Pharmacotherapy of Pain in Infants and Children

Charles Berde, MD, PhD
Boston Children's Hospital
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Overview

- Maturation of pain responses and analgesic actions.
- Scope of pediatric acute, recurrent and chronic pain and palliative care.
- Analgesics commonly prescribed in pediatrics.
- Risk-benefit considerations and roles for opioids in pediatrics acute and chronic pain management.

My Background and Clinical Focus

- MD and PhD in Biophysics at Stanford
- Residencies in pediatrics and anesthesiology
- Fellowship in pediatric anesthesiology
- 30 year clinical practice at Boston Children's Hospital in pediatric anesthesiology, pediatric critical care, pediatric palliative care, and pediatric acute and chronic pain management

My Academic and Research Focus

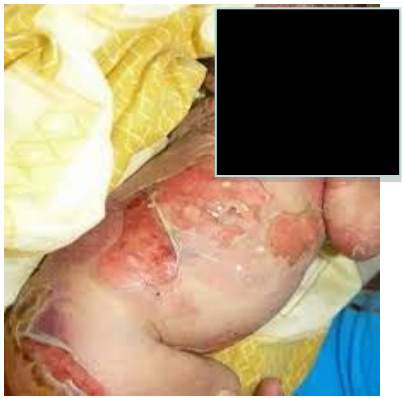
- Chief of the Division of Pain Medicine at Boston Children's Hospital; Professor at Harvard Medical School
- Research areas: pediatric acute and chronic pain management, clinical pharmacology, rehabilitative treatment of pediatric chronic pain, infant animal models for pharmacology of anesthetics and analgesics, development of novel local anesthetic s

Most Infants and Children are Healthy and Experience Brief Pain Episodes

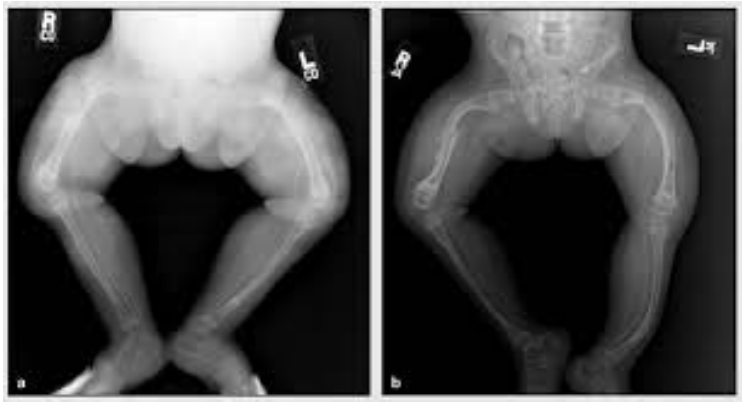
This child has a severe right supracondylar humerus fracture with complete displacement of the fracture fragments.

Some Have Severely Painful Diseases.

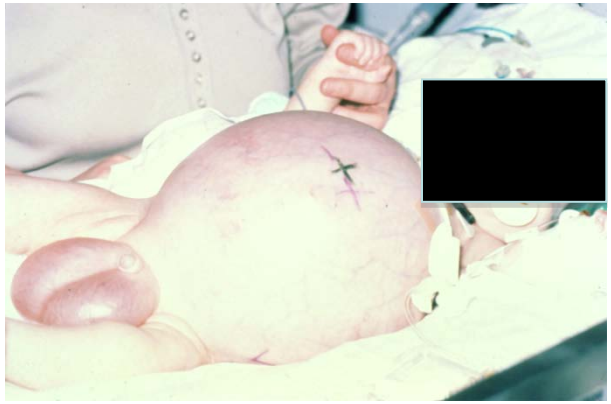
Epidermolysis Bullosa



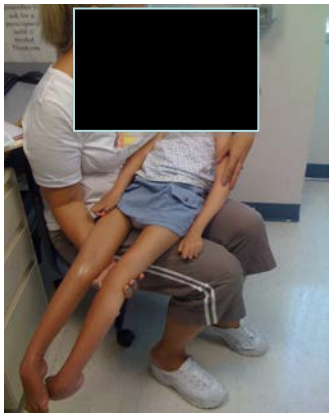
Osteogenesis Imperfecta



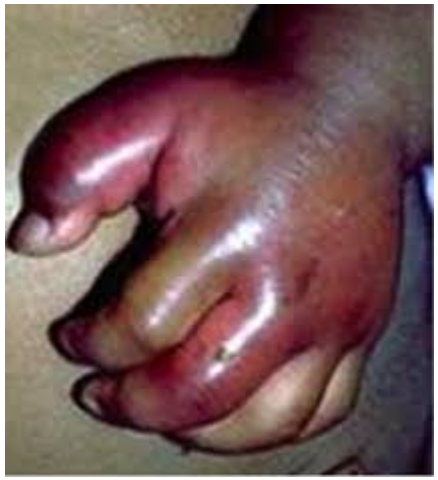
Cancer



Metabolic /Neurologic Diseases



Sickle Cell Disease: Vaso-Occlusion and Its Painful Consequences From Infancy to Adult Life



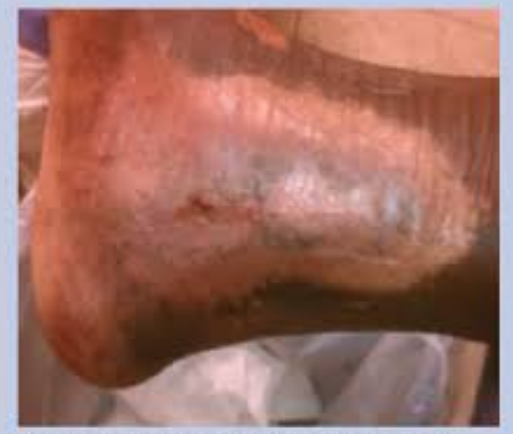
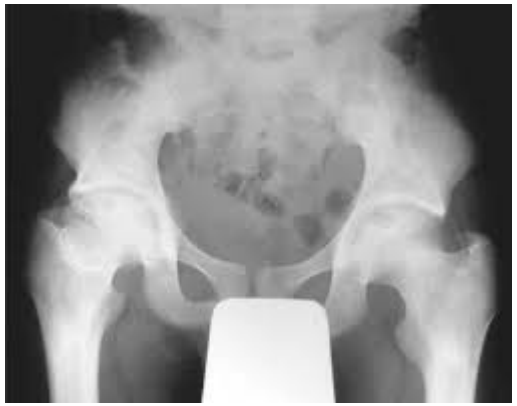
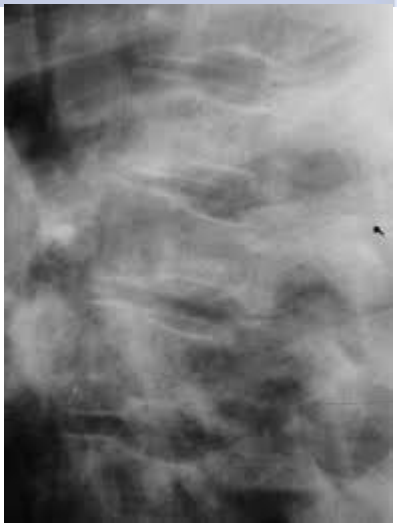


Figure 5. 7 weeks after complete epithelialization



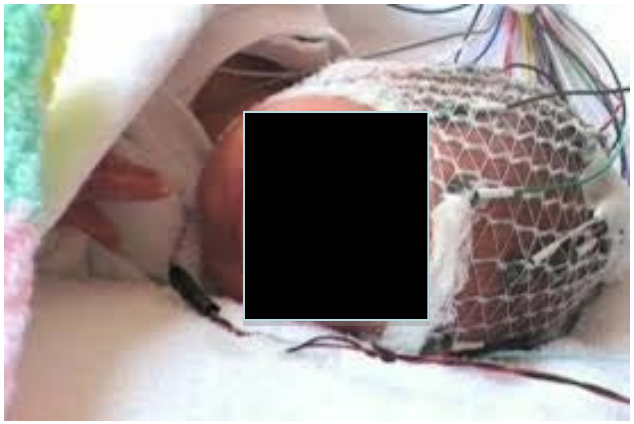


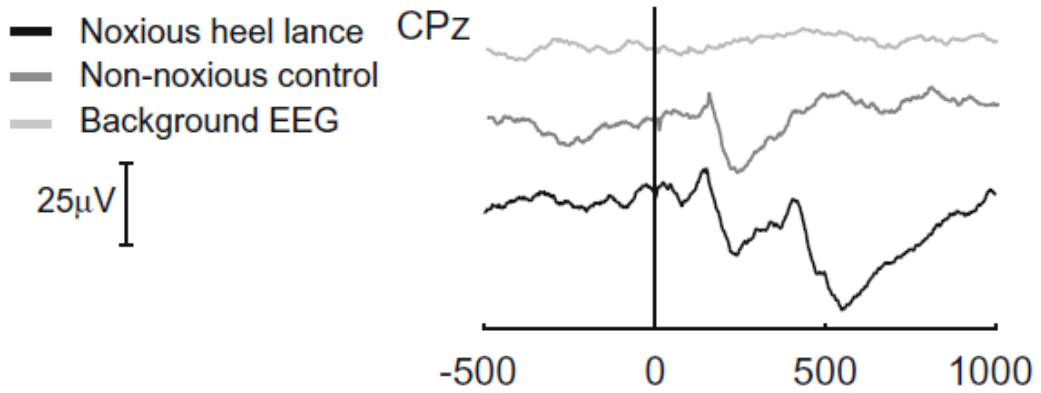
Development of Pain in Neonates

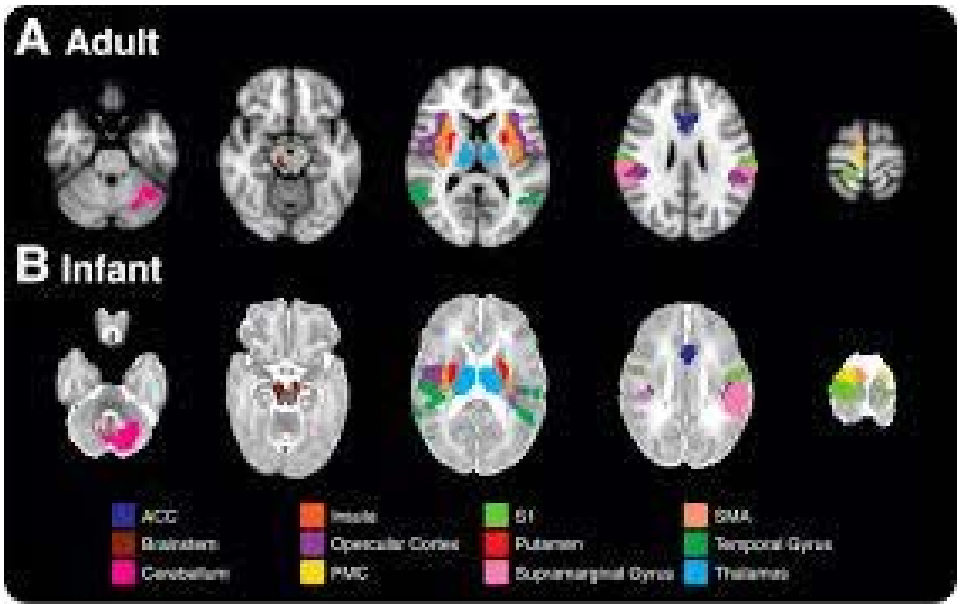
- Maturation during third trimester.
- Responses are less localized, lower threshold
- Behavior: facial expression, limb posture
- Autonomic responses, hormonal-metabolic responses.

Facial expression of physical distress and pain in the infant

Non-Invasive Studies of Brain Responses to Clinically Required Heelsticks in Neonates (EEG, EP, MRI)

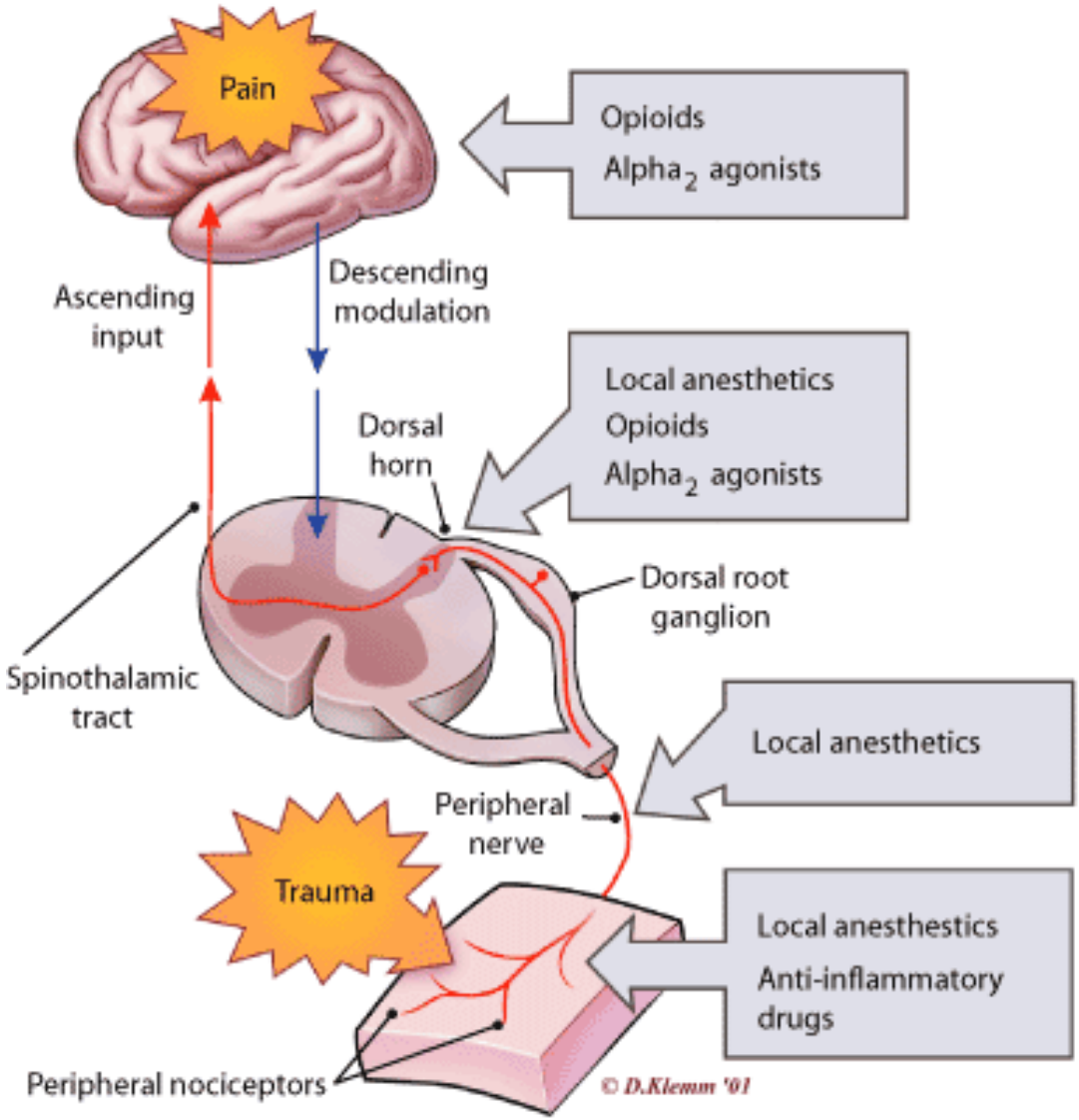






Goksan et al
eLife 2015;4:e06356

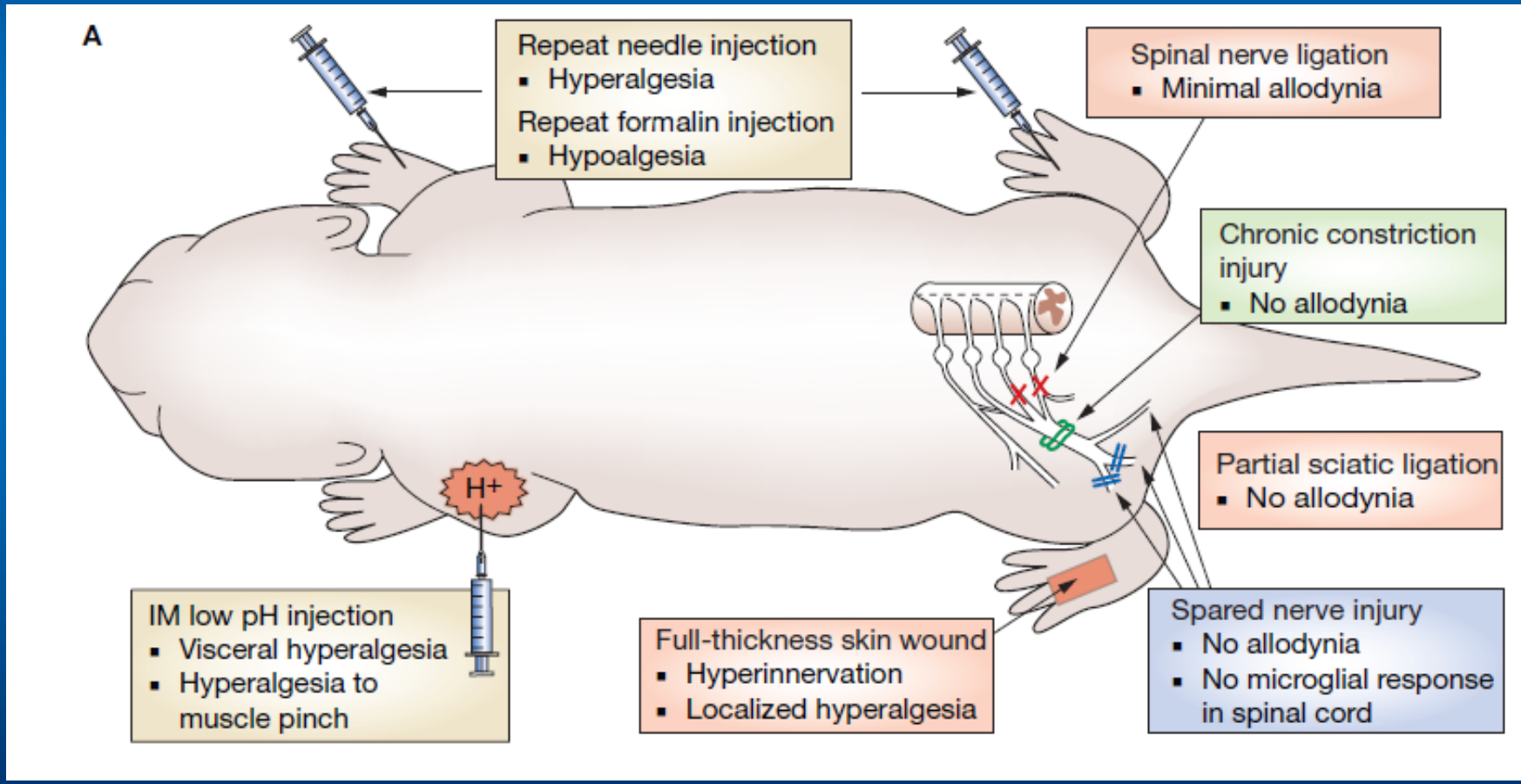
Developmental Changes in Analgesic Receptors and Pathways Influence Efficacy, Safety and Side-Effects.



Ontogeny of Analgesic Actions:

- Efficacy:
  Are receptors present?
  Are receptors coupled?
  Are pathways connected?
- Safety
  Age-specific toxicities?
  Immediate or late? Common or rare?
  Predicted by infant animal models?
  Examples: general anesthetics, opioids,
  local anesthetics

Infant Rat Models for Pain, Analgesia, and Anesthesia



Walker (2013) Clin Perinatol; Fitzgerald & Walker (2009) Nat Neurol Rev

Specific Classes of Analgesics

- Acetaminophen
- NSAIDs
- Local Anesthetics
- Opioids
- Medications for neuropathic pain
  (e.g. anticonvulsants)

Acetaminophen

- Most widely prescribed
- Mechanism remains unknown.
- PK and some safety data at all ages
- Positive efficacy trial in postoperative infants
- Low side-effect profile
- Controversies: asthma, 5HT-3 antagonists
- Overall, very good safety track record, but can cause acute hepatic failure

Morphine Sparing Increases with Acetaminophen Dose

(Korpela et al Anesthesiology 1999)

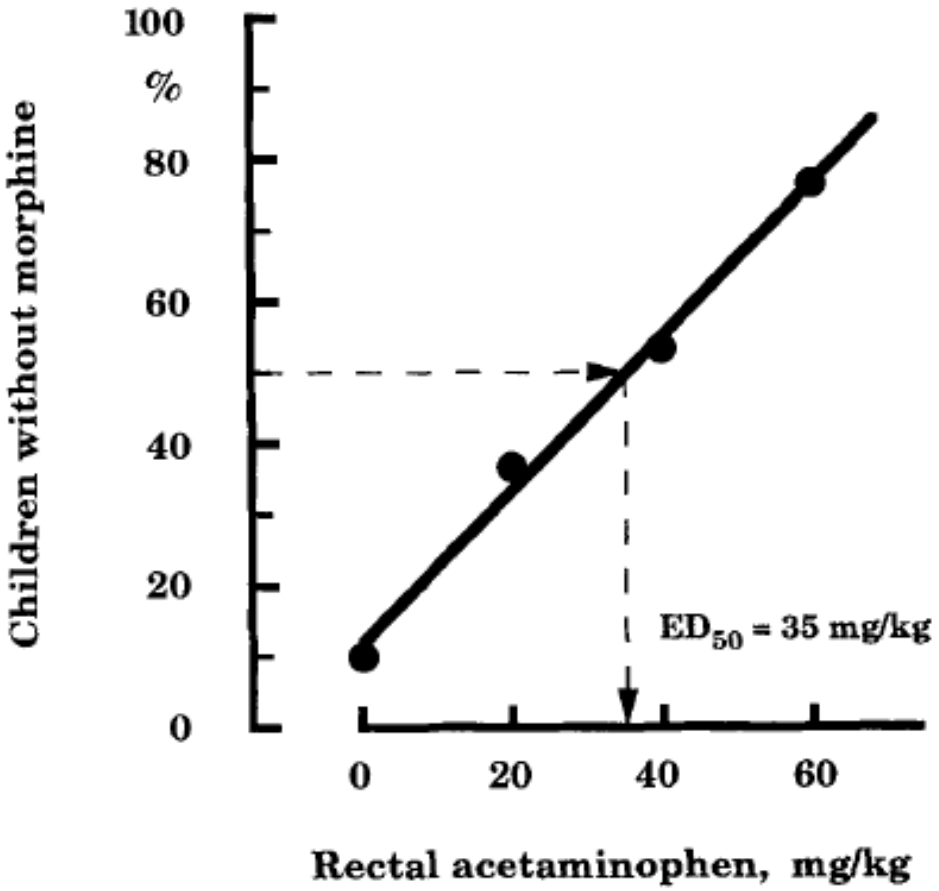


Fig. 1. Correlation between the dose of rectal acetaminophen in a pediatric day-case surgery and the percentage of children who did not need postoperative rescue morphine.

IV Acetaminophen in Postoperative Infants: Morphine-Sparing

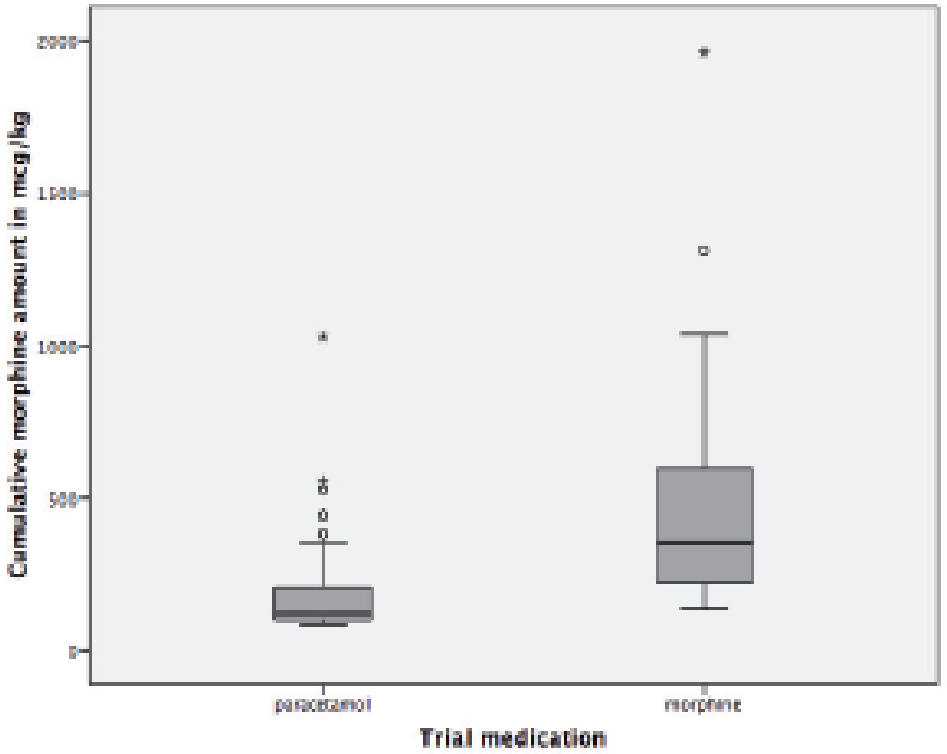


FIGURE 3. Cumulative morphine dose for both morphine and paracetamol study groups over 48 hours postoperative. Asterisks depict outliers, in the paracetamol group we identified two: the first a boy, 68 days old, who underwent surgery for a long gap esophageal atresia and subsequently needed a chest tube for a pneumothorax. The second is a boy, newborn, with a gastroschisis for which a silo was placed. In the morphine group one outlier is identified, a girl, 355 days old, who underwent surgery for a recurrence of a Congenital Diaphragmatic Hernia (CDH).

