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Opioid use in children's surgery: Awareness, current state, and advocacy

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ABSTRACT

In response to the ongoing opioid epidemic, many surgeons who care for children have reflected upon current practices and the history of our own prescribing. In this editorial review, we provide a brief summary of the origins of opioid use in medicine and surgery, we describe how the ongoing opioid epidemic specifically impacts children and adolescents, and we explore contemporary efforts underway to facilitate evidence-based opioid prescribing. Resources for pediatric surgeons including national guidelines related to safe opioid prescribing and web-based toolkits that may be used to implement change locally are highlighted. The goal of the present manuscript is to introduce opioid stewardship as a guiding principle in pediatric surgery.
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Contents

Overdose deaths involving prescription opioids have quadrupled since 2000 [1], and nonfatal opioid overdoses have led to increasing emergency department visits and hospital admissions [2]. Overdose and poisoning now surpass motor vehicle related deaths as the leading cause of accidental death in the U.S. [3] This is a direct result of excess opioid prescribing by healthcare providers [4]. These staggering figures require the entirety of healthcare system to reflect on our contribution to the current epidemic. What is our role as children's surgery specialists in the current opioid crisis? Have we contributed to the opioid epidemic and its deadly consequences? How can we participate in the solution?

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Though the answers to these questions are complicated, our patients and their families deserve our professional commitment to this issue.

This editorial review summarizes presentations delivered during a breakout session dedicated to the opioid epidemic during the American Pediatric Surgery Association's (APSA) annual meeting in May 2019. This review will outline the history of opioid use in the United States, describe the current state of the opioid epidemic as it impacts pediatric populations, and explore ongoing opioid stewardship efforts. Specifically, we will discuss the pharmaceutical industry's influence on opioid use, policies to treat pain as a 5th vital sign, and highlight many of the cautionary flags related to opioid use in children. Finally, we will introduce multiple surgeon-led opioid stewardship efforts and provide resources for surgeons to continue similar efforts locally.

1. The history of opioid use in the United States

1.1. Epidemic of the 1880s

In the 18l0's, physicians began to use tincture of opium, and its derivative morphine, to treat everything from teething babies, maladies of menstruation, and traumatic Civil War injuries [5, 6]. With the immigration of Chinese workers hired to build American railroads in the 1870's, "opium dens" became common among the immigrant communities prompting the first regulation by San Francisco to contain the spread of growing addiction [6]. By 1909, the public perception of opium smoking and social degeneracy led to federal bans on prescribing opioids for addiction treatment and finally, The Harrison Narcotics Tax Act of 1914 [7]. Ultimately, the concerted efforts of pharmacists, physicians, legislators along with law enforcement were able to contain the opium epidemic in the early 20th century. Consequently, opioids were infrequently prescribed during the decades following, with most physicians concerned about the addictive nature of opioids and possible litigation associated with opioid prescribing.

1.2. Purdue Pharma & Pai7n As The 5th Vital Sign

In 1980, a brief letter to the editor written by Dr. Hershel Jick and his assistant Jane Porter was published in the *New England Journal of Medicine* highlighting a single hospital's experience administering opioids in an inpatient setting [8]. The authors highlighted the very small number of individuals who developed opioid addiction after their inpatient stay and concluded that when opioids are appropriately used to treat pain, there is minimal risk of addiction. This 101-word, five sentence letter was largely relegated to the archives until nearly a decade later.

Then, in 1995, the U.S. Food and Drug Administration (FDA) approved use of a new form of extended-release oxycodone (brand name: OxyContin®), and highlighted its delayed absorption as reducing the abuse potential of the drug [9, 10]. Purdue Pharma then marketed OxyContin as a "safe" opioid alternative that had low addictive potential, citing the Porter and Jick's study as an original research paper and underscoring the FDA's approval.

Indications for OxyContin broadened to include low back pain, fibromyalgia and arthritis and concordantly, opioid prescribing during the late 1990's began to rise. Purdue representatives often cited Porter and Jick's letter as evidence that opioids used properly for pain management were non-addictive, a dramatic misrepresentation of the inpatient data with no detail regarding opioid dosing, duration of exposure, and long-term follow up. Recently, a bibliometric analysis performed in 2017 demonstrated 608 citations peaking after the introduction of OxyContin, many of which misrepresented the conclusions of the letter [11]. In 2007, in a Virginia federal court, Purdue the maker of OxyContin paid a $600 million fine for misleading doctors and patients about OxyContin's negative effects [12]. The impact to the company was nominal given the billions of dollars in profit accumulated in sales from OxyContin by Purdue.

