Prescription Opioid Abuse and Related Outcomes in the Pediatric Population

Joint Meeting of the Drug Safety and Risk Management Advisory Committee
and the Pediatric Advisory Committee

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Background and Objectives

- **Background**: For all regulatory questions involving opioids, FDA considers the public health risks associated with misuse and abuse of these drugs
- **Objective:** Review available epidemiologic data to inform considerations of these risks relating to pediatric opioid use

Outline

1. Defining Misuse and Abuse
2. Descriptive Epidemiology of Pediatric Opioid Misuse/Abuse
3. Literature on Risk of Misuse/Abuse and Substance Use Disorders Following Pediatric Prescription Opioid Therapy
4. Limitations
5. Overall Summary

Defining Misuse and Abuse

- **Misuse:** Intentional use, for therapeutic purposes, of a drug in a way other than prescribed or by an individual for whom it was not prescribed
- **Abuse:** Intentional, non-therapeutic use of a drug for its desirable psychological or physiological effects

Terminology varies by data source

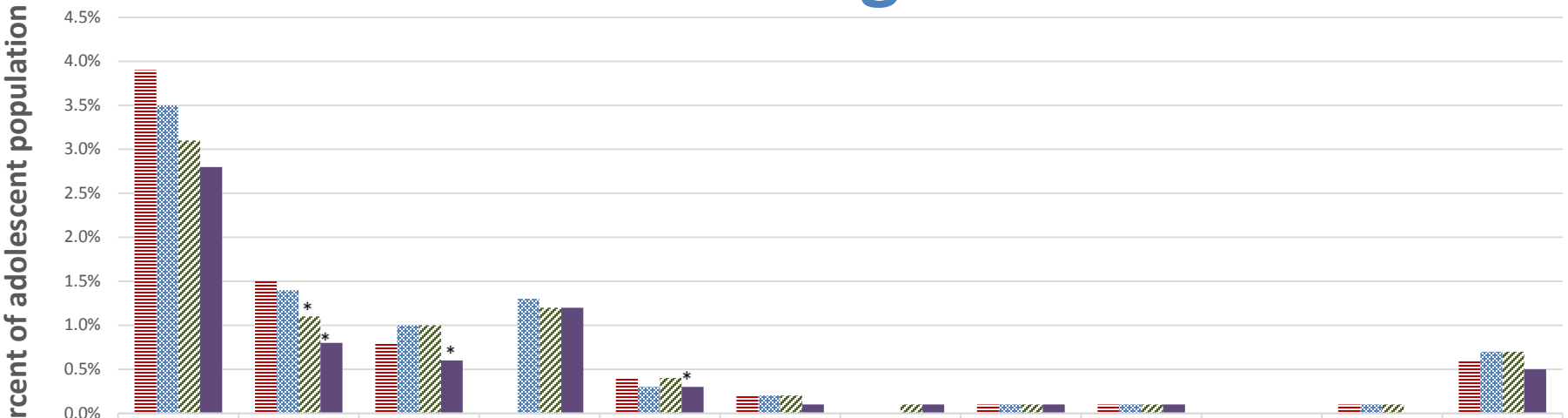
Source: FDA, Drug Abuse and Dependence Section of Labeling for Human Prescription Drug and Biological Products: Guidance for Industry (2019)

Descriptive Epidemiology of Pediatric Opioid Misuse/Abuse

Data Sources

- **Prevalence of misuse/abuse**
  - National Survey on Drug Use and Health (NSDUH): 2015-2017
  - Monitoring the Future (MTF): 2010-2018
- **Emergency Department visits**
  - National Electronic Injury Surveillance System - Cooperative Adverse Drug Event Surveillance (NEISS-CADES): 2016-2017
- **Calls to U.S. Poison Control Centers**
  - National Poison Data System (NPDS): 2000-2015
- **Drug Overdose Deaths**
  - National Vital Statistics System mortality files: 2016-2017

