Opioid Misuse Behaviors in Adolescents and Young Adults in a Hematology/Oncology Setting

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Objective To describe the occurrence and psychosocial correlates of aberrant opioid-associated behavior (AOB) in adolescent and young adult (AYA) hematology and oncology patients prescribed opioid therapy. **Methods** Structured retrospective chart reviews were conducted for AYA patients ($N = 398$) accepted for active treatment at a large pediatric hematology/oncology institution over a 17-month period. Opioid therapy was documented in the records of 94 out of the 398 patients. The records of those 94 patients were further reviewed to identify documented AOB and documented correlates of AOB. **Results** Of the 94 patients prescribed opioid therapy, 11.7% exhibited AOB. At least one psychosocial risk factor was identified in 90.9% of patients with AOB. Concurrent use of multiple opioids was significantly associated with AOB ($p = .003$). **Conclusions** Hematology/oncology AYA patients may exhibit AOB despite a legitimate clinical indication for opioid therapy. Clinicians should consider young patients' psychosocial risk factors when using opioid therapy.

Key words adherence; cancer and oncology; drug abuse and exposure; hematology.

Introduction

Opioid misuse, abuse, diversion, addiction, and accidental overdose has increased dramatically in recent decades (Casty, Wieman, & Shusterman, 2013; Caudill-Slosberg, Schwartz, & Woloshin, 2004; Compton & Volkow, 2006; Edlund et al., 2010; Joranson, Ryan, Gilson, & Dahl, 2000). In a 2002 survey, 4.7% of U.S. residents older than 12 years of age acknowledged having abused an opioid, and the number of admitted opioid abusers increased from 628,000 to 2.4 million between 1990 and 2001 (Compton & Volkow, 2006). Aberrant opioid-associated behaviors (AOBs) often indicate opioid misuse or abuse (Anghelescu, Ehrentraut, & Faughnan, 2013; Compton & Volkow, 2006; Passik, 2009; Passik, Portenoy, & Ricketts, 1998; Pergolizzi et al., 2012; Portenoy, 1996). The range of AOB reported within the literature includes demanding more medication; claiming to have lost pills or prescriptions; seeing multiple physicians for pain medication; obtaining pain medication from the emergency room or nonmedical sources; using medications for nonprescribed purposes (e.g., relaxation, mood change, euphoria); stealing or selling drugs; prescription forgery, theft, or tampering; unauthorized dose escalation; concurrent use of alcohol; resisting changes to the medication regimen; hoarding drugs; deteriorating function; and third-party concerns about opioid use (Anghelescu et al., 2013; Passik, 2009; Passik, Portenoy, et al., 1998; Pergolizzi et al., 2012; Portenoy, 1996). Aberrant opioid-associated behaviors associated with opioid misuse can lead to addiction, respiratory depression, and death (Compton & Volkow, 2006).

Various factors are significantly associated with opioid misuse. Among adolescent and young adult (AYA) patients, these include patients' previous substance abuse (Nakawaki & Crano, 2012; Webster & Webster, 2005) or substance abuse by the patient's immediate family

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(Michna et al., 2004; Webster & Webster, 2005) or peer group (Boyd, Young, Grey, & McCabe, 2009; Lord et al., 2009), a past or current mental health diagnosis in the patient (Boyd et al., 2009; Grattan, Sullivan, Saunders, Campbell, & Von Korff, 2012; Wasan et al., 2007; Webster & Webster, 2005) or immediate family (Ahmed, Salib, & Ruben, 1999; Webster & Webster, 2005), and a history of sexual abuse (Pergolizzi et al., 2012; Webster & Webster, 2005). Furthermore, in adults, concurrent (i.e., two or more at the same time) opioid use in prescribed opioid therapy increases risk of AOB (Edlund et al., 2010).

The U.S. Food and Drug Administration has mandated that manufacturers of long-acting opioids develop a Risk Evaluation and Mitigation Strategy to ensure that the benefits of opioid therapy outweigh its risks (Edlund et al., 2010). Similarly, the American Pain Society and American Academy of Pain Medicine encourage pain therapy tailored to individualized risk assessment (Jones et al., 2012). The possibility of AOB and opioid misuse must always be considered in treatment planning, though methods for accurately measuring risk of opioid misuse can be limited, particularly in an AYA population. Despite this, identification of patients at increased risk for demonstration of AOB is imperative because it allows for the implementation of additional support to reduce opioid misuse behaviors (Jamison et al., 2010; Manchikanti, Benyamin, Datta, Vallejo, & Smith, 2010; Portenoy & Lesage, 1999; Sehgal, Manchikanti, & Smith, 2012; Trescot et al., 2008; Webster & Fine, 2010).

