Pediatric Exposure to Opioid and Sedation Medications during Terminal Hospitalizations in the United States, 2007-2011

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Objective To describe the use of opioids and sedatives to pediatric patients dying in the hospital in the 2 weeks preceding death.

Study design We conducted a retrospective study on opioid and sedation medication exposure among children who die in hospitals in the US by using large administrative data sources. We described patterns of exposure to these medications for deceased inpatients (<21 years of age) between 2007 and 2011 (n = 37 459) and factors associated with the exposure. Multivariable logistic regression models were used to estimate the ORs.

Results Overall, 74% patients were exposed to opioids or sedatives in the 14 days before death. Among patients with 6 or more hospital days before death, the daily exposure rate ranged from 73% (the sixth day before death) to 89% (the day of death). The most commonly used medications were fentanyl (52%), midazolam (44%), and morphine (40%). Older age (ORs 1.6-3.7), black race (ORs 0.8), longer hospital stay (ORs 6.6-9.3), receiving medical interventions (including mechanical ventilation, surgery, and stay in the intensive care unit, ORs 1.7-2.6), having comorbidities (ORs 1.7-2.4), and being hospitalized in children's hospitals (ORs 4.0-4.5) were associated with exposure of opioid and sedation medication on adjusted analysis.

Conclusion Although most pediatric patients terminally hospitalized are exposed to opioid and sedation medication, some patients do not receive such medications before death. Given that patient and hospital characteristics were associated with opioid/sedative exposure, these findings suggest areas of potential quality improvement and further research. *(J Pediatr 2015;166:587-93)*.

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Opioid and sedation medications are important in the treatment of patients who die in hospitals for 2 main reasons. First, opioid and sedation medications are crucial for the effective management of pain and anxiety symptoms that can cause suffering in patients who are dying. Second, because a large proportion of patients who die in the hospital experience a period of being tracheal intubated and mechanically ventilated, or undergo surgery before death, opioid and sedation medications can provide relief from the discomfort and distress of being critically ill and of undergoing invasive procedures. Substantial variation is seen in clinical practice of prescribing opioid and sedation medications in the setting of palliative sedation to hospitalized patients at end of life between medical centers and countries.[1] Consequently for adult patients, efforts have been taken to develop consensus guidelines and standards in palliative sedation practice[1-4] as well as the provision of opioid sedation for critically ill patients[5] (although this practice has also recently come under scrutiny).[6,7]

Little published data exist regarding patterns of use of opioid and sedation medications in children before death, and no treatment guidelines have been formed for refractory symptoms. The few previous studies of the use of opioid or sedation medications among hospitalized pediatric patients at the end of life have had small samples and were conducted by single institutions,[8-11] limiting generalizability.

Therefore, to better inform efforts to improve care for children who die in hospital, we conducted a retrospective study in which we examined the prescribing patterns of opioid and sedation medications among 37 459 children who died in 430 hospitals in the US 2007-2011, by using administrative data from the Pediatric Health Information System (PHIS) and the Premier Perspective Database (PPD). We sought to better understand the current prescribing practice of opioid and sedation medications among hospitalized children in their final days. The knowledge gained from this study may

CCC	Complex chronic condition
ICU	Intensive care unit
LOS	Length of stay
MV	Mechanical ventilation
PHIS	Pediatric Health Information System
PPD	Premier Perspective Database

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subsequently contribute to promoting standard care for those children with a terminal hospitalization.

Methods

This study of deidentified data was deemed by the institutional review board of The Children's Hospital of Philadelphia to not constitute human subjects research. Administrative data from PHIS and PPD were used in this study. The PHIS has administrative discharge data from children's hospitals for most of the major metropolitan areas across the US and is maintained by the Children's Hospital Association (Kansas City, Kansas). The PPD collects data from a broad array of academic medical centers, community-based hospitals, and a large multihospital system distributed throughout the urban and rural US and is maintained by Premier, Inc (San Diego, California). Both data sources contain detailed information for each patient hospitalization, including demographics, diagnoses, pharmacy activity, procedures, laboratory tests, and diagnostic and therapeutic services.

