

Prescription Opioids in Children: Importance of Accurate Labeling and Treatment of Pain

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INTRODUCTION

- Pediatric Oncologist
- Board certified in Clinical Pharmacology
- Treat pediatric patients with cancer
- Member, AAP Committee on Drugs

TWO GROUPS IN DESPERATE NEED

Taking opioids in a harmful manner

Enduring severe pain

NEED A BALANCED
APPROACH

GOAL:

STOP OPIOID MISUSE & HARM



THE OPIOID ADDICTION EPIDEMIC

- 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 problematic opioid use
- 17% of ED visitors are prescribed opioids at discharge
- Opioid use disorders cost \$72 billion in medical costs annually



CHILDREN AND THE OPIOID EPIDEMIC

- 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 > 12 years either misused or were dependent on opioid painkillers in 2013
- Opioid-related illicit drug use in teenagers
 - 79% of significant morbidity
 - 100% of deaths



GOAL:
EFFECTIVE TREATMENT
OF SEVERE PAIN

SEVERE REFRACTORY PAIN CONDITIONS IN PEDIATRICS

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



EXAMPLE CASE

- 15 year old with recurrence of Ewing sarcoma
 - T7 with compression fracture
- Admitted to hospital on morphine PCA for intractable pain
- Converted to oral long acting morphine ER 30 mg BID, with 30 mg short acting for breakthrough
- Discharged with prescription to cover 2 weeks of each

EXAMPLE CASE

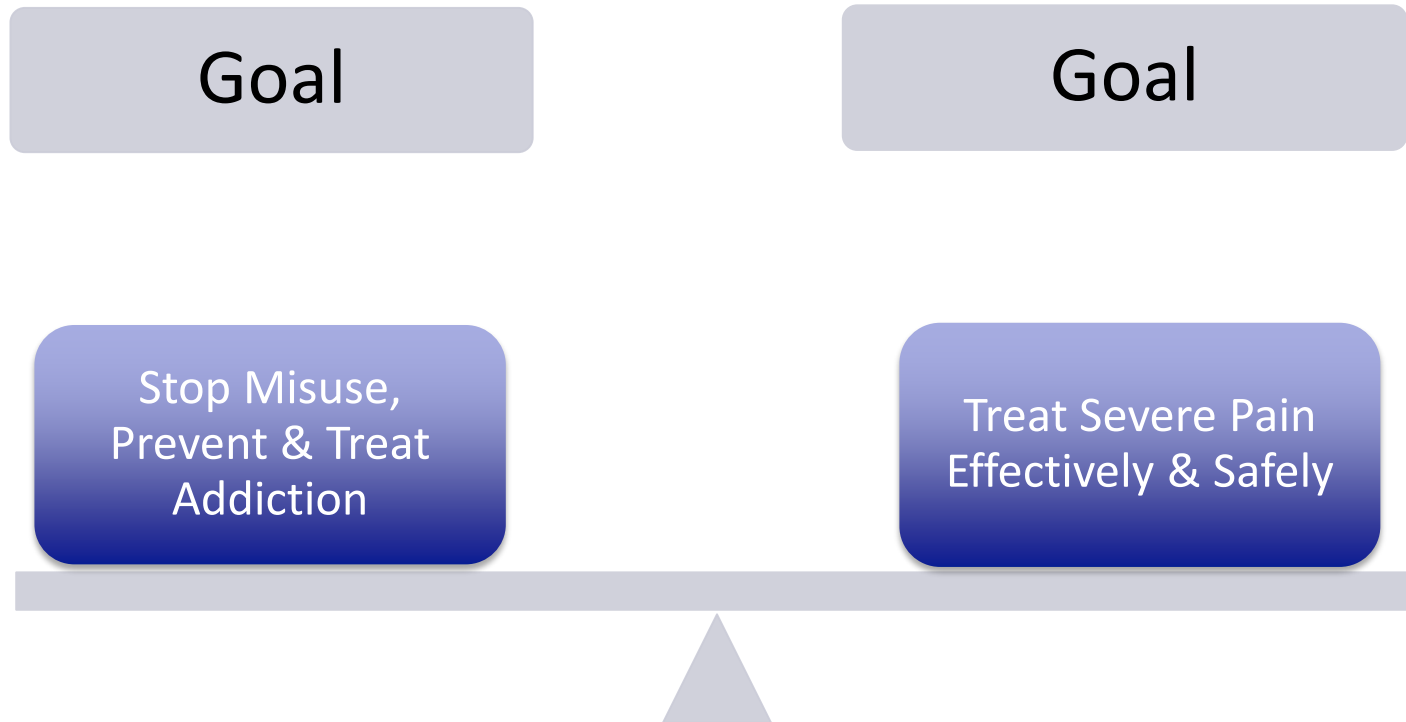
- Insurance denied the long acting formulation
 - dad paid full price out of pocket for 10 pills
- Prior auth was accepted
- Four days later her pain was significantly worse
- We increased the long acting to 60 mg BID
 - She ran out of long acting 30 mg tabs before the 2 week supply.