From I. Ceelie,
PhD Thesis
Erasmus University

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

- Efficacy in over 300 pediatric clinical trials.
- Effective by oral, rectal, or intravenous routes.
- In general, they improve pain scores and reduce opioid requirements by 30-40%
- No NSAID is uniquely “stronger”.
- Short-term safety in healthy children (Lesko and Mitchell, …)
- Extensive PK for children, limited PK for neonates (ibuprofen, indomethacin)

NSAIDs: Controversies/Unknowns

- Efficacy for newborns
- Risks (GI, renal…) with chronic use in children, especially with risk-factors
- Effect on bleeding after tonsillectomy (Riggin et al 2013 38: 115-129 Clinical Otolaryngology largest meta-analysis: reassuring conclusion)
- Bone formation in orthopedic surgeries (laboratory vs. clinical relevance, depends on clinical context) Dodwell et al 2010; Pountos et al 2012

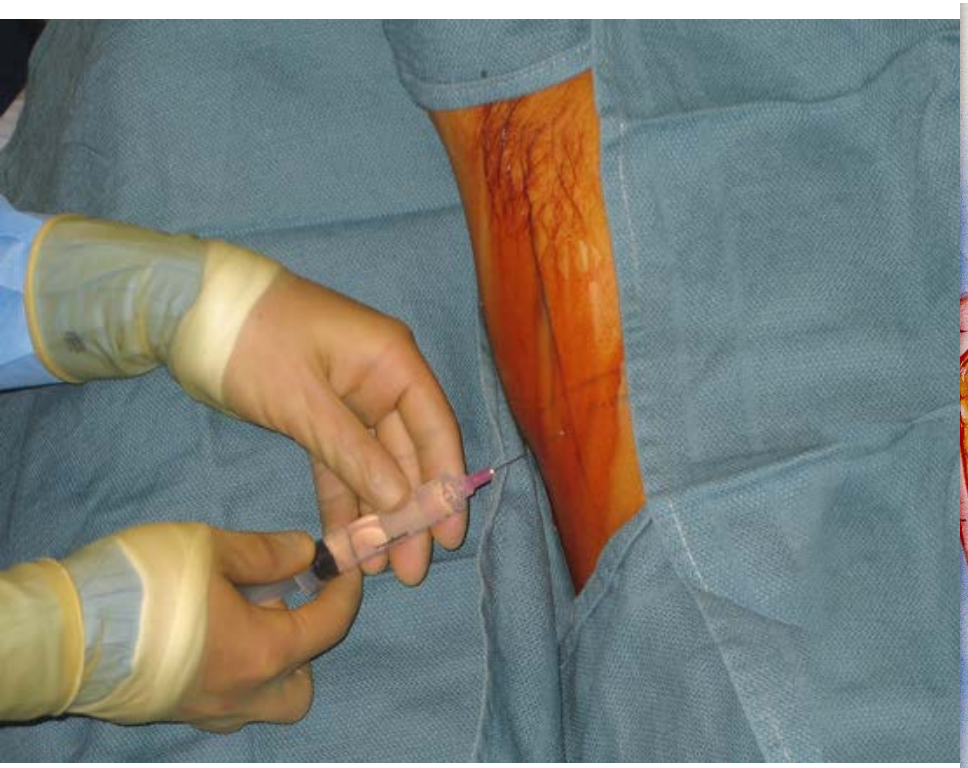
Local Anesthetics in Pediatrics

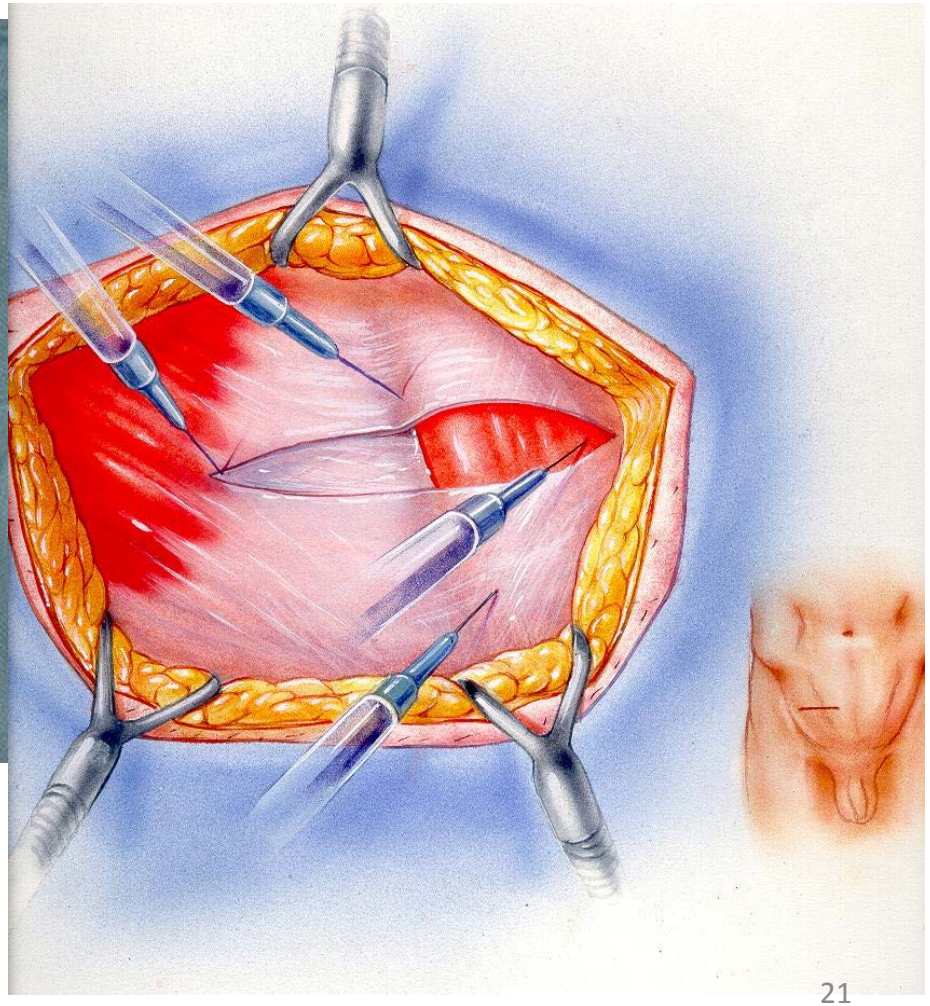
- Topical and Mucosal Analgesia
- Infiltration for Procedures
- Regional Anesthesia and Wound Infiltration for Surgery and Postoperative Analgesia

Local Anesthetics: PK and Safety

- Amino-amides are cleared very slowly in neonates.
- Bupivacaine t ½ e neonates: 8-12 hours.
- Chloroprocaine is cleared rapidly, even in preterm neonates.
- Topical local anesthetics show excellent safety for infant needle procedures.
- Pediatric Regional Anesthesia Network (PRAN) Multi-center database, > 100,000 cases: overall very good safety.

Wound Infiltration During Surgery

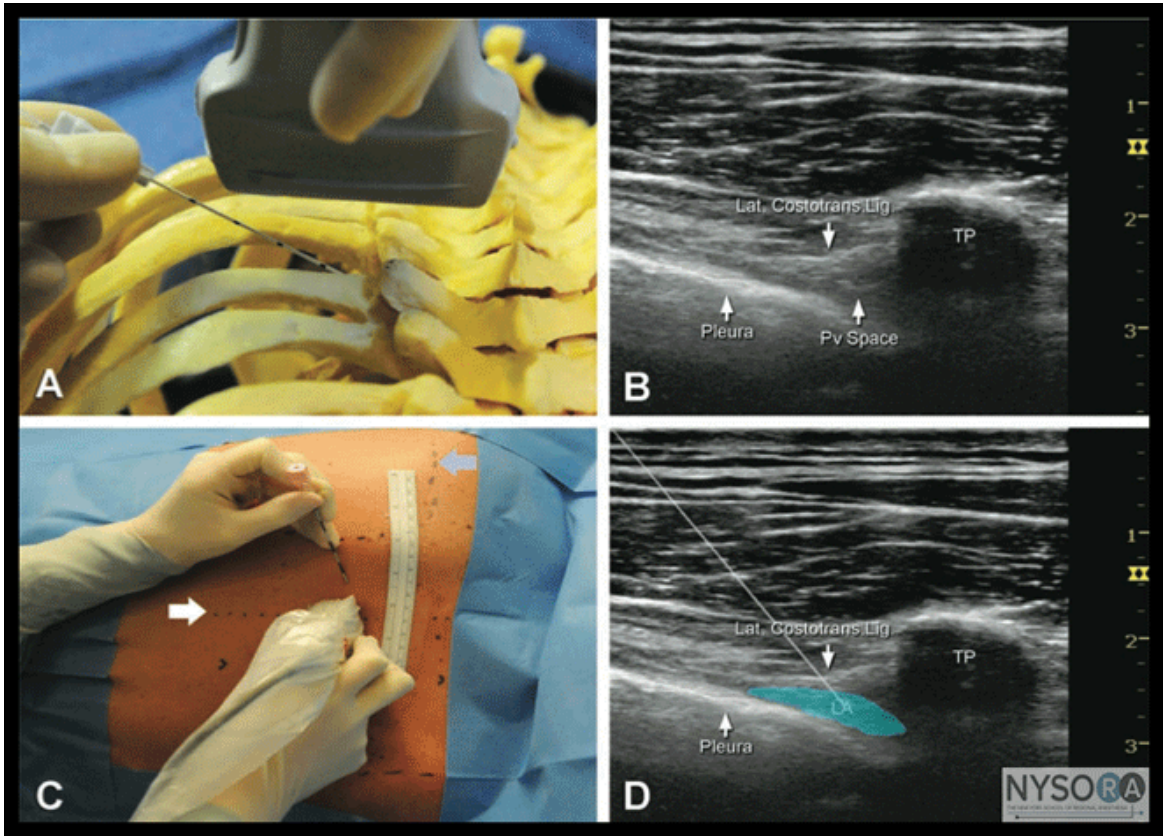




Pediatric Regional Anesthesia:

- Peripheral and plexus blocks and epidural analgesia produce excellent analgesia and favorable impact on postoperative recovery.
- Requires pediatric-specific technical expertise, knowledge of pediatric local anesthetic pharmacology, protocols, and systematic approaches to postoperative management.

Ultrasound-Guidance Has Revolutionized Regional Anesthesia: Paravertebral Blockade for Infant Thoracotomy



Multi-modal Opioid-Sparing Approach to Pediatric Postop Analgesia

- Regional anesthesia wherever feasible
- Additives or systemic adjuncts to prolong regional anesthesia.
- Round the clock acetaminophen **+** NSAID (**not** prn)
- Opioid as rescue, less as primary analgesic

Walther-Larsen et al Pediatric Anesthesia 2016; 26: 151-7
Chalkiadis and Berde Pediatric Anesthesia 2016; 26: 120-1

Is it Effective or Safe to Combine Acetaminophen and NSAIDs?

- Adults: Ong et al Anesthesia and Analgesia 2010; 110: 1170-9
- Systematic Review of 21 studies, 1909 patients
- 85% of studies show significantly improved analgesia compared to acetaminophen alone, 65% of studies show significantly improved analgesia compared to NSAID alone

Opioids Have Essential Uses in Pediatrics.

- Cancer pain (mucositis and tumor-related)
- Life-limiting illnesses/end of life care,
  for pain and dyspnea
- Post-operative pain
- Sickle cell acute vaso-occlusive episodes
- Critical illness and mechanical ventilation

Opioid Pharmacokinetics in Infants

- Newborns: hepatic and renal immaturity, accumulation of parent drug and metabolites
- Newborns: increased brain entry
- Maturation over the first 6 – 12 months
- Morphine infusion postoperative dosing guidelines established for all age groups (mg/kg/hr)

  - Older infants and children 0.03
  - 1 month – 3 months . 0.015
  - Term – 1 month 0.01
  - < 36 weeks PCA 0.005

Postoperative Opioids in Infants

- GI side-effects are relatively common.
- Apnea risk varies with age and disease status.
- Which opioid???
- What to give infants receiving mechanical ventilation?
- What constitutes a “monitored setting”?
- Which infants can receive opioids and go home after ambulatory surgery?

Reasons to Avoid Prescribing Codeine

- Codeine is a pro-drug, inert by itself.
- Poor analgesia: Slow-metabolizing variant or drugs that block CYP2D6 Many other drugs block CYP2D6, rendering codeine inert.
- Overdose and death: ultra-rapid CYP2D6 variant
- Lexus-Nexus (legal) databases, pediatric tonsillectomy:

  > 28 opioid-related deaths from 1984 – 2010

Recurrent Pain in Community Pediatrics

- Recurrent episodic pain is very common;
  daily persistent pain is less common.
- Headaches (tension, migraine), abdominal pains, chest pain and limb pains affect 5-20% of children.
- Diagnostic evaluation guided by Hx and PE
- Pain-related disability: school absence
- Episodic school absence is common, dropping out of school for pain is less common.
- Estimate: 20% of missed school days are due to headaches and abdominal pain.

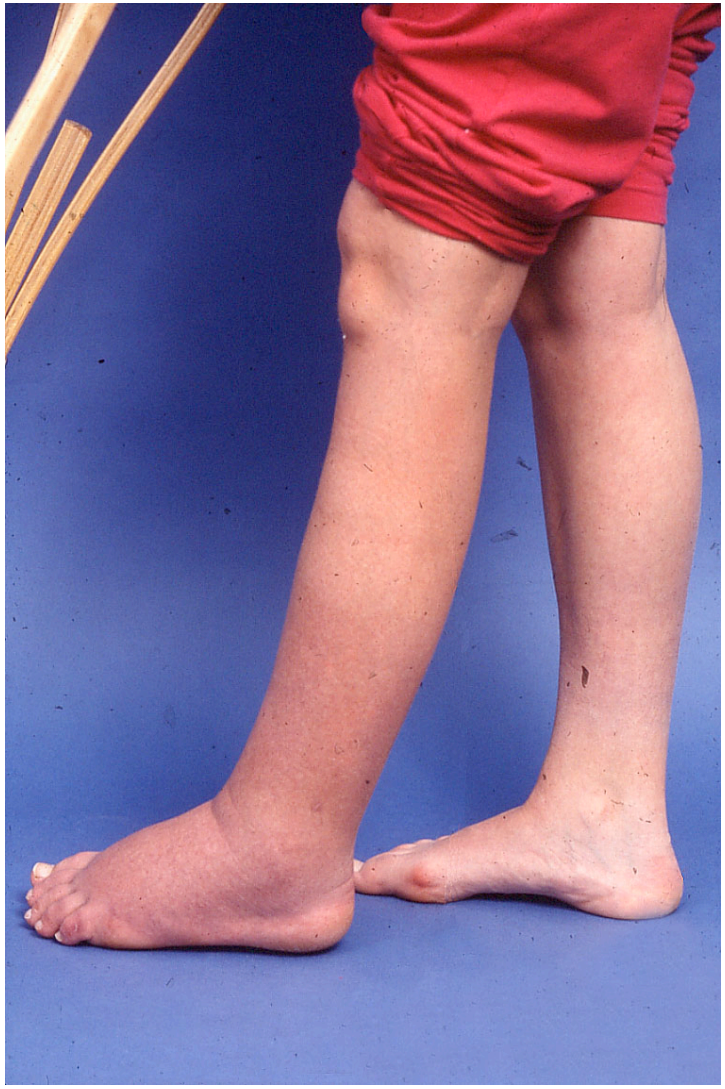
Recurrent Pain in Community Pediatrics: Treatment

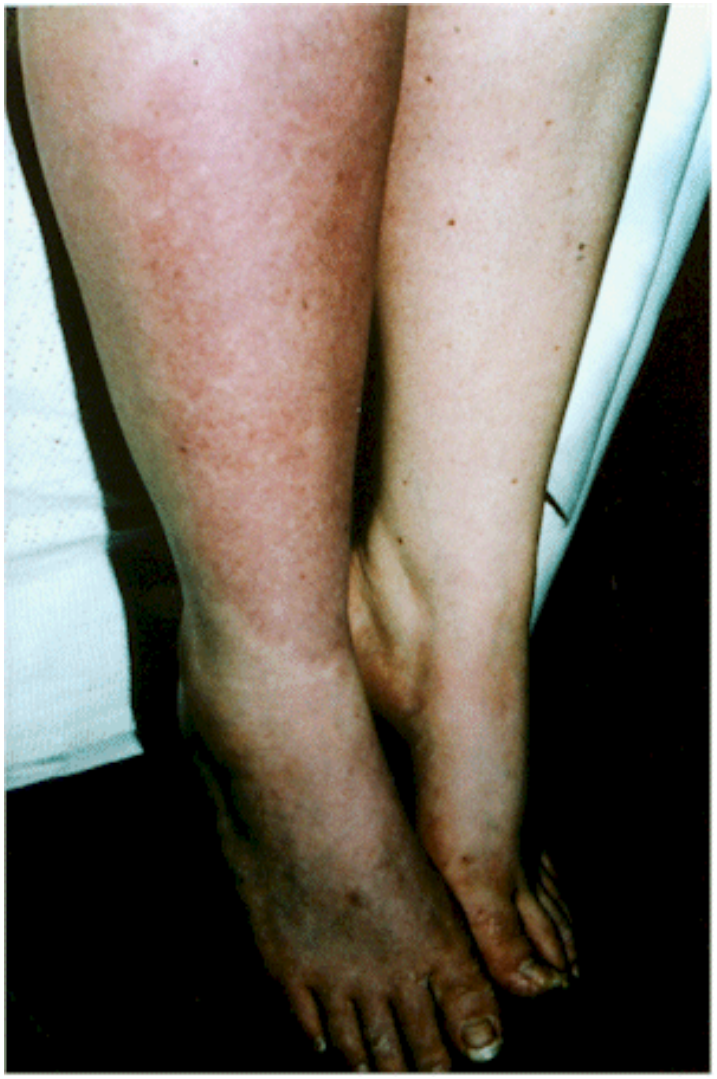
- Robust evidence for cognitive-behavioral therapy (CBT), lifestyle changes, exercise, impact on measures of pain
- Major goal: keeping kids in school
- Circumscribed role for analgesics.

Neuropathic Pain

- Pain associated with injuries to nerves or abnormal excitability in the nervous system.
- Biology and incidence are very age-dependent.
- Pediatrics: peripheral nerve trauma, post-surgical, post-amputation pain, complex regional pain syndromes (see next slide)…

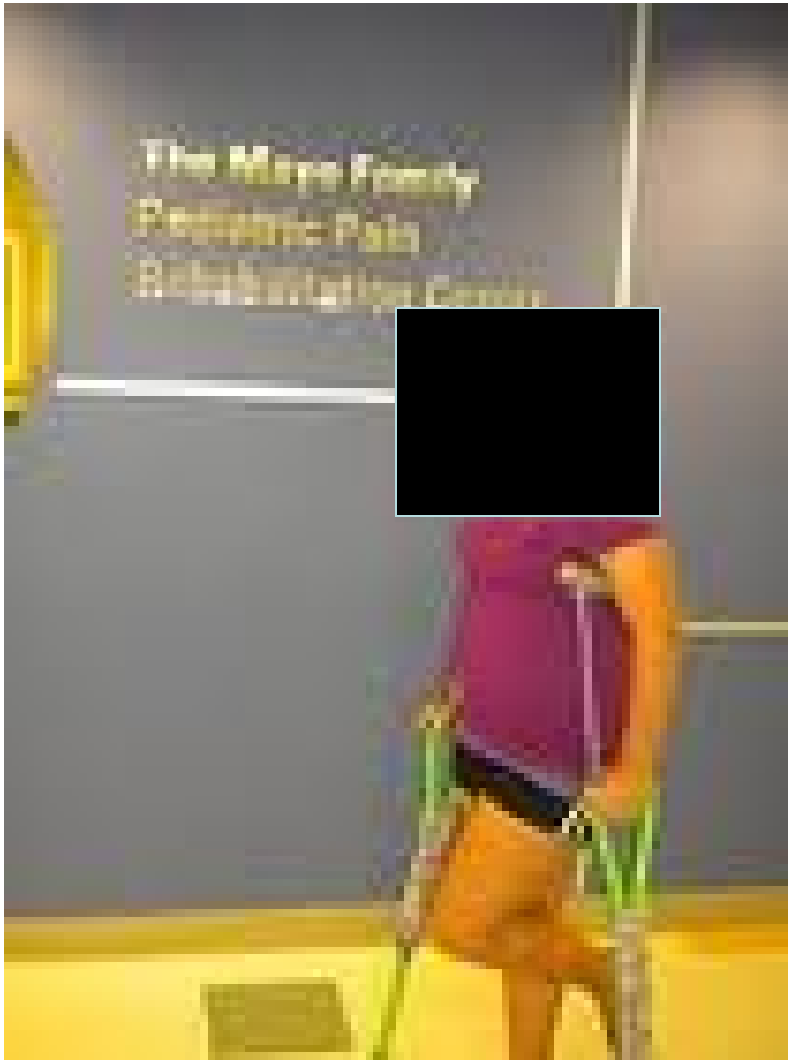
Complex Regional Pain Syndromes (CRPS), Two Adolescent Girls with Extreme Pain With Light Touch (Allodynia)





Rehabilitative Treatment of Pediatric CRPS

- Most patients improve with a regimen of intense physical and occupational therapy, intense exercise, and cognitive-behavioral therapy.
- MRI evidence for brain structural and functional abnormalities that partially improve with rehabilitative treatment.
- Similar rehabilitative treatment benefits several other types of chronic pain (fibromyalgia, widespread musculoskeletal pain).


The Mayo Family
Pediatric Polio

Medications for Neuropathic Pain

- Adults: Several anticonvulsants and anti-depressants have partial efficacy, with frequent side-effects.
- Children: Very sparse data, mostly extrapolated from:

  adult trials for chronic pain

  pediatric trials for epilepsy and mood

Opioids for Children with Advanced Cancer

- Several case series and a small number of clinical trials indicate good effectiveness.
- Most frequent side-effects: constipation, fatigue, mental clouding.
- Some via oral route, some parenteral (IV, subcutaneous, transdermal).
- Many children need switching among opioids, most dosing is extrapolated from adults or from pediatric short-term studies.

Opioid Tolerance and Hyperalgesia: The downside of neuroplasticity

- Tolerance: larger doses are required to achieve the same analgesic effect.
- Opioid-Induced Hyperalgesia: chronic opioid dosing resets pain responsiveness. Everything hurts more.
- Tolerance and hyperalgesia develop more rapidly in younger animal and younger humans compared to older animals and older humans, respectively.

Opioid Tolerance and Hyperalgesia in Pediatrics

- Profound opioid tolerance and withdrawal syndromes in critically ill infants and children in the NICU and PICU.
- Children with advanced cancer: a subset show profound opioid tolerance/resistance Collins et al J Pediatrics 1996

Chronic Prescribing of Opioids for Pain in Non-Life-Limiting Conditions

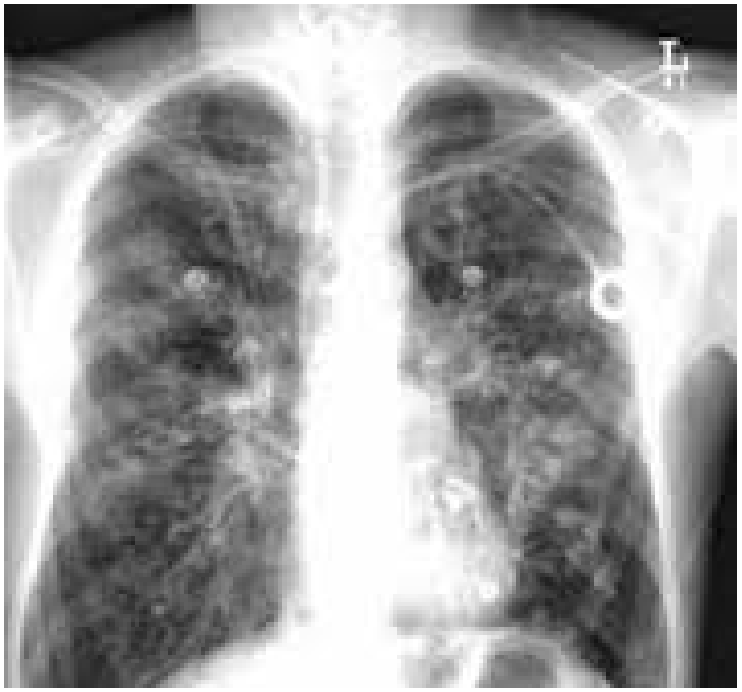
- Adults with Low Back Pain: Studies generally show lack of long-term benefit on pain, function or disability
- Pediatrics: Additional concerns:

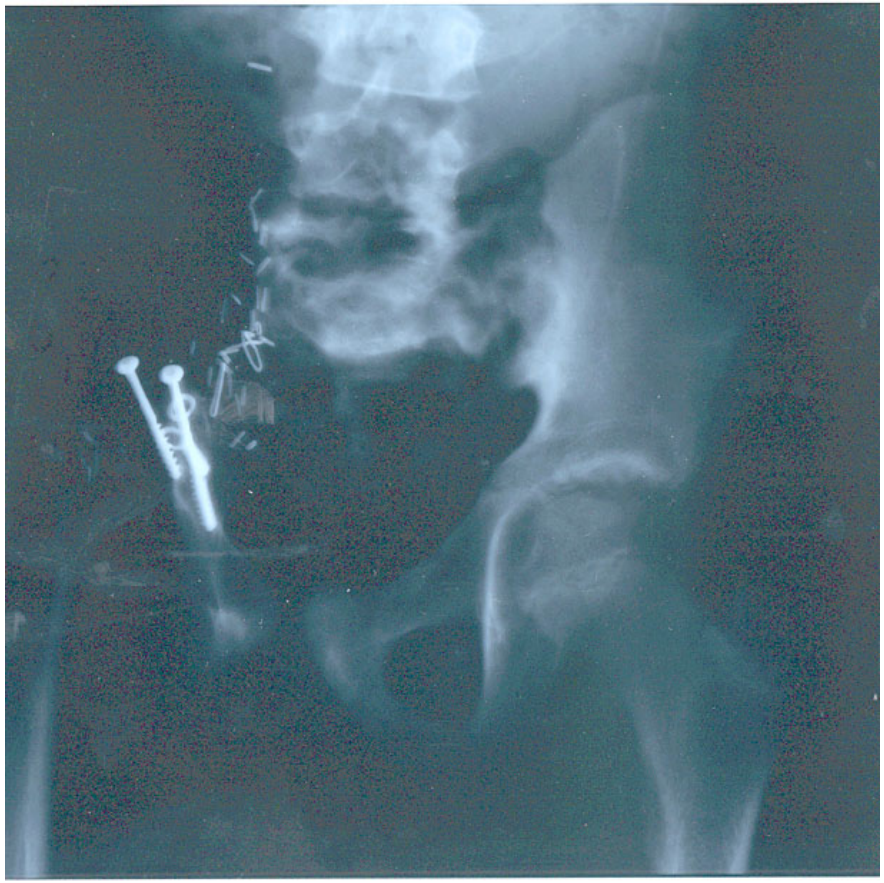
  effects on cognition, mood, and endocrine development,

  tolerance and opioid-induced hyperalgesia

What is a Life-Limiting Disease?
Example: Changes in Prognosis for Cystic Fibrosis

Year	Median Age at Death (years)
1980	19
2016	> 40





Example:
Radiograph from a
30 Year old Woman,
treated at Age 3
for Ewing's Sarcoma.
Tumor-free.

Note the missing
hemi-pelvis on the
right.

Daily pain for 27 years.

Conclusions

- Acute and chronic pain in pediatrics has important differences from adults in epidemiology and biology.
- Evidence supports safe and effective prescribing of several analgesics in pediatrics, but there are major information gaps.
- Pediatric clinical trials are needed to improve how we prescribe analgesics in the overall care of children with acute and chronic pain.

Ethical Framework for Considering Pediatric Opioid Policy

Chris Feudtner, MD PhD MPH
Director, Department of Medical Ethics
The Children's Hospital of Philadelphia
Professor, Pediatrics, Medical Ethics & Health Policy
The University of Pennsylvania Perelman School of Medicine

Introduction

- I am Chris Feudtner, MD PhD MPH
- Pediatrician who cares for children with complex conditions, providing when needed palliative care
- I have spoken previously about the role of opioids in pediatric palliative care
- I am also a pediatric ethicist
- I speak today focusing on the ethical issues raised by our response to the opioid misuse epidemic

Let me briefly reiterate several points I made last time, as they are ethically relevant

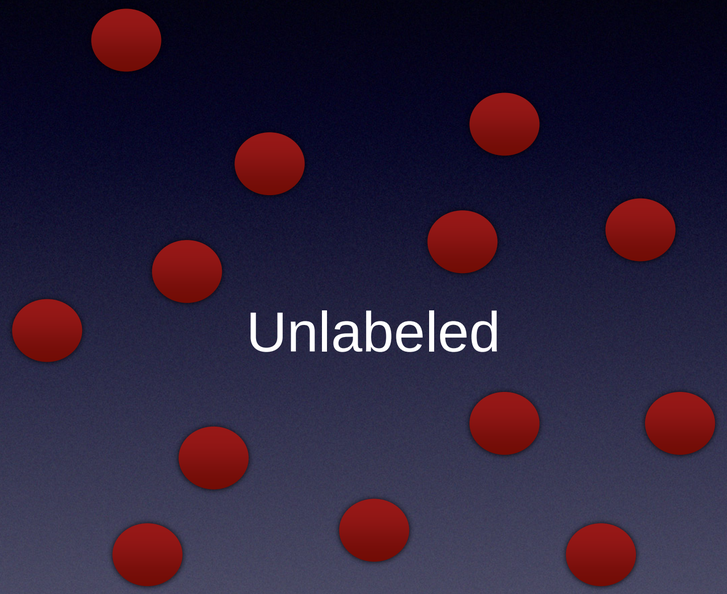
Two Groups in Desperate Need

- We serve 2 vulnerable populations of infants, children, adolescents, and young adults at risk of:
  - Group 1: Taking opioids in a prohibited & harmful manner
  - Group 2: Enduring inadequately relieved severe pain

To serve both of these groups,
we need a clear-sighted, balanced, and forthright
policy response.

Labeling as Evidence Based Guidance

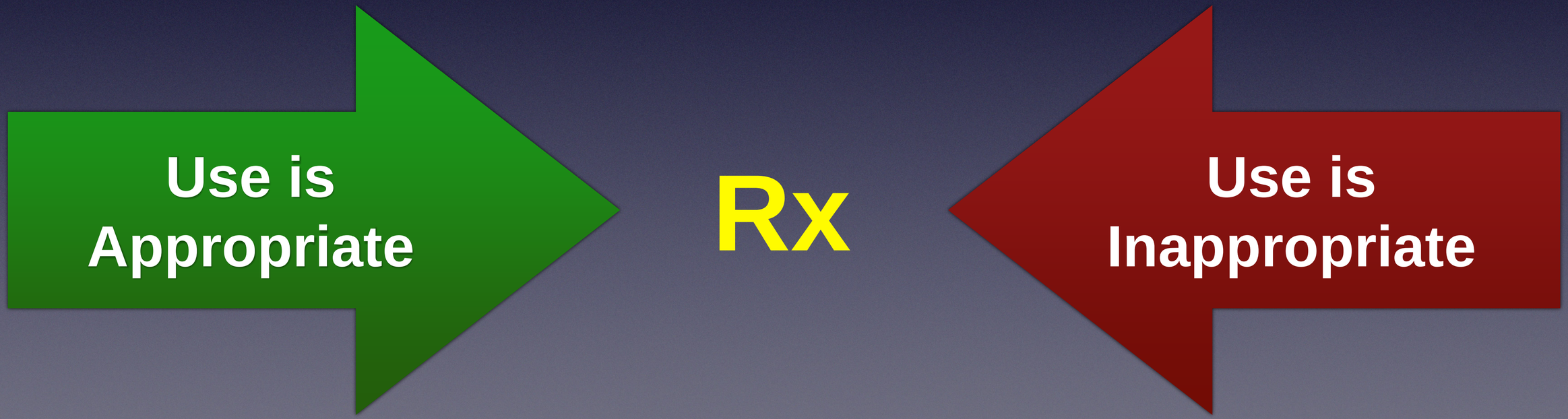
Labeling to Improve Clinical Practice



Widely Varying Practice

Safer & More Effective Practice

Labeling as a Confirmation & Constraint on Clinical Practice



Oxycontin Labeling: Confirmation & Constraints

OXYCONTIN is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in:

- Adults; and
- Opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent.