Simultaneously, a more aggressive approach to pain management gained increasing acceptance in the medical community. In 1992, the Agency for Healthcare Quality Research declared that half of all surgical patients did not receive adequate pain control after surgery [13]. Hydrocodone plus acetaminophen soon became the most prescribed drug of any category with over a 100 million prescriptions written [14]. Scientific studies categorizing chronic pain from a nonmalignant source as a disease process were increasingly published while clinicians felt emboldened to more aggressively treat chronic pain. In 1994, a diagnosis of chronic pain was formalized by the International Association for the Study of Pain. The World Health Organization recognized chronic pain as causing a four-fold increased likelihood of depression, anxiety, difficulty working and unemployment [15]. As chronic pain became recognized as a public health problem, opioids were increasingly perceived as a preferred method for comprehensive pain management.

Finally, the "pain as the 5th vital sign" movement solidified the medical community's new commitment to address the needs of patients experiencing acute and chronic pain. In 1996, Dr. James Campbell stated during his presidential address at the American Pain Society's annual meeting, "Vital signs are taken seriously. If pain were assessed with the same zeal as other vital signs are, it would have a much better chance of being treated properly. We need to train doctors and nurses to treat pain as a vital sign. Quality care means that pain is measured and treated." [16] In 2001, in an effort to be more humane to hospitalized patients in the Veteran's Administration Hospital, the Joint Commission promoted the idea of pain as a 5th vital sign [17].

Clinicians however, had little data, poor guidance and limited training about how to prescribe opioids to avoid addiction and overdose. After years of opioid over-prescribing, the rising death toll from opioid overdose has affected nearly every community in our nation [18]. Since 2000, the age-adjusted drug overdose death rate has more than tripled. In 2017, an estimated 18 million people in the U.S. misused prescription opioids, depressants, or stimulants in the last year [19].

In the same year, 17.4% of the U.S. population received one or more opioid prescriptions, with the average person receiving 3.4 prescriptions [20], and there were 70,237 drug overdose deaths in the United States [21].

1.3. Warnings from the US Food and Drug Administration (FDA): Codeine and tramadol

Codeine and tramadol are two opioid medications historically thought to be safer for pediatric use, with codeine plus acetaminophen elixir commonly prescribed to younger children. Unfortunately, the FDA has issued several pediatric safety communications regarding opioid use, based on post-market deaths dating back to 2012 [22]. The FDA's strongest recommendations, designated as *contraindications*, include to the drug labels of codeine and tramadol alerting that codeine should not be used to treat pain or cough and tramadol should not be used to treat pain in children younger than 12 years [23]. Furthermore, a *contraindication* warns against tramadol use in children younger than 18 years to treat pain after surgery to remove the tonsils and/or adenoids [23].

The next level of FDA recommendations is *warnings*. There are *warnings* against codeine and tramadol use in adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease, which may increase the risk of serious breathing problems [24]. Another key warning is that health care professionals should limit prescribing opioid pain medicines with benzodiazepines or other central nervous system depressants [25].

Unfortunately, avoidance of tramadol and codeine administration in children has not been universally adopted. As recently at 2015, Cochrane published a systematic review endorsing use of tramadol in children [26]. Further efforts to disseminate FDA warnings for codeine and tramadol in care of the pediatric surgical patient are vital.

2. Impact of opioid prescription on children

2.1. Vulnerability of the pediatric populations

Unfortunately, the increased number of opioid prescriptions, opioid misuse and opioid related overdose observed adults is mirrored in the pediatric population. Between 1999 and 2016, 73% of opioid related deaths in children between 1999 and 2016 involved prescription opioids [27]. In 2017, over 10% of all adolescents report receiving an opioid prescription within the last year [20]. Overdose death rates primarily affect adolescents, aged 15–19, but are also increasing among younger children [27]. Pediatric hospitalizations related to opioid poisonings and opioid-related critical care unit admissions are similarly increasing [28, 29].

In addition to the direct effects of opioids on children in terms of adverse events, opioid use also poses developmental, addiction, and dependency risks for children. Historically, as opioid prescribing has become more common in youth, so has opioid misuse – defined as taking a higher dose of prescription that was given or taking opioid prescription pills to "get high" [30]. In 2012, there were over 2.8 million new users of illicit drugs and over half (54.1%) were under 18 years of age [31]. Currently, prescription opioid misuse is decreasing in youth (5% now, down from 12% at height of epidemic), but has not reached the pre-opioid epidemic levels (<1%) [32].

