Need for Human Abuse Potential Studies for Evaluation of NDA 209-653

James M. Tolliver, PhD
Pharmacologist
Controlled Substance Staff
Office of the Center Director
CDER, FDA

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Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee

NDA 209-653

- Intellipharmaceutics Corp. (Sponsor) has submitted NDA 209-653 in support of intravenous abuse deterrent claims for Oxycodone HCl Extended Release Tablets.

- Under the original NDA 209-653 Sponsor submitted Category 1 physical manipulation and chemical extraction studies, but no Category 2/3 oral or intranasal human abuse potential studies for manipulated product.

- Within the Sponsor's open session background package, Sponsor notes:
  - On page 8 the need to conduct clinical human abuse potential studies to obtain abuse-deterrent labeling incorporating Category 2 and 3 claims for oral and intranasal routes of abuse.
  - On page 51 under "Post-Marketing Plans" that post-approval, oral and intranasal human abuse potential studies will be completed and submitted under a supplement to NDA 209-653 to obtain abuse deterrent labeling by additional routes of administration.

2015 Final Guidance for Industry – Abuse-Deterrent Opioids – Evaluation and Labeling

- Notes the need to understand the potential for abuse of abuse deterrent formulations by multiple routes of administration such as oral, intranasal, and intravenous.

- Delineates the importance of Category 2 and 3 clinical studies as part of the overall pre-market oral and intranasal abuse deterrent assessment. Totality of data (Category 1, 2, and 3 studies) must be examined.
  - The focus in Category 2 studies is on pharmacokinetic (PK) parameters of the active pharmaceutical ingredients (API) of the formulation but generally not subjective reinforcing effects.
  - The focus of Category 3 studies is documenting subjective reinforcing effects usually along with PK data on the API of the formulation.

- Notes that the results of Category 1 studies should be used in the development of Category 2 and 3 studies involving oral or intranasal administration.

Oxycodone HCL ER Tablets

- With dosage strengths ranging from 10 mg to 80 mg oxycodone HCl, compromise of the extended release mechanism for Oxycodone HCL ER Tablets could make available considerable amounts of immediate release oxycodone for purposes of oral or intranasal abuse.

- The results of Category 1 physical manipulation and chemical extraction studies should be evaluated to determine if Oxycodone HCL ER Tablets are susceptible in particle size reduction and compromise of the controlled release properties for oxycodone HCl. If so, consideration should be given to evaluating manipulated product for abuse by oral and intranasal routes of administration.

- Category 2/3 oral and intranasal human abuse potential studies would be important in the proper assessment of Oxycodone HCL ER Tablets for abuse by oral and intranasal routes, respectively.

Importance of Category 2 and 3 Studies in Premarket Abuse-Deterrent Assessments

- Allows for the examination of the effects of manipulation and routes of administration in non-dependent, opioid experienced population.
  - PK parameter of the API(s)
  - Subjective reinforcing effects such as Drug Liking, High, Take Drug Again, and Overall Drug Liking.

- Allows for assessing food effects on the PK of the APIs and on subjective reinforcing effects following oral administration of abuse-deterrent formulations.

- Allows for determination of the percentage of a dose of manipulated product(s) that individual study subjects are able to insufflate. For each subject, this percentage can be further correlated to subjective reinforcing effects.

Importance of Category 2/3 Studies in Premarket Abuse-Deterrent Assessments

- Allows for evaluating the effects of particle size on the PK of API(s) for the formulation and on subjective reinforcing effects following insufflation. Fine versus coarse particle size produced by different manipulations may be compared.

- Allows for investigator and subject-rated assessments of nasal tolerability as a function of time following insufflation of manipulated products.
  - Evaluation of abuse deterrent formulations with or without excipients intended to serve as nasal irritants (i.e., aversive agent).
  - Nasal tolerability scores may be correlated to subjective reinforcing effects.

- At this time the Sponsor has not submitted clinical study reports to the Agency examining the possible oral or intranasal abuse deterrent effects attributable to dye in the formulation. Later today, you will have the opportunity to discuss possible approaches to this novel area of research.

Conclusions

- In support of deterrent claims to intravenous abuse for Oxycodone HCL ER Tablets under NDA 209-653, Category 1 physical manipulation and chemical extraction studies.

- In keeping with the recommendations of the final 2015 guidance for industry – Abuse Deterrent Opioids – Evaluation and Labeling document, a complete abuse deterrent assessment should cover multiple routes of administration such as oral, intranasal and intravenous abuse.

- Category 2 and 3 studies provide important information for the evaluation of abuse deterrent formulations with respect to oral and intranasal abuse that cannot be derived from Category 1 studies alone. These studies have not yet been provided with respect to Oxycodone HCL ER tablets.

- The totality of data generated from Categories 1, 2, and 3 studies should be used to assess the deterrent effects of Oxycodone HCL ER tablets to oral and intranasal abuse.