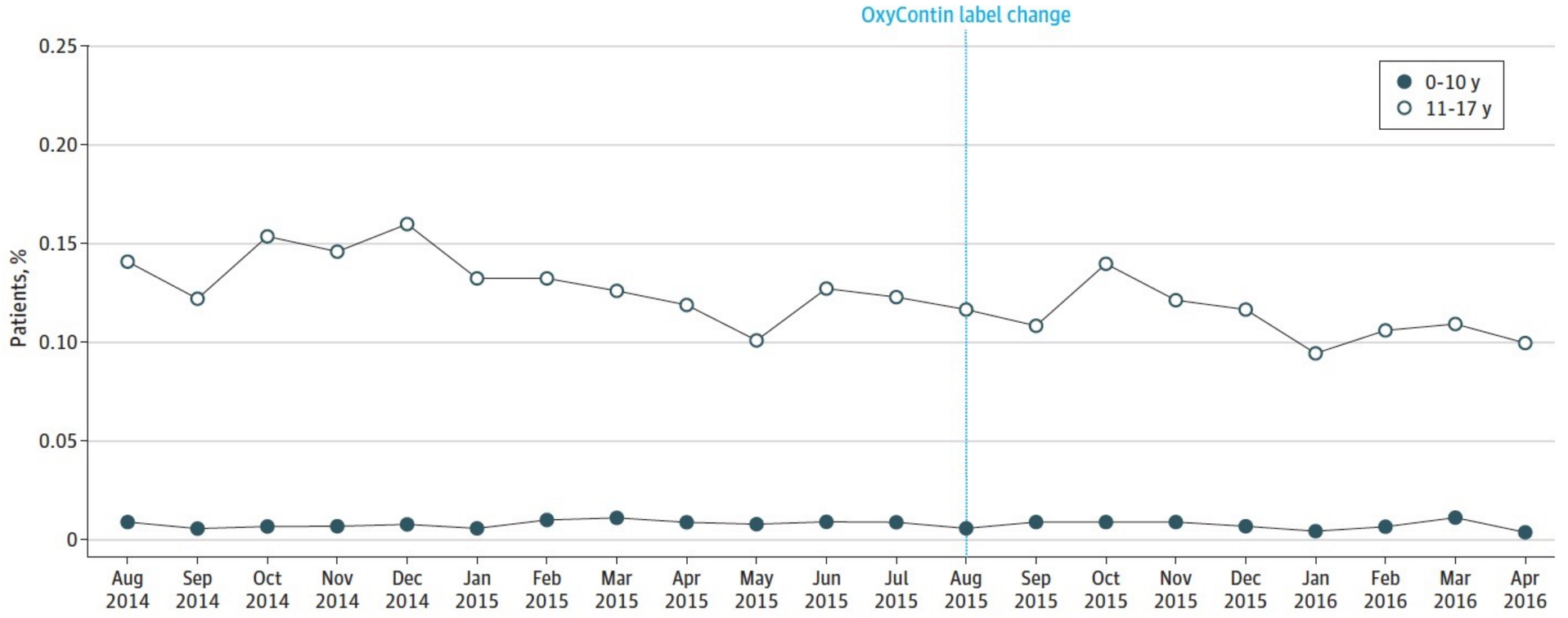
Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations *[see Warnings and Precautions (5.1)]*, reserve OXYCONTIN for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- OXYCONTIN is not indicated as an as-needed (prn) analgesic.

http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022272s027lbl.pdf

Recent Finding Underscoring "Constraint" Effect

Figure 2. Percentage of Oxycodone Extended-Release Prescriptions Dispensed to Pediatric Patients From Retail Pharmacies, August 2014-April 2016



Data were extracted in August 2016.[6]

[Effect of US Food and Drug Administration–Approved Pediatric Labeling on Dispensing of Extended Release Oxycodone in the Outpatient Retail Setting](#)
Jing Xu, PhD, MA; Rajdeep Gill, PharmD; Marisa Cruz, MD; et al. JAMA Pediatrics (2016).

What are some of the
ethical insights and implications
of the focus on labeling
as a response to the opioid epidemic?

Pieces of the Opioid Epidemic Solution: Policy and Clinical Practice

Science	Drug Development	Drug Studies	Non-Drug Studies
Clinical Practice	**Medication Labeling**	Non-Opioid Alternatives	Quality Improvement & Payment
Illicit Sources	Over Prescribers	Excessive Amounts Prescribed	Home Medicine Cabinets
Addiction Treatment	Prevention & Screening	Access to Levels of Treatment	Harm Reduction

Ethical Framework for Pediatric Opioid Policy

- Aspects of the situation
- Detection of problems
- Deliberation
  - At the level of individual patients
  - At the level of populations of persons
  - At the level of having to synthesize these different levels
- Conclusion

Aspects of the Situation

Patients & Persons

- Pediatric patients in pain
- Pediatric patients at risk of misuse
- Adolescents at risk of misuse

Interacting Systems

- Health care
- Insurance and payment
- Police & drug enforcement
- FDA

Multiple Levels

- Individual patients
- Populations of persons

Importance of Knowledge

- To weigh individual risks/benefits
- To weigh population-level impact

Detection of Problems

Individual Patients

- Risk of suffering due to pain
- Risk of subsequent misuse

Patient vs Population

- Patient in pain without opioid
- Persons accessing opioid & misusing

Interacting Systems

- Blame game focused on pills, not on coordinated solutions to misuse problem
- Pediatric misuse deaths prompt narrow focus on pediatric opioid restrictions
- Insufficient payment for non-opioid pain management induces “quick fix” pill-based responses

Problems of Knowledge / Thinking

- Risk of use-induced misuse
- Not thinking of the interacting systems
- Individual vs population tradeoffs

Deliberation #1

Trading off Entirely at the INDIVIDUAL level

Patient's risk of pain

vs

Patient's risk of subsequent misuse

Individual Level

			Treatment Options		
		???	No treatment	???	Opioid treatment
???					

Individual Level

<u>Ethics job #1</u>
Clarify the goals that patients are pursuing via treatment

			Treatment Options		
		???	No treatment	???	Opioid treatment
GOALS	Reduce pain in short term				
	Reduce pain in long term				
	Avoid opioid side effects				
	Minimize risk of opioid misuse				

Ethics job #2
Clarify the value weights that patients place on goals

Individual Level

			Treatment Options		
		Preference Weights	No treatment	**???**	Opioid treatment
GOALS	Reduce pain in short term				
	Reduce pain in long term				
	Avoid opioid side effects				
	Minimize risk of opioid misuse				

Individual Level

Ethics job #3
Make sure all valid options are being considered

		Preference Weights	Treatment Options: No treatment	Treatment Options: **Non-opioid treatment**	Treatment Options: Opioid treatment
GOALS	Reduce pain in short term				
	Reduce pain in long term				
	Avoid opioid side effects				
	Minimize risk of opioid misuse				

Patient with acute pain

			Treatment Options		
		Preference Weights	No treatment	Non-opioid treatment	Opioid treatment
GOALS	Reduce pain in short term	+++			
	Reduce pain in long term	0			
	Avoid opioid side effects	+			
	Minimize risk of opioid misuse	+++			

Patient with chronic pain

			Treatment Options		
		Preference Weights	No treatment	Non-opioid treatment	Opioid treatment
GOALS	Reduce pain in short term	++			
	Reduce pain in long term	+++			
	Avoid opioid side effects	++			
	Minimize risk of opioid misuse	+++			

Patient with advanced cancer pain

			Treatment Options		
		Preference Weights	No treatment	Non-opioid treatment	Opioid treatment
GOALS	Reduce pain in short term	+++			
	Reduce pain in long term	++			
	Avoid opioid side effects	+			
	Minimize risk of opioid misuse	+			

Individual Level

The patient largely determines this

Patient & doctor decide upon this

		Preference Weights	Treatment Options: No treatment	Non-opioid treatment	Opioid treatment
GOALS	Reduce pain in short term				
	Reduce pain in long term				
	Avoid opioid side effects				
	Minimize risk of opioid misuse				

Patient & doctor deliberate regarding how well different options are likely to accomplish important goals

Individual Level

What does the FDA do at the individual level?

		Preference Weights	Treatment Options: No treatment	Treatment Options: Non-opioid treatment	Treatment Options: **Opioid treatment**
GOALS	Reduce pain in short term				
	Reduce pain in long term				
	Avoid opioid side effects				
	Minimize risk of opioid misuse				

The FDA serves (among other things) as an authoritative clearing house of the data that informs this part of the deliberation, namely the likelihood that a specific treatment will achieve a specific goal via **LABELING**

Deliberation #2

Impact at POPULATION level

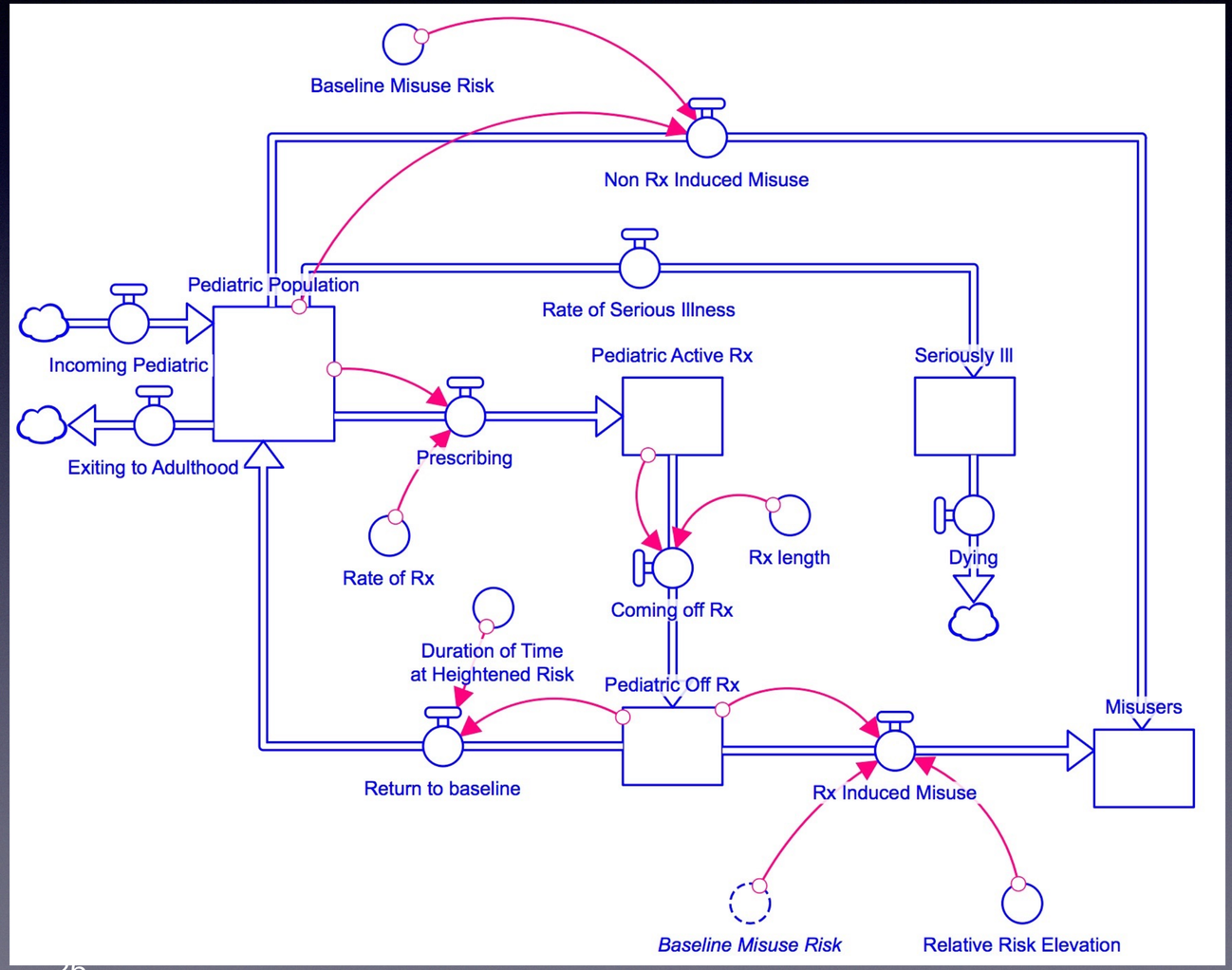
Numbers of Misusers

Amount of Opioid Diversion

Population Level

Opioid Misusers

Simple Model:
Incomplete & Inaccurate, but Hopefully Enlightening



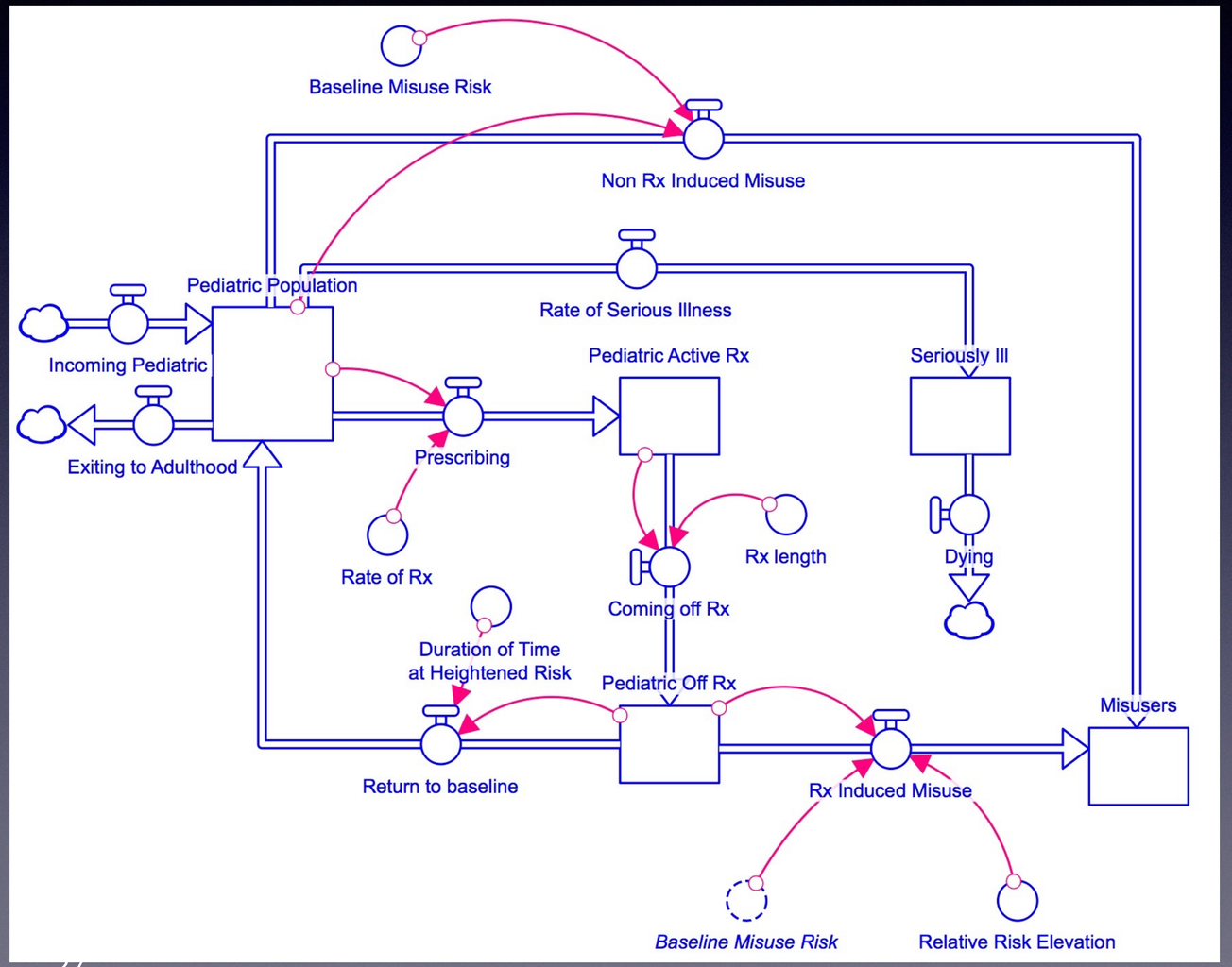
Population Level

Baseline Misuse Risk: 0.09

Opioid Misusers

Simple Model:
Incomplete & Inaccurate,
but Hopefully Enlightening

Relative Risk Elevation: 1.33



Miech et al.
Prescription Opioids in Adolescence and Future Opioid Misuse (2015)
www.pediatrics.org/cgi/doi/10.1542/peds.2015-1364

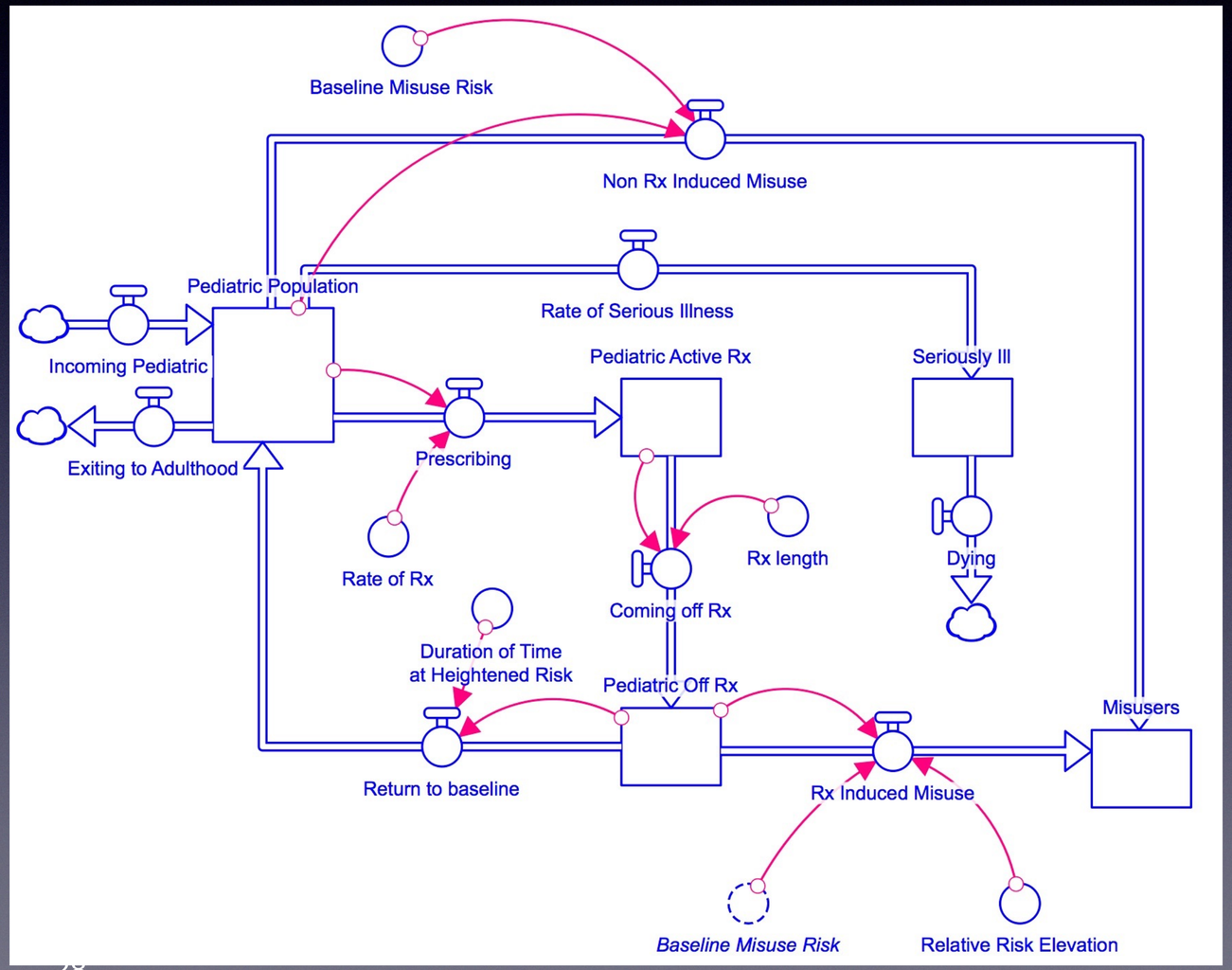
Population Level

Baseline Misuse Risk: 0.09

Lifetime opioid use by 12th grade

Question: "On how many occasions (if any) have you taken narcotics other than heroin on your own; that is, without a doctor telling you to take them?" Note: question includes an extensive list of example prescription opioids that is updated from year to year.

None	0.91 (0.0035)
1–2	0.041 (0.0025)
3–5	0.018 (0.0016)
6–9	0.010 (0.0012)
10–19	0.010 (0.0011)
20–39	0.005 (0.0008)
40+	0.006 (0.0008)



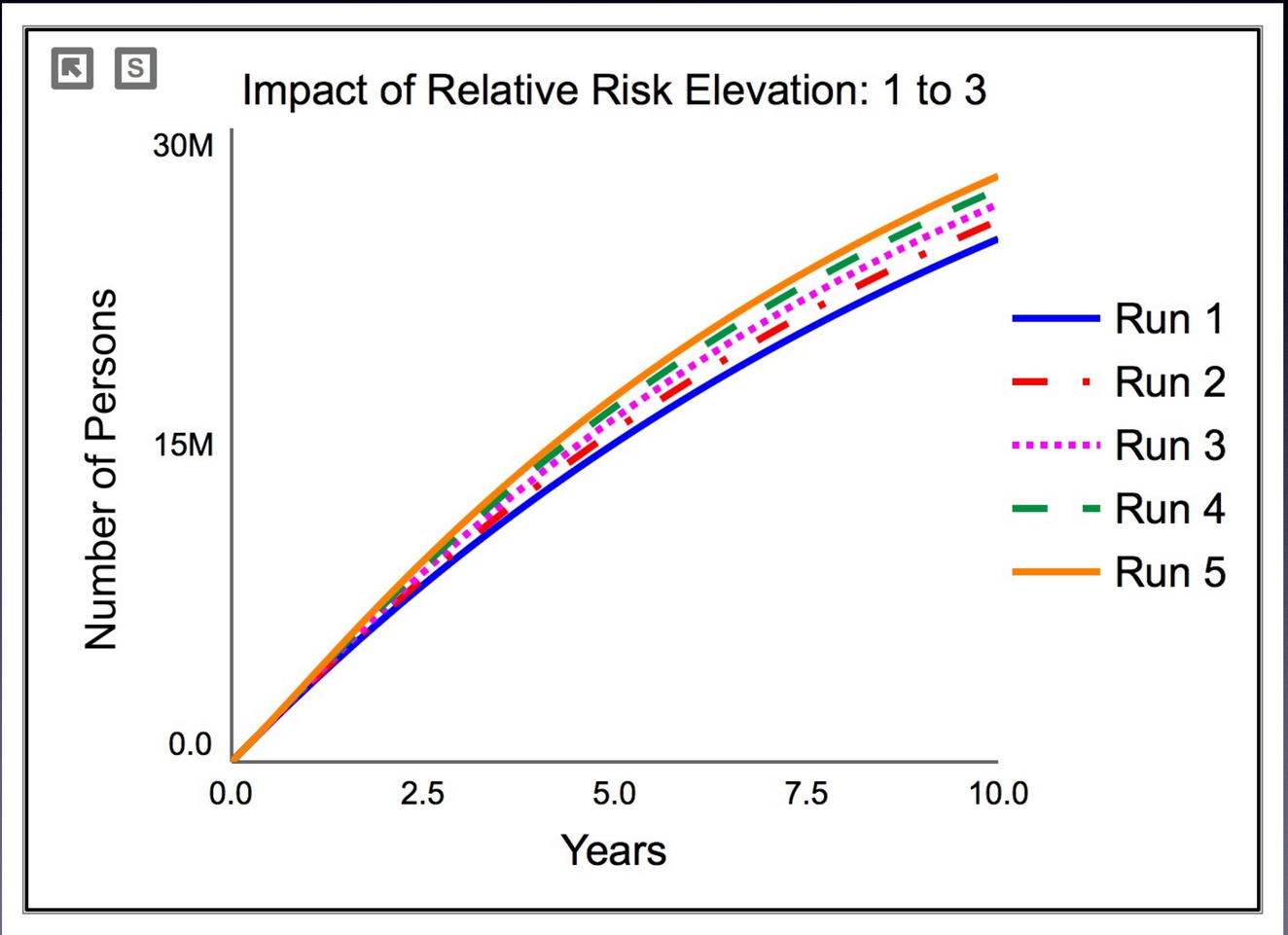
Relative Risk Elevation: 1.33

Miech et al.
Prescription Opioids in Adolescence and Future Opioid Misuse (2015)
www.pediatrics.org/cgi/doi/10.1542/peds.2015-1364

Population Level

Baseline Population Risk

0.09



Marginal Risk Elevation Due to Rx Use

Run 1	1
Run 2	1.5
Run 3	2
Run 4	2.5
Run 5	4

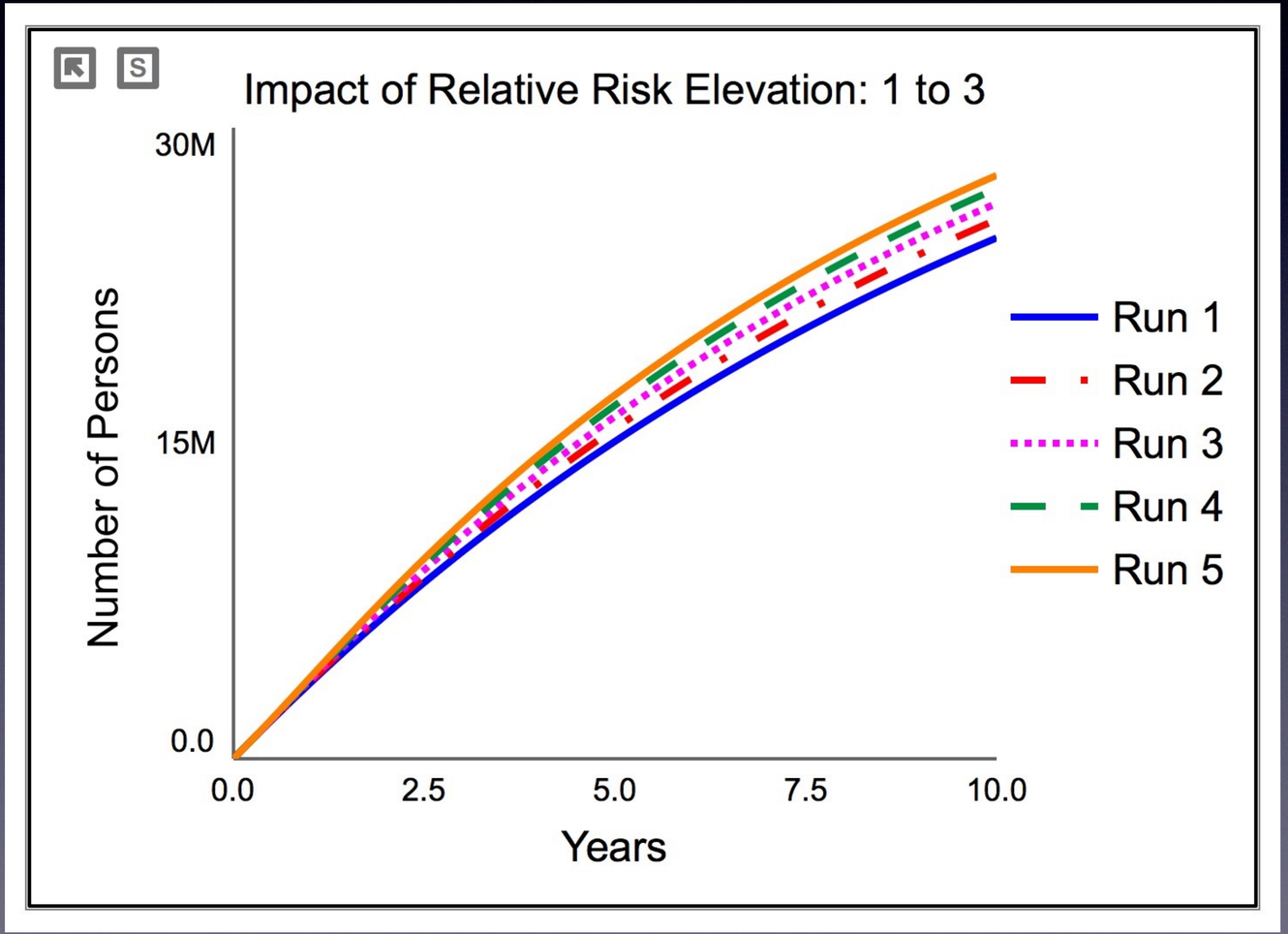
Fortuna RJ, Robbins BW, Caiola E, Joynt M, Halterman JS. Prescribing of controlled medications to adolescents and young adults in the United States. Pediatrics. 2010 Dec;126(6):1108-16. doi: 10.1542/peds.2010-0791. Epub 2010 Nov 29. PubMed PMID: 21115581.