Exposure to prescription opioids in childhood/early adolescence is a risk factor for prescription opioid misuse, which may impact neurocognitive development [33–36], and increase the likelihood of later high risk substance abuse behaviors. Results from a nationally representative longitudinal survey among 12th grade students showed a 33% increase in opioid misuse following prescribed use. The risk was particularly prevalent among students with no history of drug use and who even expressed strong disapproval of illegal drug use [35, 36]. Furthermore, in a longitudinal cohort survey of youth in Los Angeles, CA, nonmedical prescription opioid use was prospectively associated with subsequent heroin use initiation [37].

Adolescents are a particularly vulnerable population in the opioid epidemic. Immaturity of the adolescent brain makes youth more vulnerable to addiction, as relatively fewer exposures result in substance use disorder [38]. In addition, adolescents can be more susceptible to the negative influence of peer substance use [39, 40]. The risk of prescription drug abuse and dependence increases with earlier onset of non-medical use by children [41]. The risk of addiction is particularly worrisome due to the increased availability of more dangerous synthetic opioids, such as fentanyl, which are frequently involved in overdose deaths among adolescents [42]. These risks, and the fact that substance abuse initiation most frequently occurs in childhood, underscore the importance of preventive activities targeting this vulnerable population [43].

2.2. Surgery as an Initial Exposure to Opioids

Opioids prescribed following surgery are often a child's first contact with opioids. Surgeons write nearly 10% of all opioid prescriptions (28.3 million prescriptions in 2012) and often prescribe more opioids than necessary following minor procedures with more than 50% of prescribed pills remaining unused [44, 45]. New, persistent, opioid use among opiate naïve children who undergo surgery is estimated at 4.8% and ranges from 2.7% for inguinal orchidopexy to 15.2% for colectomy [46].

2.3. Diversion of Excess Opioids

Many adolescents obtain opioids from family and friends [47]. Overprescription of opioids may result in excess opioids being stored in homes with children, becoming accessible for diversion to nonmedical use [48–50]. It is critical for opioid prescribers to have candid discussions with patients and families regarding proper use of these medications and risks of non-prescribed use. This can be a challenging proposition as nearly half of physicians report that it is difficult for them to discuss prescription drug abuse with their patients [51]. Preoperative counseling and shared decision making surrounding the use of prescription opioids have been described and utilized to reduce opioid prescription fills and overall use [52–54].

3. Role of Pediatric Surgery in Opioid Prescribing

3.1. Current guidelines and recommendations

Currently, there are no widely accepted guidelines for pediatric surgery acute or perioperative pain management. While the World Health Organization developed guidelines for "persisting pain in children", they specifically exclude perioperative pain [55]. The Centers for Disease Control and Prevention's (CDC's) guidelines on opioid prescribing are limited to chronic pain and only include patients over age 18 years [56]. The American Pain Society (APS) developed clinical practice guidelines for postoperative pain management, for both adults and children. Recommendations include use of multi-modal analgesia with non-pharmacological interventions and use of non-opioid drugs such as acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs). However, these recommendations were primarily based on trials conducted among adults.

Some specific recommendations for children, such as education of parents and use of specific pain assessment scales, are based on low-quality evidence [57]. Recently, the Society for Pediatric Anesthesiology published broad recommendations for the use of opioids in the perioperative period, such as adjusting morphine dosing based on age and monitoring for respiratory depression after opioid dosing in infants less than 3 months of age [58]. Use of non-opioid adjuncts, such as ketorolac and acetaminophen, are recommended but recommendations for post-surgical opioid use and outpatient treatment duration were not included. This paucity of recommendations and guidelines is likely due to a lack of available evidence on opioid use and outcomes in pediatric populations. Current evidence is emerging from single-center studies and often addressing isolated procedures [59–62].

3.2. Current efforts within pediatric surgery

Evidence for improved opioid stewardship within pediatric surgery is emerging from single-center studies addressing discrete procedures such as appendectomy, tonsillectomy, or umbilical hernia repair [59–62]. A study evaluating opioid prescriptions following common outpatient surgeries found that most children used less than 50% of prescribed doses to control their pain [44, 61]. Use of epidurals, regional nerve blocks, and cryoablation have all been used as part of multimodal approaches to pain management after pectus excavatum procedures [63, 64]. Enhanced recovery protocols incorporating non-opioid analgesics and regional nerve blocks for more complex procedures in children and adolescents also decrease opioid use in the operating room and at discharge [65, 66].