Several validated opioid-specific misuse risk-assessment tools for use in adults with nonmalignant pain exist (Sehgal et al., 2012). Moore et al. found that diagnostic/clinical interviews provide the most sensitive opioid risk assessment (0.77) when compared with three other commonly cited adult tools (Moore, Jones, Browder, Daffron, & Passik, 2009). Conversely, no opioid misuse screening instruments have been created or validated specifically for use with general pediatric patients (Koyyalagunta, Burton, Toro, Driver, & Novy, 2011) or for use with pediatric hematology/oncology patients (Anghelescu et al., 2013). Instead, McCabe and colleagues (2012) recommend use of measures that pertain to substance abuse more globally, such as the Drug Abuse Screening Test, Short Form, and the CRAFFT Screening Tool for Adolescent Abuse (Knight et al., 1999) when considering opioid therapy for an adolescent. Although use of these more general substance abuse screening measures certainly have merit and could prove useful when considering opioid therapy in pediatrics, development of refined instruments specifically created and validated for use with pediatric patients who experience pain and require opioid therapy is prudent.

Research that examines the occurrence of opioid therapy and psychosocial correlates of AOB in pediatric populations should inform refined and streamlined clinical evaluation of risks; however, as noted above, research on opioid misuse in pediatric populations, as opposed to nonmedical use of opioids in adolescents, is scant to nonexistent. Moreover, opioids often are prescribed for pediatric patients with cancer (Gudin, 2012; Portenoy & Lesage, 1999), making the hematology and oncology population important to study. Therefore, the research goals of this study are (1) to describe the use of opioid therapy among newly diagnosed AYA hematology and oncology patients admitted to a large pediatric research institution over a 17-month period; (2) to identify potential psychosocial risk factors associated with opioid misuse that were documented within the medical record before the introduction of opioid therapy and to inform next steps in AYA hematology/oncology opioid risk assessment instrument development and validation efforts; and (3) to compare the presence of identified risk factors among AYA patients who had AOB documented within the medical record to those without AOB documented in the medical record and to explain the relative risk ratio associated with concurrent opioid use. It was hypothesized that (1) a sizable portion of AYA patients would be prescribed opioid therapy; (2) patients prescribed opioid therapy may have risk factors for opioid misuse; (3) some of the patients with identified risk factors would display AOB, as documented in the medical records; and (4) concurrent opioid use (i.e., two or more opioids prescribed at the same time) would be associated with increased risk of AOB.

Methods

Participants

After this study was approved by our institutional review board, the medical records of all new patients aged $\geq$12 years who were accepted for active treatment (i.e., exclusion of consult-only patients) at a large pediatric hematology/oncology institution between January 1, 2012 and May 31, 2013 were reviewed ($N = 398$). The only exclusion criterion was age $<$12 years, 0 months at time of acceptance for active treatment. Of note, the overall sample ($N = 398$) was only used to evaluate what proportion of AYA was prescribed opioid therapy. Data from the opioid therapy subsample ($n = 94$) were used to answer the remaining research questions.

Demographic characteristics of patients can be seen in Table I, presented as the entire group and the opioid therapy subsample. Age at time of acceptance for active treatment ranged from 12.0 to 33.5 years ($M = 16.3$, $SD = 2.82$), and just less than half of the 398 participants were female (46%).

Table I. *Demographics of All Patients Versus Those Receiving Opioid Therapy*

	All patients	Patients prescribed opioid therapy
Sex	*n* (%)	*n* (%)
Male	216 (54.3)	51 (54.3)
Female	182 (45.7)	43 (45.7)
Total	398 (100)	94 (100)
Age (years)[a]		
Mean	16.3	16.3
Standard deviation	2.82	0.28
Range	12.0–33.5	12.2–28.0
Primary diagnosis	*n* (% total)	*n* (% Opioid Tx)
Leukemia/lymphoma	107 (26.9)	47 (50.0)
Hodgkin lymphoma	33	13
Acute lymphoblastic	29	16
leukemia	16	6
Acute myeloid leukemia	11	6
Other leukemia	18	6
Other lymphoma		
Solid tumor	74 (18.6)	35 (37.2)
Osteosarcoma	13	12
Rhabdomyosarcoma	10	3
Ewing sarcoma	5	5
Melanoma	4	0
Other solid tumor	16	2
Carcinoma	13	7
Other sarcoma	13	6
Hematologic malignancy	64 (16.1)	4 (4.3)
Bleeding/clotting disorder	40	2
Sickle cell disease	7	1
Other hematologic	17	1
Brain tumor	53 (13.3)	6 (6.4)
Astrocytoma/glioma	23	1
Craniopharyngioma	6	0
Medulloblastoma	5	4
Ependymoma	5	1
Other brain tumor	14	0
Infectious disease	60 (15.1)	2 (2.1)
Rule out malignancy	40 (10.1)	0 (0)

Note. [a]Age at presentation to our institution.