Population Level

Baseline Population Risk

0.09

This risk affects the entire 44M population of adolescents



Marginal Risk Elevation Due to Rx Use

Run 1	1
Run 2	1.5
Run 3	2
Run 4	2.5
Run 5	4

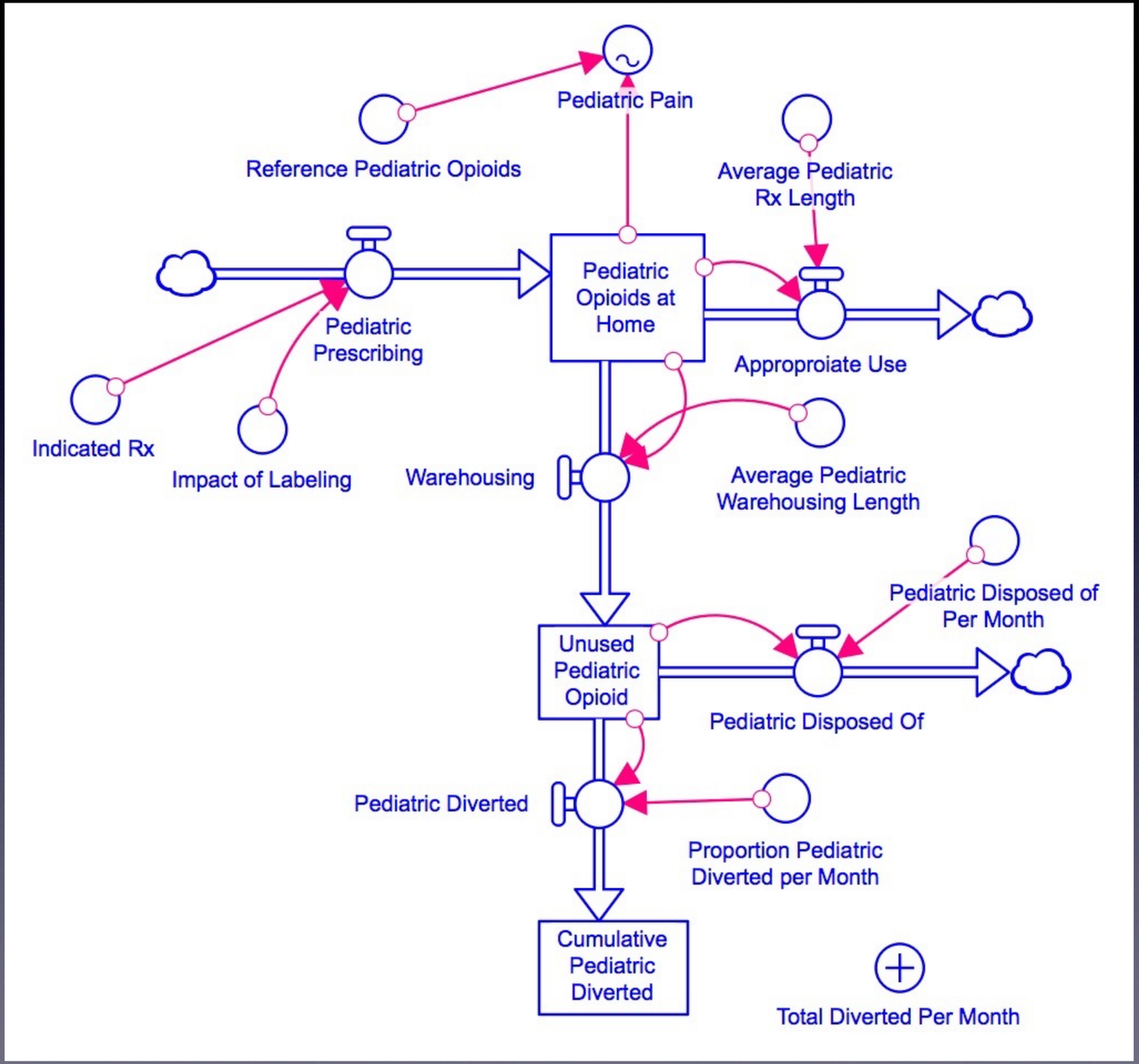
This risk affects the 15% of population treated for pain with an opioid

Fortuna RJ, Robbins BW, Caiola E, Joynt M, Halterman JS. Prescribing of controlled medications to adolescents and young adults in the United States. Pediatrics. 2010 Dec;126(6):1108-16. doi: 10.1542/peds.2010-0791. Epub 2010 Nov 29. PubMed PMID: 21115581.

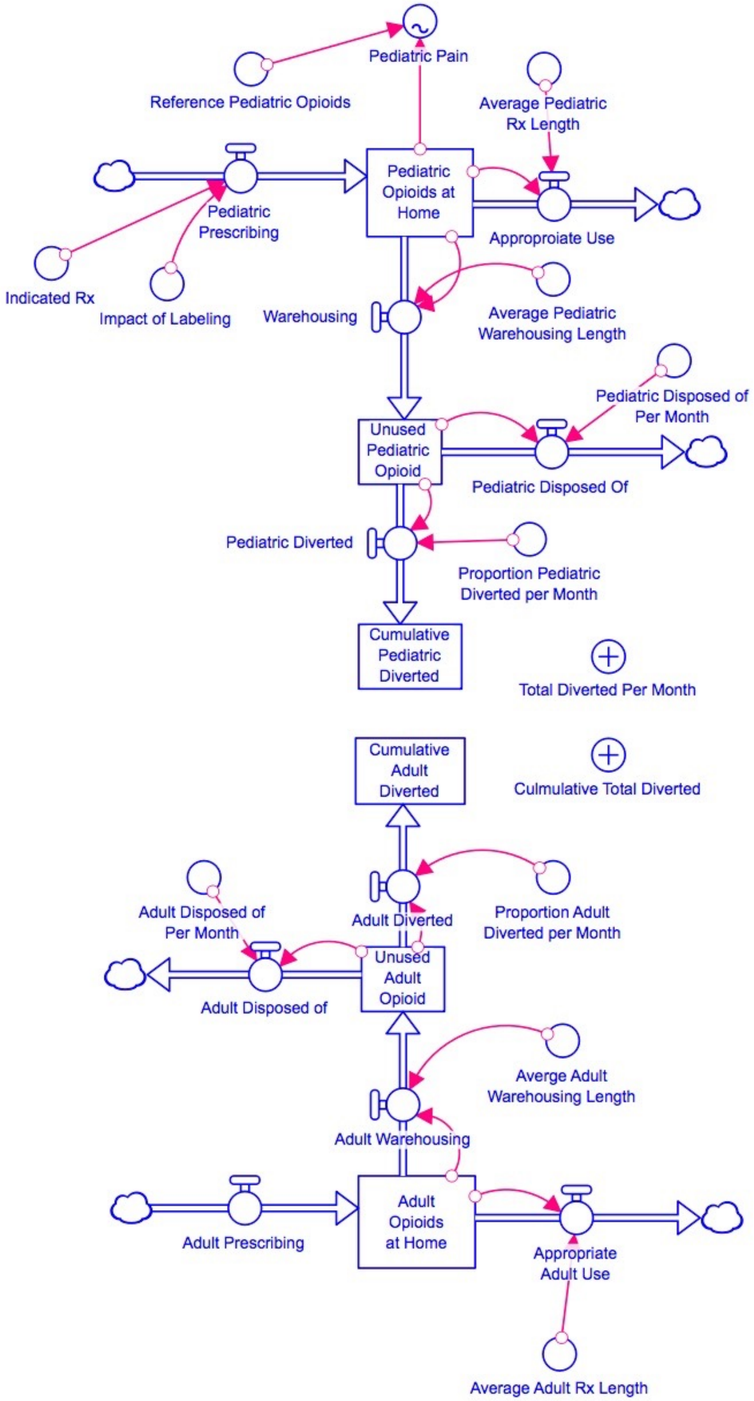
Population Level

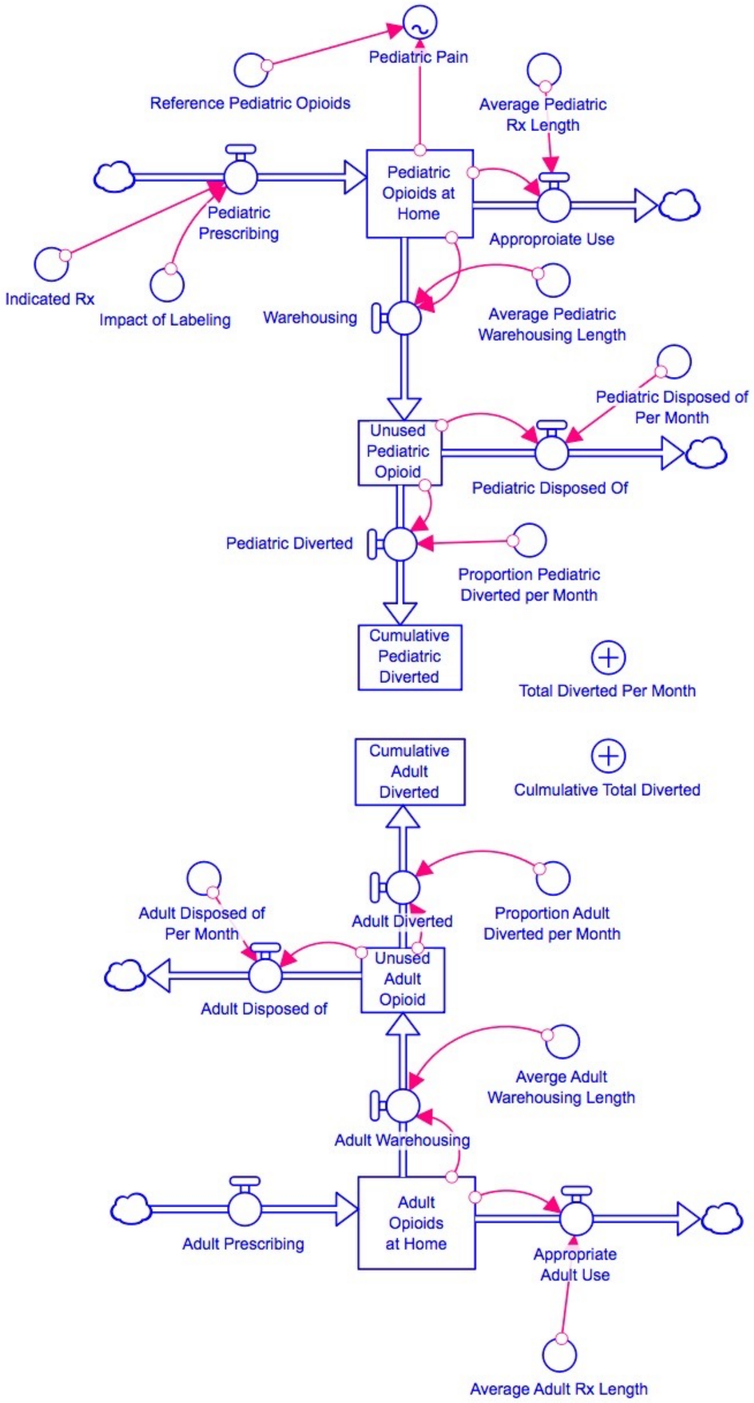
Opioid Pill Diversion

Simple Model:
Incomplete & Inaccurate, but Hopefully Enlightening

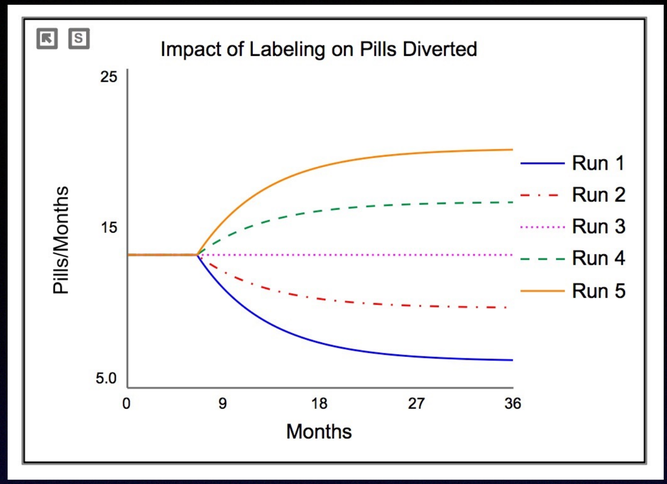


Population Level





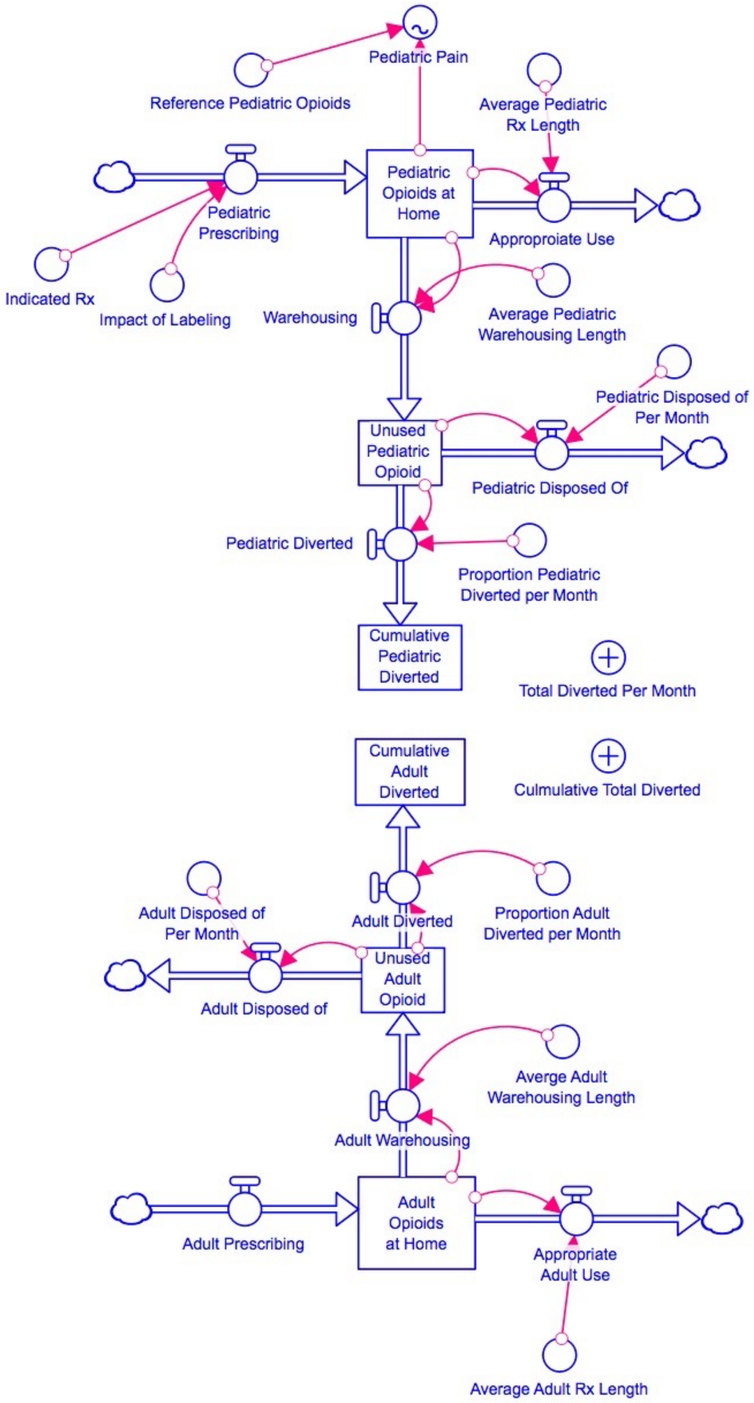
Population Level

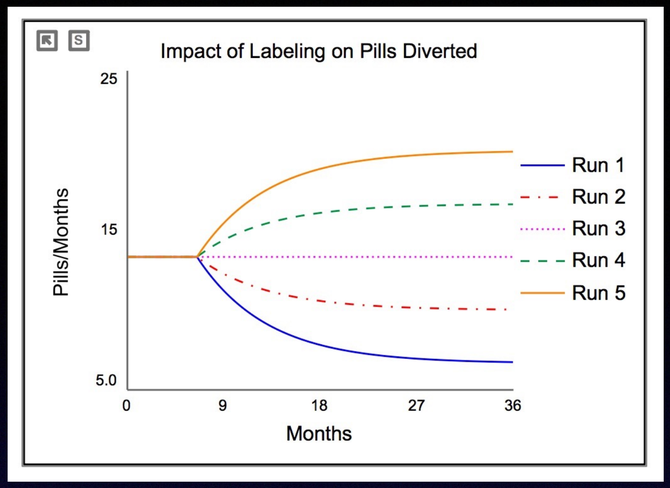


Run 1 = 0.5
Run 2 = 0.75
Run 3 = 1
Run 4 = 1.25
Run 5 = 1.5

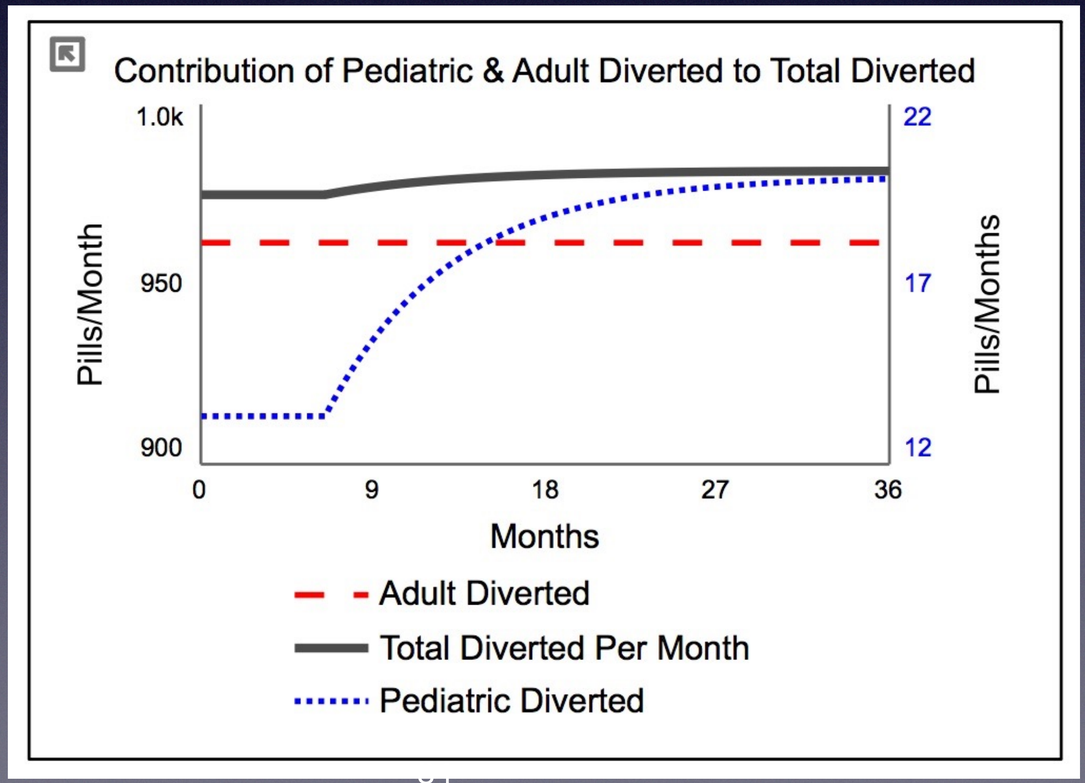
Different estimates of the impact of labeling on decreasing or increasing amount of opioid pills dispensed

Population Level





Run 1 = 0.5
Run 2 = 0.75
Run 3 = 1
Run 4 = 1.25
Run 5 = 1.5



Different estimates of the impact of labeling on decreasing or increasing amount of opioid pills dispensed

Deliberation #3

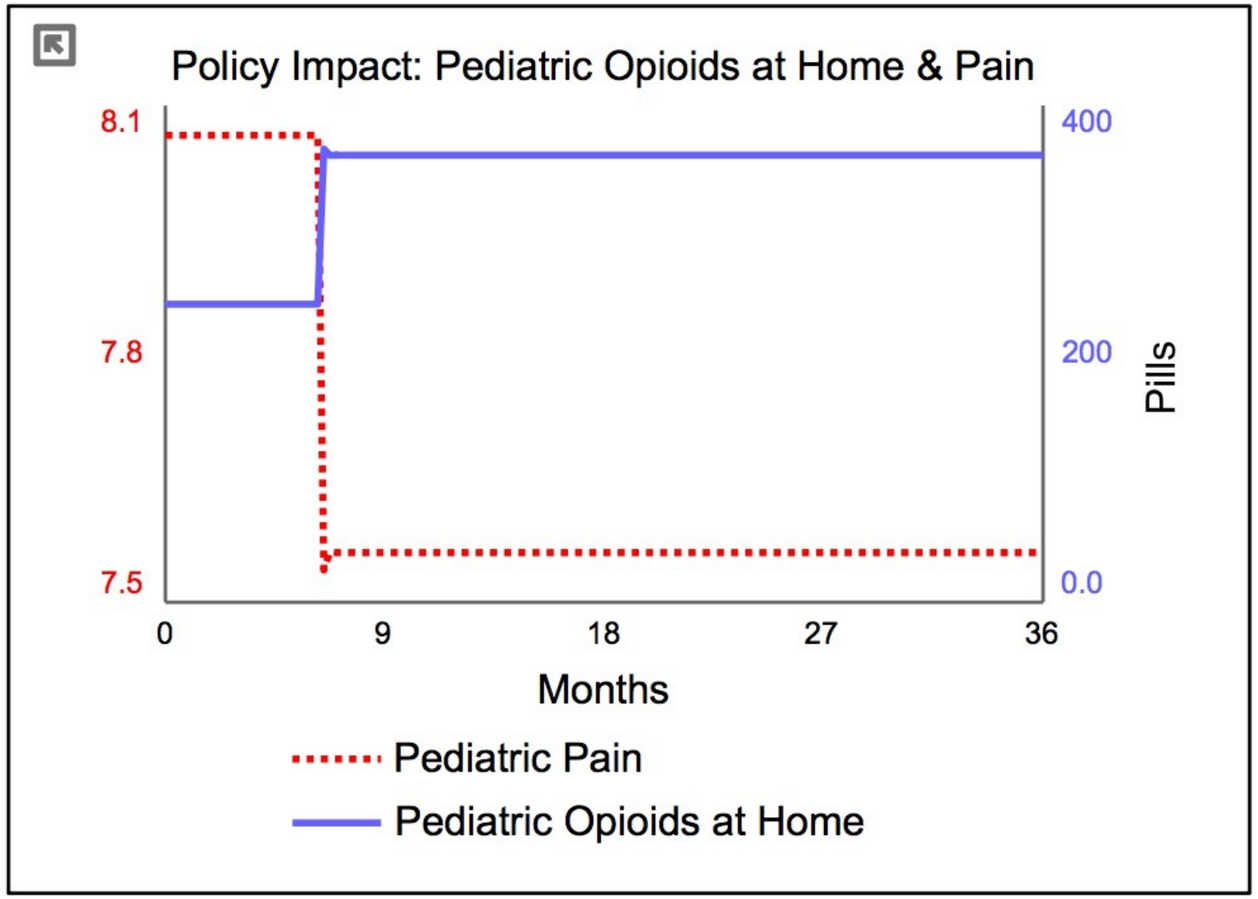
Trading off ***Between*** the INDIVIDUAL vs POPULATION level

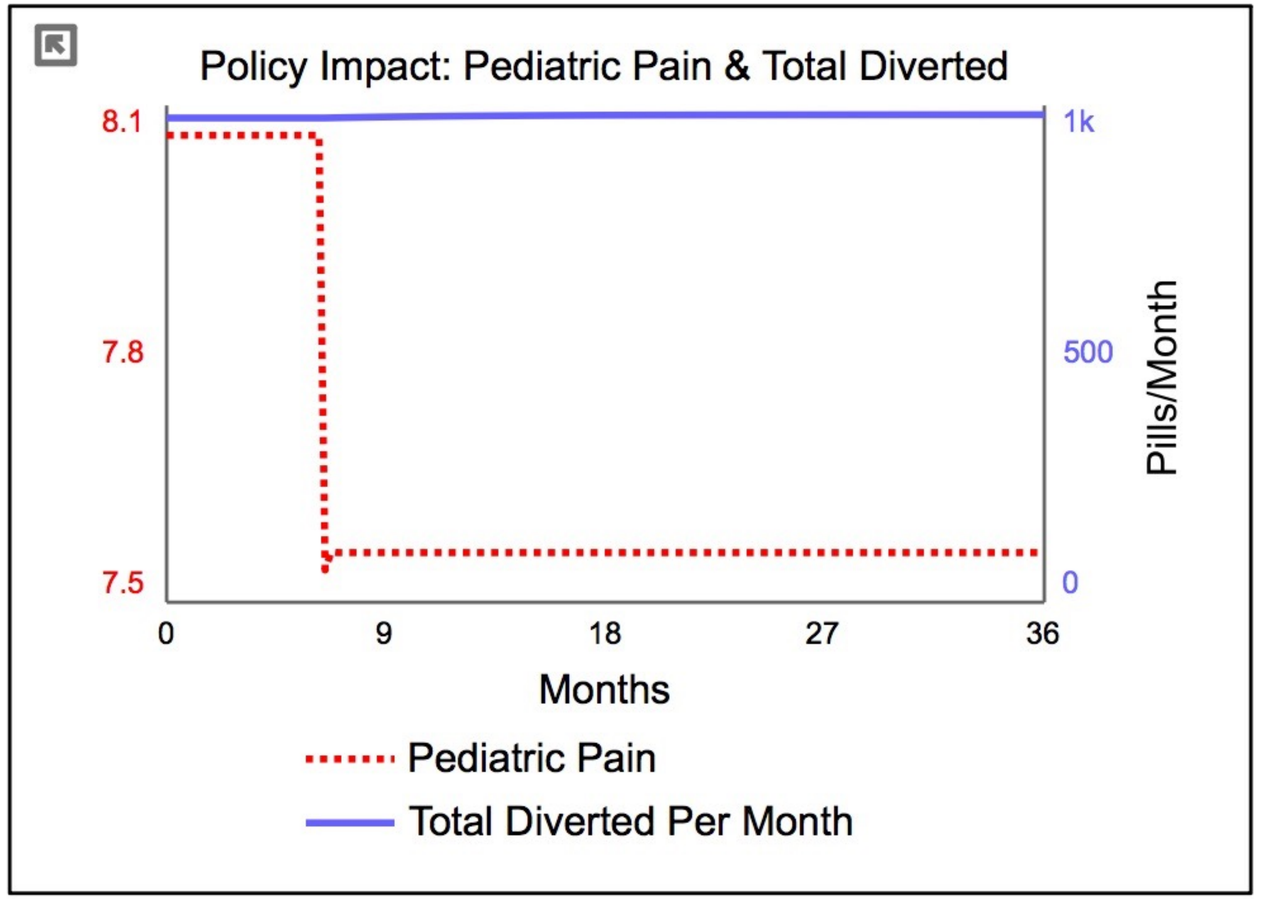
Potential BENEFITS to INDIVIDUAL patients

vs

Potential HARMS to POPULATIONS

Individual vs Population





Individual vs Population

Role for the FDA?
And for labeling?

		Preference Weights	Treatment Options: No treatment	Non-opioid treatment	Opioid treatment
GOALS ???	**INDIVIDUAL**: Reduce pain	???			
	INDIVIDUAL: Avoid misuse	???			
	POPULATION: Curb epidemic	???			
	POPULATION: Reduce deaths	???			

↖ ↑ ↗

What platform to advocate for best pain management practices?

What data & modeling informs the population analysis?

Individual vs Population

Role for the FDA?
And for labeling?

		Preference Weights	Treatment Options: No treatment	Non-opioid treatment	Opioid treatment
GOALS ???	**INDIVIDUAL**: Reduce pain	???	**LABELING**		
	INDIVIDUAL: Avoid misuse	???	Labeling should be focused on individual level considerations and guidance		
	POPULATION: Curb epidemic	???			
	POPULATION: Reduce deaths	???			