Utilization Trends of Oxycodone ER and Other Extended-Release/Long-Acting Opioid Analgesics, 2012-2016

Jennie Wong, PharmD
Drug Utilization Analyst
Division of Epidemiology II
Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology
CDER, FDA

July 26, 2017

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee

Outline

- Sales distribution
- Outpatient retail utilization
  - Prescription data
  - Prescriber Specialty
  - Diagnoses Associated with Use
- Limitations
- Summary of Findings

Selected Opioid Analgesics

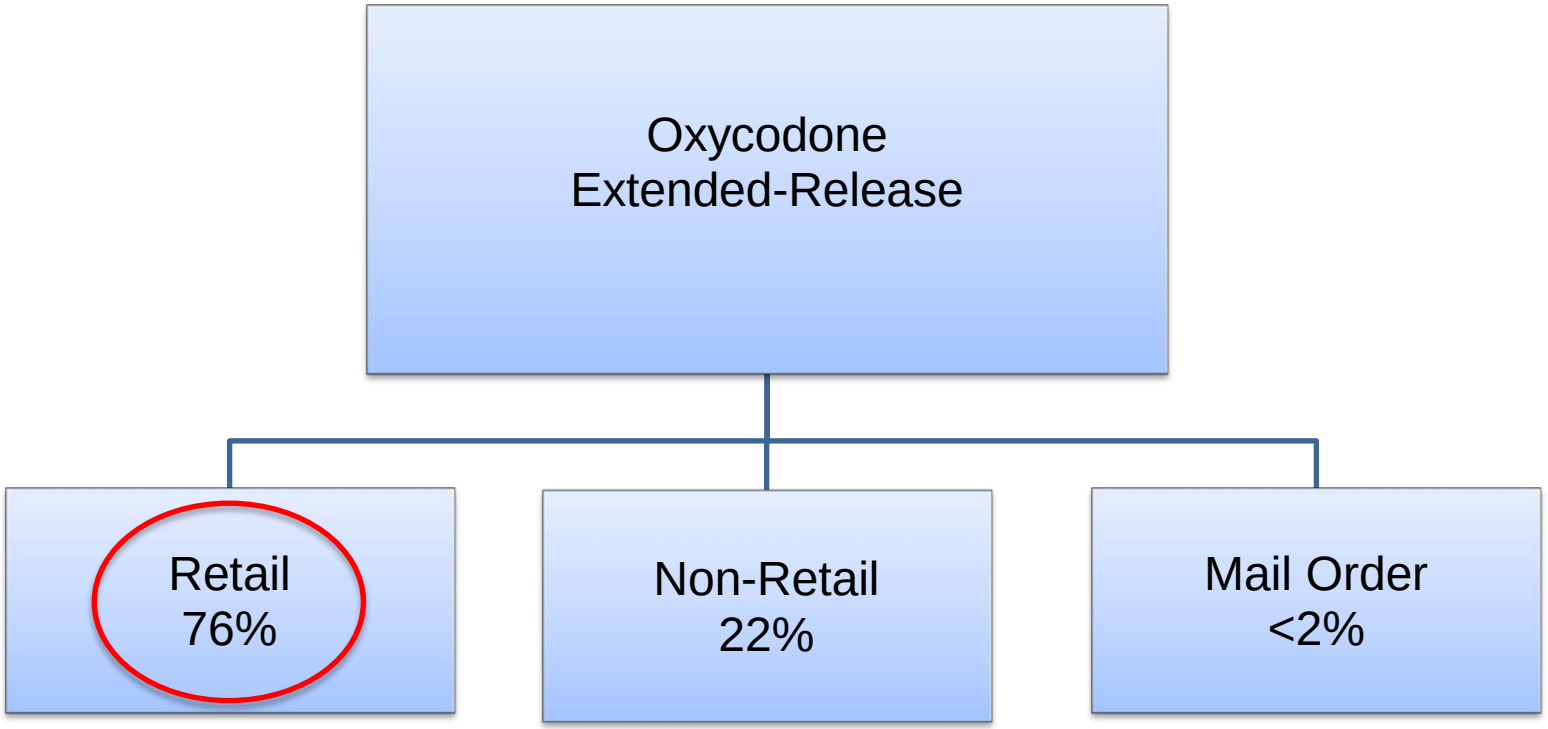
- **Extended-Release/Long-Acting (ER/LA) Products:**
  - **Transdermal (TD) Products**
    - **Buprenorphine TD**
    - **Fentanyl TD**
  - **Oral**
    - **Buprenorphine Buccal Film**
    - **Hydrocodone ER**
    - **Hydromorphone ER**
    - **Methadone**
    - **Morphine ER**
    - **Morphine-Naltrexone ER**
    - **Oxycodone ER**
    - **Oxycodone-Acetaminophen ER**
    - **Oxycodone-Naloxone ER**
    - **Oxycodone-Naltrexone ER**
    - **Oxymorphone ER**
    - **Tapentadol ER**
- **Oral Single-Ingredient (SI) Oxycodone Immediate-Release (IR) products**

Opioid Analgesic Products with Abuse-Deterrent Labeling

- **Extended-Release/Long-Acting Products**
  - Arymo (morphine)
  - Embeda (morphine-naltrexone)*
  - Hysingla (hydrocoodne)*
  - MorphaBond (morphine)
  - Vantrela (hydrocodone)
  - OxyContin (oxycodone)*
  - Xtampza (oxycodone)*
  - Targiniq (oxycodone-naloxone)
  - Troxyca (oxycodone-naltrexone)
- **Immediate-Release Products**
  - Roxybond (oxycodone)

* Currently, launched in the market in the examined time period.

