified in a subset of the overall opioid users, ranging from 7% of post-operative women meeting criteria for new persistent opioid users [22] to 90% of parents of children and adolescents with cancer reporting unsafe opioid storage techniques [30]. These behaviors were by definition determined to put an individual at increased risk of opioid misuse. Among these five studies, four examined factors associated with this outcome [21–24]. Though two of these studies did not identify significant associations, two did report increased risk associated with prior mental health diagnosis, substance use disorders, and/or prior opioid use [12, 23, 24, 30].

Discussion

Through a systematic review of the literature, we identified 12 studies describing opioid use and misuse in children and AYAs with cancer. The study designs, settings, and outcomes were not consistent across studies, and the proportion prescribed opioids varied widely by where they were in the cancer treatment continuum. Importantly, our findings suggest that children and AYAs who use opioids may be at risk for opioid misuse, particularly those who become long-term survivors.

All of the included studies reported the proportion of participants who received opioids. The lowest rates, ranging from 6 to 12%, were reported in survivors of childhood cancer [31, 32]. These numbers are consistent with other studies of opioid use in adults with cancer or post-operatively [33, 34]. Smitherman's study, however, also reported a 46% rate of opioid use among survivors of bone tumors, suggesting a difference by disease type as the 12% rate was reported among survivors of childhood leukemia. This may be related to certain tumor types, such as bone tumors, requiring more intensive surgical treatment and subsequent pain management, compared with other cancers such as leukemia. In addition, the lowest reported rate of 6%, from the Childhood Cancer Survivor Study, relied on self-report compared with other studies that utilized insurance claims or hospital databases.

The variability in opioid use supports the need for clinical practice guidelines on opioid prescribing and effective pain management for children and AYAs across the cancer treatment continuum and not just at the end-of-life, as is currently available [35, 36]. The American Society of Clinical Oncology recently published a clinical practice guideline for pain management for adult survivors of cancer [37]. Similar guidance directed toward pain

management for younger people with cancer, particularly into survivorship, is needed to support safe prescribing for effective pain management while mitigating the risk of opioid misuse and overdose.

Studies where more prevalent opioid use was reported were primarily in the active therapy setting [25, 28], or at the end-of-life setting [26, 29]. These studies often focused on patients who may be expected to use opioids, such as those being seen by the palliative care program or those in the last week or month of life. The high proportion of opioid use is expected given that these patients have a high burden of pain, and opioids are clinically indicated for acute pain. In fact, because opioids are often an integral and necessary component of high-quality palliative care, we considered excluding end-of-life pain management from this review. We realized, however, that the paucity of studies on opioid use in children and AYAs with cancer warranted a complete review regardless of disease status to establish the current knowledge gaps.

Although opioid misuse and aberrant behaviors that may put a child or AYA at increased risk of opioid misuse were examined in a subset of the studies, it is important to note that neither the definition of opioid misuse nor aberrant behaviors was standardized. Persistent use of opioids following treatment for cancer, as reported in both Cheung and Smitherman's studies, signifies that AYA survivors may either already be misusing opioids or are at an elevated risk of future misuse and perhaps overdose. Further, Madden et al.'s study highlighted another important definition of misuse by characterizing opioid storage and use behaviors in the home of children and adolescents with cancer [30]. With 90% of parents reporting unsafe opioid storage techniques, further research is needed both to educate recipients of opioids about safe storage and to improve safe prescribing techniques, such as not overprescribing quantity of tablets or providing safe disposal options when the opioids are no longer needed. These strategies have been developed in other settings and should be explored in this population [38, 39].

Although only four studies examined factors associated with opioid misuse, we identified a trend toward increasing risk in patients with prior mental health diagnosis, substance use disorders, or prior opioid use [12, 23, 24, 30]. These findings are corroborated in studies of older cancer patients and non-oncology AYAs [6, 8, 10, 11] and although largely unmodifiable can support future screening initiatives and prediction models to identify at-risk patients early in their treatment. These potential risk factors also support the need for a multidisciplinary approach, including psychosocial support, to effectively manage pain and manage potential opioid misuse. With early identification, tailored interventions may be more effective at reducing risk of future misuse and/or overdose.

Though we conducted our systematic review using rigorous methodology, there are limitations to acknowledge. We included broad search terms to identify any relevant studies about children and AYAs and opioid use and/or misuse, but it is possible that some relevant studies were not identified. To mitigate this risk, we did include a subsequent search of Web of Science using the Citation Index for each of our included 12 studies, and no new studies were identified. Further, as stated previously, we included all stages of cancer treatment, rather than limiting to studies of survivors and/or non-end-of-life settings. We view this as

strength, as this review provides a full scope of the knowledge gap about opioid use and misuse in children and AYAs with cancer.

In conclusion, this systematic review identified a highly relevant gap in knowledge about opioid use and misuse in children and AYAs with cancer. The paucity of data around this topic highlights a need to explore and better understand the prevalence of opioid use/misuse among this population. A better understanding of opioid use and misuse is necessary to develop effective and targeted interventions to mitigate opioid-specific negative outcomes for children and AYAs with cancer.