Individual vs Population

			Treatment Options		
		Preference Weights	No treatment	Non-opioid treatment	**Opioid treatment**
GOALS ???	**INDIVIDUAL**: Reduce pain	**???**	**LABELING** Labeling should be focused on individual level considerations and guidance		
	INDIVIDUAL: Avoid misuse	**???**			
	POPULATION: Curb epidemic	**???**			
	POPULATION: Reduce deaths	**???**			

Conclusions

- **Narrow Depictions of the Situation and Problems are Ethically Problematic (*Truthfulness*)**
  - The ethical framework for considering pediatric opioid policy should start with a full depiction of the current situation, identifying the various problems that are driving the opioid epidemic

Conclusions

- **Simplistic Thinking at the Population Level is Ethically Problematic (*Truthfulness*)**

  - While the individual deliberation of the pros and cons of opioid therapy for severe pain is demanding, the deliberation regarding population level implications is orders of magnitude more complicated and less certain

  - The pursuit of beneficence and non-maleficence is still important, yet we need to remain aware of our uncertainty about which actions optimize these goals

Conclusions

- **Solving Population Level Problems on the Backs of Vulnerable Individuals Is Ethically Problematic (*Justice*)**
  - The needs of children in severe pain cannot be lost in efforts to restrict access to opioids in order to curb the opioid epidemic (efforts that are likely to have a small impact anyway)

Conclusions

- **Expanding the purpose of labeling beyond individual-level guidance to include population-level considerations erodes patient autonomy**

  - Labeling should be exclusively focused on providing the highest level of individual-level guidance regarding effective and safe practice

Thank you

The Challenges of Conducting Opioid Clinical Trials In Pediatrics

Steven J. Weisman, MD
Jane B. Pettit Chair in Pain Management
Children's Hospital of Wisconsin
Professor of Anesthesiology and Pediatrics
Medical College of Wisconsin
Milwaukee, WI

Children's Hospital of Wisconsin

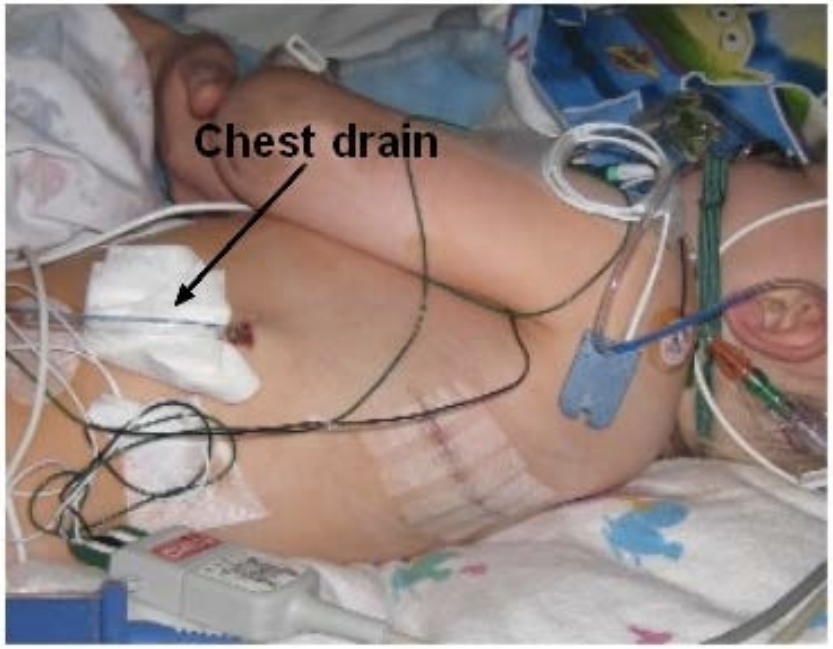
Medical College of Wisconsin

Objectives

- Review challenges of selecting and enrolling patients to participate in opioid trials
- Discuss model trial designs for opioid trials
- Discuss the inherent risks of investigators conducting opioid trials in children

Why Is This Important?

3.5 kg baby born with a large left congenital pulmonary adenomatous malformation who underwent lateral thoracotomy for resection. Pain was initially managed with a thoracic epidural catheter. The endo-tracheal tube was removed and the baby is ready to begin oral analgesia. What is the safe and effective dose of oxycodone to administer to this baby, who is already receiving acetaminophen and ketorolac (off-label) and has pain scores of 8/10?



Why do we not have sound scientific data on the efficacy and safety of opioid analgesics in pediatric patients?

Analgesics Approved For Kids(US)

Acetaminophen, Aspirin, NSAIDs

- Oral APAP (birth-adult)
- IV APAP (≥2 y)
- ASA
- Ibuprofen (≥ 6 m)

JIA indication (not pain per se)

- Celecoxib
- Diflunisal
- Etodolac XL
- Indomethacin
- Ketorolac
- Mefenamic acid
- Meloxicam
- Naproxen
- Oxaprozin
- Tolmetin
- [Rofecoxib was on the list]

Opioids

- Fentanyl transdermal (≥2 y)
- OxyContin (>11 y)
- Fentanyl citrate injection
- Buprenorphine injection
- Meperidine

Combination Products

- Codeine/APAP (≥ 3 y)
- Hydrocodone/APAP (≥2 y)
- Oxycodone/Ibuprofen
- Pentazocine/APAP
- Dihydrocodeine/ASA/Caffeine
- Codeine/ASA/Butalbital/Caffeine
- Pentazocine/Naloxone
- Carisoprodol/ASA/Codeine
- Butalbital/APAP
- Butalbital/APAP/Caffeine

Children As Special Populations

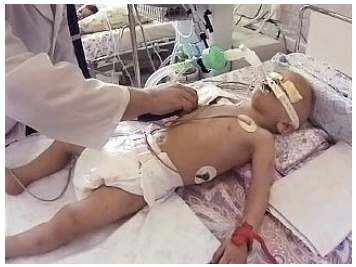
- Neonates/Infants

- Children/Adolescents
- Patients with developmental delay/ cognitive impairment

- Pregnancy/Breast feeding women

Population Challenges

- Critically ill patients



- Violence injured

- Substance abusing patients

- Immigrants/non-native speaking families

What Children Can We Study For Acute Pain Trials?

2012 Surgery Data from all HCUP States

All surgeries

		# of cases ambulatory surgery	# of cases inpatient surgery
All surgeries		8,358,909	7,915,119
Age group	<1	68,691	875,887
	1-17	846,400	235,459
	18-44	2,121,529	2,065,708
	45-64	2,791,153	2,191,899
	65-84	2,258,342	2,179,585
	85+	271,817	365,346
	Missing	977	1,235

Ref: HCUP Clinical Classifications Software for Services and Procedures. Healthcare Cost and Utilization Project (HCUP). 2012. Agency for Healthcare Research and Quality, Rockville, MD. http://www.hcup-us.ahrq.gov/toolssoftware/ccs_svcsproc/ccssvcproc.jsp. Accessed August 20, 2016

There Are Very Few Potential Study Patients

2012 Surgical procedures **Discharged Hospitalized patients**

Age group = <1			Total number of discharges
Rank	CCS principal procedure category and name		
1	115	Circumcision	891,863
5	9	Other OR therapeutic nervous system procedures	4,902
6	99	Other OR gastrointestinal therapeutic procedures	3,477
7	96	Other OR lower GI therapeutic procedures	3,463
9	85	Inguinal and femoral hernia repair	2,995
12	78	Colorectal resection	2,157
13	75	Small bowel resection	1,945
14	112	Other OR therapeutic procedures of urinary tract	1,712
Age group = 1-4			**Total number of discharges**
Rank	CCS principal procedure category and name		
1	30	Tonsillectomy and/or adenoidectomy	7,165
2	9	Other OR therapeutic nervous system procedures	3,715
3	80	Appendectomy	3,655
4	148	Other fracture and dislocation procedure	3,610
5	33	Other OR therapeutic procedures on nose, mouth and pharynx	3,507
6	112	Other OR therapeutic procedures of urinary tract	3,310

Discharge diagnoses from the HCUPnet database survey of inpatient discharge diagnoses. **Candidate procedures for acute pain trials are highlighted.**

Ref: HCUP Clinical Classifications Software for Services and Procedures. Healthcare Cost and Utilization Project (HCUP). 2012. Agency for Healthcare Research and Quality, Rockville, MD. http://www.hcup-us.ahrq.gov/toolssoftware/ccs_svcsproc/ccssvcproc.jsp. Accessed 08/20/16.

There Are Very Few Potential Study Patients

2012 Surgical Procedures **Ambulatory Surgery** patients

Age group = <1			Total number of discharges
Rank	**CCS all-listed procedure category and name**		
1	23	Myringotomy	26,402
2	118	Other OR therapeutic procedures, male genital	12,937
3	115	Circumcision	7,175
4	85	**Inguinal and femoral hernia repair**	**7,062**
5	109	**Procedures on the urethra**	**2,835**
6	33	**Other OR therapeutic procedures on nose, mouth and pharynx**	**2,687**
Age group = 1-17			**Total number of discharges**
Rank	**CCS all-listed procedure category and name**		
1	30	**Tonsillectomy and/or adenoidectomy**	**263,797**
2	23	Myringotomy	201,556
3	118	**Other OR therapeutic procedures, male genital**	**38,870**
4	33	**Other OR therapeutic procedures on nose, mouth and pharynx**	**31,269**
5	160	**Other therapeutic procedures on muscles and tendons**	**30,702**
6	161	**Other OR therapeutic procedures on bone**	**30,131**
7	85	**Inguinal and femoral hernia repair**	**27,306**

Discharge diagnoses from the HCUPnet database survey of inpatient discharge diagnoses. **Candidate procedures for acute pain trials are highlighted.**

Ref: HCUP Clinical Classifications Software for Services and Procedures. Healthcare Cost and Utilization Project (HCUP). 2012. Agency for Healthcare Research and Quality, Rockville, MD. http://www.hcup-us.ahrq.gov/toolssoftware/ccs_svcsproc/ccssvcproc.jsp. Accessed August 20, 2016.

Study Recruitment: PRN-Pain

(Pediatric Research Network for Pain)

- Alberta Children's Hosp
- British Columbia Children's Hosp
- Children's Hosp Atlanta
- Children's Hosp Boston
- Children's Hosp Colorado
- Children's Hosp LA
- Children's Hosp Minnesota
- Children's Hosp of Eastern Ontario
- Children's Hosp Philadelphia
- Children's Hosp Seattle
- Children's Hosp St. Louis
- Children's Hosp Stanford University
- Children's Hosp Wisconsin
- Children's Med Ctr Dallas
- Children's Mercy Hosp
- Children's National Med Ctr
- Cincinnati Children's Med Ctr
- Connecticut Children's Med Ctr
- Duke Children's Hosp
- Hosp for Sick Children
- IWK Health Centre
- Johns Hopkins Children;s Ctr
- Kosair Children's Hosp
- Lurie Children's Hosp
- Mattel Children's Hosp
- Mayo Clinic
- Phoenix Children's Hosp
- Riley Hosp for Children
- Shriners Hosp for Children Portland
- St. Jude's Children's Hosp
- Texas Children's Hosp

Chronic Pain in Adults

Table 2. Organization of Chronic Pain Disorders to Be Included in the AAPT*

Peripheral and central nervous systems
Peripheral neuropathic pain
Central neuropathic pain
Musculoskeletal pain system
Osteoarthritis
Other arthritides (eg, rheumatoid arthritis, gout, connective tissue diseases)
Musculoskeletal low back pain
Myofascial pain, chronic widespread pain, and fibromyalgia
Other predominantly musculoskeletal pain
Orofacial and head pain system
Headache disorders*
Temporomandibular disorders
Other orofacial pain
Visceral, pelvic, and urogenital pain
Visceral pain: abdominal, pelvic, and urogenital pain
Disease-associated pains not classified elsewhere (eg, pain associated with active cancer, with sickle cell disease, or with Lyme disease)

*AAPT will not develop diagnostic criteria for headache condition, because the ICHD-2 already exists and provides an evidence-based classification that is highly consistent with the AAPT template.

Fillingim, et al **The Journal of Pain, Vol 15, No 3 (March), 2014: pp 241-249**
(ACTTION–American Pain Soc. Pain Taxonomy)

Chronic Pain In Children

Table 2
Summary of prevalence rates by pain type.

Pain type	Prevalence range	Median quality criteria met	Age differences	Sex differences	Psychosocial/demographic factors associated with increased prevalence
Headache	8–82.9%	9	Older > younger	Girls > boys	Presence of anxiety and depression; low self-esteem (girls only); positive family history of headache; low SES (conflicting findings)
Abdominal pain	3.8–53.4%	8	Younger > older	Girls > boys	SES (conflicting findings); emotional symptoms; school stress
Back pain	13.5–24%	7	Older > younger	Girls > boys	Emotional symptoms (conflicting findings); relation between back pain and sociodemographic/psychosocial factors is unclear
Musculoskeletal/ limb pain	3.9–40%	7	Older > younger	Girls > boys	Feeling sad (girls only)
Multiple pains	3.6–48.8%	8	Unclear	Girls > boys	Chronic health problems; frequent change of residence; frequent television watching; poor school performance; fewer interactions with peers
Other/general pain	5–88%	8	Unclear – possible age × sex interaction	Girls > boys	Poor self-rated health; feeling low or irritable; bad temper; feeling nervous

SES, socioeconomic status.

Children's Hospital of Wisconsin New Clinic Patients:

500/year

30% Headache

20% Recurrent Abdominal Pain

24% Back/generalized pain

15% Miscellaneous pain problems

6% Complex Regional Pain Syndrome

5% Cancer Pain/Sickle Cell Pain

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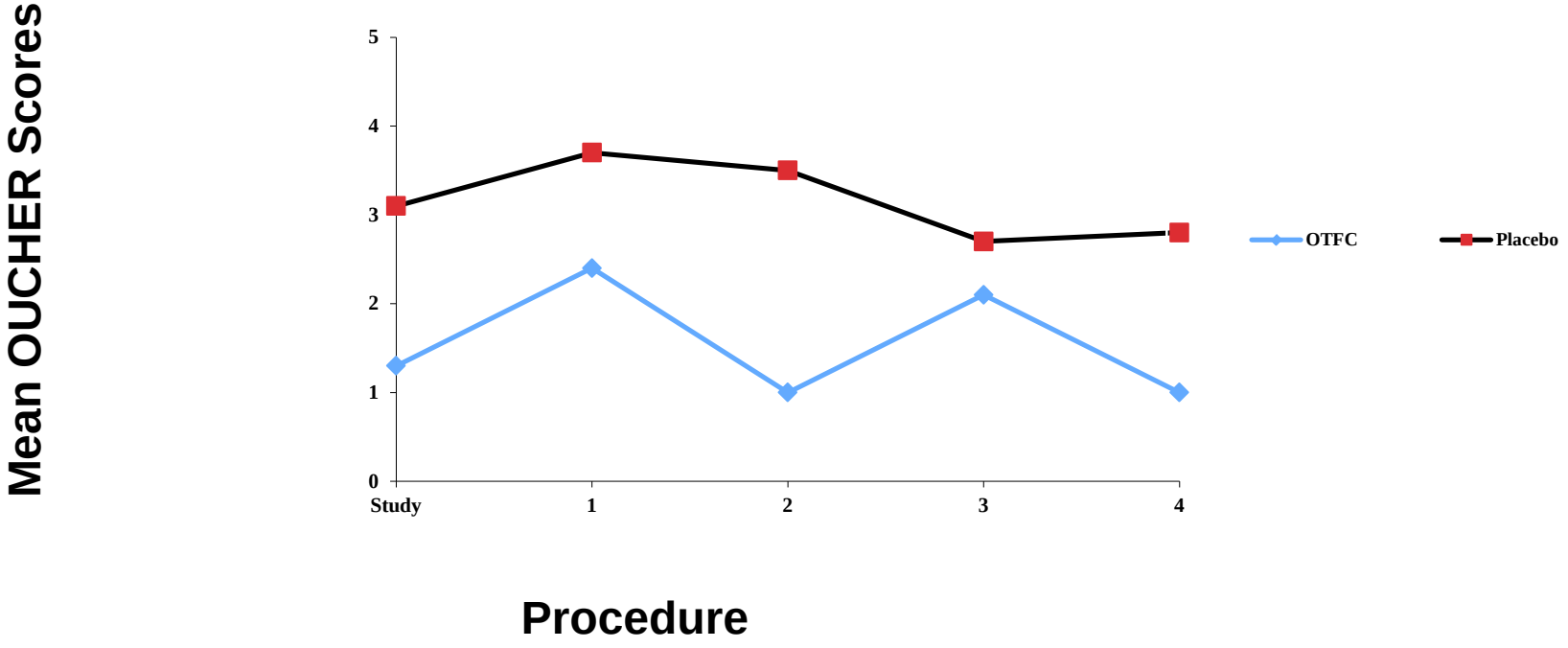
Proposed Dimensions Pain Taxonomy

- Dimension 1: Event or Core Criteria
  - Children < 8 yrs cannot offer self-report as means to define pain type; Acute v. Chronic
    - Acute illness (appendicitis, strep throat)
    - Trauma (penetrating, burn, fracture)
    - Surgery (T & A, hernia)
    - Procedures (needles, biopsy)
    - Disease (Cancer, infection, arthritis, Sickle Cell)
    - Treatment-related (ChemoTx, RadiationTx, Mab therapy)
    - Ischemic pain (Compartment syndromes)

Fillingim, RB, et al The ACTTION-American Pain Society Pain Taxonomy J of Pain 2014;15: 241-249 (Analgesic, Anesthetic, and Addiction Clinical Trials Translations Innovations Opportunities and Networks (ACTTION))

Dimension 2: Host/Risk Factors

- Susceptible populations may have altered acute pain responses (neonates/premies)
- Prior pain experience



Weisman S.J., et al. The Consequences of Inadequate Analgesia During Painful Procedures in Children. Arch Pediatr Adol Med 152:147-149, 1998.

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Dimension 3: Pain Quality

- In children, this is not considered an acute pain domain (PedIMMPACT J of Pain, 2008)
- Impossible to characterize in many of these special populations (language, ICU, developmental delay)

Dimension 4: Environmental Context

- Acute/chronic associated with cancer treatment
- Acute pain with injuries from violence
- Immigrant/refugee population with acute injuries

Dimension 5: Pathophysiology

- Largely similar across populations
- Pathophysiology does not necessarily result in pain in pediatric population (ie Diabetic neuropathy)
  - Neonates (Anand and Hickey, NEJM, 1992)
  - Elderly Hip Fractures (Morrison, et al Pain, 2003)

Dimension 6: Impact (Function)

- Children have quite variable baseline functional (developmental) levels
- Emotional responses may be immeasurable in the extremes of age, in the ICU and may vary by culture and milieu

Enrollment Challenges: The 6 P's

- **Parents:** Access for consent; Consent "under the influence"
- **Physicians:** Pediatric providers continue to underestimate pain from procedures and diseases
- **Placebos:** Impossible treatment paradigm
- **Pills:** Formulation of analgesics; PREA
- **Phlebotomy:** Sampling is challenging in pediatrics
- **Pretreatment:** Many studies with opioids require long term prior use that is not prevalent in pediatrics

The Myth of Opioid Use in Children

Diagnostic groups (Opioid use >29days)	N	%
Cancer Care	50	37.88
Cardiac: Surgery	24	18.18
NICU with Surgery; No Ventilation	16	12.12
NICU with Ventilation and Surgery	15	11.36
Cardiac: No Surgery	9	6.82
Ventilated and Surgery	9	6.82
Surgery; No Ventilation	5	3.79
Ventilated and No Surgery	3	2.27
NICU with Ventilation; No Surgery	1	0.76
TOTAL	132	1.61 (of all patients)

8,179 unique patients; 3559 (43.5%) received opioids

Walco, Gove, Phillips, Weisman, Submitted

Completed Chronic Opioid Trials

- Transdermal Fentanyl (2-16 years):
  - 66 sites; 10 countries
  - 199 patients/173 completed

- Oxycodone ER (6-16 years):
  - 101 sites; 15 countries (only 44 enrolled)
  - 173 patients/155 completed
  - Permitted enrollment with 5 days exposure
  - 2034 screened for eligibility rate of 8%
  - **4 YEARS!!**
  - Target 40% age 6-11but only 27/155; 17.4%
  - 89/155 (57.4%) were post-surgical

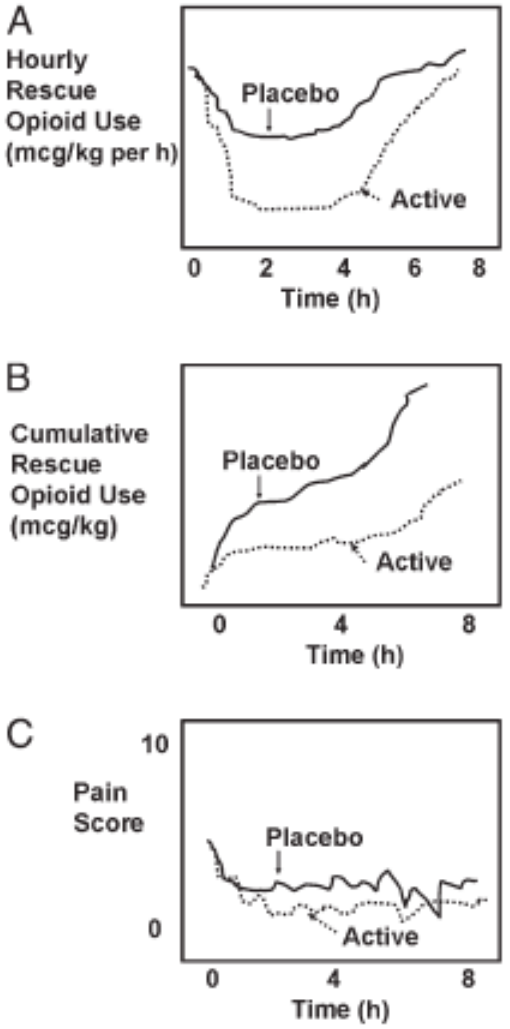
Analgesic Clinical Trial Designs

- **PK, dose response, safety (toxicity):** All ages
- **Efficacy** with known mechanism of action:
  - $<$ 2 yrs required
  - $\geq$ 2 years extrapolate from adult
- **Efficacy** with unknown: required all ages

Berde, et al Pediatrics 2012; 129:354
Kossowsky, Donado, Berde Anesthesiology 2015; 122:150

How We Can Conduct Pediatric Trials

- Immediate-rescue with PCA
- Addresses ethics of placebo exposure
- Can be patient or nurse activated, to allow model for young patients
- NCA use has been extended down to the newborn age
- Usually requires hospitaliza-tion



Children's Hospital of Wisconsin

Medical College of Wisconsin

Inherent Risk to Investigators

- Investigators are advising the drug industry with the hope of helping to design scientifically sound studies in children
- Publicity casts investigators negatively
- Impugns them and their institutions
- Results in retreat from participation
- PRN-Pain group retreated from a plan to study oxycodone for acute pain management in infants 6-24 mo of age

Conclusions

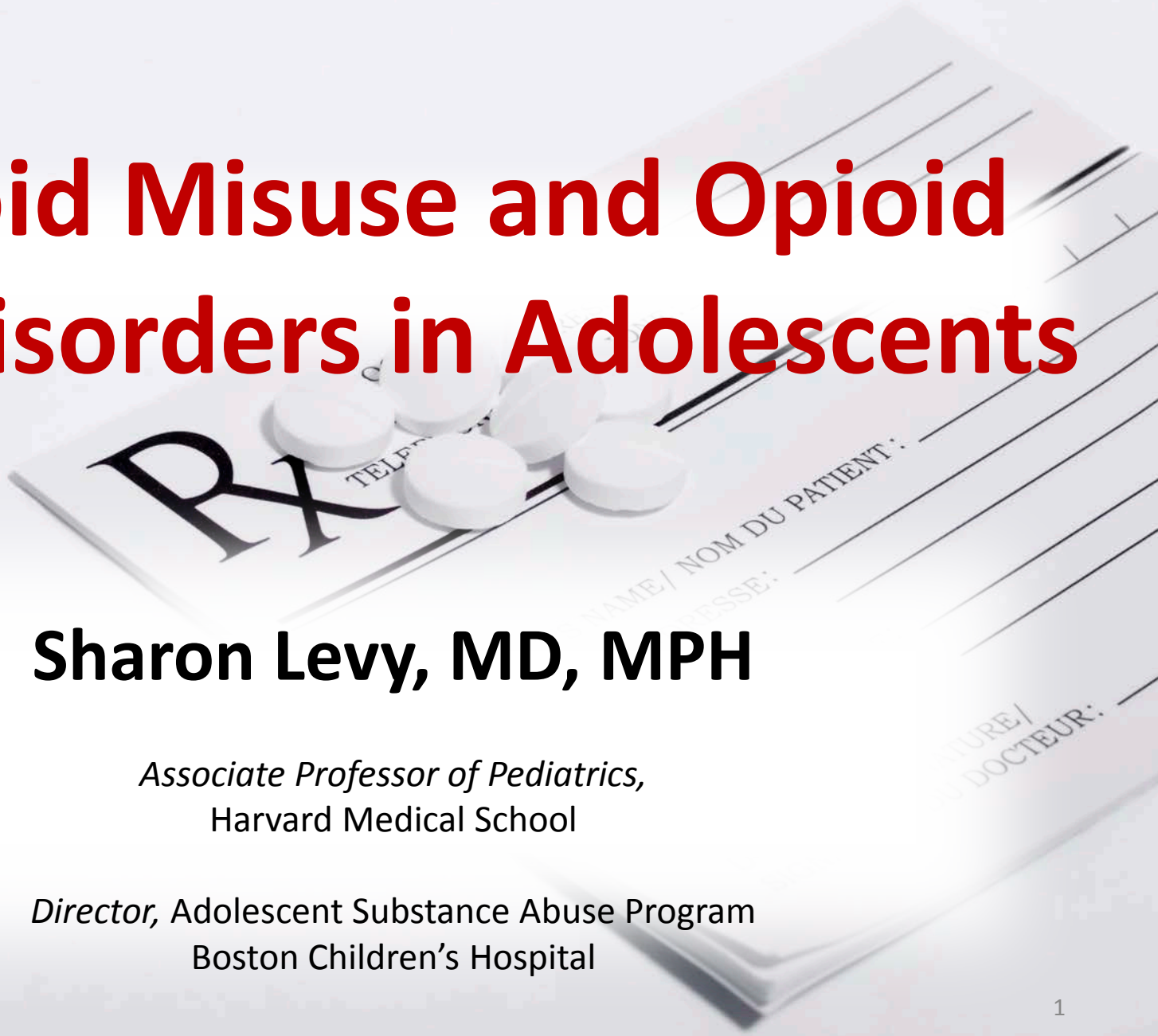
- Clinical trials for opioids in pediatrics have significant challenges
- Patient recruitment is difficult
- The regulatory environment of the FDA results in challenging study design
- There are significant costs, without clear sources of funding, for these projects
- Investigators are sparse and fearful of negative media representation of their work

In The End: Who Suffers?

"If we know that pain and suffering can be alleviated and we do nothing about it, we, ourselves, are tormentors."

– Primo Levi

Opioid Misuse and Opioid Use Disorders in Adolescents



Sharon Levy, MD, MPH

Associate Professor of Pediatrics,
Harvard Medical School

Director, Adolescent Substance Abuse Program
Boston Children's Hospital

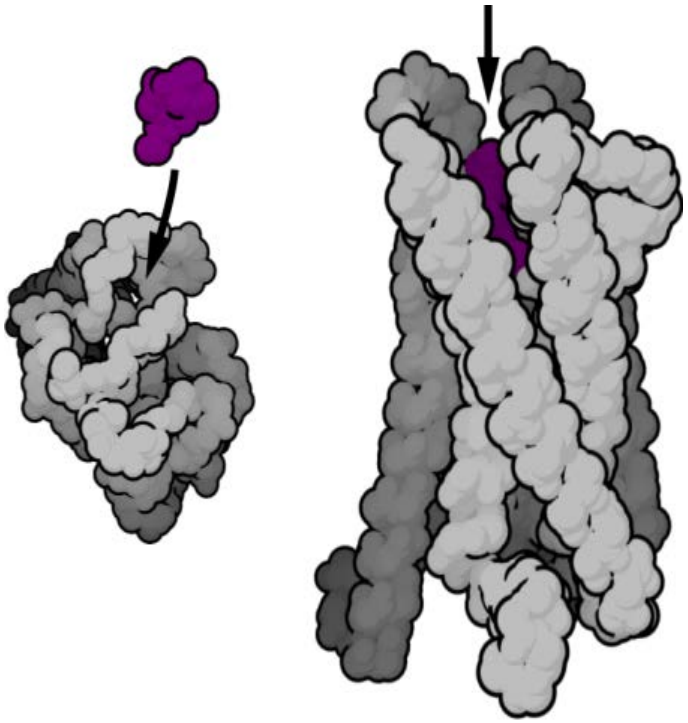
Disclosures

I, Sharon Levy, have no relevant financial or commercial relationships to disclose.