Sales Distribution Data
2016



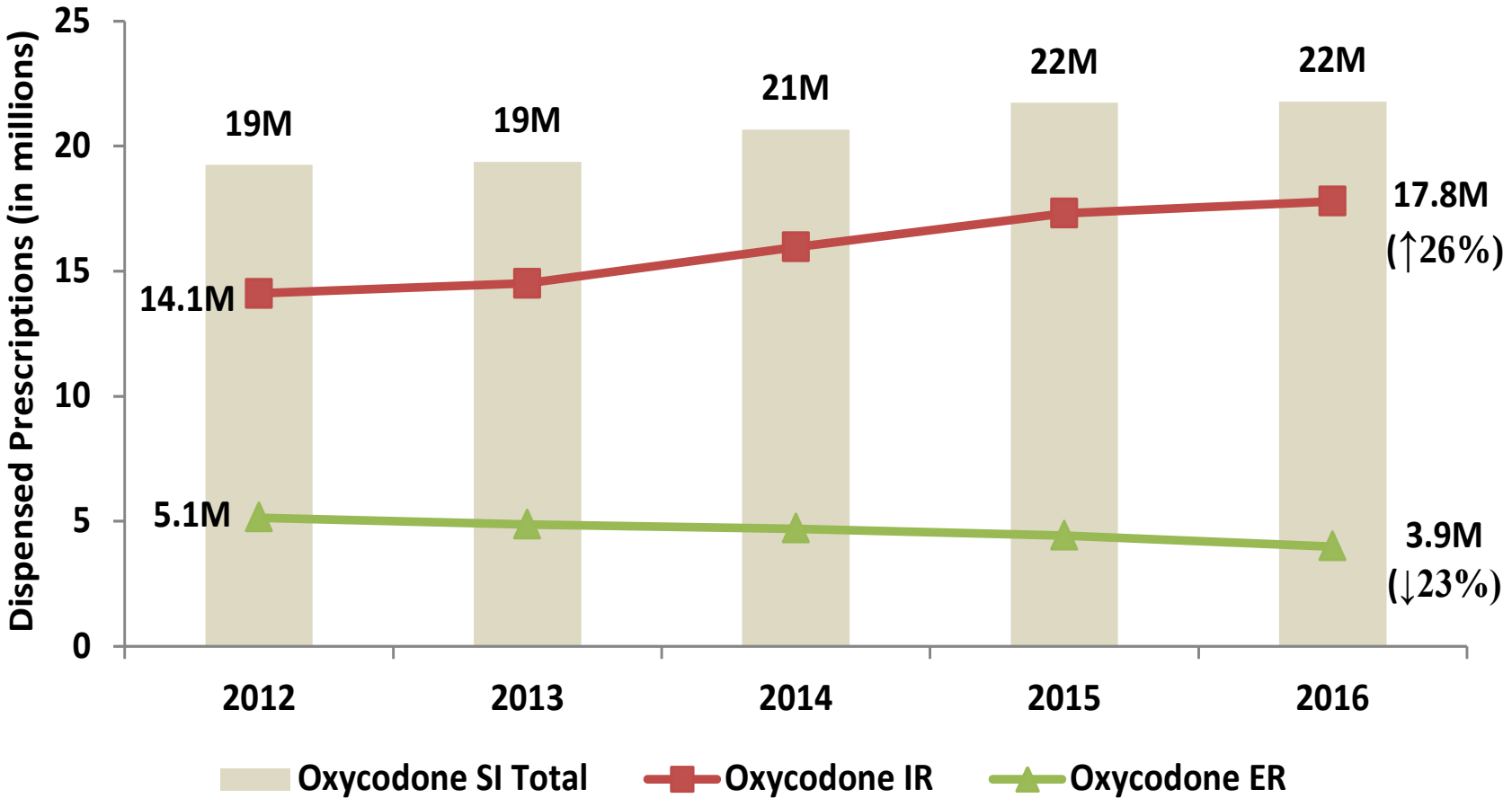
Source: QuintilesIMS National Sales Perspective™. Data Extracted April 2017.

Database Description

Prescription Utilization and Prescriber Specialty Data:

- QuintilesIMS Health, National Prescription Audit™(NPA) Database
- Measures dispensing of prescriptions out of retail pharmacies into the hands of consumers
- Data are projected to provide national estimates of utilization
- Data can be stratified by prescriber specialty