Current efforts to curtail opioid overprescribing involve education of healthcare providers and families combined with increased use of opioid-sparing pain management strategies. Table 1 provides a brief list of resources on opioid stewardship available to healthcare providers caring for children who require surgery. The American Pediatric Surgical Association (APSA) Quality & Safety Committee recently identified opioid stewardship as a target for improvement. Materials outlining opioid stewardship projects conducted at APSA member institutions are available through a web link on the APSA website (Practices & Resources, Quality & Safety Toolkit) or directly through a shared web-based drive (https://sites.google.com/view/apsaqsc/home). Surgeons and hospitals interested in spearheading their own opioid stewardship program can

Table 1
Publically available opioid stewardship related resources available to pediatric surgical care providers.

Topic/Description	Target	Source	Web-link
Examples of successful opioid stewardship efforts using quality improvement methodology	Pediatric surgical care providers	American Pediatric Surgical Association (APSA) Quality & Safety Committee	https://sites.google.com/view/apsaqsc/home
Tips for safe pain control after surgery for children and teens	Patients/families	APSA and the American College of Surgeons	https://www.facs.org/-/media/files/education/patient-ed/safe_pain_control_pediatric.ashx
Safe opioid disposal	Providers and patients/families	Food and Drug Administration (FDA)	https://www.fda.gov/drugs/safe-disposal-medicines/disposal-unused-medicines-what-you-should-know#Medicines_recommended

log on to the website and immediately download materials successfully integrated into other hospital settings.

In addition, APSA's Outcomes and Evidence-Based Committee recently conducted an exhaustive literature review to generate opioid prescribing and perioperative pain management recommendations for children who require surgery (presented at APSA 2019 meeting). This process involved iterative input from a multidisciplinary stakeholder team that included representatives from surgery, anesthesiology, nursing, general surgery training, addiction science and parent and patient advocates. Members also included representatives of the American Academy of Pediatrics Section on Surgery and the American College of Surgeons (ACS) Education Committee. In a general sense, the guidelines highlight the risks of opioid misuse and abuse in adolescents, underscore the need for non-opioid alternatives to be used in the perioperative setting, and emphasize that education of patients and families is paramount to maintain a patient-centered approach. Guideline statements are currently under review with publication anticipated in the next year.

The ACS has also identified opioid stewardship as a key component of evidence-based practice. In the last year, ACS created targeted educational brochures for patients regarding pain management and opioid use after surgery (https://www.facs.org/~/media/files/education/patient%20ed/safe_pain_control.ashx). The ACS partnered with APSA to create a brochure for specifically for children and their families entitled *Safe and Effective Pain Control After Surgery for Children and Teens* and is available at https://www.facs.org/-/media/files/education/patient-ed/safe_pain_control_pediatric.ashx.

3.3. Proper disposal of unused opioids

Another key aspect to decreasing opioids available for nonmedical use and diversion is proper disposal of excess opioids. A systematic review found that across a diverse group of surgical patients, 67%–92% reported having unused opioids [67]. Three fourths of these patients reported that they did not store unused opioids in locked cabinets and few appropriately disposed of the unused opioids [67]. Proper disposal should be part of the counseling process when prescribing opioids to families with children.

To this end, the FDA had created a toolkit for safe opioid disposal that is available at https://www.fda.gov/drugs/safe-disposal-medicines/disposal-unused-medicines-what-you-should-know#Medicines_recommended [68]. There are three main ways to safely dispose of opioids. The first and preferred method is to identify a medicine take-back option offered in some communities and by some hospitals. Surgeons and other prescribers should investigate if Drug Enforcement Agency (DEA) registered and approved options are available and can campaign to partner with community stakeholders to establish these types of programs locally [69]. Periodic drug "take-back" events are also held in conjunction with the DEA [70]. A second option is to review the "flush list" to determine if the medication can be flushed down the toilet. This list currently includes many varieties of hydrocodone, hydromorphone, oxycodone, and others [68]. There a negligible negative environmental impact of flushing these medications [71]. A third option is to dispose of opioids in household trash following simple directions that include:

- Mixing medicines (do not crush tablets or capsules) with an unpalatable substance such as dirt, cat litter, or used coffee grounds;
- Placing the mixture in a container such as a sealed plastic bag;
- Throwing the container in your household trash; and
- Deleting all personal information on the prescription label of empty pill bottles or medicine packaging, then dispose of the container [68].

Finally, a randomized clinical trial found that providing drug disposal bags that enable safe disposal of opioids in the home garbage to families of children receiving postoperative opioids increased the likelihood of excess opioid disposal [72].