Past-year Misuse/Abuse: U.S. Adolescents Ages 12 to 17

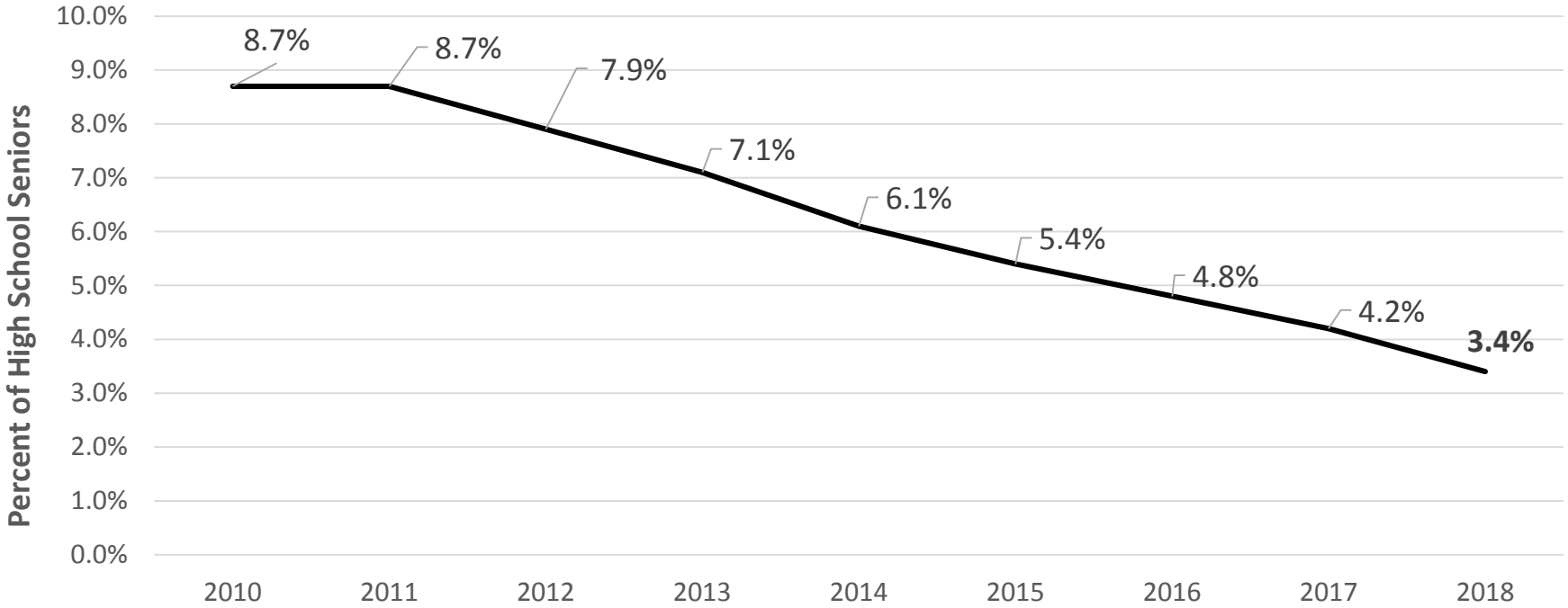


	Any	Hydro codone	Oxycodone	Codeine	Tramadol	Morphine	Fentanyl	Bupre norphine	Oxy morphone	Hydro morphone	Methadone	Other
2015	3.9%	1.5%	0.8%		0.4%	0.2%	0.0%	0.1%	0.1%	0.0%	0.1%	0.6%
2016	3.5%	1.4%	1.0%	1.3%	0.3%	0.2%	0.0%	0.1%	0.1%	0.0%	0.1%	0.7%
2017	3.1%	1.1%	1.0%	1.2%	0.4%	0.2%	0.1%	0.1%	0.1%	0.0%	0.1%	0.7%
2018	2.8%	0.8%	0.6%	1.2%	0.3%	0.1%	0.1%	0.1%	0.1%	0.0%	0.0%	0.5%

*Statistically significant decline from previous year

Source: NSDUH, SAMHSA detailed tables, Tables 1.98 A-B, 1.98D (2016-2017), Tables 1.99A-B, 1.99D (2018).