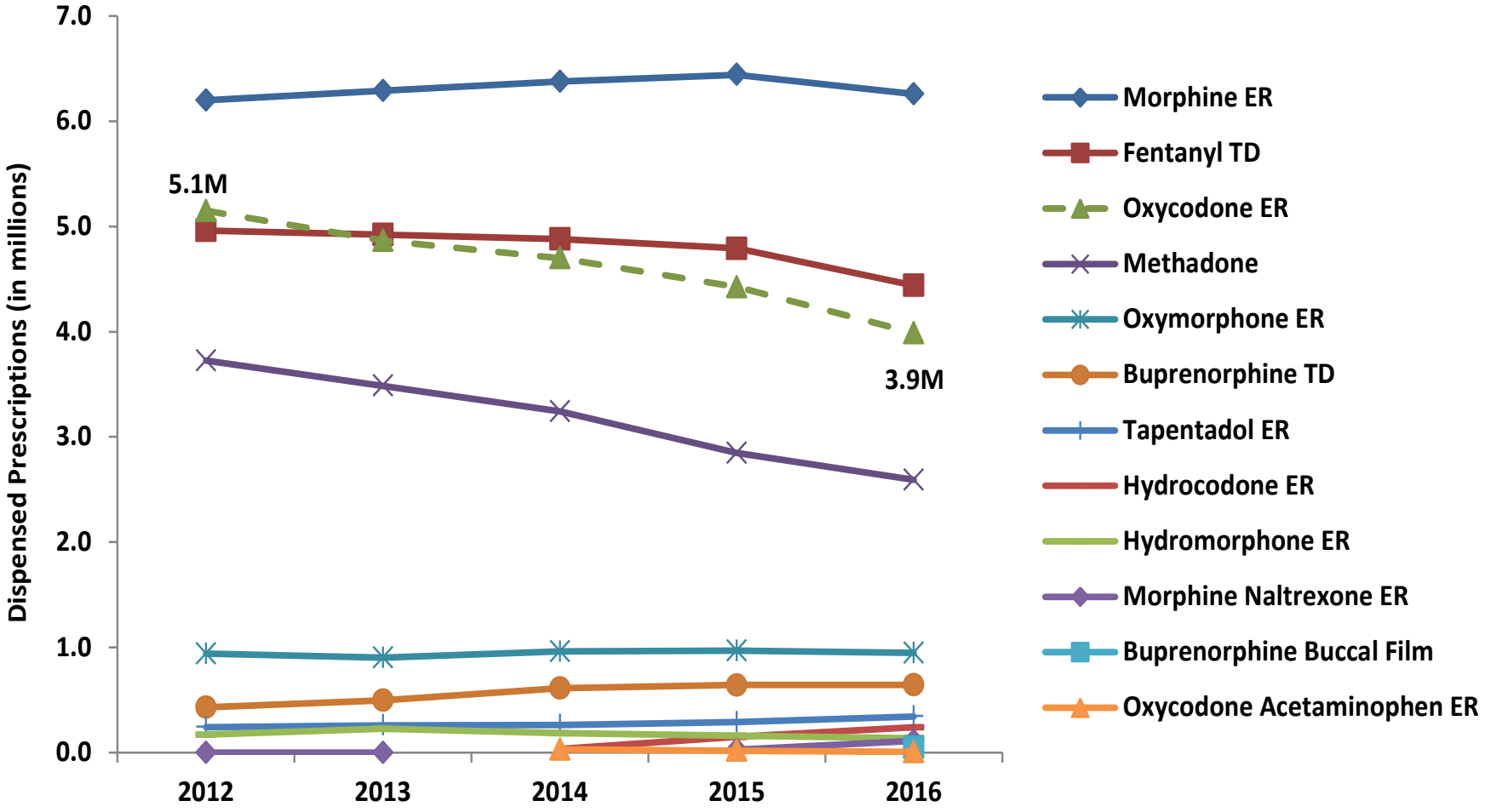
Prescription Data: Oxycodone Products



Nationally Estimated Number of Dispensed Prescriptions for Oral Single-Ingredient (SI) Oxycodone from U.S. Outpatient Retail Pharmacies

Source: QuintilesIMS, National Prescription Audit (NPA). January 2012 - December 2016. Data extracted April 2017.