The majority of the overall sample had an oncology diagnosis. Less than 1% of patients in the overall sample were diagnosed with sickle cell disease, likely because the majority of patients with sickle cell disease who are treated at this institution are accepted for active treatment and disease management in infancy or early childhood.

Definition of Opioid Therapy

Electronic prescription records were examined to determine whether outpatient opioid therapy was prescribed. The opioids included were codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, and oxycodone. Outpatient opioid therapy was defined as either (1) one or more prescriptions for opioids for seven or more consecutive days while outpatient, or (2) one opioid prescription for at least 3 days with a subsequent opioid prescription of any time length within 3 weeks while outpatient. This operational definition was determined based on clinical knowledge obtained from this institution's pain service that the overwhelming majority of patients at this institution who meet the above criteria go on to require chronic opioid therapy, which often is defined as ≥90 days (Edlund et al., 2010), during their active treatment.

Procedure—Data Collection and Measures

Data collection was structured in four categories: (1) demographic data and patient characteristics; (2) opioid therapy related data; (3) data pertaining to risk factors for AOB obtained from the psychosocial history; (4) data pertaining to AOB documented in clinic notes. Data pertaining to risk factors for AOB and identified AOB were only collected for the patients included in the opioid therapy subsample.

1. Demographic data and patient characteristics included gender, age, age category (≥18 years/≤17 years, 11 months), and oncology/hematology diagnosis.
2. The data related to opioid therapy included prescribed opioid therapy (yes/no), opioid(s) prescribed, and duration of opioid therapy.
3. The data collection for AOB risk factors was based on a checklist of risk factors developed by our clinical team—the Screen for Opioid-Associated Aberrant Behavior Risk (SOABR). The authors developed this AOB-risk checklist specifically for pediatric and adolescent oncology and hematology patients based on our clinical experience, the adult opioid misuse literature, the AYA medication misuse literature, and the AYA substance abuse literature. This checklist, the SOABR (Table II), was used to collect information related to substance abuse by the patient, immediate family, and peer group; mental health diagnoses in the patient or immediate family; and sexual abuse of the patient. Risk factors were rated as ''yes/no'' based on documentation of each risk factor included within the initial psychosocial note and/or initial psychology clinic note.
4. The data collection for AOB was based on a Documentation of AOB list. A list of potential

Table II. *Screen for Opioid-Associated Aberrant Behavior Risk (SOABR) in 94 Patients Prescribed Opioid Therapy*

	Patients with documented AOB $n = 11$ (100%)[a]	Patients without documented AOB $n = 83$ (100%)[a]	Fisher's exact test odds ratio	95% confidence interval	*p*-value
Substance use					
History or current abuse of or addiction to alcohol (including binge drinking), illicit drugs, or prescription medications, or current abuse of any of these in the:					
1. Patient[b]	2 (18.2%)	2 (2.4%)	8.614289	0.563–132.517	0.0659
2. Immediate family[c]	1 (9.1%)	10 (12.0%)	0.732229	0.015–6.261	1
3. Friend/peer group[d]	0 (0%)	2 (2.4%)	0	0.000–41.513	1
Mental health					
History or current diagnosis of anxiety, depression, ADHD, excessive impulsivity, schizophrenia, bipolar disorder, gambling addiction, and/or PTSD in the:					
4. Patient[e]	8 (72.7%)	35 (42.2%)	3.60775	0.794–22.615	0.104
5. Immediate family[f]	4 (36.3%)	33 (39.8%)	0.8671291	0.172–3.735	1
Abuse screening					
History or current experience of sexual abuse in the:					
6. Patient[g]	0 (0%)	1 (1.2%)	0	0.000–292.930	1

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[a]Sum of column is $>n$ because some patients had multiple risk factors.

[b]Nakawaki and Crano, 2012; Webster and Webster, 2005.

[c]Michna et al., 2004; Webster and Webster, 2005.

[d]Boyd et al., 2009; Lord et al., 2009.

[e]Boyd et al., 2009; Grattan et al., 2012; Wasan et al., 2007; Webster and Webster, 2005.

[f]Ahmed et al., 1999; Webster and Webster, 2005.

[g]Pergolizzi et al., 2012; Webster and Webster, 2005.

AOB, aberrant opioid-associated behavior; ADHD, attention deficit hyperactivity disorder; PTSD, posttraumatic stress disorder.