3.4. Moving forward with opioid stewardship in children's surgery

A recent systematic review examined interventions associated with changing opioid prescription practices on surgical discharge [73]. Eight studies were included in the review including 3 pre-intervention and post-intervention comparison studies, 3 controlled clinical studies, 1 time-series study, and 1 post-intervention results with a predetermined baseline. Interventions done at the organization level, including changes to electronic health records order sets and workflow, showed clear improvement in opioid use [54, 74]. Several studies propagated guidelines based on patient opioid use and reported reductions up to 53% in the quantity prescribed [54, 75, 76]. While no increases in emergency department visits and refill requests were reported in these studies, one study used check-in telephone calls after discharge and found that that 13 of 240 tonsillectomy patients (5.4%) had inadequately controlled pain [74]. Thus, opioid reduction efforts should be balanced with patient reported outcomes.

Furthermore, there is an emerging body of literature suggesting that postoperative opioid prescriptions may be safely eliminated for many common surgical procedures in children including umbilical hernia repair, appendectomy and adenoidectomy [77–79]. These efforts must be balanced to ensure that pain is being adequately treated. Surgeons aiming to reduce opioid prescribing within their healthcare system should track medication refills and follow up with patients/families [80], to ensure that risks associated with excess opioid prescribing are minimized while satisfactory postoperative recovery is ensured.

4. Conclusion

This editorial review briefly describes the history of the opioid epidemic in the United States and the unique vulnerabilities seen in pediatric surgical populations. Literature highlighting opioid stewardship for children and adolescents who require surgery is increasing. Many procedures can likely be performed with local or regional anesthesia and non-opioid analgesics, thus minimizing risks associated with prescription opioids. If prescription opioids are required, routine guidance on safe disposal of unused opioids is key. As evidence for opioid stewardship and utilization of

opioid-sparing techniques matures, the pediatric surgical community must critically appraise our role in combating the opioid epidemic in order to provide the best care to our patients.