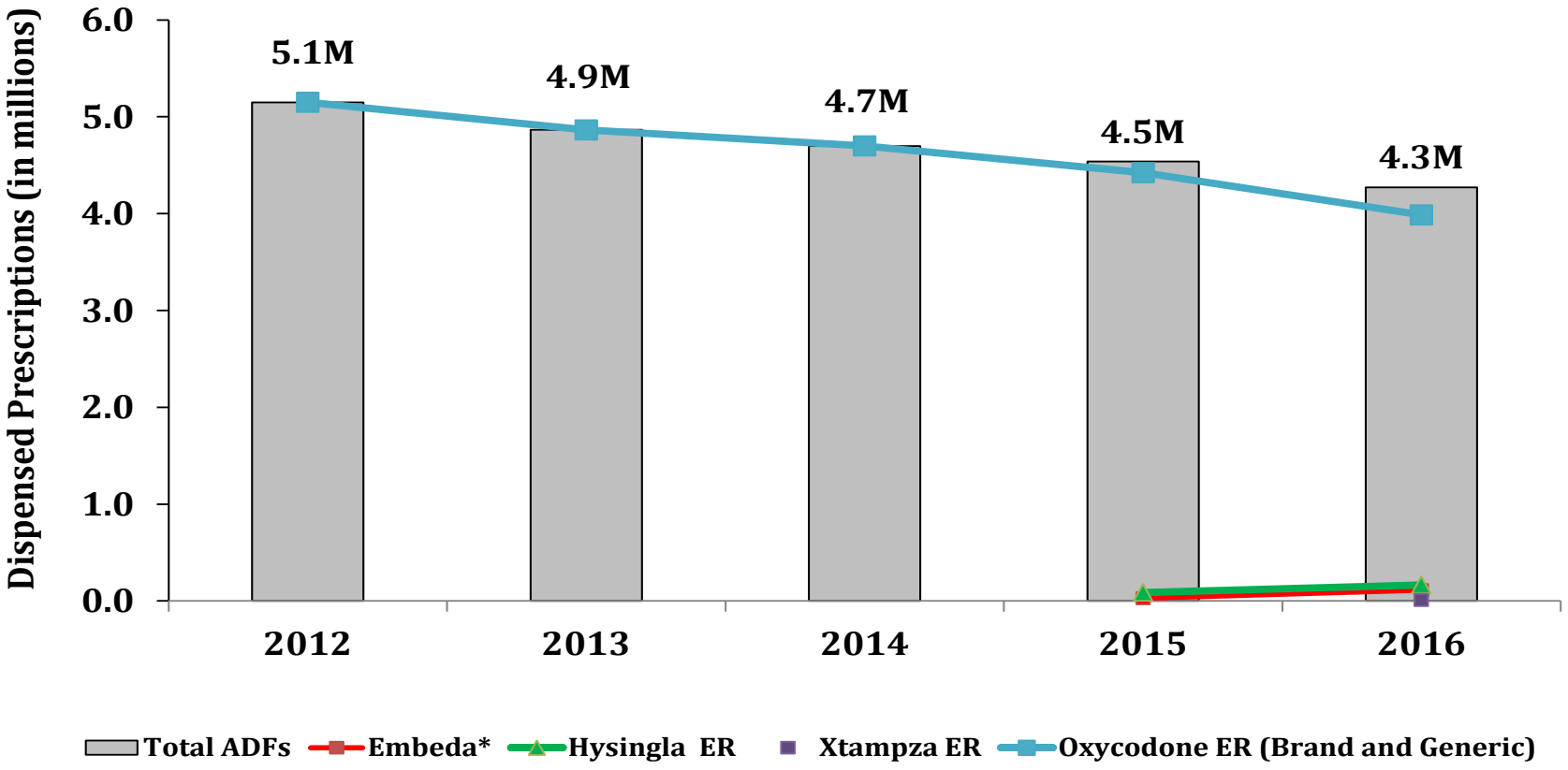
ER/LA Opioid Analgesics



Nationally Estimated Number of Dispensed Prescriptions for ER/LA Opioid Analgesics from U.S. Outpatient Retail Pharmacies

Source: QuintilesIMS, National Prescription Audit (NPA). January 2012 - December 2016. Data Extracted April 2017.