AOB was created based on the adult opioid misuse literature and clinical experience at this institution (Anghelescu et al., 2013; Passik, 2009; Passik, Portenoy, et al., 1998; Pergolizzi et al., 2012; Portenoy, 1996). This list was used to standardize our review of patients' medical records. Data related to AOB were obtained from primary and specialty clinic notes describing patient behaviors after initiation of opioid therapy. AOBs were subdivided into four categories: observable behaviors, medication noncompliance, interpersonal behaviors, and illegal behaviors; all items received equal weight in analysis. Specific items included in each of the four categories can be found in Table III and are largely self-explanatory. One item included in the category ''observable behaviors,'' however, warrants additional explanation. Much of the adult opioid misuse literature includes ''requesting specific drugs by brand name or street name'' as an AOB, highlighting that although patients may request a particular medication for a number of reasons, this behavior also commonly is indicative of drug-seeking and frequently is related to later misuse of medication (e.g., Breitbart et al., 1997; Passik, Kirsh, Donaghy, & Portenoy, 2006; Pergolizzi et al., 2012; Portenoy, 1996; Weaver & Schnoll, 2002; Ziegler, 2005). In this study, documentation of the presence of requesting a certain medication was counted as an AOB only when the request was made for the street name of the drug or when there was clear documentation that a patient was demanding a particular drug by name without providing a legitimate reason for doing so. For example, if a patient asked to be prescribed oxycodone instead of hydromorphone due to the excessive itching experienced previously with hydromorphone, this behavior would not be counted as an AOB. Conversely, if there was clear documentation that a patient demanded ''a quick push of morphine'' in the intravenous line, stating ''make sure it is pushed fast,'' this would be counted as an AOB. Similarly, if a patient requested oxycodone by the street name ''OC,'' this also would be counted as an AOB. Of note, as described in Tables III and IV, endorsement of ''requesting a medication by name'' was never the only AOB rated as present for a participant. Distinctions between ''more'' and ''less'' aberrant behaviors were not made. Each item was rated as ''yes/no'' based on clear

Table III. *Documented Aberrant Behaviors in 11 Patients on Opioid Therapy*

Behaviors reported in the literature	Distribution of AOBs
Observable behaviors ($n = 17$)	
(1) Missed, canceled, or unscheduled appointments with pain care provider	3
(2) Seeking pain treatment from multiple providers (doctor shopping) or from urgent care/emergency department	1
(3) Excessive phone calls or attempts to obtain treatment or refills without visit	3
(4) Reporting lost/stolen prescriptions or pills	3
(5) Pill count discrepancy, with or without explanation	2
(6) Requesting specific drugs by brand name or street name	5
(7) Resisting changes in regimen	3
Medication noncompliance ($n = 4$)	
(8) Unauthorized change in dose or frequency; unauthorized combinations of medications or substances to achieve additional effect	1
(9) Use of other prescriptions or substances for pain relief; use of pain medications or substances to treat nonpain symptoms (such as anxiety or insomnia)	3
(10) Patient admitting to desiring euphoric effects or purposely over-sedating oneself	0
Interpersonal behaviors ($n = 7$)	
(11) Decreased functioning in daily responsibilities related to opioid use	2
(12) Third party expressing concern over opioid use or requesting to manage patient's medications	5
(13) Hoarding drugs	0
Illegal behaviors ($n = 0$)	
(14) Illicit drug use	0
(15) Stealing or selling prescription drugs	0
(16) Obtaining opioids from nonmedical sources	0
(17) Prescription forgery or other tampering	0

Note. Reprinted with permission from *JNCCN—Journal of the National Comprehensive Cancer Network*. Behaviors included in table is based on data from: Breitbart et al., 1997; Passik et al., 2006; Pergolizzi et al., 2012; Portenoy, 1996; Weaver & Schnoll, 2002; Ziegler, 2005.

documentation in clinic notes. Documentation that was ambiguous or not clearly indicative of a specific AOB was *not* counted as documentation of an AOB. As with the SOABR items, there is no way to ensure AOBs were documented in a consistent manner by all clinicians.

The initial psychosocial history notes, all clinic notes, and all records of prescriptions included within the electronic medical record were reviewed. The data collection process was intended to mimic a clinical scenario; therefore, data for the SOABR checklist were taken from the *initial* psychosocial history conducted by a social worker (at initial presentation) or a psychologist (if psychology was immediately consulted on acceptance of the patient). Documentation related to changes in risk factors (e.g., father of patient diagnosed with an anxiety disorder subsequent to the initial psychosocial history, new knowledge of substance abuse in a patient's sibling obtained after the initial history, new information related to risky behaviors in the patient's peer group, etc.) during the course of treatment was not considered. Rather, only data related to psychosocial risk factors divulged and documented as present at acceptance to this institution were considered. This was done to ensure potential psychosocial correlates of opioid misuse were present *before* the initiation of opioid therapy.

Process to Ensure Reliability of Data Collection

Two clinical research associates independently reviewed the medical records of all participants in the opioid therapy group ($n = 94$) to ensure all participants met criteria for inclusion in the opioid therapy group. Reliability was 100%. A third clinical research associate reviewed the medical records of a random sample of 20% ($n = 19$) of participants included in the opioid therapy group to further ensure accuracy of group inclusion; reliability was 100%.