Past-year Misuse/Abuse of Prescription Opioids*: High School Seniors



Source: The Monitoring the Future Study 2018, the University of Michigan, Table 2.
*Term is “Narcotics other than heroin” in this survey

Source of Prescription Opioids for Misuse/Abuse in Adolescents Ages 12 to 17

Source	Percent of those reporting past-year misuse/abuse
Received from friends or relatives (taken/given/bought)	**49.5%**
Personal prescription	**34.1%**
Other (drug dealer, stranger, stolen)	12.9%

Source: NSDUH 2018, SAMHSA detailed tables, Tables 6.5A-B.

Source of Prescription Opioids for Misuse/Abuse: High School Seniors

Source	Percent of those reporting past-year misuse/abuse
Given for free by friend/relative	**48.2%**
Bought from friend/relative	26.1%
Took from friend/relative without asking	13.7%
Personal prescription	**31.9%**
Bought from drug dealer/stranger	17.4%
Other method	14.5%

Source: The Monitoring the Future Study 2018, the University of Michigan, Table 9-10.
NOTE: Categories are not mutually exclusive.

U.S. ED Visits for Adverse Events from Prescription Opioid Use, 2016-2017

	Average annual estimate	Annual rate per 100,000*	95% CI of rate
Prescription opioid **nonmedical use**+ (annual estimate = 127,177 visits)			
Ages 12-17	2,130	8.5	4.4-12.6
Ages 18 and older	124,980	49.9	36.2-63.6
Prescription opioid **self-harm** (annual estimate = 36,057 visits)			
Ages 12-17	2,617	10.5	6.0-14.9
Ages 18 and older	33,374	13.3	10.5-16.1

+ Includes Abuse, Therapeutic Misuse, and Overdose of Undetermined Intent
*Based on average Census population estimates
NOTE: Visits among patients ages 11 and younger not shown due to small number of cases.
Age missing for 3 cases of nonmedical use and 1 case of self-harm.

Source: NEISS-CADES Project, CDC Division of Healthcare Quality Promotion

U.S. ED Visits for Adverse Events from Therapeutic Prescription Opioid Use, 2016-2017

Age group	Average annual estimate	Annual rate per 100,000*	95% CI of rate
Therapeutic prescription opioid use‡ (Total annual estimate = 103,786 ED visits)			
Ages 0-11¥	4,600	9.5	6.3-12.6
Ages 12-17	1,522	6.1	4.0-8.2
Ages 18 and older	97,664	39.0	28.0-50.0

Source: NEISS-CADES Project, CDC Division of Healthcare Quality Promotion

*Based on average Census population estimates
‡Includes adverse events from therapeutic use (e.g., adverse effects, allergic reactions, medication errors, and unsupervised ingestions by children)
¥82.5% of these ED visits were due to unsupervised ingestions

U.S. Poison Control Calls, 2000-2015: Prescription Opioid Exposures, by Reason and Age

	Ages 0-5 years N=112,465 (%)	Ages 6-12 years N=19,723 (%)	Ages 13-19 years N=56,280 (%)
Unintentional	111,258 (98.9)	16,654 (84.4)	12,051 (21.4)
General	96,134 (85.5)	5,905 (29.9)	3,759 (6.7)
Therapeutic error	15,124 (13.4)	10,749 (54.5)	8,292 (14.7)
Intentional - overall	201 (0.1)	1,988 (10.1)	40,255 (71.5)
Suspected suicide	46 (0.0)	**360 (1.8)**	**19,239 (34.2)**
Abuse	40 (0.0)	**447 (2.3)**	**11,721 (20.8)**
Misuse	86 (0.1)	**670 (3.4)**	**6,297 (11.2)**