References

[1] Seth P, Rudd RA, Noonan RK, et al. Quantifying the epidemic of prescription opioid overdose deaths. Am J Public Health 2018;108(4):500–2.
[2] Centers for Disease Control and Prevention. Annual Surveillance Report of Drug-Related Risks and Outcomes — United States. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services; 2018; 2018 August 31, 2018.
[3] Rudd RA, Aleshire N, Zibbell JE. Increases in Drug and Opioid Overdose Deaths — United States, 2000-2014. MMWR Morb Mortal Wkly Rep 2016.
[4] Kanouse AB, Compton P. The epidemic of prescription opioid abuse, the subsequent rising prevalence of heroin use, and the federal response. J Pain Palliat Care Pharmacother 2015;29(2):102–14.
[5] Trescot AM, Datta S, Lee M, et al. Opioid pharmacology. Pain Physician 2008;11(2 Suppl):S133–53.
[6] Musto DF. The American disease: Origins of narcotic control. 3 ed. Oxford university press; 1999.
[7] Hohenstein K. Just What the Doctor Ordered: The Harrison Anti-Narcotic Act, the Supreme Court, and the Federal Regulation of Medical Practice, 1915–1919. *Journal of Supreme Court History, The Federal Regulation of Medical Practice*; 2001; 231–56.
[8] Porter J, Jick H. Addiction rare in patients treated with narcotics. N Engl J Med 1980; 302(2):123.
[9] U.S. government accountability office (GAO). Prescription drugs: OxyContin abuse and diversion and efforts to address the problem GAO-04-110: published: Dec 19, 2003. Publicly Released: Jan 22; 2004.
[10] Van Zee A. The promotion and marketing of oxycontin: commercial triumph, public health tragedy. Am J Public Health 2009;99(2):221–7.
[11] Leung PTM, Macdonald EM, Stanbrook MB, et al. A 1980 letter on the risk of opioid addiction. N Engl J Med 2017;376(22):2194–5.
[12] United States v. Purdue Frederick Co., Inc., 495 F. Supp. 2d 569 (W.D. Va. 2007).
[13] Acute pain management: operative or medical procedures and trauma, Part 1. Agency for Health Care Policy and Research. Clin Pharm. 1992;11(4):309–331.
[14] Manchikanti L. National drug control policy and prescription drug abuse: facts and fallacies. Pain Physician 2007;10(3):399–424.
[15] Chwastiak LA, Von Korff M. Disability in depression and back pain: evaluation of the World Health Organization disability assessment schedule (WHO DAS II) in a primary care setting. J Clin Epidemiol 2003;56(6):507–14.
[16] Campbell JN. APS 1995 Presidential address. J Pain 1996;5(1):85–8.
[17] Baker DW. The joint Commission's pain standards: Origins and evolution. Oakbrook Terrace, IL: The Joint Commission; 2017.
[18] Chen LH, Hedegaard H, Warner M. Drug-poisoning Deaths Involving Opioid Analgesics: United States, 1999–2011. NCHS Data Brief 2014(166):1–8.
[19] Center for Behavioral Health Statistics and Quality. Results from the 2017 National Survey on Drug Use and Health: Detailed Tables. Rockville (MD): SAMHSA; 2018 Available at: https://www.samhsa.gov/data/report/2017-nsduh-detailed-tables Last July 2, 2019.
[20] Centers for Disease Control and Prevention. 2018 Annual Surveillance Report of Drug-Related Risks and Outcomes — United States. Surveillance Special Report. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. Published August 31, 2018. Accessed July 5, 2019 from https://www.cdc.gov/drugoverdose/pdf/pubs/2018-cdc-drug-surveillance-report.pdf.
[21] Hedegaard H, Miniño AM, Warner M. Drug overdose deaths in the United States, 1999–2017. NCHS data brief, no 329. Hyattsville, MD: National Center for Health Statistics; 2018; 1–7.
[22] FDA U.S. Food & Drug Administration. FDA Pediatric Safety Communications. https://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/ucm300090.htm; 2019, Accessed date: 19 February 2019.
[23] FDA U.S. Food & Drug Administration. FDA Drug Safety Communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. 2017; https://www.fda.gov/Drugs/DrugSafety/ucm549679.htm. Accessed 02–19, 2019.
[24] FDA U.S. Food & Drug Administration. FDA Drug Safety Communication: FDA evaluating the risks of using the pain medicine tramadol in children aged 17 and younger. 2015; https://www.fda.gov/Drugs/DrugSafety/ucm462991.htm. Accessed 04-16-2019, 2019.
[25] FDA U.S. Food & Drug Administration. FDA Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. 2015; https://www.fda.gov/Drugs/DrugSafety/ucm518473.htm. Accessed 04-16-2019, 2019.
[26] Schnabel A, Reichl SU, Meyer-Friessem C, et al. Tramadol for postoperative pain treatment in children. Cochrane Database Syst Rev 2015;3:CD009574.
[27] Gaither JR, Shabanova V, Leventhal JM. US National Trends in pediatric deaths from prescription and illicit opioids, 1999-2016. JAMA Netw Open 2018;1(8):e186558.
[28] Gaither JR, Leventhal JM, Ryan SA, et al. National Trends in hospitalizations for opioid poisonings among children and adolescents, 1997 to 2012. JAMA Pediatr 2016;170(12):1195–201.
[29] Kane JM, Colvin JD, Bartlett AH, et al. Opioid-related critical care resource use in US Children's hospitals. Pediatrics 2018;141(4).
[30] Sung HE, Richter L, Vaughan R, et al. Nonmedical use of prescription opioids among teenagers in the United States: trends and correlates. J Adolesc Health 2005;37(1):44–51.
[31] NIDA. Nationwide trends. Retrieved from https://www.drugabuse.gov/publications/drugfacts/nationwide-trends; 2015, June 25. on 2019, July 5.
[32] Vaughn MG, Nelson EJ, Salas-Wright CP, et al. Racial and ethnic trends and correlates of non-medical use of prescription opioids among adolescents in the United States 2004-2013. J Psychiatr Res 2016;73:17–24.
[33] Crews F, He J, Hodge C. Adolescent cortical development: a critical period of vulnerability for addiction. Pharmacol Biochem Behav 2007;86(2):189–99.