One clinical research associate subsequently randomly reviewed the medical records of 20% of patients not included in the opioid therapy subgroup ($n = 61$) to determine if exclusion criteria (i.e., not prescribed opioid therapy as operationally defined by this study) had been appropriately assigned. Reliability was 100%.

Table IV. *Demographic and Clinical Characteristics of 11 Patients With Documented AOB*

Age[a]	Sex	Diagnosis	SOABR elements	Opioids taken	AOB type[b]
12.2	M	Osteosarcoma	Mental health—Patient	Hydromorphone Methadone Morphine Oxycodone	1, 3, 6
12.7	F	Osteosarcoma	Mental health—family	Methadone	4, 5, 6
15.5	M	Acute promyelocytic leukemia	Substance Abuse—family Mental health—patient Mental health—family	Hydromorphone Morphine	7, 12
17.1	F	Hodgkin lymphoma	None	Oxycodone	4, 6
17.4	F	Acute lymphoblastic leukemia	Mental health—patient	Hydromorphone Morphine	6, 7
17.6	M	Ewing sarcoma	Mental health—patient	Hydromorphone Methadone Morphine	9
18.0	M	Acute lymphoblastic leukemia	Substance abuse—patient Mental health—patient	Hydromorphone	9
19.6	F	Acute myeloid leukemia	Mental health—patient	Hydromorphone Morphine	1, 3, 6, 7, 11, 12
19.9	M	Osteosarcoma	Mental health—patient Mental health—family	Methadone	11, 12
20.7	M	Hodgkin lymphoma	Mental health—patient Mental health—family	Oxycodone	3, 9, 12
20.8	M	Hodgkin lymphoma	Substance abuse—patient	Methadone Morphine Oxycodone	1, 2, 4, 5, 8, 12

Note. [a]Age at presentation to our institution.
[b]See corresponding numbers in Table III for AOB type.

Finally, the first author reviewed the medical records of a random sample of 20% of participants included in the opioid therapy group ($n = 19$) to further ensure reliability of additional variables of interest. Reliability of AOB documentation was 100%; reliability of documentation of risk factors as defined by the SOABR was 100%. Reliability of concurrent use of opioid therapy was 95%; reliability related to additional demographic and descriptive data was 100%. Overall reliability of data abstraction was 98%.

Based on these processes, the authors are confident that assignment of the participants to the opioid therapy group and exclusion from the opioid therapy group was accurate.

Statistical Data Analysis Methods

All data were analyzed by a biostatistician; $p < .05$ was prospectively determined as indicative of statistically significant differences for all statistical tests run. The median age of participants prescribed opioid therapy who had AOB documented in their medical records ($n = 11$) was compared with the median age of participants prescribed opioid therapy who did not have AOB documented in their medical records ($n = 83$) using the Wilcoxon rank sum test; medians, rather than means, were compared because the medians were more robust than the means.

A chi-square test was used to compare gender distributions among patients prescribed opioid therapy who had AOB documented in their medical records ($n = 11$) to patients who were prescribed opioid therapy who did not have AOB documented in their medical records ($n = 83$), as well as to examine the association between AOB and concurrent opioid use. Due to small cell counts, the association between AOB and each individual risk factor included on the SOABR was evaluated using Fisher's exact test; Spearman's rank correlation coefficient and its corresponding permutation test were used to determine whether the number of risk factors identified was correlated with the presence and number of AOB and whether the number of AOBs was correlated with age.

Results

Of the 398 AYA patients included in our initial sample, 94 (23.6%) were prescribed opioids and represented the

opioid therapy subsample. As with the overall sample, the opioid therapy subsample included a comparable number of females (45.7%) and males (54.3%). Almost twice as many participants included in the opioid therapy subsample had a diagnosis of leukemia or lymphoma (50.0%) as compared with those in the overall sample (26.9%). Similarly, a higher proportion of patients with malignant solid tumors were prescribed opioid therapy (37.2%) when compared with the overall sample (18.6%).

Of the 94 AYA patients prescribed opioid therapy, 11.7% ($n = 11$) had AOB documented in their medical records; 90.9% of the 11 patients with documented AOB had risk factors, as described by the SOABR checklist, also documented in their medical records.

SOABR Checklist Items and AOB

As highlighted in Table II, mental health problems were the most frequent risk factor among patients with documented AOB. Three of the 11 (27.3%) had mental health difficulties as well as a similarly affected family member. Two patients with documented AOB also had documented substance abuse problems, and one had at least one immediate family member with a substance abuse history. Despite this and contrary to what was hypothesized, the relationship between documented AOB and each individual risk factor described by the SOABR checklist was not statistically significant (see Table II), possibly due to the small sample size ($n = 11$). Similarly, the presence of one or more SOABR checklist item(s) documented in the medical record was not significantly associated with documented AOB ($p = .165$); the number of SOABR items identified was not significantly correlated with the presence of documented AOB in the medical record (Spearman's rank correlation rho = .150, $p = .150$) or with the number of AOBs documented (rho = .146, $p = .160$), again possibly due, at least in part, to the small sample size of patients prescribed opioid therapy who had AOB documented in their charts. The correlations between the number of AOBs and patient age (Spearman's rank correlation, rho = .176, $p = .090$) and between the number of AOBs and age category ($\geq$18 years) at presentation (rho = .197, $p = .057$) were approaching statistical significance.