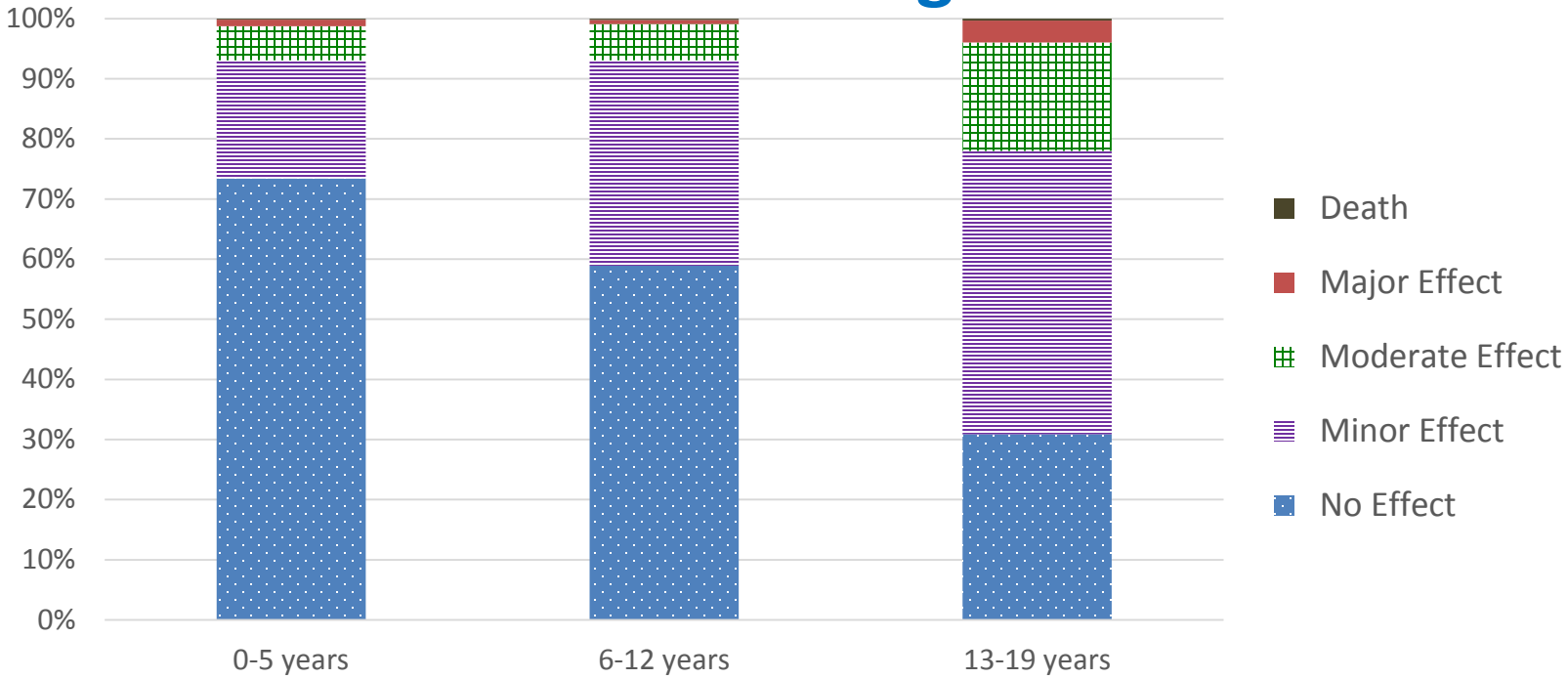
Source: Table 1, Allen (2017)

U.S. Poison Control Calls, 2000-2015: Prescription Opioid Exposure Rates

- The rate* of these exposures increased from 2000 to 2009, then declined from 2009 to 2015 for both children and adolescents
- This trend was not consistent across all reasons for prescription opioid exposure
  - Rate of **suspected suicide** among teenagers increased by **52.7%** from 2000 to 2015

*Number of prescription opioid PCC calls per 100,000 population by age group
Reference: Allen (2017)

U.S. Poison Control Calls 2000-2015: Prescription Opioid Exposures, by Medical Outcome and Age



Source: Table 2, Allen (2017)

Rate of Drug Overdose Death Involving Prescription Opioids, by Age, U.S.