[34] Cerda M, Santaella J, Marshall BD, et al. Nonmedical Prescription Opioid Use in Childhood and Early Adolescence Predicts Transitions to Heroin Use in Young Adulthood: A National Study. J Pediatr 2015;167(3):605–12 e601–602.
[35] Miech R, Johnston L, O'Malley PM, et al. Prescription opioids in adolescence and future opioid misuse. Pediatrics 2015;136(5):e1169–77.
[36] Groenewald C, Palermo T. Legitimate opioid prescription increases the risk for future opioid misuse in some adolescents. Evid Based Nurs 2016;19(3):83.
[37] Kelley-Quon LI, Cho J, Strong DR, et al. Association of Nonmedical Prescription Opioid Use With Subsequent Heroin Use Initiation in Adolescents. JAMA Pediatr 2019 Jul 8:e191750. https://doi.org/10.1001/jamapediatrics.2019.1750 [Epub ahead of print].
[38] Benowitz NL. Nicotine addiction. N Engl J Med 2010;362(24):2295–303.
[39] Needle R, McCubbin H, Wilson M, et al. Interpersonal influences in adolescent drug use–the role of older siblings, parents, and peers. Int J Addict 1986;21(7):739–66.
[40] Mason MJ, Zaharakis NM, Rusby JC, et al. A longitudinal study predicting adolescent tobacco, alcohol, and cannabis use by behavioral characteristics of close friends. Psychol Addict Behav 2017;31(6):712–20.
[41] McCabe SE, West BT, Morales M, et al. Does early onset of non-medical use of prescription drugs predict subsequent prescription drug abuse and dependence? Results from a national study. Addiction 2007;102(12):1920–30.
[42] Curtin SC, Tejada-Vera B, Warmer M. Drug Overdose Deaths Among Adolescents Aged 15–19 in the United States: 1999–2015. NCHS Data Brief 2017(282):1–8.
[43] Levy S. Youth and the opioid epidemic. Pediatrics February 2019;143(2):e20182752.
[44] Voepel-Lewis T, Wagner D, Tait AR. Leftover prescription opioids after minor procedures: an unwitting source for accidental overdose in children. JAMA Pediatr 2015;169(5):497–8.
[45] Levy B, Paulozzi L, Mack KA, et al. Trends in opioid analgesic-prescribing rates by specialty, U.S., 2007-2012. Am J Prev Med 2015;49(3):409–13.
[46] Harbaugh CM, Lee JS, Hu HM, et al. Persistent opioid use among pediatric patients after surgery. Pediatrics 2018;141(1).
[47] Boyd CJ, McCabe SE, Cranford JA, et al. Prescription drug abuse and diversion among adolescents in a Southeast Michigan school district. Arch Pediatr Adolesc Med 2007;161(3):276–81.
[48] Groenewald CB, Rabbitts JA, Gebert JT, et al. Trends in opioid prescriptions among children and adolescents in the United States: a nationally representative study from 1996 to 2012. Pain 2016;157(5):1021–7.
[49] Makary MA, Overton HN, Wang P. Overprescribing is major contributor to opioid crisis. BMJ 2017;359:j4792.
[50] Abou-Karam M, Dube S, Kvann HS, et al. Parental Report of Morphine Use at Home after Pediatric Surgery. J Pediatr 2015;167(3):599–604 e591–592.
[51] McCabe SE, Boyd CJ, Couper MP, et al. Mode effects for collecting alcohol and other drug use data: web and U.S. mail. J Stud Alcohol 2002;63(6):755–61.
[52] Sugai DY, Deptula PL, Parsa AA, et al. The importance of communication in the management of postoperative pain. Hawaii J Med Public Health 2013;72(6):180–4.
[53] Holman JE, Stoddard GJ, Horwitz DS, et al. The effect of preoperative counseling on duration of postoperative opiate use in orthopaedic trauma surgery: a surgeon-based comparative cohort study. J Orthop Trauma 2014;28(9):502–6.
[54] Stanek JJ, Renslow MA, Kalliainen LK. The effect of an educational program on opioid prescription patterns in hand surgery: a quality improvement program. J Hand Surg Am 2015;40(2):341–6.
[55] World Health Organization. WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses. Geneva (Switzerland): WHO Press; 2012.
[56] Schechter NL, Walco GA. The potential impact on children of the CDC guideline for prescribing opioids for chronic pain: above all, Do No Harm. JAMA Pediatr 2016;170(5):425–6.
[57] Chou R, Gordon DB. de Leon-Casasola OA, et al. Management of Postoperative Pain: a clinical practice guideline from the American pain society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' committee on regional anesthesia, executive committee, and administrative council. J Pain 2016;17(2):131–57.
[58] Cravero JP, Agarwal R, Berde C, et al. The Society for Pediatric Anesthesiology Recommendations for the use of opioids in children during the perioperative period. Paediatr Anaesth 2019 Jun;29(6):547–71.
[59] Anderson KT, Bartz-Kurycki MA, Ferguson DM, et al. Too much of a bad thing: discharge opioid prescriptions in pediatric appendectomy patients. J Pediatr Surg 2019;53(12):2374–7.
[60] Horton JD, Munawar S, Corrigan C, et al. Inconsistent and excessive opioid prescribing after common pediatric surgical operations. J Pediatr Surg 2018;54(7):1427–31.
[61] Monitto CL, Hsu A, Gao S, et al. Opioid prescribing for the treatment of acute pain in children on hospital discharge. Anesth Analg 2017;125(6):2113–22.
[62] Cartmill RS, Yang DY, Fernandes-Taylor S, et al. National variation in opioid prescribing after pediatric umbilical hernia repair. Surgery 2019 Apr;165(4):838–42.
[63] Graves CE, Moyer J, Zobel MJ, et al. Intraoperative intercostal nerve cryoablation during the Nuss procedure reduces length of stay and opioid requirement: A randomized clinical trial. J Pediatr Surg 2019 Nov;54(11):2250–6.
[64] Frawley G, Frawley J, Crameri J. A review of anesthetic techniques and outcomes following minimally invasive repair of pectus excavatum (Nuss procedure). Paediatr Anaesth 2016;26(11):1082–90.
[65] Short HL, Heiss KF, Burch K, et al. Implementation of an enhanced recovery protocol in pediatric colorectal surgery. J Pediatr Surg 2018;53(4):688–92.