AOB and Other Variables of Interest

The distribution of AOB is summarized in Table III. The most frequent AOBs were requesting drugs by brand name or street name ($n = 5$) and third-party concern about opioid misuse and requests for its management ($n = 5$). Some AOBs were not identified; notably, no illegal AOBs were documented in any medical records reviewed. Two patients exhibited only a single AOB; the majority exhibited two or more (Table IV).

As demonstrated using a chi-square test, the association between AOB and gender was not statistically significant ($\chi^2 = 0.12$, $p = .732$). Similarly, results from the Wilcoxon rank sum test indicated the median age of participants prescribed opioid therapy who had AOB documented in their medical records was not significantly different from the median age of participants prescribed opioid therapy without documented AOB (W = 601.5, $p = .089$).

Only 19% of patients without documented AOB, but 55% of those with AOB documented in their charts, received two or more opioids, either concurrently or in sequence. Consistent with what was hypothesized, concurrent use of two or more opioids was significantly associated with one or more AOBs documented in the medical record ($\chi^2 = 8.69$, $p = .003$). Patients who were concurrently receiving two or more opioids were 6.1 times more likely to exhibit AOB as those taking one opioid or multiple opioids consecutively (as opposed to concurrently).

Discussion

This study is the first, to our knowledge, to report the incidence of AOBs in a population of AYA with hematology and oncology diagnoses and to review the association between potential opioid misuse risk factors and AOB, demographic variables, and opioid treatment patterns in this population. No previous studies have addressed AOB specifically in pediatric cancer, and no validated risk assessment tool for use with this specific pediatric patient population currently exists (Koyyalagunta et al., 2011).

A substantial proportion of the patients in this sample were prescribed opioid therapy; however, this is not surprising given the well-known disease- and treatment-related pain commonly reported in patients with diagnoses of leukemia, lymphoma, or solid malignant tumors. One major finding of this study is that AYA may demonstrate AOB even when they legitimately need opioid therapy, as in the context of cancer. This finding is consistent with previous research examining opioid abuse in other AYA populations, though it is the first, to our knowledge, to examine this type of behavior in a pediatric hematology and oncology group. Specifically, among patients with noncancer diagnoses, adolescents and young adults are more likely than older adults to abuse opioids (Ives et al., 2006; Pergolizzi et al., 2012) and illicit substances (Manchikanti et al., 2006; Pergolizzi et al., 2012). Although the incidence of AOB (11.7%) in the current study was

surprisingly high given that opioid prescription practices are closely monitored and multidisciplinary support is readily available at this pediatric institution, these findings cannot be compared directly with other recent reports in AYA, which have focused largely on illicit opioid use. More specifically, opioid therapy, when used in the treatment of patients whose charts were reviewed for the current study, was indicated as necessary and was legitimately prescribed and provided in this AYA hematology and oncology sample.

Nationally, the rate of opioid dependence or abuse among persons 12 years of age and older is 0.7% and this rate has increased over the past decade (Substance Abuse and Mental Health Services Administration, 2012). Although the prevalence and correlates of opioid misuse and abuse among pediatric patients with oncology or hematology diagnoses have not been previously reported, Anghelescu and colleagues reported preliminary observations of AOB in this population at a rate of 4.2% when patients were prescribed opioid therapy by a specialized multidisciplinary pain service (Anghelescu et al., 2013). Thus, rates of AOB in the present study of 11.7% are significantly higher than expected given previous estimates and national norms. Perhaps the age of patients included in the current study contributed to this, as patients whose charts were included in this retrospective study were in the age-groups that most commonly abuse opioids recreationally (12–17 and 18–25 years) (Manchikanti, Fellows, Ailinani, & Pampati, 2010). As such, the findings of this study underline the importance of monitoring patients' clinical opioid use and evaluating abuse risk before initiation of opioid therapy, as recommended by the American Pain Society and American Academy of Pain Medicine, in AYA hematology/oncology patients. Furthermore, as pediatric cancer survival rates continue to rise, survivors may face chronic cancer- or treatment-related pain that requires opioid therapy (Anghelescu et al., 2013); however, adolescents and young adults with AOB may be more susceptible to addiction and drug abuse problems during the later stages of life (Anghelescu et al., 2013; Chambers, Taylor, & Potenza, 2003). Because opioid therapy has been linked to opioid misuse, abuse, and AOB (Manchikanti et al., 2006; Passik, Narayana, & Yang, 2014; Pergolizzi et al., 2012), pediatric cancer patients with prolonged exposure to opioids may be at even greater risk (Anghelescu et al., 2013). This again highlights the need for continued research in this area.