Opiates

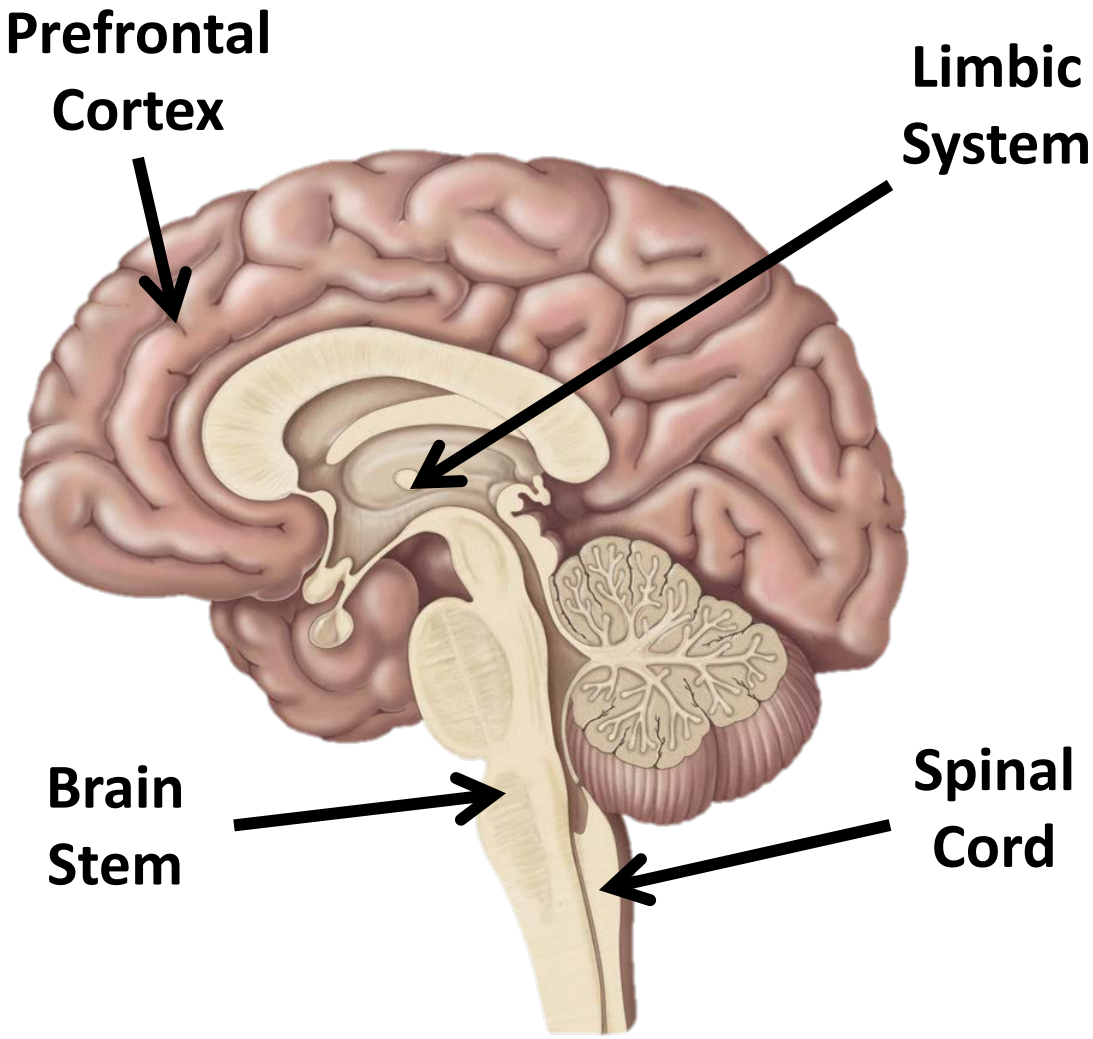
Opioids

Opioid pharmacology



Opioid μ-receptor and agonist

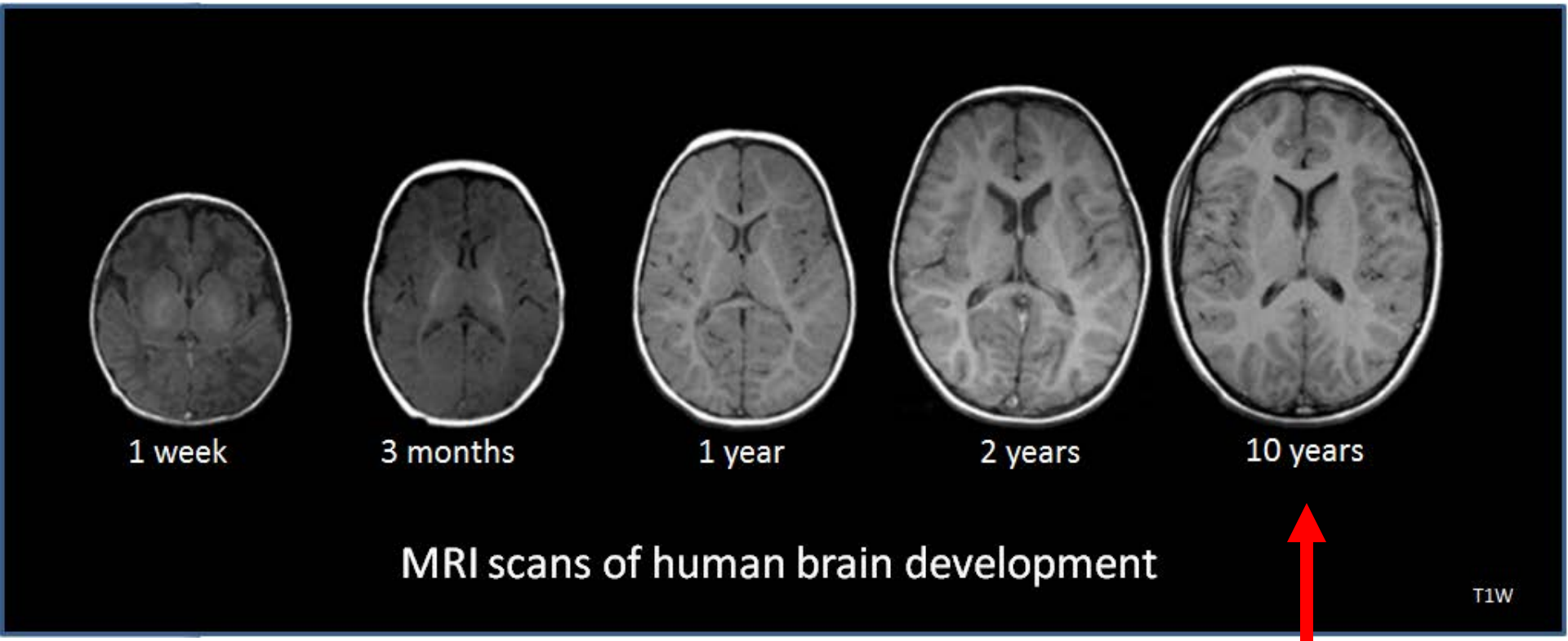
Opioid neurobiology



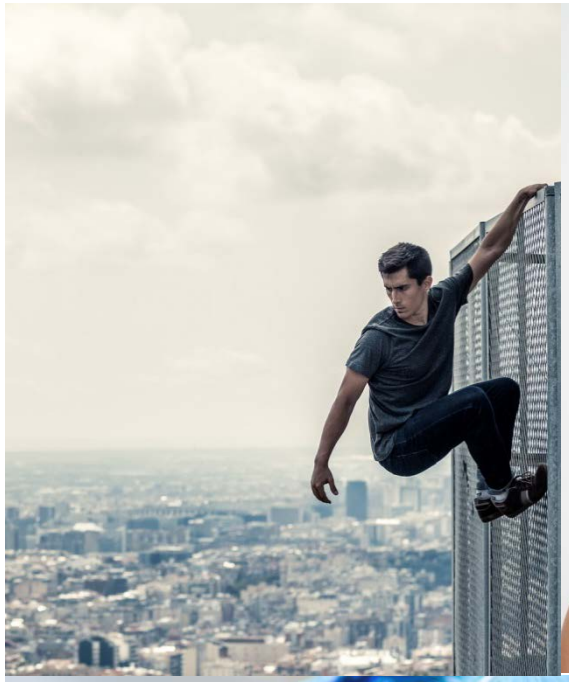
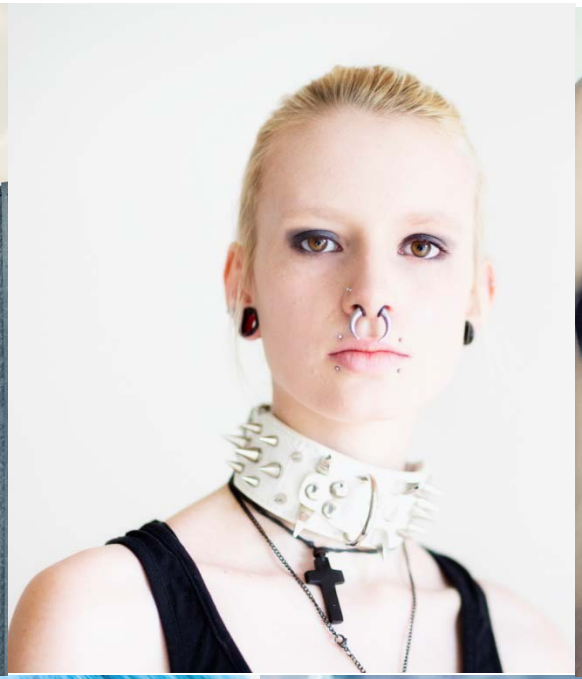
ADDICTION

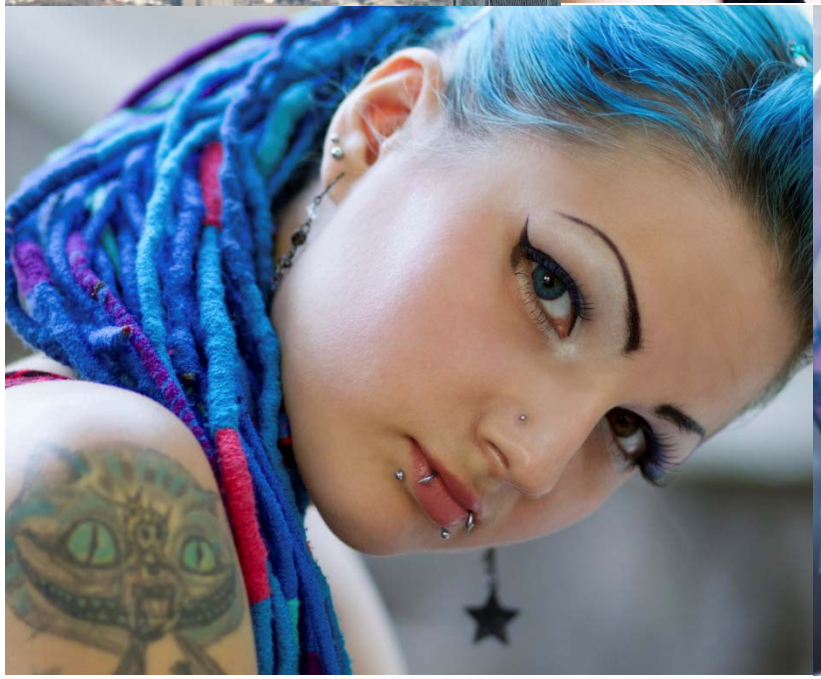
Adolescents are **developmentally primed** to use drugs

Brain weight by age



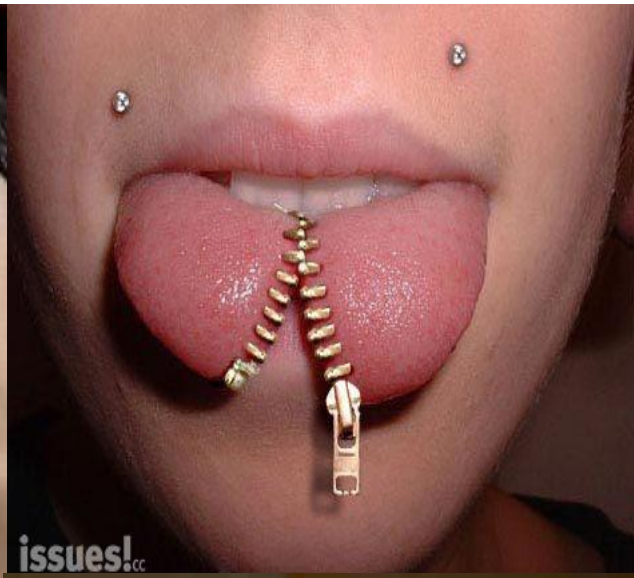
Source: Dekaban, A.S. and Sadowsky, D. *Annals of Neurology*, 4:345-356, 1978
Image retrieved from: http://www.pediatricmri.nih.gov/nihpd/info/image_gallery.html#





issues!.cc


issues!.cc


My Fashiony

Neuron growth in brain development

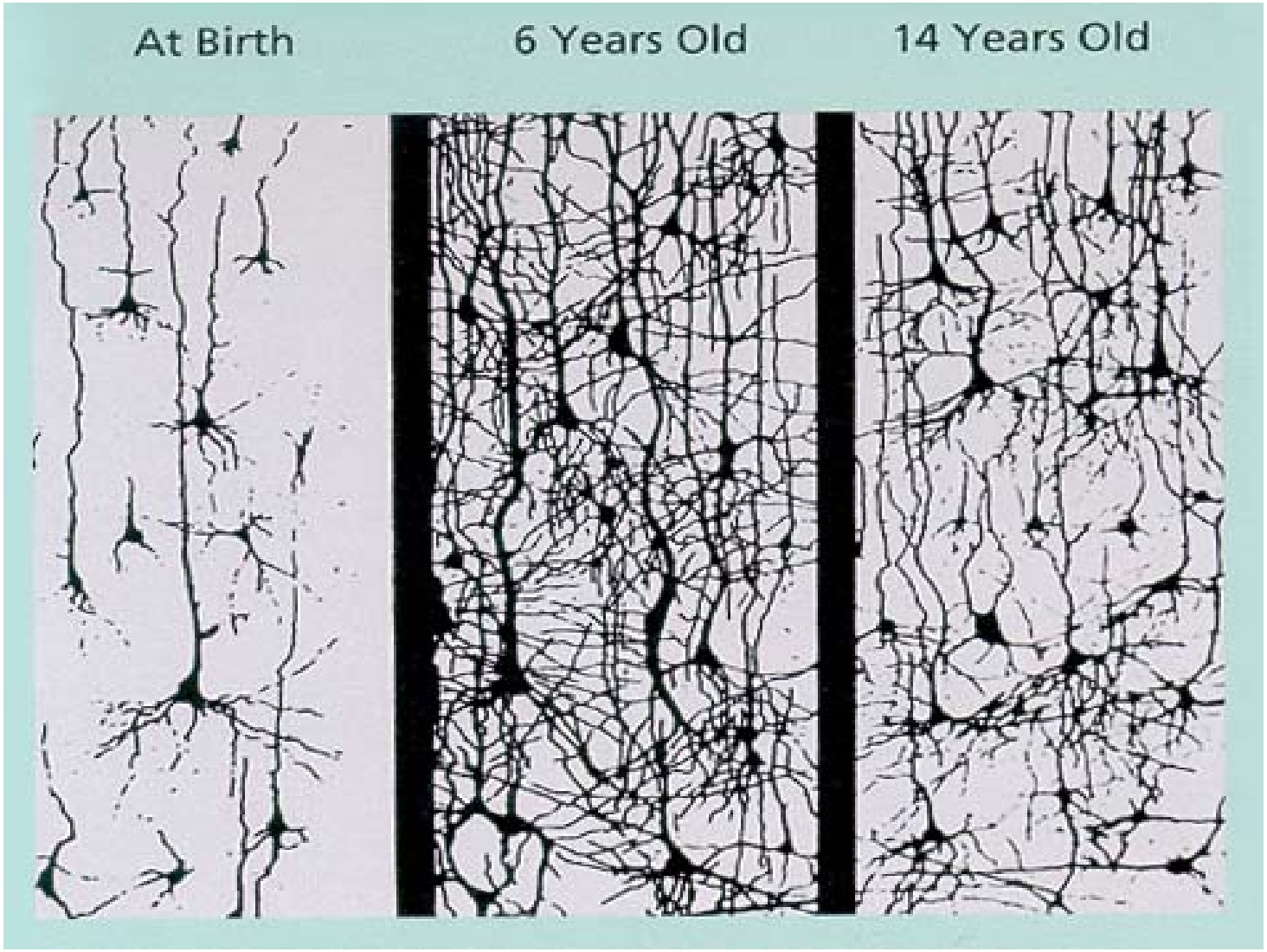
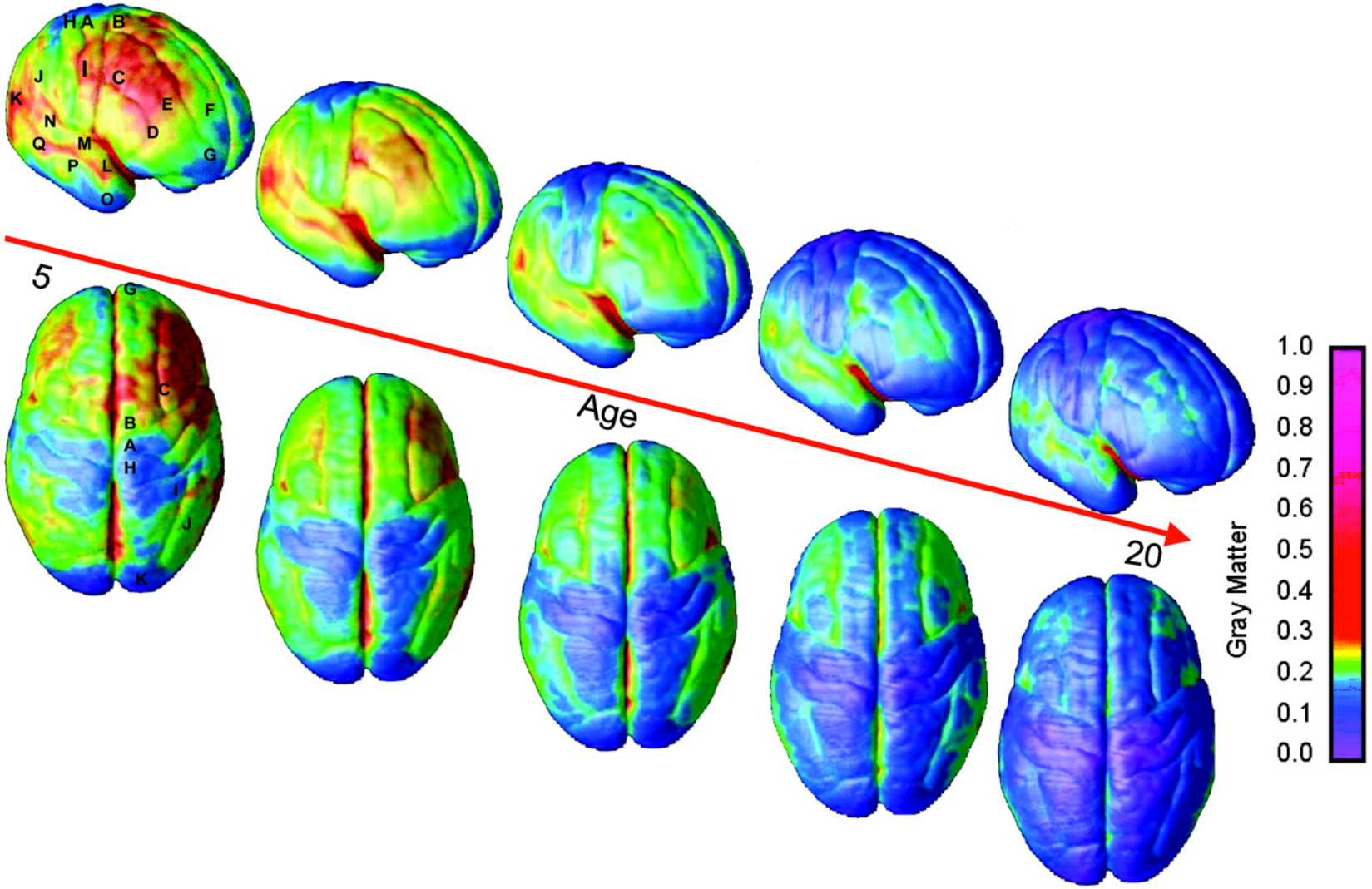
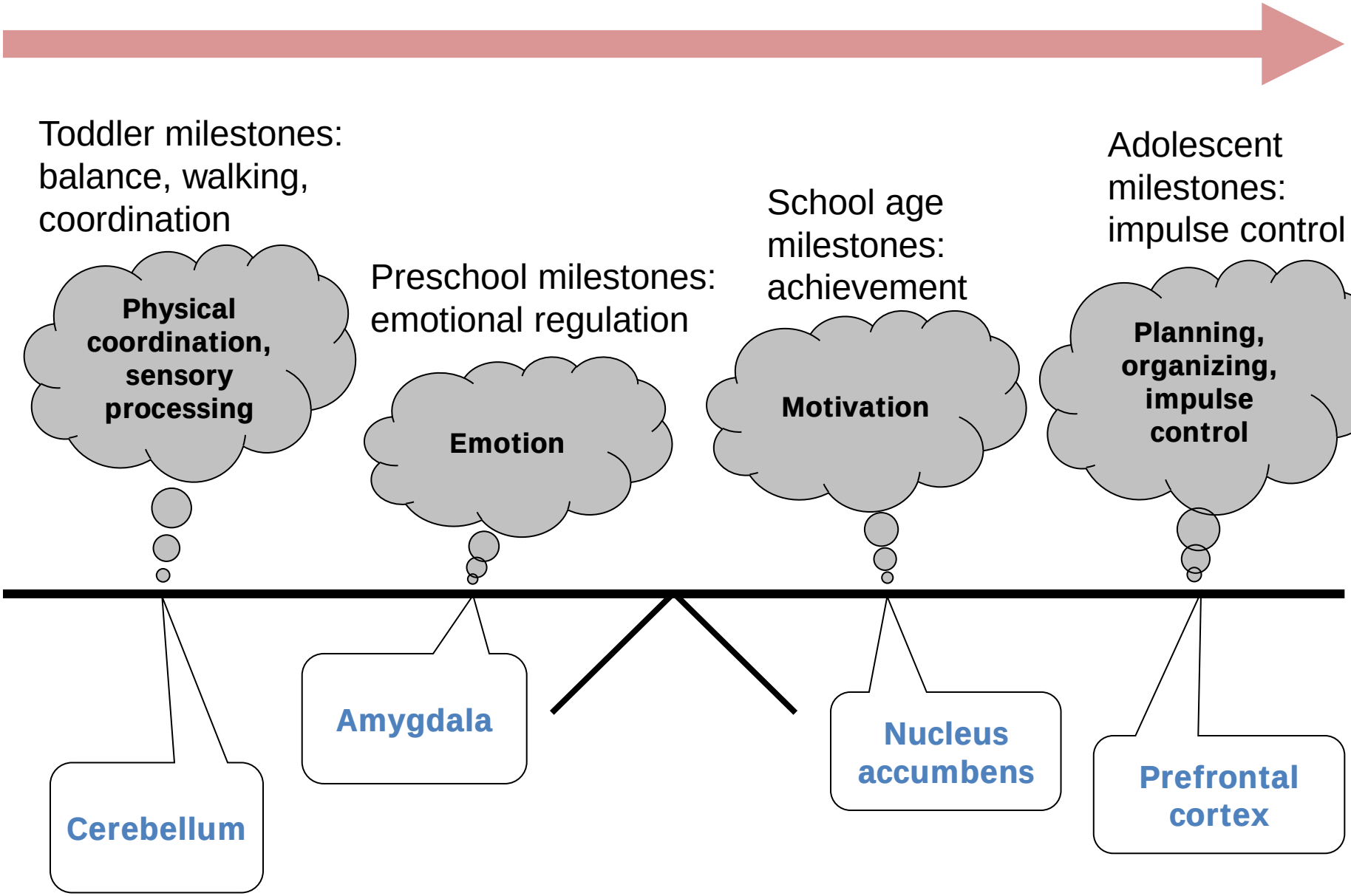


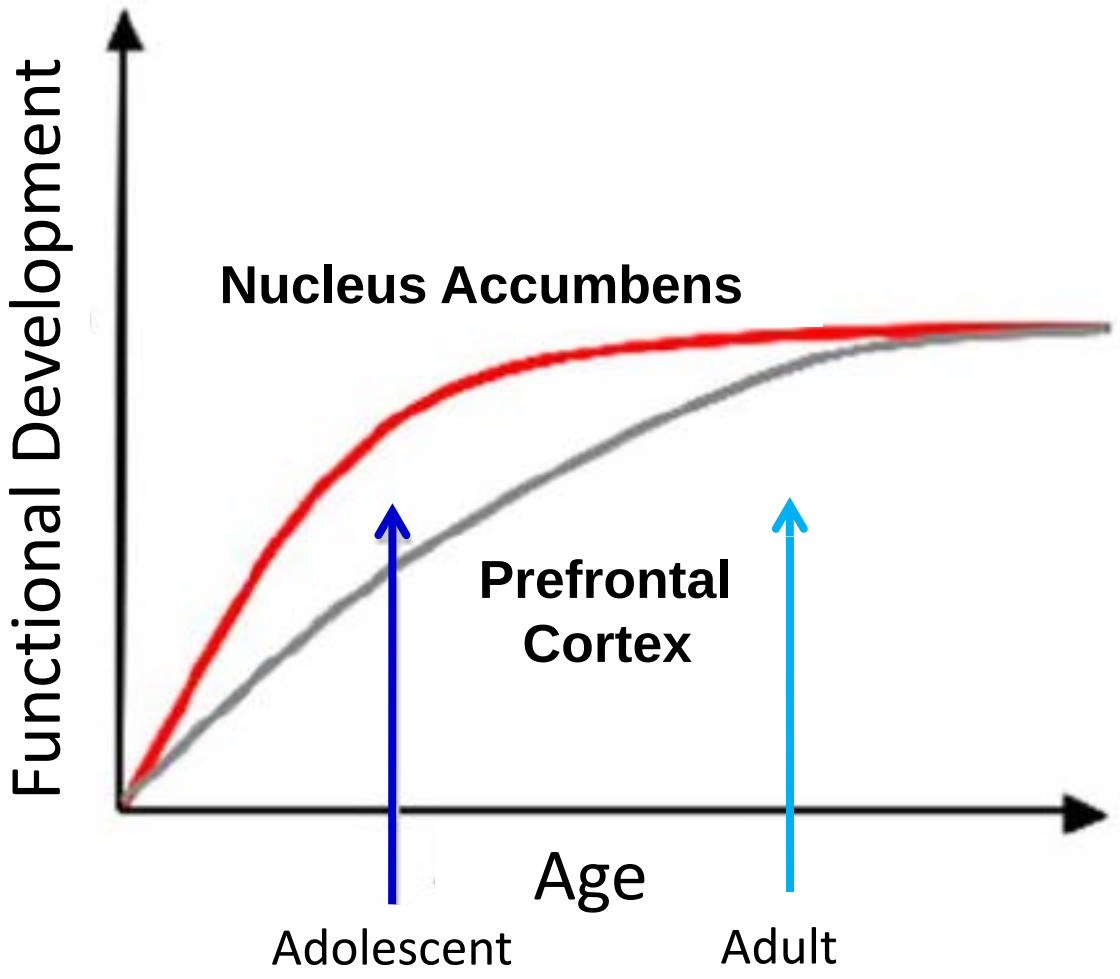
Image retrieved from: http://etec.ctlt.ubc.ca/510wiki/Brain-based_Learning



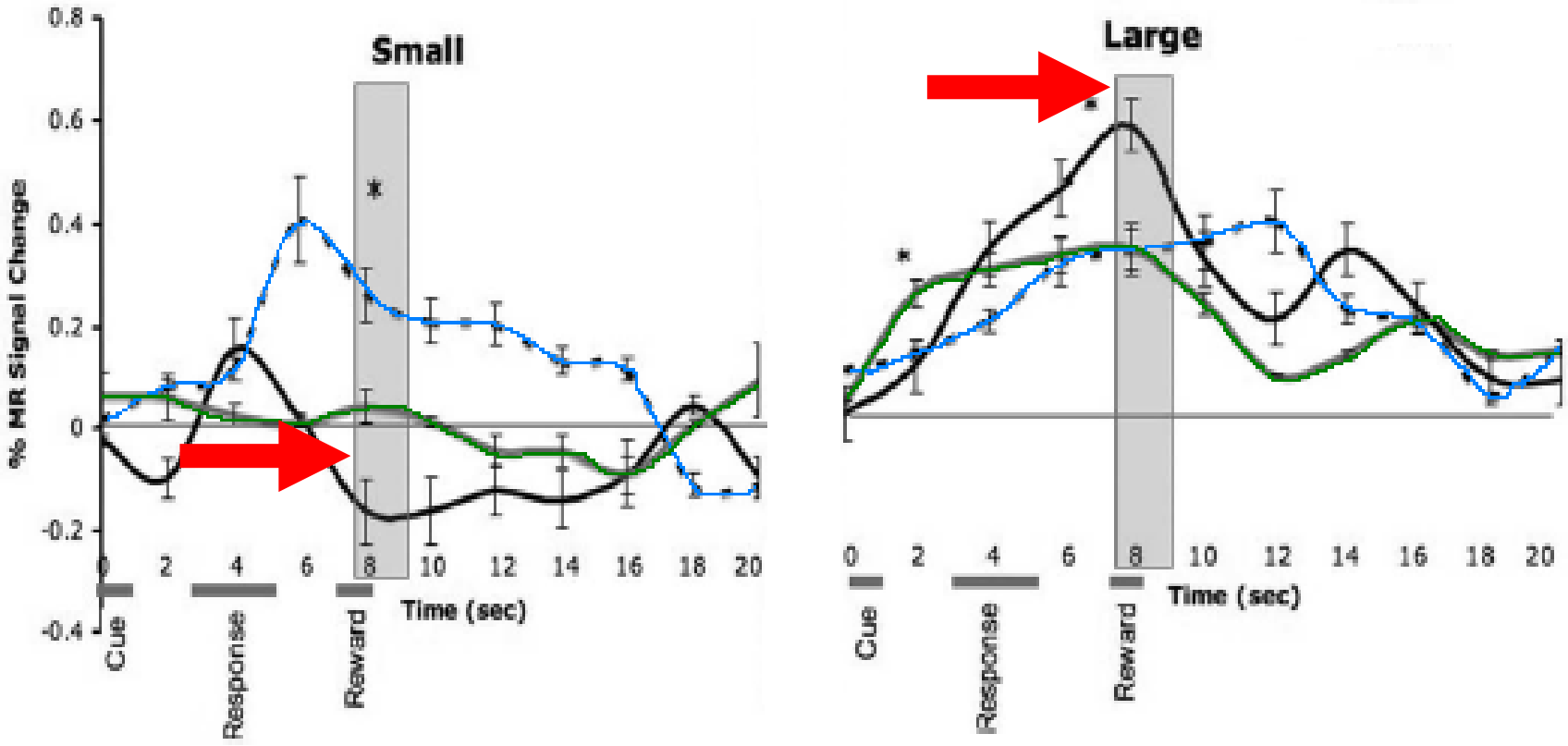
Source:Copyright (2004) National Academy of Sciences, U.S.A
Gogtay et al. PNAS. 2004:101(21):8174-8179. Retrieved on February 17, 2015 from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC419576/figure/fig3/
Permission received from PNAS



Slide adapted from Ken Winters, PhD.