Opioid Analgesic Products with Abuse-Deterrent Labeling

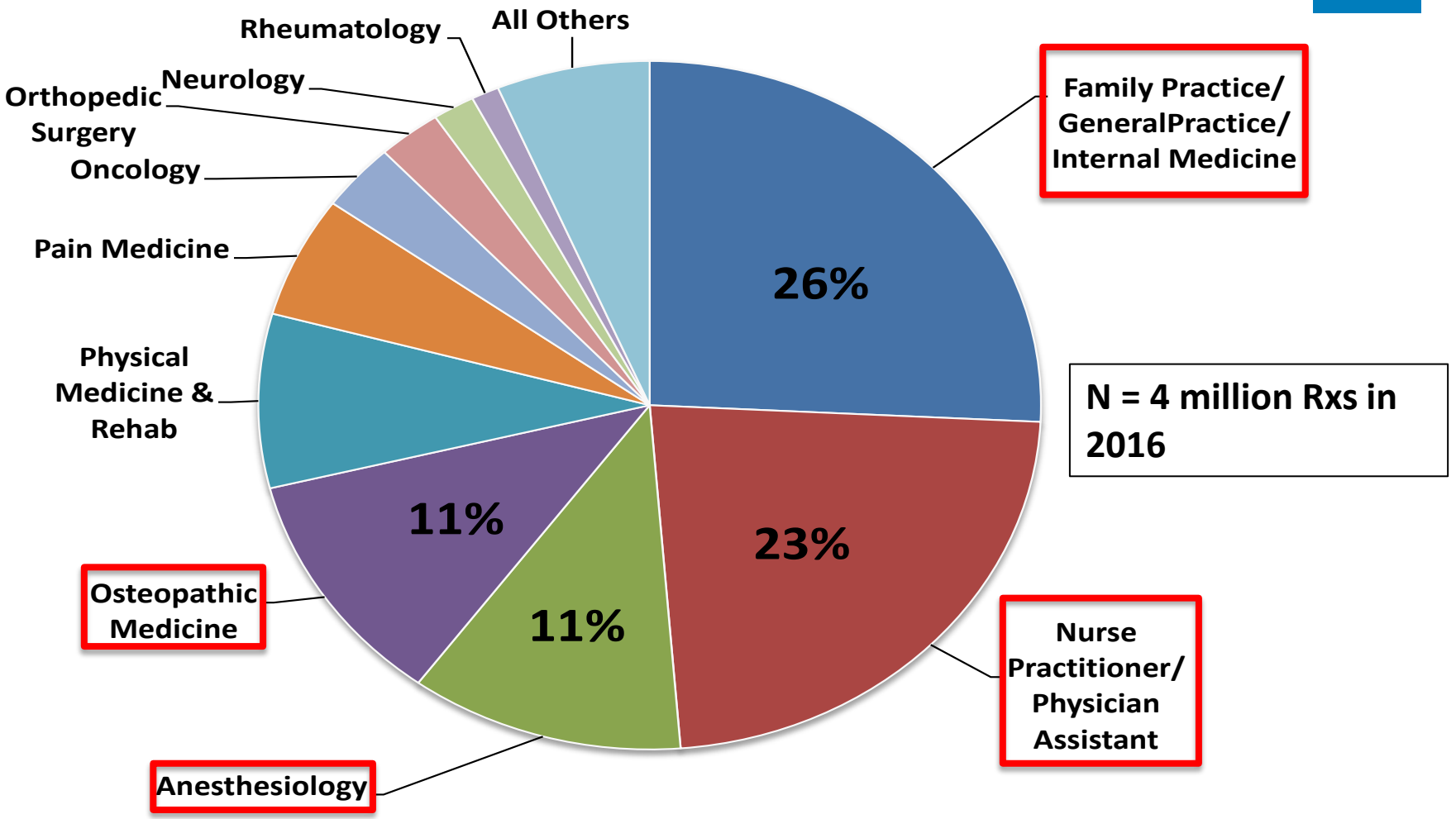


Nationally Estimated Number of Prescriptions Dispensed for Opioid Analgesic Products* with Formulations Designed to Deter Abuse from U.S. Outpatient Retail Pharmacies

Source: QuintilesIMS National Prescription Audit™, Years 2009-2016. Data Extracted March 2017.

***Not marketed during study period: Targiniq (oxycodone/naloxone ER) - Approved 07/2014; MorphaBond (morphine ER) - Approved 10/2015; Troxyca (oxycodone/naltrexone ER) - Approved 08/2016 ; Arymo (morphine ER) – Approved 01/2017; Vantrela (hydrocodone ER) – Approved 01/2017; Roxybond (oxycodone IR) – Approved 04/2017**

Top Prescriber Specialties



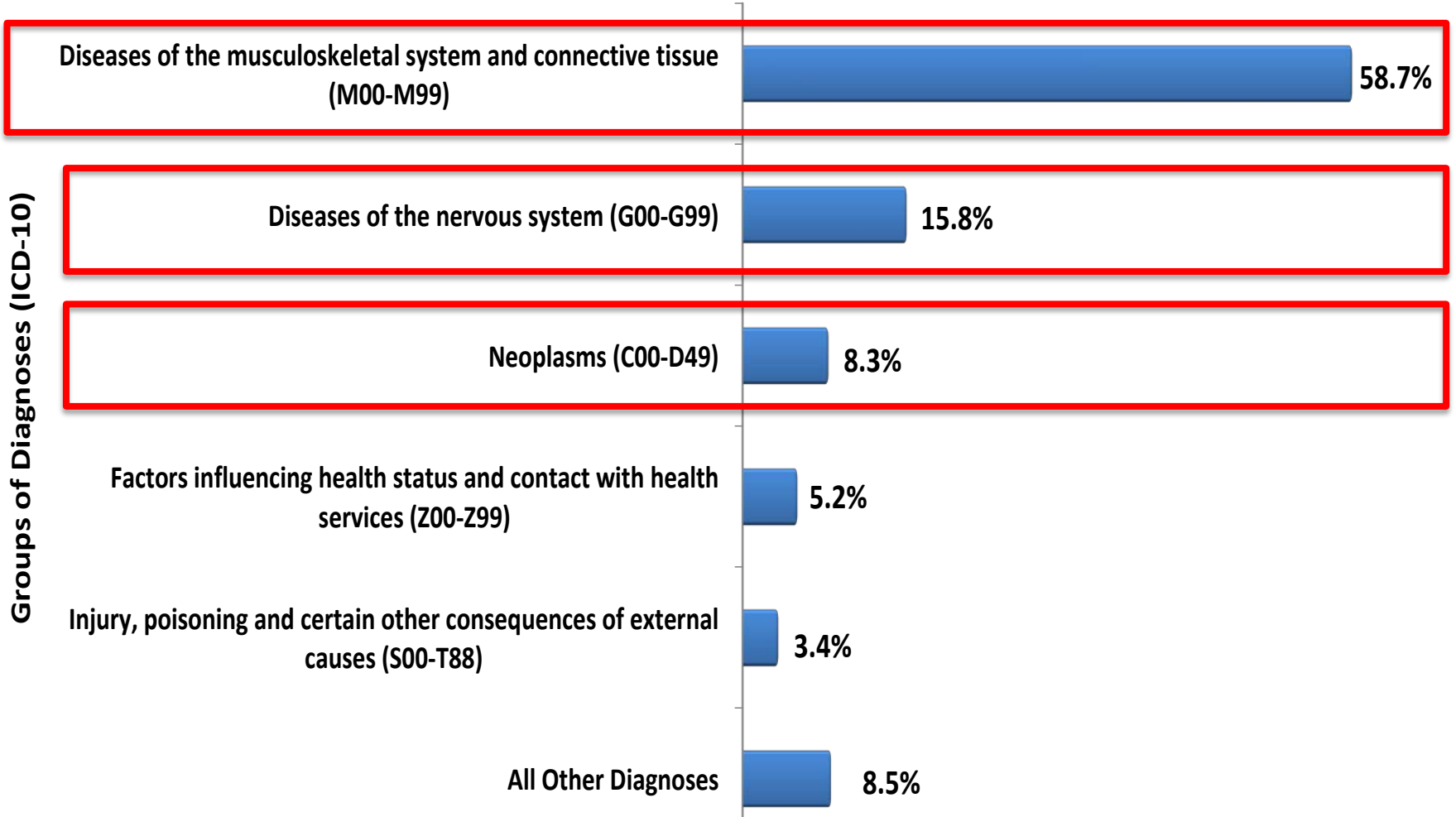
Nationally Estimated Number of Dispensed Prescriptions for Single-Ingredient Oxycodone ER from U.S. Outpatient Retail Pharmacies, Stratified by Top 10 Prescriber Specialties, Year 2016

Source: QuintilesIMS Health, National Prescription Audit (NPA). January 2016 - December 2016. Data Extracted April 2017.