Just as chronic opioid therapy is associated with increased risk of opioid misuse, abuse, and aberrant behaviors (Manchikanti et al., 2006; Passik et al., 2014; Pergolizzi et al., 2012), a pleathora of other correlates of opioid misuse is suggested within the adult nonmalignant pain literature and the AYA nonmedical substance use literature. The SOABR checklist includes many of these additional risk factors for AOB. The most frequently cited risk factor associated with opioid abuse is a past or current mental health diagnosis (Boyd et al., 2009; Grattan et al., 2012; Wasan et al., 2007; Webster & Webster, 2005). In the current study, 46% of patients receiving opioid therapy were in this category and 37% had an immediate family member in this category; though not directly comparable, these proportions are higher than those reported in the general population of individuals $\geq$18 years of age (26.2%) (Kessler, Chiu, Demler, Merikangas, & Walters, 2005). Eight of our 11 patients exhibiting AOB had documented mental health diagnoses before initiation of opioid therapy, and four had immediate family members with a past or current mental health diagnosis.

In a study of adolescents, mental illness and substance use disorder comorbidity rates ranged from 60 to 75%, with the most commonly cited concurrent mental health diagnoses being depression, conduct disorder, oppositional defiant disorder, attention-deficit/hyperactivity disorder, and posttraumatic stress disorder (Griswold, Aronoff, Kernan, & Kahn, 2008; Hoffmann, Bride, MacMaster, Abrantes, & Estroff, 2004; Turner, Muck, Muck, Stephens, & Sukumar, 2004). Although the current study did not directly examine which mental health diagnoses were most common among the 11 patients who demonstrated AOB, future studies could explore the most common mental health diagnoses concurrent with opioid misuse in pediatric hematology and/or oncology patients. Moreover, untreated psychological problems, especially depression, have been linked to increased pain (Kadan-Lottick, Vanderwerker, Block, Zhang, & Prigerson, 2005; Passik, Dugan, et al., 1998). In one study of adolescents with noncancer pain who were publicly and privately insured, patients were 41 and 37%, respectively, more likely to be prescribed opioids if they had comorbid mental health diagnoses (Richardson et al., 2011). Edlund et al. showed that increased rates of opioid (odds ratio [OR] = 5.48, $p < .001$) and nonopioid (OR = 4.48, $p < .001$) misuse among users of prescribed opioids were mediated partially by mental health problems such as anxiety and depression (Edlund, Sullivan, Steffick, Harris, & Wells, 2007). This, again, highlights the need to screen for potential psychosocial correlates of opioid misuse before initiation of opioid therapy.

Three of our 11 patients with AOB had past or current substance abuse problems or immediate family members or peers with those problems. Adolescents who persistently use illicit substances, such as marijuana and inhalants, are

more likely to engage in nonmedical use of opioids (Nakawaki & Crano, 2012). Documented substance abuse history only demonstrated a trend toward association with AOB in the present study; however, the relationship of substance abuse history to AOB remains clinically meaningful and should not be disregarded in assessing the risk of opioid misuse. The 2011 National Survey on Drug Use and Health found that 8.0% of the U.S. civilian noninstitutionalized population age ≥12 years exhibited substance dependence or abuse problems during the past year (Substance Abuse and Mental Health Services Administration, 2012). Current prescription abuse and misuse literature suggests gathering data regarding substance use, and abuse history is necessary in clinical opioid therapy practice.

While a history of sexual abuse may be a predictor of opioid misuse (Pergolizzi et al., 2012; Turk, Swanson, & Gatchel, 2008; Webster & Webster, 2005), it has not been thoroughly evaluated as a risk factor in youth with a hematology or oncology diagnosis. One of our 94 patients receiving opioid therapy had a documented history of sexual abuse but that patient did not exhibit AOB. However, given that the manner in which data related to previous sexual abuse victimization were obtained by clinicians and that accurate documentation of information cannot be guaranteed by the authors due to the retrospective design of this study, it is imperative that a history of sexual abuse not be discounted as a potential predictor of, or risk factor for, opioid misuse based solely on the current findings.