The quality and reliability of PHIS data are assured through a joint effort between the Children's Hospital Association and participating hospitals. Data are accepted into the PHIS database only when classification errors occur in fewer than 2% of a hospital's quarterly data. Upon receiving data from participating hospitals, PPD undertakes an extensive 7-phase data validation and correction process that includes >95% quality assurance checks. Deidentified data were extracted from both databases and used for statistical analysis.

We obtained prescription records of opioids and sedatives for all pediatric inpatients who died in PHIS and PPD hospitals between 2007 and 2011 retrospectively. We examined exposure to opioids and sedatives in terminal hospitalized patients within 14 days before death (regardless of the total length of stay [LOS]). Specifically, we examined the percentage of patients exposed each day (daily exposure percentage) and the distinct number of opioid and sedation medications that patients received on each of the last 6 days before death. Because longer hospital stay may be associated with more exposure to these medications, we also examined the daily exposure patterns among patients who had at least 6 hospital days.

We examined the associations of patient- and hospital-level factors with the exposure to opioids and sedatives by using a multivariable logistic regression model. A random intercept was included to account for the multilevel data structure and the clustering of observations within hospitals. The patient and hospital level factors evaluated included patients' age, sex, race, calendar year of death, geographical region, primary payer, the existence and number of complex chronic conditions (CCCs),[12-14] LOS, and invasive interventions (intensive care unit [ICU] stay, mechanical ventilation [MV], and surgery) received during the stay, and hospital characteristics (children's vs general, and teaching vs nonteaching). All 43 PHIS hospitals and 30 PPD hospitals were identified as children's hospitals, and the remaining 357 hospitals from the PPD were identified as general hospitals.

The cohort was assessed for exposure to the following opioid medications: fentanyl, hydromorphone, meperidine, meperidine and promethazine, methadone, morphine, oxycodone, oxymorphone, propoxyphene, remifentanil, sufentanil, and unspecified narcotic analgesic combinations; and for the following sedative medications: amobarbital, amobarbital and secobarbital, butabarbital, chloral hydrate, chlordiazepoxide and amitriptyline, chlordiazepoxide, clonazepam, dexmedetomidine, diazepam, estazolam, flurazepam, haloperidol, ketamine, lorazepam, midazolam, oxazepam, pentazocine, pentobarbital, phenobarbital, propofol, secobarbital, thiopental, unspecified nonnarcotic analgesic and barbiturates, and unspecified sedative hypnotics.

All statistical analyses were conducted using SAS 9.3 (SAS Institute Inc, Cary, North Carolina) and Stata 13.1 (StataCorp, College Station, Texas).

Results

A total of 37 459 pediatric patients from 430 PHIS and PPD hospitals died during a hospitalization in 2007-2011 (**Table I**). Sixty-six percent of the patients were infants (<1 year of age); 56% were male; 43% were white, and 21% were black. Thirty-seven percent of the patients died on the first day of hospitalization, and 40% of patients spent 7 or more days in hospital before death. Sixty-four percent of patients had at least 1 CCC, and 12% had more than 3 CCCs. Most patients received invasive interventions during their terminal hospitalization: 81% had an ICU stay, 69% were on MV, and 39% underwent surgery. Sixty-one percent of patients died in children's hospitals, and 84% in teaching hospitals.

Overall, 74% patients were exposed to opioid and sedation medications (69% to opioids, 63% to sedatives, and 58% to both) within 14 days before death. The daily exposure to opioid and sedation medications in the last 6 days is shown in **Figure 1**. Overall, slightly less than one-half of patients received both opioids and sedatives on any given day near the end of life (**Figure 1**). The exposure percentages were stable or increased slightly toward the end of life, and then decreased a bit on the day of death. The percentage exposed to any opioids or sedatives increased from 73% to 75% from the sixth day to the first before death but decreased to 69% on the day of death. However, in the subset of patients who had least 6 days of hospitalization (n = 16 010), the daily exposure percentage to any opioids or sedatives continued increasing at the end of life until the day of death (**Figure 1**), from 73% on the sixth day before death to 89% on the day of death.

The top panel of **Figure 2** (available at www.jpeds.com) displays the pattern of exposures to distinct opioid