[66] Baxter KJ, Short HL, Wetzel M, et al. Decreased opioid prescribing in children using an enhanced recovery protocol. J Pediatr Surg 2019 Jun;54(6):1104–7.
[67] Bicket MC, Long JJ, Pronovost PJ, et al. Prescription opioid analgesics commonly unused after surgery: a systematic review. JAMA Surg 2017;152(11):1066–71.
[68] FDA U.S. Food & Drug Administration. Disposal of Unused Medicines: What You Should Know. 2018. https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/EnsuringSafeUseofMedicine/SafeDisposalofMedicines/ucm186187.htm; 2018, Accessed date: 7 May 2018.
[69] Shealy KM, Ritter MS, Wyatt AS, et al. Trends in potentially abused medications returned during medication take-back days. J Am Pharm Assoc (2003) 2019;59(4):575–8.
[70] Stewart H, Malinowski A, Ochs L, et al. Inside Maine's medicine cabinet: findings from the drug enforcement Administration's medication take-Back events. Am J Public Health 2015;105(1):e65–71.
[71] Khan U, Bloom RA, Nicell JA, et al. Risks associated with the environmental release of pharmaceuticals on the U.S. Food and Drug Administration "flush list". Sci Total Environ 2017;609:1023–40.
[72] Lawrence AE, Carsel AJ, Leonhart KL, et al. Effect of Drug Disposal Bag Provision on Proper Disposal of Unused Opioids by Families of Pediatric Surgical Patients: A Randomized Clinical Trial. JAMA Pediatr 2019 Jun 24:e191695.
[73] Wetzel M, Hockenberry J, Raval MV. Interventions for postsurgical opioid prescribing: a systematic review. JAMA Surg 2018;153(10):948–54.
[74] Luk LJ, Mosen D, MacArthur CJ, et al. Implementation of a pediatric Posttonsillectomy pain protocol in a large group practice. Otolaryngol Head Neck Surg 2016;154(4):720–4.
[75] Hill MV, Stucke RS, McMahon ML, et al. An educational intervention decreases opioid prescribing after general surgical operations. Ann Surg 2018 Mar;267(3):468–72.
[76] Howard R, Waljee J, Brummett C, et al. Reduction in opioid prescribing through evidence-based prescribing guidelines. JAMA Surg 2018;153(3):285–7.
[77] Harbaugh CM, Vargas G, Streur CS, et al. Eliminating unnecessary opioid exposure after common Children's surgeries. JAMA surgery 2019 Sep 4. https://doi.org/10.1001/jamasurg.2019.2529 [Epub ahead of print].
[78] Sonderman KA, Wolf LL, Madenci AL, et al. Opioid prescription patterns for children following laparoscopic appendectomy. Ann Surg 2018 Dec 22. https://doi.org/10.1097/SLA.0000000000003171 [Epub ahead of print].
[79] Piper KN, Baxter KJ, Wetzel M, et al. Provider education decreases opioid prescribing after pediatric umbilical hernia repair. J Pediatr Surg 2019 May 11. https://doi.org/10.1016/j.jpedsurg.2019.04.035 pii: S0022-3468(19)30344-6. [Epub ahead of print].
[80] Wetzel M, Hockenberry JM, Raval MV. Opioid Fills in Children Undergoing Surgery from 2011 to 2014: A Retrospective Analysis of Relationships Among Age, Initial Days Supplied, and Refills. Ann Surg 2019 Jun 7. https://doi.org/10.1097/SLA.0000000000003387 [Epub ahead of print].