Although not significant, possibly due to the small sample size, almost two-thirds of our 11 patients with documented AOB were male despite similar gender distribution in patients receiving opioid therapy. This finding is consistent with much of the literature (Edlund et al., 2010; Lord et al., 2009; Michna et al., 2007; Sehgal et al., 2012; Turk et al., 2008), yet gender as an AOB risk factor remains contentious. Specifically, some studies have found no difference between male and female opioid usage and AOB (Manchikanti, Fellows, et al., 2010), while others have shown that adolescent females are more likely to be lifetime nonmedical users of all types of prescription drugs (Nakawaki & Crano, 2012). An adult study cited women as more likely than men to *report* opioid misuse; however, that does not necessarily indicate a higher rate of abuse (Pergolizzi et al., 2012). Therefore, additional research related to gender as a risk factor in AYA hematology/oncology opioid misuse is needed.

The two most frequent AOB we observed were requesting specific drugs and third-party concern. Although these behaviors in and of themselves may not necessarily indicate misuse or abuse is currently happening, there are no empiric data defining the boundaries of AOB (Kirsh, Whitcomb, Donaghy, & Passik, 2002; Passik, Portenoy, et al., 1998). Instead, research suggests a spectrum of behaviors, some less aberrant and others more aberrant (Kirsh et al., 2002). Given this, it may be more useful for clinicians and researchers to also focus on the number of potentially concerning behaviors present. For example, a majority of patients in the current study who had AOB documented in their medical records ($n = 9$, 81.8%) had documentation of multiple AOB. Despite this, one must also consider that some patients on opioid therapy may have had AOBs that were unknown to the medical team or were not well documented. Thus, the percentage of AYA hematology/oncology patients who misused their opioids might actually have been greater than 11.7%. Conversely, some AOBs may have reflected more on the patient's family or peers than the patient. For example, documented missing medications or discrepant pill counts could have been due to a family member stealing the patient's opioids without the patient's knowledge, thus counting as an AOB but not truly reflecting aberrant behavior on the part of the patient.

Regardless of the etiology of the documented AOB, 55% of patients on opioid therapy with AOB and 19% of patients prescribed opioid therapy without AOB were concurrently or consecutively exposed to two or more opioids. Patients concurrently prescribed two or more opioids were 6.1 times more likely to exhibit AOB. This significant finding is comparable with the results of Edlund and colleagues, who found that use of multiple types of opioids was related to a higher risk of opioid misuse in adults (Edlund et al., 2010). Moreover, this finding suggests patients prescribed opioids concurrently should be monitored closely.

Despite the strong contributions to the current literature the authors believe this study provides, a few limitations should be considered. The retrospective design is certainly a limitation of which to remain mindful. Indeed, in some cases documentation of certain aspects of treatment was inconsistent, or notes within the medical record lacked detail and/or needed information. Other challenges include the potential reluctance of patients and families to disclose their misuse of opioids and/or use of illicit drugs or alcohol. Seemingly irrelevant *detailed* information related to additional opioid misuse risk factors may not be initially volunteered from a family faced with a child's new cancer diagnosis, or it may not be solicited by care providers in a detailed fashion. In either case, the difficulties related to obtaining an accurate psychosocial history at the beginning of treatment of a catastrophic

pediatric illness and evaluating patient compliance with the opioid-related treatment plan should be considered in future studies. The SOABR was created and used to collect these data retrospectively; therefore, the authors are unable to ensure information pertaining to SOABR items was asked of each patient in the same manner and then documented with perfect consistency. Furthermore, the SOABR checklist is not a validated pediatric opioid-misuse risk assessment measure, and the current study is not intended as a validation study of the SOABR. Rather, this checklist was created based on clinical experience and relevant literature, and was solely used to aid in identification of potential risk factors in the current retrospective study. Although a tool such as the SOABR could help identify psychosocial risk factors present in AYA hematology/oncology patients before initiation of opioid therapy in the future, much more rigorous scale development and validation research would be necessary.

The authors recognize some psychosocial risk factors may not have been reported despite being present initially. Nevertheless, the authors preferred a conservative approach to collection of data related to potential risk factors in an attempt to avoid inadvertent inclusion of a psychosocial correlate that occurred *after* the initiation of opioid therapy. Of note, we did not collect and analyze data regarding the presence of risk factors for AOB in the group of patients who did not receive opioid therapy; therefore, we cannot appreciate if there were differences between groups.

Another limitation was the small sample size: 94 of 398 new patients were prescribed opioid therapy, and 11 of those 94 had documented AOB. Perhaps, with a larger sample size, statistical significance between individual and/or combined SOABR checklist items and AOB would be more likely. Future research should examine this possibility.

Conclusion

This study demonstrated a relatively high incidence of AOB among adolescents and young adults at a pediatric hematology/oncology institution. Many of the patients who exhibited AOB and/or their immediate family members had current or past mental health diagnoses and/or substance abuse histories. Results indicate that the risk of AOB in pediatric hematology/oncology is real and that it is important to monitor adolescents and young adults receiving opioid therapy. Furthermore, results highlight the overwhelming need for pediatric hematology and oncology opioid risk-assessment instrument development and validation.

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