	2017		2016-2017
Decedent Age	Number	Rate	% Change in rate
0-14	50	**0.1**	0.0
15-24	1,050	**2.4**	-7.7
25-34	3,408	7.5	-2.6
35-44	3,714	9.1	-1.1
45-54	4,238	10.0	-1.0
55-64	3,509	8.4	0.0
≥65	1,055	2.1	+10.5

Rates are per 100,000 population
Source: Table 1, Scholl *(*2019)

Literature Review

Literature: Medical Use of Prescription Opioids and Risk of Opioid Analgesic Misuse or Abuse

- Compared to adolescents who did not use any opioids, adolescents who used prescription opioids only as medically directed were more likely to misuse or abuse opioids in the future
  - In early adulthood (Adjusted RR = 1.33, CI: 1.04-1.70)[1]
  - In early mid-life (Adjusted OR = 1.74, CI: 1.10-2.76)[2]
- For high school seniors with a history of both medical use and misuse of opioids, medical use most often preceded initiation of misuse[3]

Sources: [1]Miech (2015), [2]McCabe (2016), [3]McCabe (2017)

Medical Use or Misuse/Abuse of Prescription Opioids and Future Substance Use Disorder Symptoms

Lifetime use of prescription opioids at age 18	Any substance use disorder symptoms at age 35 (AOR*)
No use	1.00 [Reference]
Medical use only	1.12 [0.895-1.39]
Medical use before misuse/abuse	1.18 [0.82-1.72]
Medical use after misuse/abuse	2.35 [1.46-3.77]
Misuse/abuse only	2.47 [1.74-3.52]

*Adjusted for race/ethnicity, sex, parental education, region, metropolitan area, cohort year, past alcohol, marijuana, or other drug use at age 18

Source: McCabe (2019)

Dentist Prescriptions for Opioids and Risk of Opioid Analgesic Misuse or Abuse

- Examined opioid abuse-related administrative claims* in 12 months following dental opioid prescription in adolescents and young adults (16-25 years old)
- Patients who received an opioid prescription more likely to have a subsequent abuse-related claim* compared to non-exposed (5.8% vs. 0.4%)
  - Adjusted** risk difference: 5.3% [CI: 5.0-5.7]

*Defined as an ICD-9/10 healthcare claim diagnosis code for opioid abuse, opioid use disorder, or opioid overdose
**Adjusted for patient race/ethnicity and history of past other substance use

Source: Schroeder (2019)

Key Limitations (1)

- Survey-based studies
  - Possible inaccurate reporting/recall
  - Individuals with more advanced SUD may be underrepresented
  - Longitudinal studies: Confounding by indication
- ED visit data
  - Only captures misuse/abuse cases resulting in an ED visit
  - Excludes fatal cases
- Poison center call data
  - Analysis limited to single-substance exposures

Key Limitations (2)

- Administrative claims studies
  - Do not capture actual opioid use or exposure resulting from someone else's prescription
  - Poor capture of misuse/abuse and substance use disorders
  - Death outcomes incompletely captured
  - Potential unmeasured confounding
    - Undocumented family/personal history of substance abuse

Summary of Findings (1)

- Approximately 3% of adolescents report having misused or abused prescription opioids in the past year
  - Adolescent prescription opioid misuse and abuse have been declining
  - Most commonly, adolescents obtain prescription opioids for misuse/abuse from a friend or relative, but about a third receive them from their own prescription

Summary of Findings (2)

- Among adolescents, opioid-related ED visits due to self-harm occur at similar rates as nonmedical use
- Most opioid-related poison center exposure calls involve unintentional exposures in children ages ≤5 years
  - Calls in adolescents are more likely to be due to misuse/abuse or suicide attempts and to result in more severe medical outcomes
  - Calls involving adolescent suicide attempts involving prescription opioids have been increasing

Summary of Findings (3)

- Medical use of opioid analgesics may place adolescents at increased risk of future misuse/abuse
- Prescription opioid misuse/abuse in adolescence is associated with substance use disorders (SUDs) in adulthood
  - But, medical opioid use alone (with no misuse/abuse) is not a risk factor for later SUD
- Further research is needed to understand the relationships between medical use and future misuse, abuse, SUD, and related outcomes.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