Source: Casey BJ, et al., Development Reviews. 2008; 28: 62-77.



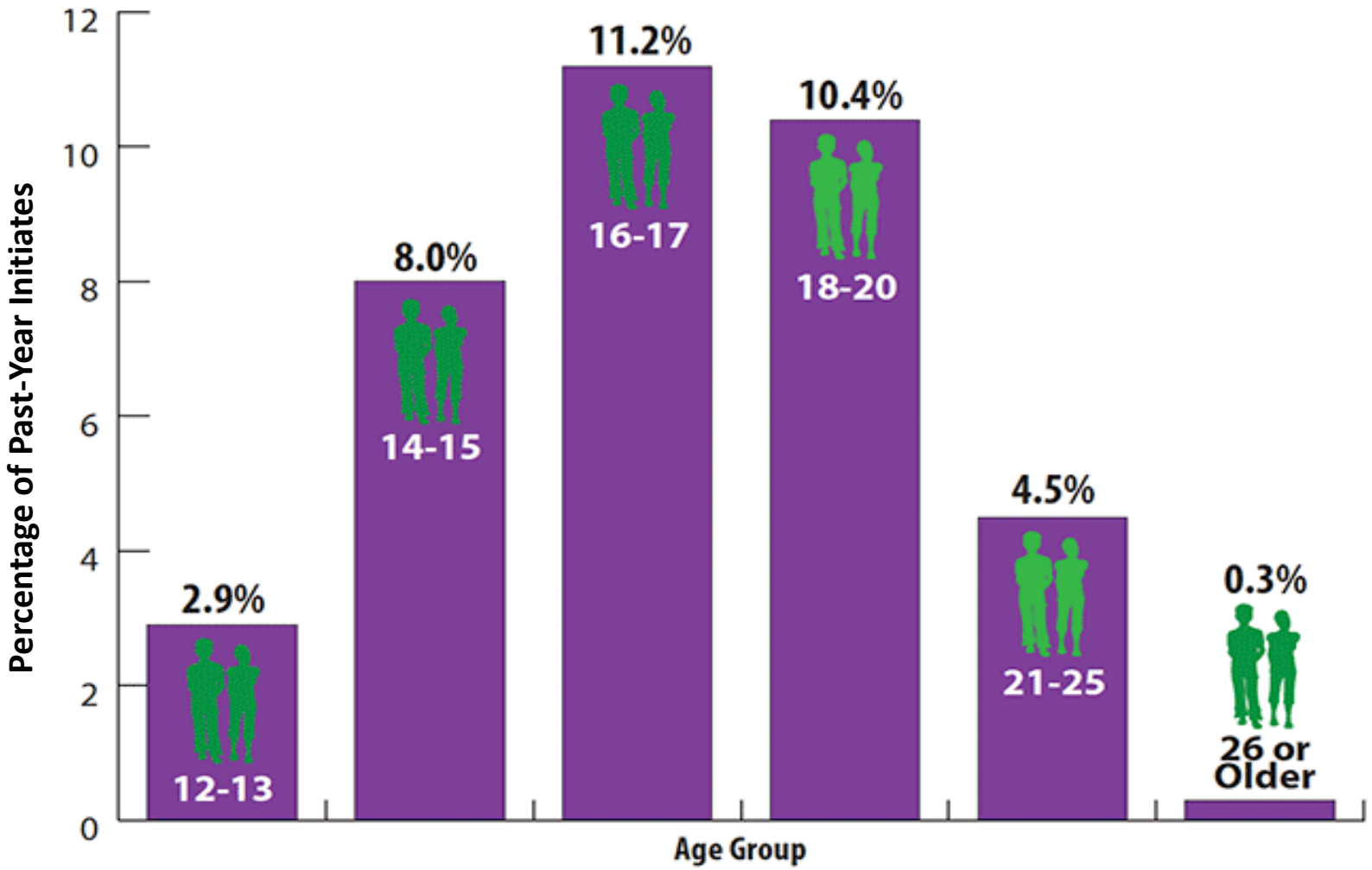
Children, ages 7-11 Teens, ages 13-17 Adults, ages 23-29

Adriana Galvan et al. J. Neurosci. 2006;26:6885-6892

The Journal of Neuroscience

Image retrieved on February 17, 2015, from http://www.drugabuse.gov/publications/teaching-packets/neurobiology-drug-addiction/section-iv-action-cocaine/7-summary-addictive-drugs-activate-reward

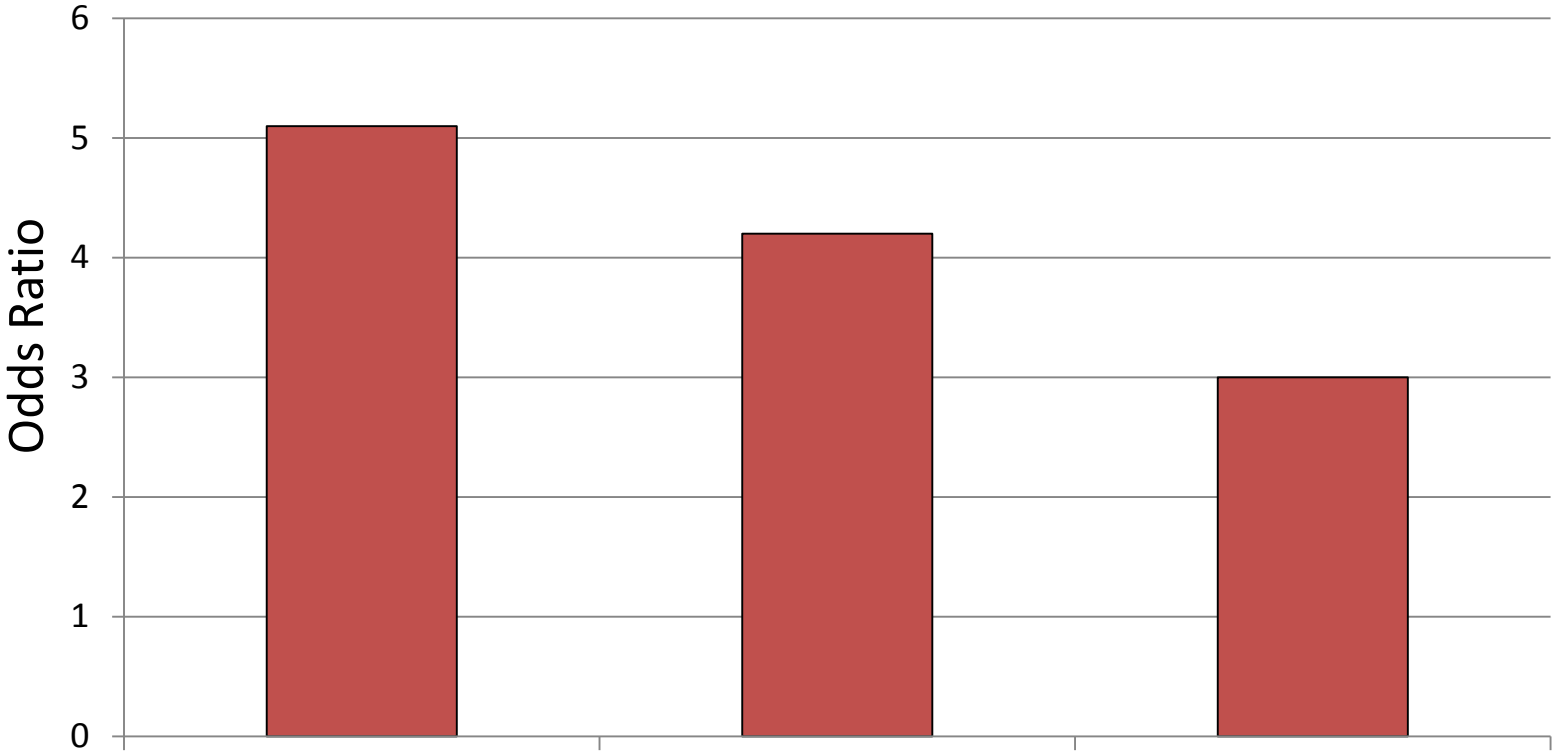
Most drug use starts in adolescence



Source: SAMHSA, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health, 2011 and 2012.

Gateway to opioid misuse

Odds of Prescription Opioid Misuse as a Function of Other Substance Use Behaviors



Source: McCabe SE, West BT, Boyd CJ. Medical Use, Medical Misuse, and Nonmedical Use of Prescription Opioids: Results from a Longitudinal Study. *Pain* 2013 154(5):708-713.

Adolescents are **developmentally vulnerable** to develop substance use disorders

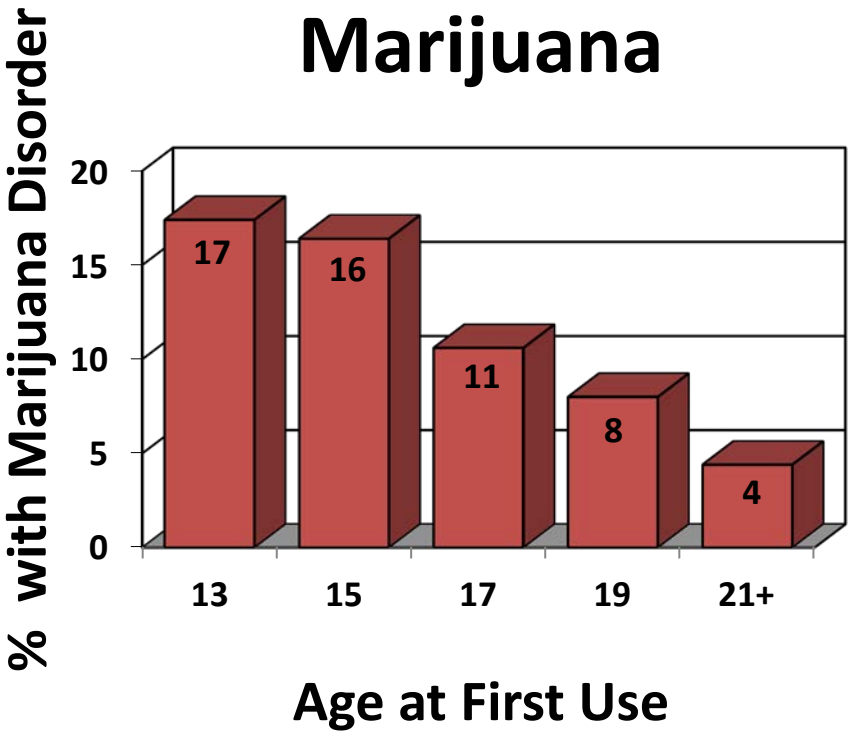
Younger age*

*AOR decreases by 5% each year that non-medical use is delayed

(after one year, **AOR: 0.95** with 95% CI 0.94-0.97)

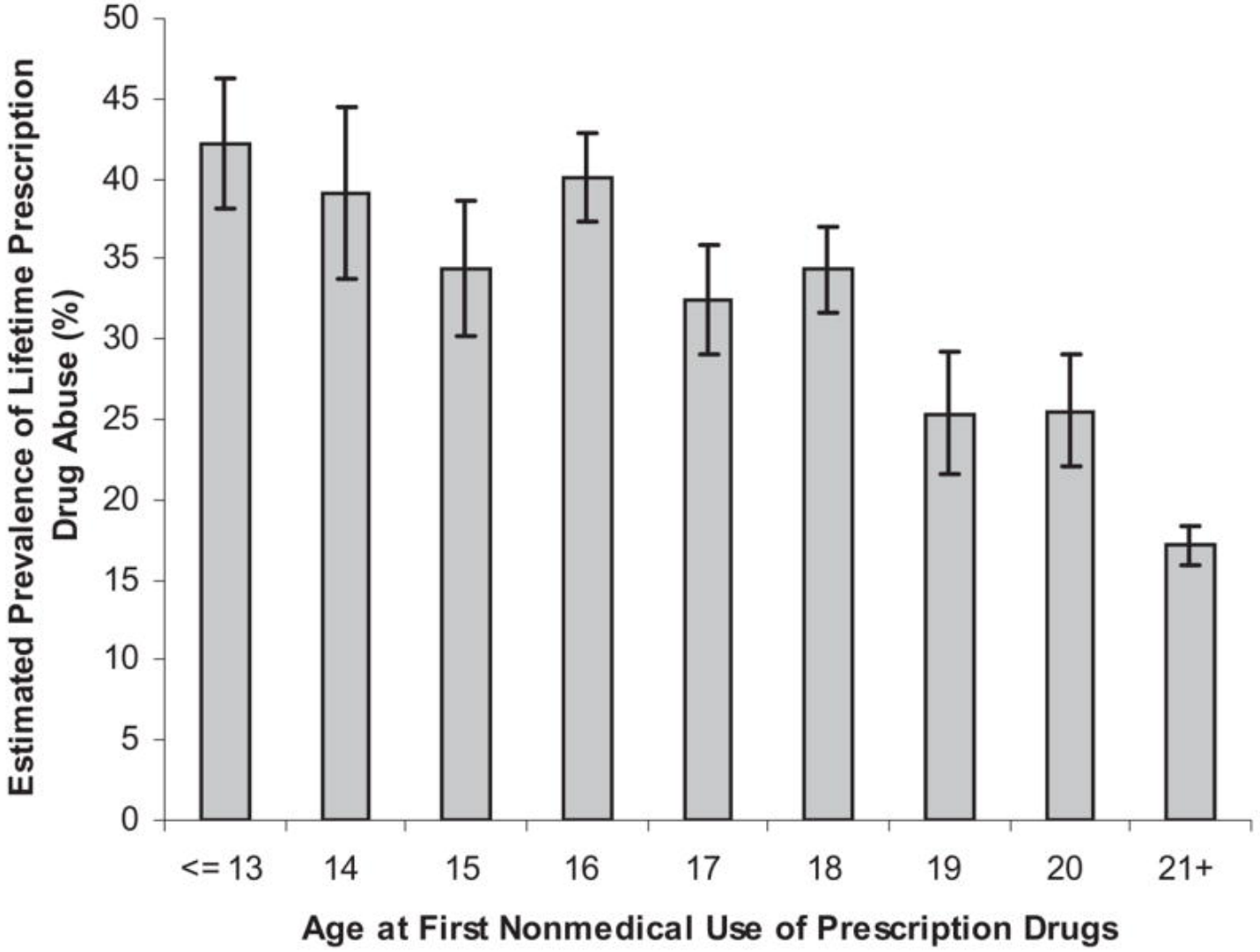
Sources: Johnson, et al. (2015). Prescription Opioids in Adolescence and Future Opioid Misuse. Lynskey, et al. (2003). Escalation of drug use in early-onset cannabis users versus co-twin controls. McCabe et al. (2007). Does early onset of non-medical use of prescription drugs predict subsequent prescription drug abuse and dependence? Boyd et al. (2009). Non-medical use of prescription analgesics. Boyd et al. (2006). Adolescents' Motivations to Abuse Prescription Medications.

Age at first use and later risk



Source: Hingson RW, Heeren T, Winter MR. Age at drinking onset and alcohol dependence. *Arch Pediatr Adolesc Med.* 2006;160:739-746.

Age of onset of non-medical use of prescription drugs



Source: McCabe SE 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):1920-1930.

Younger age*

Exposure to marijuana

AOR: 3.67

(95% CI 1.02-13.14)

Cigarette smoking

AOR: 2.2

(95% CI 1.3-3.5)

*AOR decreases by 5% each year that non-medical use is delayed

(after one year, **AOR: 0.95** with 95% CI 0.94-0.97)

Sources: Johnson, et al. (2015). Prescription Opioids in Adolescence and Future Opioid Misuse. Lynskey, et al. (2003). Escalation of drug use in early-onset cannabis users versus co-twin controls. McCabe et al. (2007). Does early onset of non-medical use of prescription drugs predict subsequent prescription drug abuse and dependence? Boyd et al. (2009). Non-medical use of prescription analgesics. Boyd et al. (2006). Adolescents' Motivations to Abuse Prescription Medications.

Tobacco and opioids

PDS Pharmacoepidemiology & Drug Safety

Official Journal of the International Society for Pharmacoepidemiology

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2011; 20: 90–98
Published online 1 December 2010 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/pds.2066

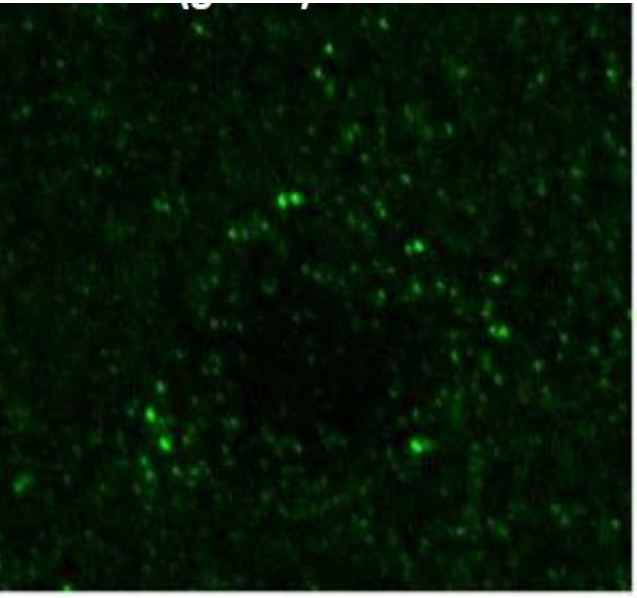
ORGINAL REPORT

The association between smoking and subsequent repeated use of prescribed opioids among adolescents and young adults—a population-based cohort study

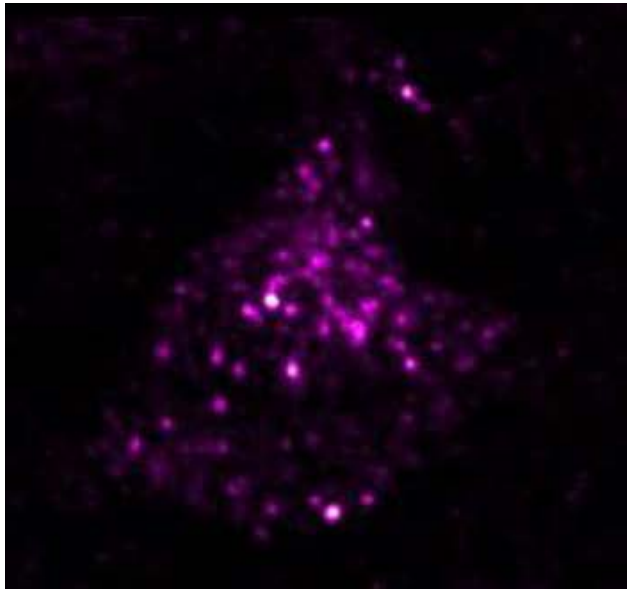
Tomas Log[1]*, Ingeborg Hartz[2,3], Marte Handal[3], Aage Tverdal[3], Kari Furu[1,3] and Svetlana Skurtveit[3,4]

"Daily smoking [of tobacco] at 15-16 years of age was associated with increased risk of incident repeated use of prescribed opioids later in life. **Our study suggests that smoking dependence in adolescents may predict longer lasting and/or higher levels of opioid use**."

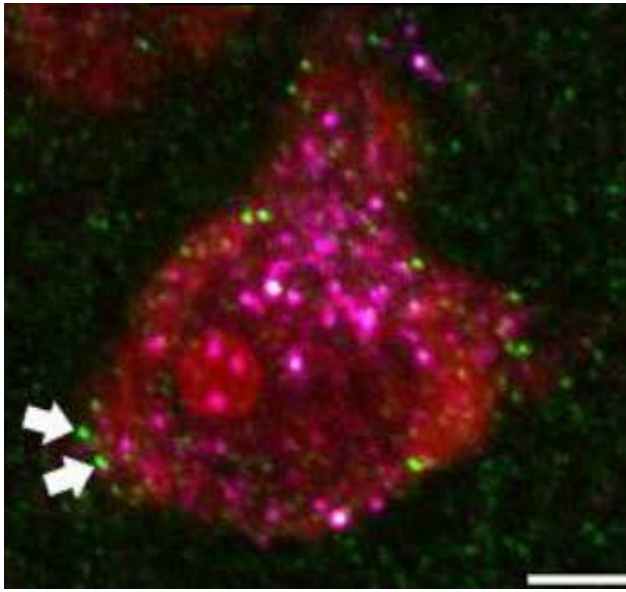
Marijuana and opioids



Cannabinoid Receptors



Opioid Receptors



BOTH

Younger age*

*AOR decreases by 5% each year that non-medical use is delayed (after one year,

AOR: 0.95

with 95% CI 0.94-0.97)

Exposure to marijuana

AOR: 3.67

(95% CI 1.02-13.14)

Cigarette smoking

AOR: 2.2

(95% CI 1.3-3.5)

Recreational use

AOR: 3.42

(95% CI 1.45-8.07)

Unprescribed pain relief

AOR: 1.8

(95% CI 1.20-2.60)

Prescribed pain relief

AOR: 1.33

(95% CI 1.04-1.70)

Sources: Johnson, et al. (2015). Prescription Opioids in Adolescence and Future Opioid Misuse. Lynskey, et al. (2003). Escalation of drug use in early-onset cannabis users versus co-twin controls. McCabe et al. (2007). Does early onset of non-medical use of prescription drugs predict subsequent prescription drug abuse and dependence? Boyd et al. (2009). Non-medical use of prescription analgesics. Boyd et al. (2006). Adolescents' Motivations to Abuse Prescription Medications.

Major depression, anxiety disorder, or panic disorder

Opioid use **OR: 4.43**

(95% CI 3.64-5.38)

Familial alcohol problem/drug use

Hard drug abuse/dependence

OR: 7.89-7.92

PTSD

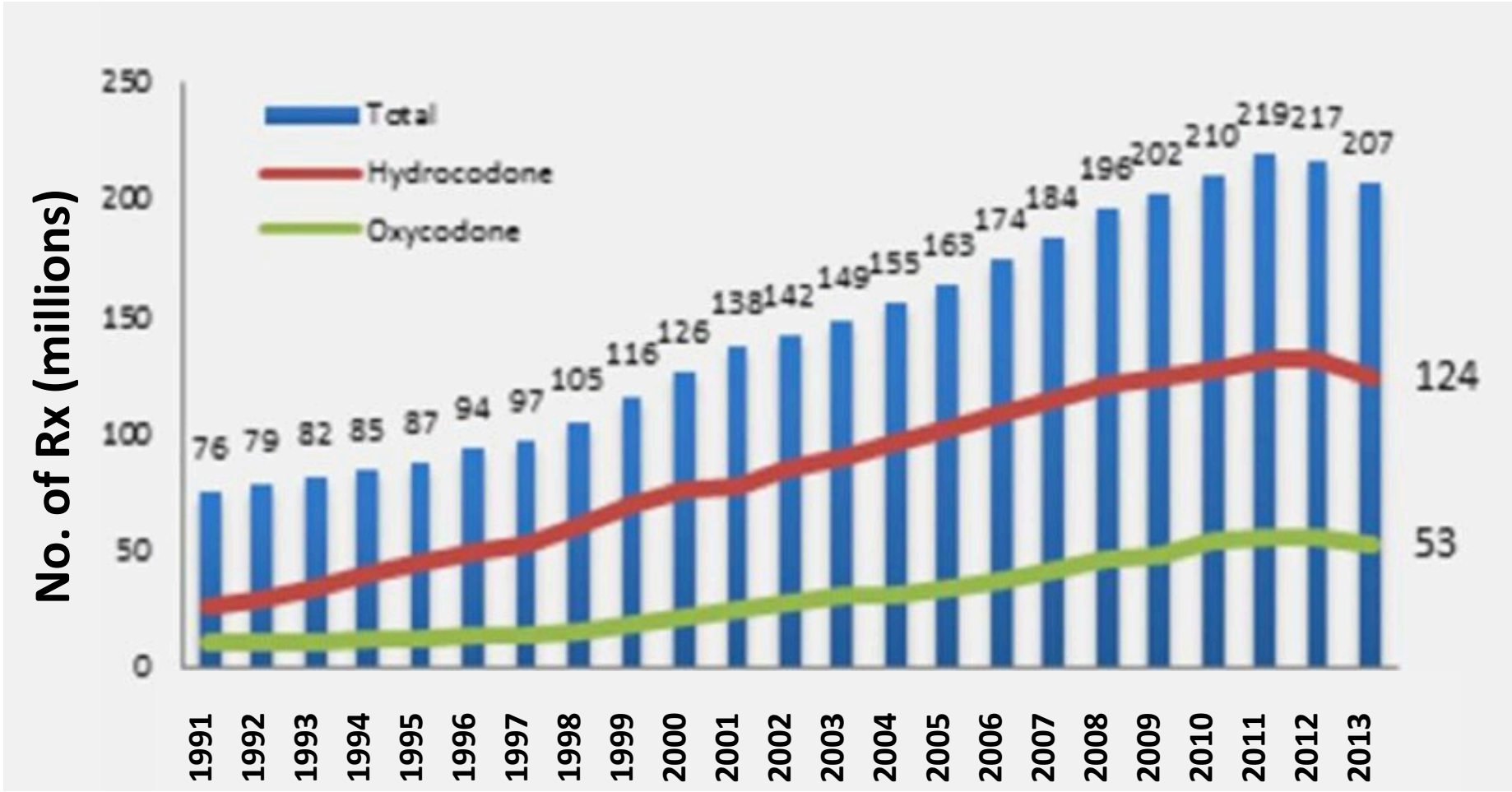
Hard drug abuse/dependence

OR: 8.68

Sources: Kilpatrick DG, Acierno R, Saunders B, Resnick HS, Best CL, Schnurr PP (2000). Risk Factors for Adolescent Substance Abuse and Dependence: Data From a National Sample. J Consult and Clin Psych 63(1):19-30. Sullivan MD, Edlund MJ, Zhang L, Unützer J, Wells KB (2006). Association Between Mental Health Disorders, Problem Drug Use, and Regular Prescription Opioid Use. *Arch Intern Med* 166(19):2087-2093.