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Appendix.: Search strategy in PubMed in February, 2020 (re-run in May, 2020 and again in December, 2020 to ensure no new findings)

("analgesics opioid"[Pharmacological Action] OR "analgesics, opioid"[MeSH Terms] OR ("analgesics"[All Fields] AND "opioid"[All Fields]) OR "opioid analgesics"[All Fields] OR "opioid"[All Fields]) AND ("prescriptions"[MeSH Terms] OR "prescriptions"[All Fields] OR "prescription"[All Fields]) AND ("young adult"[MeSH Terms] OR ("young"[All Fields] AND "adult"[All Fields]) OR "young adult"[All Fields] OR ("young"[All Fields] AND "adults"[All Fields]) OR "young adults"[All Fields] OR ("adolescent"[MeSH Terms] OR "adolescent"[All Fields] OR "adolescents"[All Fields]) OR ("child"[MeSH Terms] OR "children"[All Fields] OR "pediatric"[All Fields])) AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields])

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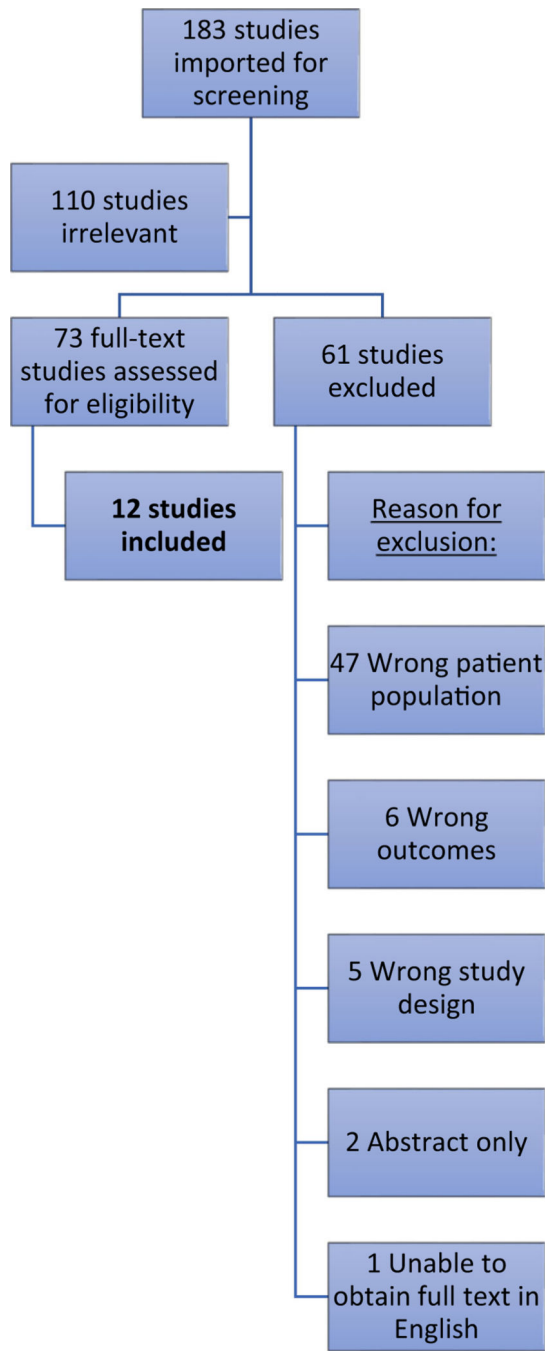


