

Prescription Opioids in Children Towards a Safer and Pain-free Tomorrow



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INTRODUCTION

- Pediatric Emergency Medicine Specialist
- Treat patients with severe pain
 - Motor vehicle crashes and Burns
 - Sickle cell pain crises
 - Breakthrough pain in post-op patients
- Also treat patients with
 - Acute drug overdose
- Member, AAP Committee on Drugs



AMERICAN ACADEMY OF PEDIATRICS

- A non-profit organization of 66,000 pediatricians, pediatric medical sub-specialists, and pediatric surgical specialists
- Dedicated to the health, safety, and well-being of infants, children, adolescents, and young adults
- AAP policy since 1977 that it is not only ethical but also imperative that new drugs to be used in children be studied in children under controlled circumstances



BPCA AND PREA

- The Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) have revolutionized pediatric therapeutics
- More than 637 pediatric label changes have been made as a result of BPCA and PREA
- BPCA and PREA made permanent in 2012 giving children a permanent seat at the drug development table



TIMELINE: BPCA AND PREA

Date	Action
1977	AAP Policy Statement <i>Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations</i>
1997	Pediatric incentive enacted as part of <i>FDAMA</i>
1998	Pediatric Rule published
2002	Federal district court strikes down Pediatric Rule
2003	Pediatric Research Equity Act enacted
2007	BPCA and PREA reauthorized together as part of <i>FDAAA</i>
2012	BPCA and PREA made permanent law as part of <i>FDASIA</i>



WHAT BPCA AND PREA TAUGHT US

- Increased experience and understanding of pediatric clinical trial design, extrapolation, and formulations
- Drugs previously thought to be safe in children turned out not to be.
- Under-/Over-Dosing
- New indications for children discovered
- Today 50% of drugs used in children are off-label (before BPCA and PREA it was 80%).
- Absence of approved FDA labeling a barrier to access to therapies for children



Prescription Opioids



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THE PROBLEM

- In 2013, there were $\frac{3}{4}$ million persons treated for nonmedical use of prescription pain relievers
- 18,893 Opioid analgesic overdose fatalities (2014)
 - Increase by 5 times since 1999
- 7,000 people treated daily in EDs for incorrect opioid use
- 17% of ED visitors are prescribed opioids at discharge
- Opioid use disorders → \$72 billion in medical costs annually



From: **Seeking Balance Between Pain Relief and Safety: CDC Issues New Opioid-Prescribing Guidelines**

JAMA Neurol. 2016;73(5):513-514. doi:10.1001/jamaneurol.2016.0535

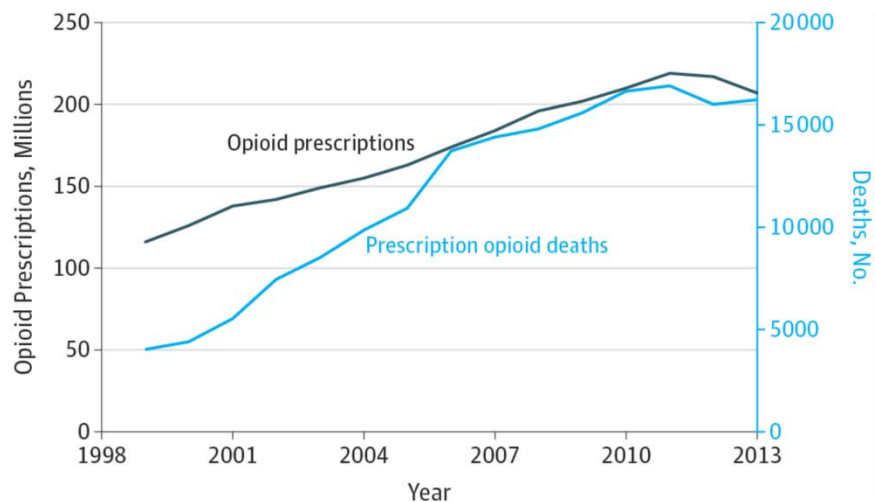


Figure Legend:

Opioid Prescriptions and Opioid-Related Deaths From 1999-2013 Data compiled from National Institute on Drug Abuse, 2014, and National Prescription Audit, 1997-2013.

WHY CHILDREN SHOULD BE PART OF THE NATIONAL DIALOGUE

- Children < 18 years of age represent 25% of the US population
- Rate of Opioid prescriptions in adolescents 15 to 19 years of age doubled from 1994-2007
- 2 million Americans \geq 12 years either abused or were dependent on opioid painkillers in 2013
- Opioid-related illicit drug use in teenagers
 - 79% of significant morbidity
 - 100% of deaths



THE NEED FOR EFFECTIVE PEDIATRIC OPIOID MISUSE & ADDICTION COUNTERMEASURES

- AAP Committee on Substance Use and Prevention is working to:
 - Promote use of screening, brief intervention and referral to treatment for adolescent substance use in the primary care setting
 - Develop clinical practice guidelines for the treatment of opioid use disorder specifically for adolescents
- AAP also strongly supported the passage of the Protecting Our Infants Act
 - Advances federal government activities to improve treatment and identification of babies with neonatal abstinence syndrome
 - Improves care for pregnant women using opioids



SEVERE REFRACTORY PAIN CONDITIONS IN PEDIATRICS

- Post-operative Major Surgery
 - Spinal surgery
 - Correction of Birth Defects
- Relapsed Cancer
- Sickle Cell pain crises
- Extensive trauma