EXAMPLE CASE

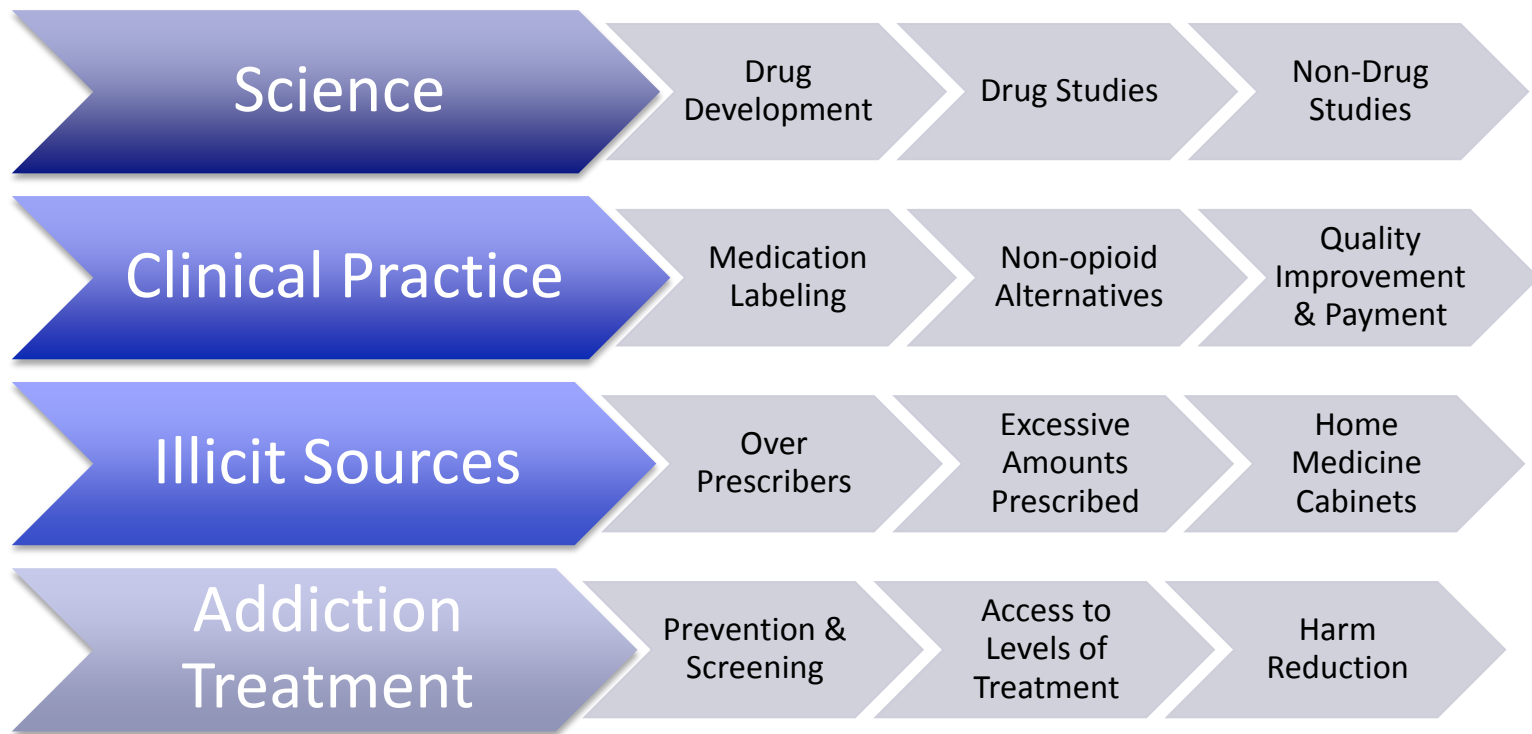
- Ordered a new prescription for 60 mg BID
 - insurance denied it because she had already been dispensed
- Eventually got insurance to cover 60 mg tablets
- Pharmacist refused to dispense the medication when dad went to get it because "she had just received 30 mg tabs less than 2 weeks prior"



BALANCED POLICY AND CLINICAL PRACTICE



PIECES OF THE SOLUTION: POLICY AND CLINICAL PRACTICE



THE NEED FOR 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
- Abuse deterrent formulations



THE NEED FOR EFFECTIVE PEDIATRIC OPIOID MISUSE & ADDICTION COUNTERMEASURES

CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

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Codeine: Time to Say “No”

Joseph D. Tobias, MD, Thomas P. Green, MD, Charles J. Coté, MD, SECTION ON
ANESTHESIOLOGY AND PAIN MEDICINE, COMMITTEE ON DRUGS