U.S. Office-Based Physician Survey Data

- inVentiv Health Research & Insights, LLC., TreatmentAnswers™ Database
- Monthly surveys of 3,200 office-based physicians representing 30 specialties across the United States
- Data nationally projected to reflect national prescribing patterns
- Help characterize use of drug products in clinical practice

Diagnoses Data
2016



Top Groups of Diagnoses (ICD-10) Associated with Mentions of Single-Ingredient Oxycodone ER Products as Reported by Office-Based Physician Surveys, Year 2016

Source: inVentiv Health Research and Insights LLC., TreatmentAnswers™ with Pain Panel. 2016. Data extracted May 2017.

Limitations

- Only dispensing patterns in the outpatient retail setting was assessed
- Diagnoses information are not linked to dispensed prescriptions
- Diagnoses data were derived from surveys of office-based physician practices

Summary of Findings

- Outpatient utilization of oxycodone ER decreased
- Third most frequently dispensed ERLA opioid in 2016
- Accounted for vast majority of ADF opioid prescriptions
  - Total of 10 ADF products approved but not all marketed
- Top prescribers were primary care physicians, followed by mid-level practitioners
- Top diagnoses were for pain related to diseases of the musculoskeletal system and connective tissue

Thank you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Excipients in Oral Opioid Analgesics and IV Abuse - A Regulatory Perspective

Ellen Fields, MD, MPH
Deputy Director
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Office of New Drugs, CDER, FDA

July 26, 2017
Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee

Introduction

- Concerns raised at prior AC meetings regarding safety of excipients in oral opioid analgesics that are abused parenterally
- There have been unintended consequences of abuse-deterrent formulations, such as the recent experience of Opana ER and TTP-like illness in persons who abuse by IV route
- Oxycodone ER tablets - excipients
- Requirements for assessment of excipients
- Labeling and its impact
- Trends in IV abuse of prescription opioids

Oxycodone HCl ER Tablets

- Formulated to resist chemical extraction, dose-dumping with alcohol, to form a viscous hydrogel when in contact with aqueous environment, and to deter nasal abuse
- Excipients intended to convey abuse-deterrent (AD) properties
  - Polyethylene oxide (PEO) - gelling agent
  - Sodium lauryl sulfate (SLS) - nasal irritant
  - Blue dye - staining skin and clothes
- Other excipients (proprietary)

Oxycodone HCl ER Tablets

- Excipients in all drug products should have a specific intended purpose and excipients that do not serve a specific purpose for a product only result in unnecessary exposure to the materials.
  - USP Chapter <3> www.usp.org/sites/default/files/usp_pdf/EN/USPNF/chapter3.pdf
- We are still reviewing the safety of the excipients in Oxycodone Extended-Release Tablets for the intended oral use.

Oxycodone HCl ER Tablets

- The current formulation contains excipients that may present risks by parenteral routes of administration.
- Parenteral administration of excipients extracted from the product could result in adverse local and potentially systemic effects.

Agency Approach to Studying Excipients

- Excipients in drug products are assessed for safety for the intended route(s) of administration
  - (FDA guidance for industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf
- Drugs intended for parenteral administration cannot contain coloring agents (i.e., dyes)
  - USP Chapter <1> http://www.pharmacopeia.cn/v29240/usp29nf24s0_c1.html
- The Agency does not require that oral drug product excipients be assessed for safety for intravenous or other unintended routes

Labeling

- **Section 9.2 Abuse**
- Risks Specific to TRADENAME

  Include language specific to the risks of abusing the drug with regard to excipients, disease transmission
- A number of opioid products contain excipients with known risk in the setting of parenteral abuse
- Examples…..

Labeling

- Many products contain talc
  - MS Contin, Kadian,

Due to the presence of talc as one of the excipients in MS CONTIN, parenteral abuse can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Labeling

- Morphabond (morphine sulfate ER tablets)
- OxyContin (oxycodone HCl ER tablets)

Risks Specific to Abuse of TRADENAME

Parenteral abuse of TRADENAME can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Labeling

- Opana ER (oxymorphone ER tablets)

Risks Specific to Abuse of OPANA ER

With parenteral abuse, cases of thrombotic microangiopathy (a condition characterized clinically by thrombocytopenia and microangiopathic hemolytic anemia) have been reported; many cases resulted in hospitalization and treatment with plasmapheresis.

Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Impact of Labeling

- Doesn’t reach abuse population
  - Just saying excipients are in the solution doesn’t appear to deter abuse
- We know that
  - people inject solutions made from products intended for oral use, even when labeled as dangerous to do so
  - People who abuse opioids over time often move from less dangerous routes (i.e. oral) to more dangerous routes (i.e., injection)

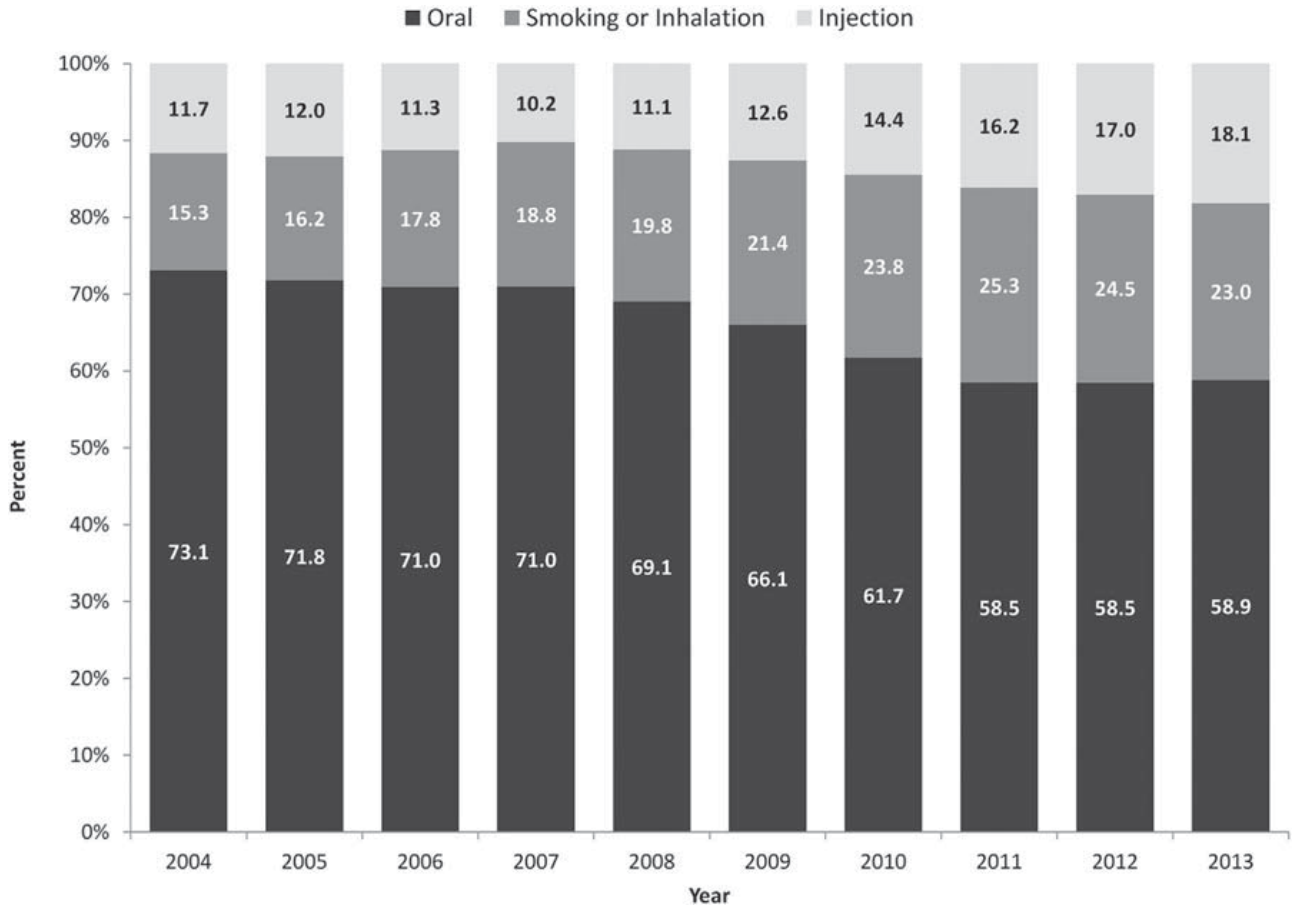
Increases in prescription opioid injection abuse among treatment admissions in the United States, 2004–2013

Christopher M. Jones[a,*], Aleta Christensen[b], R. Matthew Gladden[b]

Drug and Alcohol Dependence 176 (2017) 89-95

- Assessed trends in treatment admissions reporting injection, smoking, and inhalation abuse of prescription opioids and examined characteristics associated with non-oral routes of prescription opioid abuse in the U.S.
- Data source: Treatment Episode Data Set (TEDS)
- Prescription opioid abuse treatment admissions in the 2004–2013 were used to calculate counts and percentages of prescription opioid treatment admissions reporting oral, injection, or smoking/inhalation abuse overall, by sex, age, and race/ethnicity

Routes of Abuse Among Primary Prescription Opioid Abuse Treatment Admissions by Year, US 2004-2013



Limitations of Study

- TEDS does not capture all admissions to substance abuse treatment
- The primary, secondary, and tertiary substances of abuse reported are those that lead to treatment episode, not a complete list of all drugs used at time of admission
- TEDS data may include multiple admissions for same patient

Summary

- Excipients in drug products are assessed for safety only for the intended route(s) of administration
- Reasonable to believe that abuse of the Oxycodone HCl ER tablets via intravenous administration of extracted materials could result in adverse local and potentially systemic effects.
- Labels include risks of misuse and abuse of oral opioids with regard to excipients, but this has not effectively mitigated these risks
- Rates of abuse via injection of prescription opioids has increased
- Agency needs to consider how to approach the issue of excipients, particularly as ADF opioid analgesics may increase the opportunity for exposure to new excipients with unknown and unintended consequences.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