OVERARCHING GOALS

- Ensure that patients with pain receive appropriate analgesics in appropriate dosing for appropriate duration
- Must be equally aggressive in preventing and treating opioid use disorders

We need a **BALANCED** policy



Haddon's Matrix for the Safe Prescription of Opioids

	Agent Prescription-Opioids	Host Infant, Child, Youth	Physical Home and Social Environment
Pre-Event Primary Prevention	-FDA Drug R & D -Pediatric Labeling -DEA Enforcement	-Age, Gender, -Health Status -Parental Supervision -Impulsivity	-Family Structure -Socio-economic Status -Social and Job Inequalities -Education Attainment -Enforcement of laws
Event Secondary Prevention	-Physician Policies -EBM guidelines -Prescribing Patterns	-Access to Opioids	-Ease of Drug Diversion -Prescription Drug-monitoring Programs
Post-Event Tertiary Prevention	-Post-Market Drug Surveillance -Outcomes Research	-Availability and Access to Health Care and Rehab. -Medication – assisted Rx	-Health Systems -Family Care -Support Systems

Event = Prescription/Diversion of Opioids

NEED MORE EFFECTIVE

- Non-opioid pain management techniques
- Ways to disseminate & implement these techniques
- Prescription Drug-monitoring Programs
- Opioid return and disposal policies & practices
- Medication-assisted treatment programs
- Drug abuse prevention education & training



KEY DISCUSSION ISSUES REGARDING OPIOID ANALGESICS

- Research and Development
- Pediatric Drug Labeling
- Post-Marketing Surveillance



RESEARCH AND DEVELOPMENT



PRESCRIPTION OPIOID RESEARCH AND DEVELOPMENT IN CHILDREN

- R & D for all drugs
 - Drug absorption, metabolism and elimination
 - Drug efficacy
 - Drug adverse reactions
- Pediatric Issues
 - Effect on growth and development
 - Clinical trial study designs in pediatrics
 - Evidence of long-term efficacy of opioids for chronic pain is limited



LACK OF PUBLICATION

- Industry Sponsorship
- Industry reluctance to publish
 - Pediatric exclusivity studies typically completed late in drug life cycle
 - Economic benefits from pediatric exclusivity typically come from continued marketing protection of sales to adults.
 - Once additional marketing protection obtained sponsors may simply not see publication as a worthwhile investment



LACK OF PUBLICATION CONT'D

- Efficacy studies and those with a positive labeling change are more often published
 - Studies with negative outcomes can contain important information



MEDICATIONS IN PREMATURE BABIES AND NEONATES

- Most medications administered to preterm infants lack convincing data to support their safety and efficacy
 - > 90% not approved by FDA for prescribed indication
- Challenges
 - Ethical issues
 - Concern for long-term neurodevelopmental outcome
 - Represent a relatively small market
 - Development of permanent injuries
 - Associated with large malpractice awards whether or not adverse outcome is caused by drug



MEDICATIONS IN PREMATURE BABIES AND NEONATES

Given the considerable morbidity and mortality intrinsic to premature babies and their complex physiology, we need:

- Randomized, masked, placebo-controlled trials
- Drug superiority studies assessing improved efficacy of one drug over another
- Study short-term and long-term outcomes
 - Surveillance at least until school age



PEDIATRIC DRUG LABELING



THE OXYCONTIN STORY

- Extended Release version of Oxycodone
- Under BPCA, FDA issued a Pediatric Written Request to manufacturer to study Oxycodone and OxyContin in children; Reviewed by the FDA Pediatric Review Committee
- Safety and Pharmacokinetic studies performed in likely pediatric patients → Pediatric Labeling
- Physicians received specific information to safely manage pain in the sub-group of patients (minimum daily opioid dose: 20 mg Oxycodone)
- Negative publicity due to prescription opioid misuse
- FDA moratorium on new opioid labeling for children



PEDIATRIC LABELING OF OPIATES

- Morphine, Methadone
 - The safety and efficacy in patients less than 18 years have not been established
- Hydromorphone
 - Pharmacokinetics of hydromorphone have not been evaluated in children
- Fentanyl
 - The safety and efficacy of in children under two years of age has not been established
- Oxycodone, Hydrocodone
 - Have some pediatric dosing information



FDA's LABELING OF OPIOIDS

- Labeling changes for Extended Release (2013) and Immediate Release (2016) opioids
- Specified indications
- Added boxed warnings on risk of misuse
- Enhanced safety information
 - Drug interactions
 - Neonatal opioid withdrawal syndrome
- Post-marketing studies for extended-release opioids



POST-MARKETING DRUG SURVEILLANCE



POST-MARKETING DRUG SURVEILLANCE

- Clinical trials may not detect all possible risks
- FDA should:
 - Focus on drug safety over the drug's lifetime
 - Have specific monitoring plan considering
 - Scientific data
 - Patient's perspective
 - Ethical issues
 - Risk-benefit analysis



IN SUMMARY

- All drugs used to treat children will have age-appropriate evidence sufficient to provide information for labeling
- Work diligently to address public health crisis of opioid addiction



IN SUMMARY

- BPCA and PREA have been enormously successful in ensuring the study and labeling of drugs in children
- Advance the rational and critical study of drugs in children through conducting and/or collaborating in well-designed pediatric drug studies, including national consortium studies
- Journals should be encouraged to publish results of all well-designed investigations, including negative studies



IN SUMMARY

- Consider off-label uses of drugs when addressing various drug-related concerns, such as drug shortages
- Labeling status should not be sole criterion that determines the availability on formulary or reimbursement status for medications in children





THANK YOU

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