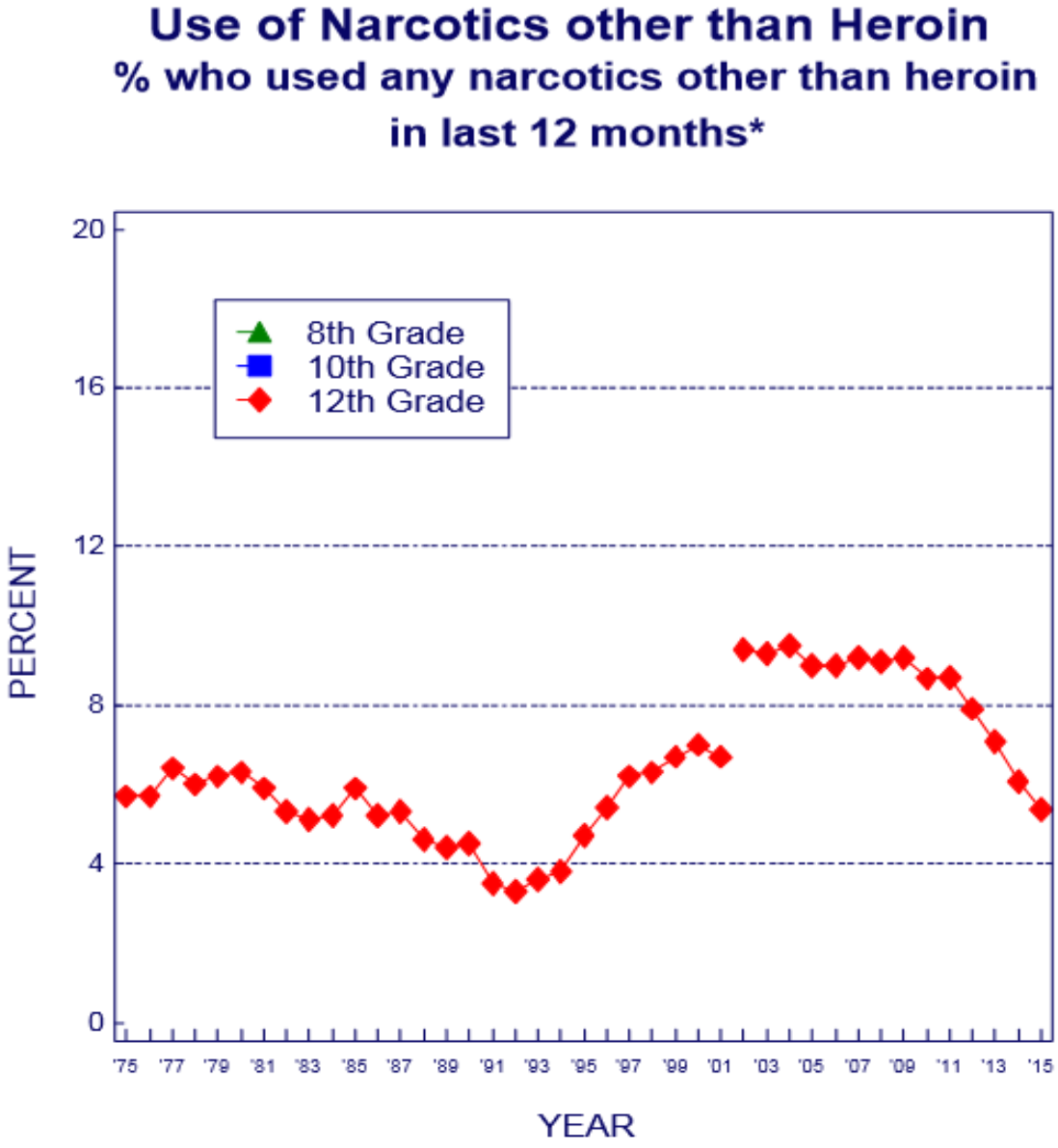
ACCESS TO OPIOIDS

Increase in opiate Rx, 1991-2013



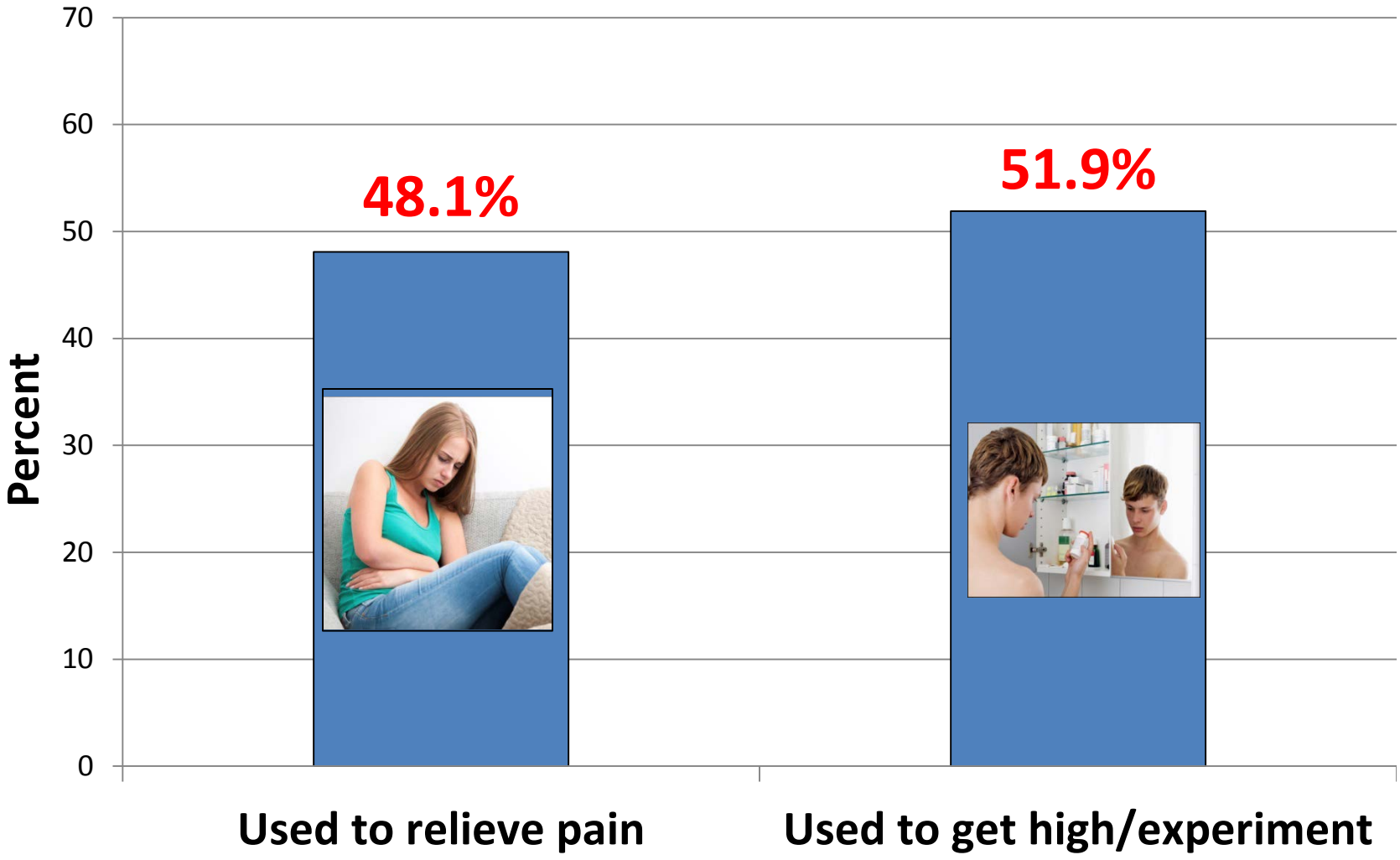
Source: Volkow ND. America's Addiction to Opioids: Heroin and Prescription Drug Abuse. *Natl. Inst. Drug Abus.* 2014.

Rates of opioid misuse by 12th graders



Source: Johnston LD, et al., Monitoring the Future – National Results on Adolescent Drug Use: Overview of Key Findings, 2011

Motivations for opioid misuse

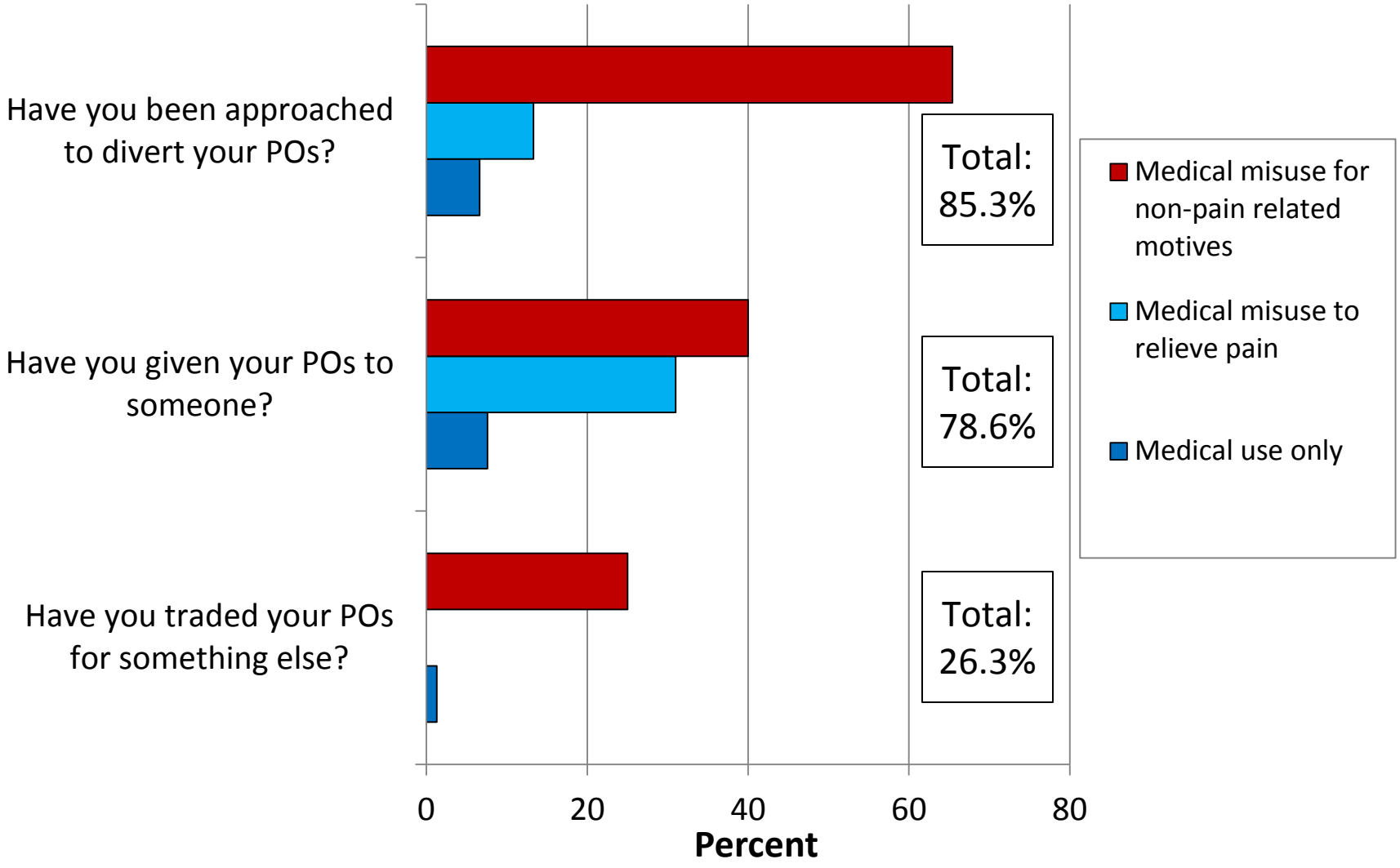


Source: McCabe et al (2012). Adolescent nonmedical users of prescription opioids: brief screening and substance use disorders. *Add Behav*.

Easy to get from medicine cabinet	62%
Available everywhere	52%
Not illegal	51%
Easy to get through other people's prescription	50%
Can claim you have a prescription if caught	49%
Cheap	43%
Safer to use than illegal drugs	35%
Less shame attached to using	33%
Easy to purchase over the Internet	32%
Fewer side effects than street drugs	32%
Parents don't care as much if you get caught	21%

Source: Partnership for a Drug-Free America. The Partnership Attitude Tracking Study (PATS): Teens in grades 7 through 12 2005; May 16, 2006.

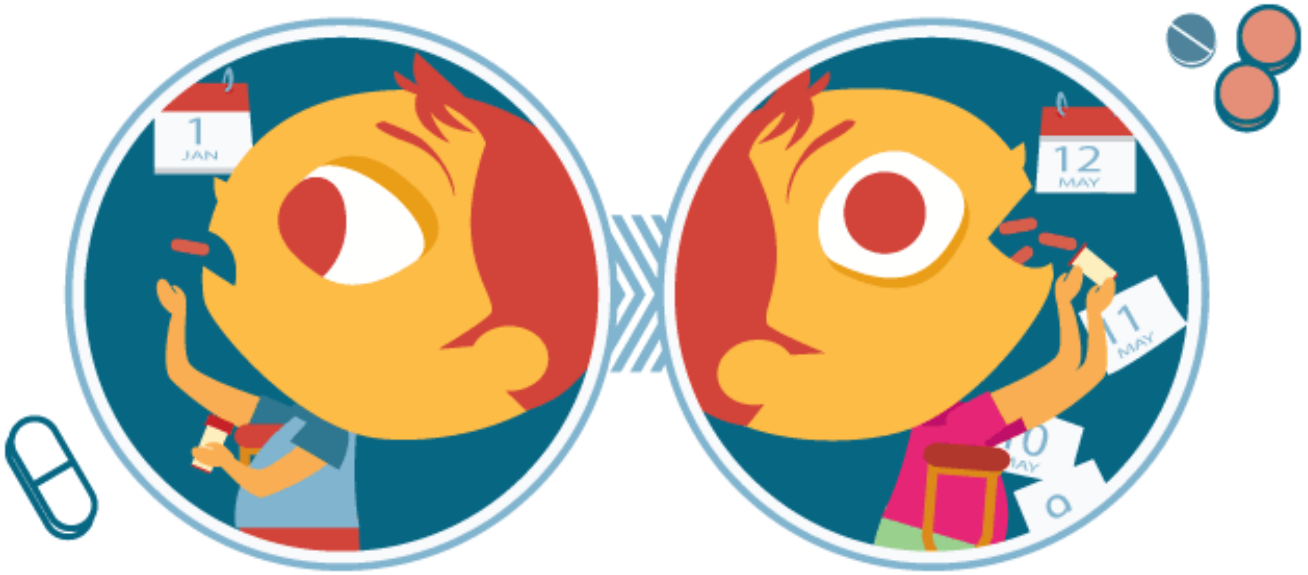
Diversion Behaviors as a Function of Motives for Misuse of Prescription Opioids (POs)



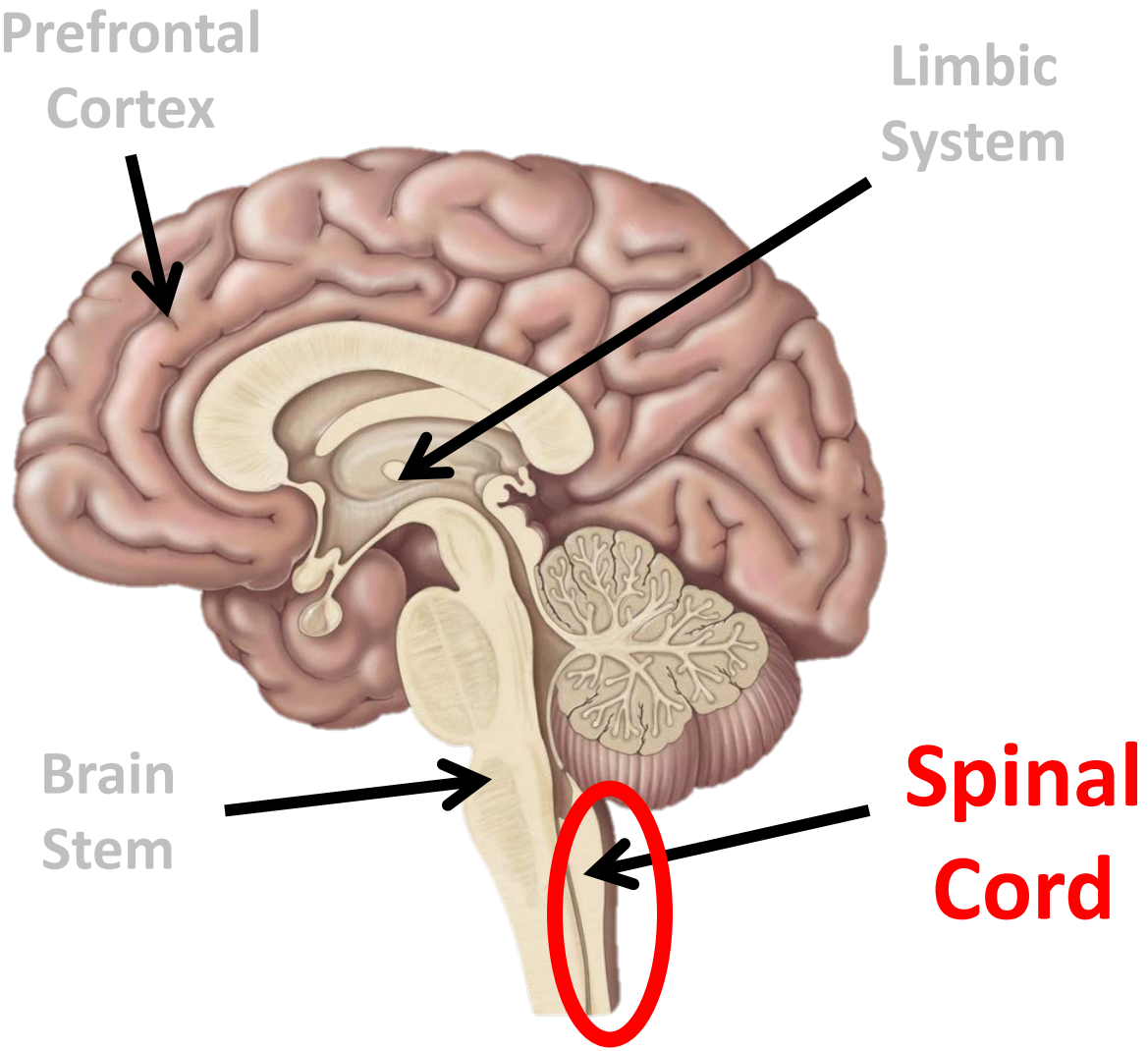
Source: McCabe SE, West BT, Boyd CJ. Motives for Medical Misuse of Prescription Opioids Among Adolescents. *Pain* 2013 14(10):1208-1216.

RECOMMENDATIONS

There is no such thing as a “safe” dose



Keep it in the spinal cord



Side effect profiles

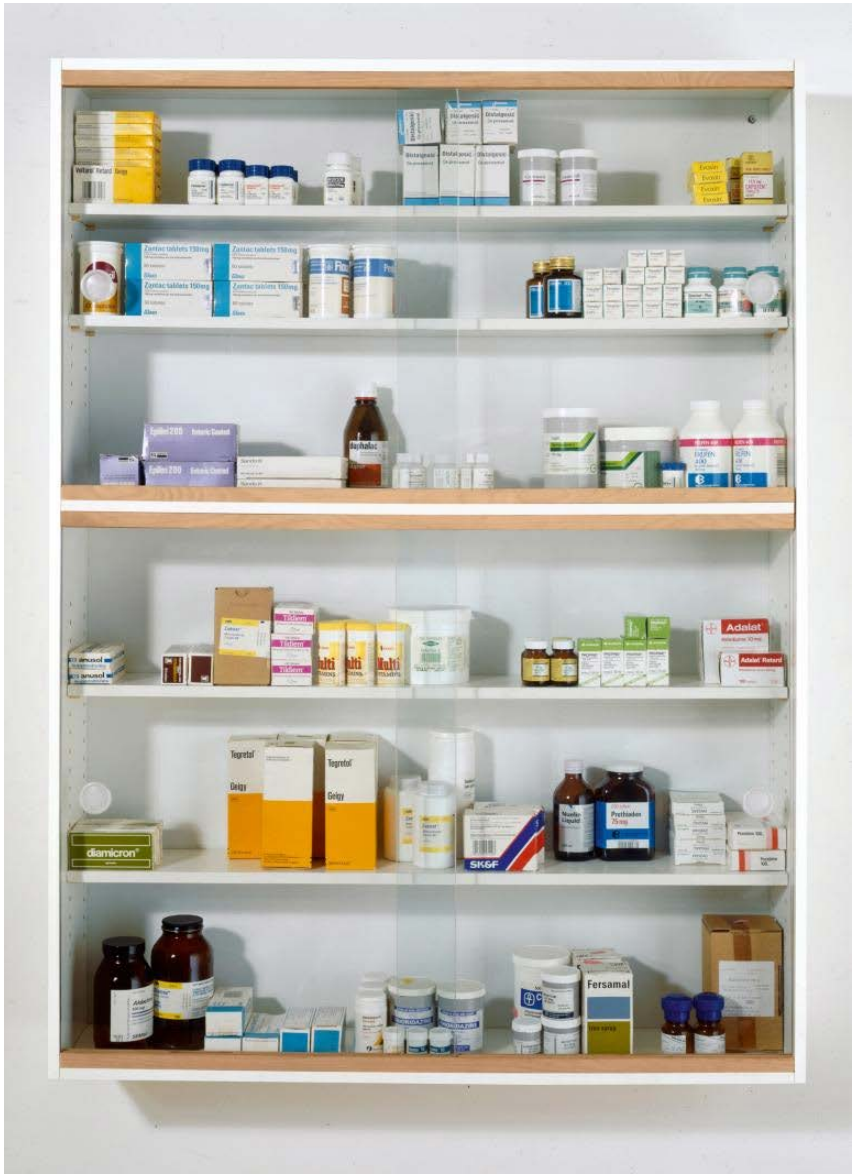
Proper assessment is critical

Patient and parent education

SUMMARY

Kids are vulnerable to drug use and addiction

The medicine cabinet *is* the problem



The opioid reservoir

84.2%

of opioids obtained by adolescents were given by or taken from a family member or peer

Source: McCabe et al (2012). Adolescent Nonmedical Users of Prescription Opioids: Brief Screening and Substance Use Disorders. *Add Behav*, *37*(5).

Take precautions

- Prescribe appropriately
- Assess risk
- Keep doses small
- Keep course of treatment short

Educate EVERY adolescent and parent

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Miriam Schizer, MD, MPH
Patricia Schram, MD

Research Collaborators
Elizabeth Harstad, MD, MPH
Sion Kim Harris, PhD
Lydia Shrier, MD, MPH
Lauren Wisk, PhD

Research Assistants
Dylan Kaye, BA
Molly Doernberg, BA

Data Manager
Qian Huang, MPH

Teaching Collaborators
Pamela Burke, PhD, RN,
Linda Malone, DNP, RN
Sarah Pitts, MD
Marianne Pugatch, MSW
Jennifer Putney, PhD

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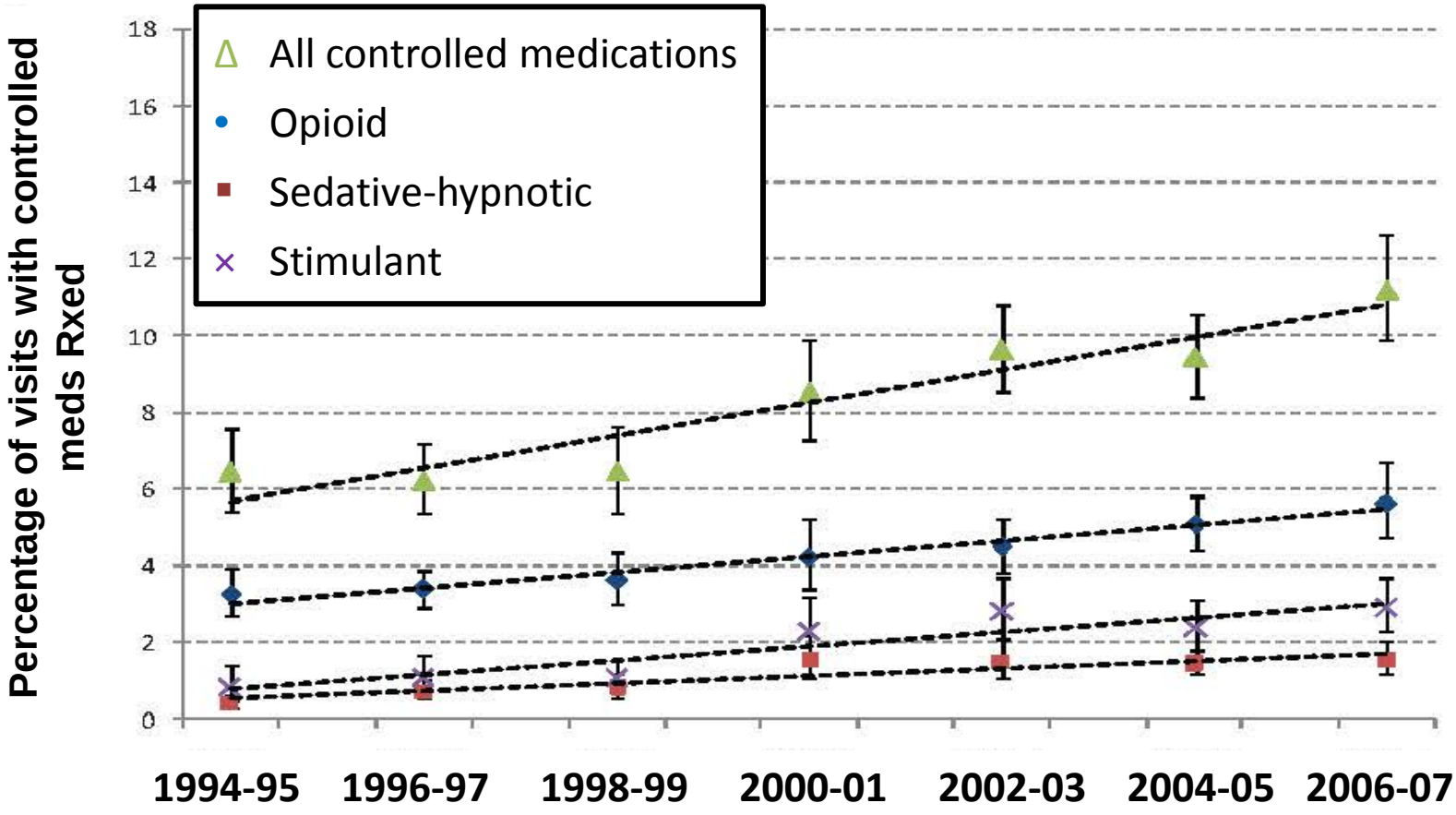
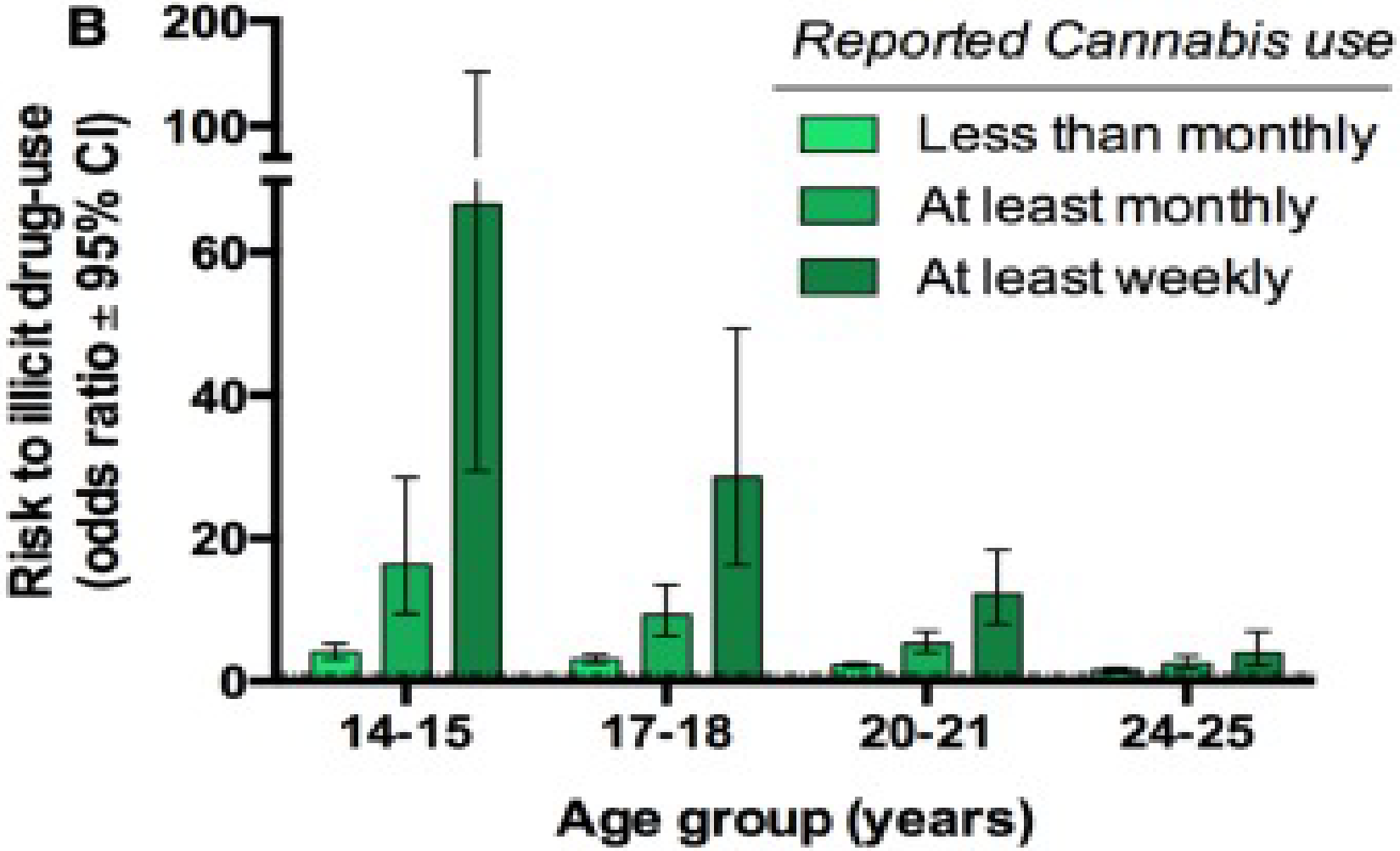
Fatma Dedeoglu, MD
Katharine Garvey, MD, MPH
Laurie Fishman, MD
Paul Hammerness, MD
Andrew MacGinnitie, MD, PhD
Jonathan Gaffin, MD

Changes in prescribing controlled meds to adolescents, 1994-2007



Source: Fortuna RJ, Robbins BW, Caiola E, Joynt M, Halterman JS. Prescribing of controlled medications to adolescents and young adults in the United States. *Pediatrics*. 2010;126(6):1108–16.



Michael T. Lynskey; Andrew C. Heath; Kathleen K. Bucholz JAMA, January 22/29, 2003—Vol 289, 427-433