Codeine has been prescribed to pediatric patients for many decades as both an analgesic and an antitussive agent. Codeine is a prodrug with little inherent pharmacologic activity and must be metabolized in the liver into morphine, which is responsible for codeine's analgesic effects. However, there is substantial genetic variability in the activity of the responsible hepatic enzyme, *CYP2D6*, and, as a consequence, individual patient response to codeine varies from no effect to high sensitivity. Drug surveillance has documented the occurrence of unanticipated respiratory depression and death after receiving codeine in children, many of whom have been shown to be ultrarapid metabolizers. Patients with documented or suspected obstructive sleep apnea appear to be at particular risk because of opioid sensitivity, compounding the danger among rapid metabolizers in this group. Recently, various organizations and regulatory bodies, including the World Health Organization, the US Food and Drug Administration, and the European Medicines Agency, have promulgated stern warnings regarding the occurrence of adverse effects of codeine in children. These and other groups have or are considering a declaration of a contraindication for the use of codeine for children as either an analgesic or an antitussive. Additional clinical research must extend the understanding of the risks and benefits of both opioid and nonopioid alternatives for orally administered, effective agents for acute and chronic pain.

abstract

FREE

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THE NEED FOR EFFECTIVE PEDIATRIC OPIOID MISUSE & ADDICTION COUNTERMEASURES

- AAP is working to:
 - Promote use of screening, brief intervention and referral to treatment for adolescent substance use in the primary care setting
 - Promote published policy recommending medication assisted treatment for adolescents with opioid use disorder



THE NEED FOR EFFECTIVE PEDIATRIC OPIOID MISUSE & ADDICTION COUNTERMEASURES

- AAP is also working to:
 - Improve treatment for pregnant women using opioids
 - Improve care for infants born with neonatal opioid withdrawal syndrome
 - Improve parental substance use treatment to help keep children out of foster care
 - Address long term impacts of parental substance use on children

THE NEED FOR EFFECTIVE PEDIATRIC REFRACTORY PAIN TREATMENT OPTIONS

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



RESEARCH AND DEVELOPMENT IN CHILDREN

- R & D for all drugs
 - Drug absorption, metabolism, elimination, and pharmacodynamics
 - 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



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

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 STUDIES AND LABELING

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OXYCONTIN

- 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

OXYCONTIN

- Physicians received specific information to safely manage pain in the sub-group of patients (minimum daily opioid dose: 20 mg Oxycodone)
- We look forward to continued discussion of Oxycontin in pediatrics today

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



POST MARKETING 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



THE NEED FOR PEDIATRIC DRUG STUDIES AND LABELING

- Congress has recognized the importance of advancing pediatric health and wellbeing through better understanding of medications
 - Best Pharmaceuticals for Children Act (BPCA)
 - Pediatric Research Equity Act (PREA)
- To date, over 805 label changes have been made under BPCA and PREA to add new pediatric information to drug labeling



WHAT WE HAVE LEARNED FROM BPCA AND PREA

- 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

WHAT WE HAVE LEARNED FROM BPCA AND PREA

- 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





POLICY STATEMENT

Off-Label Use of Drugs in Children

COMMITTEE ON DRUGS

KEY WORDS

off-label drug use, pharmaceuticals, pediatrics, infants, children, adolescents, prescribing

ABBREVIATIONS

BPCA—Best Pharmaceuticals for Children Act

FDA—US Food and Drug Administration

PREA—Pediatric Research Equity Act

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abstract



The passage of the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act has collectively resulted in an improvement in rational prescribing for children, including more than 500 labeling changes. However, off-label drug use remains an important public health issue for infants, children, and adolescents, because an overwhelming number of drugs still have no information in the labeling for use in pediatrics. The purpose of off-label use is to benefit the individual patient. Practitioners use their professional judgment to determine these uses. As such, the term “off-label” does not imply an improper, illegal, contraindicated, or investigational use. Therapeutic decision-making must always rely on the best available evidence and the importance of the benefit for the individual patient. *Pediatrics* 2014;133:563–567



PEDIATRIC DRUG LABELING

- The framework for labeling pediatric medications should be based on rigorous studies:
 - Efforts to support and expand drug studies in children need to be continued

PEDIATRIC DRUG LABELING

- Pediatric drug labeling should not:
 - Be looked upon as a solution for problems that labeling does not cause and cannot solve
 - Serve as an excuse to not grapple with effective solutions to stop the addiction epidemic



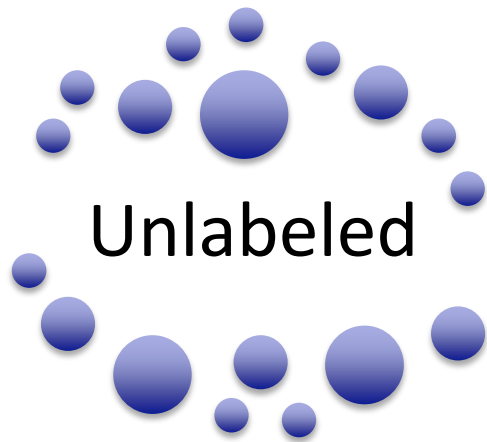
LABELING AS EVIDENCE BASED GUIDANCE

Science

Labeling

Clinical
Practice

LABELING TO IMPROVE CLINICAL PRACTICE



**Widely Varying
Practice**



**Safe & Effective
Practice**

CONCLUSION

- We need concrete solutions to address the opioid epidemic
- We also must adequately treat children with severe refractory pain
- We need balanced policy to achieve both goals

THANK YOU

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