Fig. 1.
PRISMA flow diagram for search results

Table 1

Characteristics of the 12 included studies

| Author, year | Title | Objective | Time, study design and appraisal score | Setting and sample | Opioid use | Opioid misuse and associated factors |
|------------------|--|--|---|--|--|---|
| Bertrand, 2016 | Does consumption of tobacco, alcohol, and cannabis in adolescents and young adults with cancer affect the use of analgesics during hospitalizations? | To examine how exposure to tobacco and/or cannabis and/or alcohol is associated with opioid analgesics in AYAs with cancer during hospitalizations | 6 months during 2013 Cross-sectional survey JBI Score 5 | Two cancer centers in France <i>N</i> = 30 age 15–25 years with cancer, active therapy | 40% of low-use consumers and 79% high-use consumers (of alcohol and tobacco) self-reported taking opioids | N/A |
| Cheung, 2020 | Prescription Psychoactive Medication Use in Adolescent Survivors of Childhood Cancer and Association With Adult Functional Outcomes | To estimate the prevalence of psychoactive medication use in adolescent survivors of childhood cancer and its associations with functional outcomes at young adulthood | Diagnosed with cancer between 1970 and 1999 Retrospective case control JBI Score: 7 | The Childhood Cancer Survivor Study <i>N</i> = 5665 survivors of childhood cancer ages 13–16 years; <i>N</i> = 921 siblings | 5.7% of survivors compared to 1.7% of siblings ($p < .001$) self-reported using opioids for > 1 month in the prior 2 years | N/A |
| Ehrentraut, 2014 | Opioid misuse behaviors in adolescents and young adults in a hematology/oncology setting | To examine opioid misuse behaviors in AYAs treated for cancer at a large, pediatric oncology center and to identify risk factors for aberrant use | Jan 2012–May 2013 Retrospective cohort JBI Score: 7 | TN, USA <i>N</i> = 398 age 12–33 years with cancer, active therapy | 24% were prescribed opioids | 12% exhibited aberrant behaviors No significant association between aberrant behaviors and MH/family hx of SU but trend toward significance ($p = 0.06$) |
| Getz, 2018 | Opioid utilization among pediatric patients treated for newly diagnosed acute myeloid leukemia | To examine opioid prescribing and utilization for children with newly diagnosed AML | 2000–2014 Retrospective cohort JBI Score: 8 | PHIS database <i>N</i> = 1600 age 1–20 years with AML, active therapy | 78% received opioids | N/A |
| Hewitt, 2008 | Opioid Use in Palliative Care of Children and Young People with Cancer | To examine opioid use for children and adolescents with cancer during the last month of life | 20-month period Prospective, longitudinal cohort JBI Score: 6 | 3 cancer centers in UK <i>N</i> = 185 age 0–19 years, end-of-life | 90% received opioids | N/A |
| Madden, 2020 | Patterns of Storage, Use, and Disposal of Prescription Opioids by Parents of Children with Cancer | To describe opioid use and storage patterns reported by parents of children with cancer | Feb–Nov 2018 Cross-sectional survey JBI Score: 6 | TX, USA <i>N</i> = 109 parents of children age <18 years with cancer, active therapy | 97% self-reported their children used opioids | 90% did not store safely; 21% did not use safely with patient; 6% gave to other than patient |
| Monteiro, 2005 | Clinical Aspects and Treatment of Pain in Children and Adolescents with Cancer | To examine pain control and analgesic prescribing for children and adolescents with cancer and non-procedure related pain | 2000–2003 Prospective, longitudinal cohort JBI Score: 7 | Pediatric hospital in Brazil <i>N</i> = 135 age 1–20 years, active therapy | 88% received opioids | N/A |

| Author, year | Title | Objective | Time, study design and appraisal score | Setting and sample | Opioid use | Opioid misuse and associated factors |
|--------------------|---|--|---|---|--|--|
| Murphy, 2019 | Pain and opioid prescriptions vary by procedure after breast surgery. | To examine post-operative pain and opioid prescribing for women after breast surgery | 2010–2016 Retrospective cohort JBI Score: 8 | 3 cancer centers in US $N = 4021$ 18 years+ women s/p mastectomy (5% age 18–39 years) | 94% were prescribed opioids | 22% received higher discharge dose (Q4 MME) Age 30–39 y had 1.85 higher odds of receiving higher dose compared to age > 80 years ($p < 0.05$) |
| Orsey, 2009 | Variation in receipt of opioids by pediatric oncology patients who died in children's hospitals | To describe daily opioid use compared to intermittent use during last week of life for children with cancer who died in the hospital | 2001–2005 Retrospective cohort JBI Score: 7 | PHIS database $N = 1466$ age 0–24 years with cancer, end-of-life | 56% received daily opioids | N/A |
| Smitherman, 2018 | Early Post-Therapy Prescription Drug Usage among Childhood and Adolescent Cancer Survivors | To examine prescription types and quantities for survivors of childhood cancer | Completed treatment between 2000 and 2011 Retrospective case control JBI Score: 8 | Marketscan database $N = 1414$ mean age 9.3–17.4 years at least 3 years off-therapy | 12–46% were prescribed opioids by disease type (highest proportion in bone tumors) | N/A |
| Thienprayoon, 2017 | Risk Stratification for Opioid Misuse in Children, Adolescents, and Young Adults: A Quality Improvement Project | To use an opioid bundle to increase risk stratification for opioid misuse among patients who present for follow up with Pediatric Advanced Care Team | 2014–2015 Prospective, pre-post JBI Score: 6 | Single cancer center in OH, USA $N = 106$ age 3–33 years with cancer/BMT; $n = 62$ were risk-stratified, active therapy | 58% received opioids | 34% were classified as high-risk for opioid misuse |
| Wright, 2019 | Use and Misuse of Opioids After Gynecologic Surgical Procedures | To examine the rate of opioid use for gynecologic surgical procedures and to investigate persistent opioid use among those women who received an initial opioid prescription | 2009–2016 Retrospective cohort JBI Score: 7 | Marketscan database $N = 729,000$ women 6.1% age 18–29 years 25.1% age 30–39 years | Among 18–29 years: 64.5% were prescribed Among 30–39 years: 63.1% were prescribed opioids | Among 18–29 years: 9.8% were new, persistent users post-operatively Among 30–39 years: 7.7% were new, persistent users post-operatively Younger patients, Medicaid recipients, and patients with depression, anxiety, and substance use disorder all associated with new persistent use ($p < .001$) |