Outpatient Drug Utilization Patterns For Selected Opioid Analgesics in the U.S., Years 2007-2011

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Anesthetic and Analgesic Drug Products Advisory Committee
December 7, 2012

Selected Opioid Analgesics

- Combination Immediate-Release (IR)
  - Hydrocodone Combination Products
  - Oxycodone Combination Products
- Single Ingredient Extended-Release/Long-Acting (ER/LA)
  - Oxycodone ER
  - Oxymorphone ER
  - Morphine ER
  - Hydromorphone ER

Outline

- Sales Distribution
- Prescription and Patient Trends
- Prescriber Specialty
- Duration of Therapy
- Diagnosis
- Limitations
- Summary

Sales Data

Year-2011

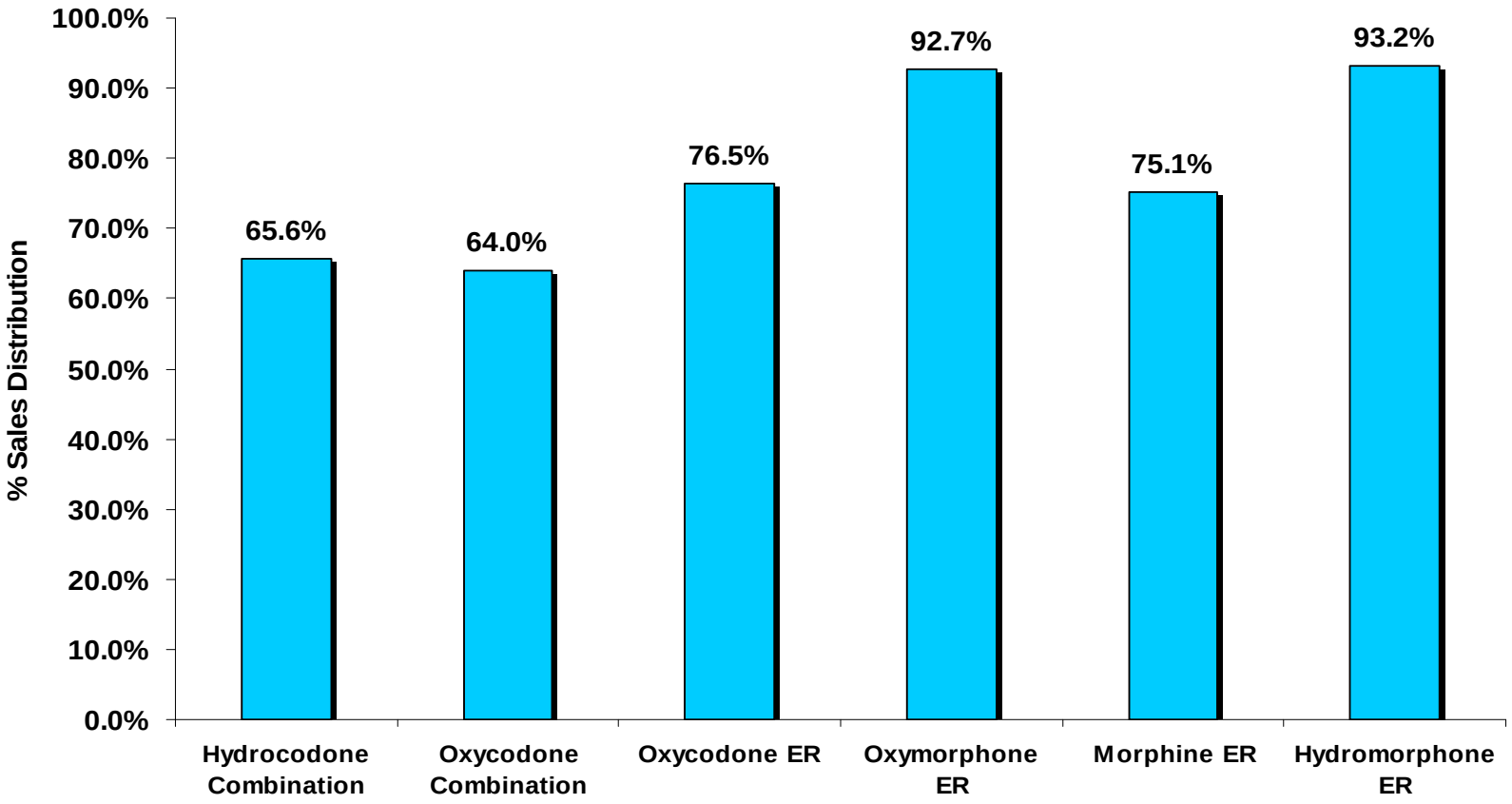
IMS Health, IMS National Sales Perspective™

IMS Health, IMS National Sales Perspectives™

Measures sales data from *manufacturer to retail and non-retail channels of distribution*

- Retail Channels - chain, independent, mass merchandisers, food stores with pharmacies
- Non-Retail Channels - federal facilities, non-federal hospitals, clinics, long-term care facilities, home health care, HMOs, miscellaneous channels (prisons, universities, other)

Sales Distribution of Selected Opioid Analgesics to U.S. Outpatient Retail Pharmacies, Year 2011



IMS Health, National Sales Perspective™, Extracted November 2012

Prescription and Patient Level Data Outpatient Retail Pharmacies

Years 2007-2011

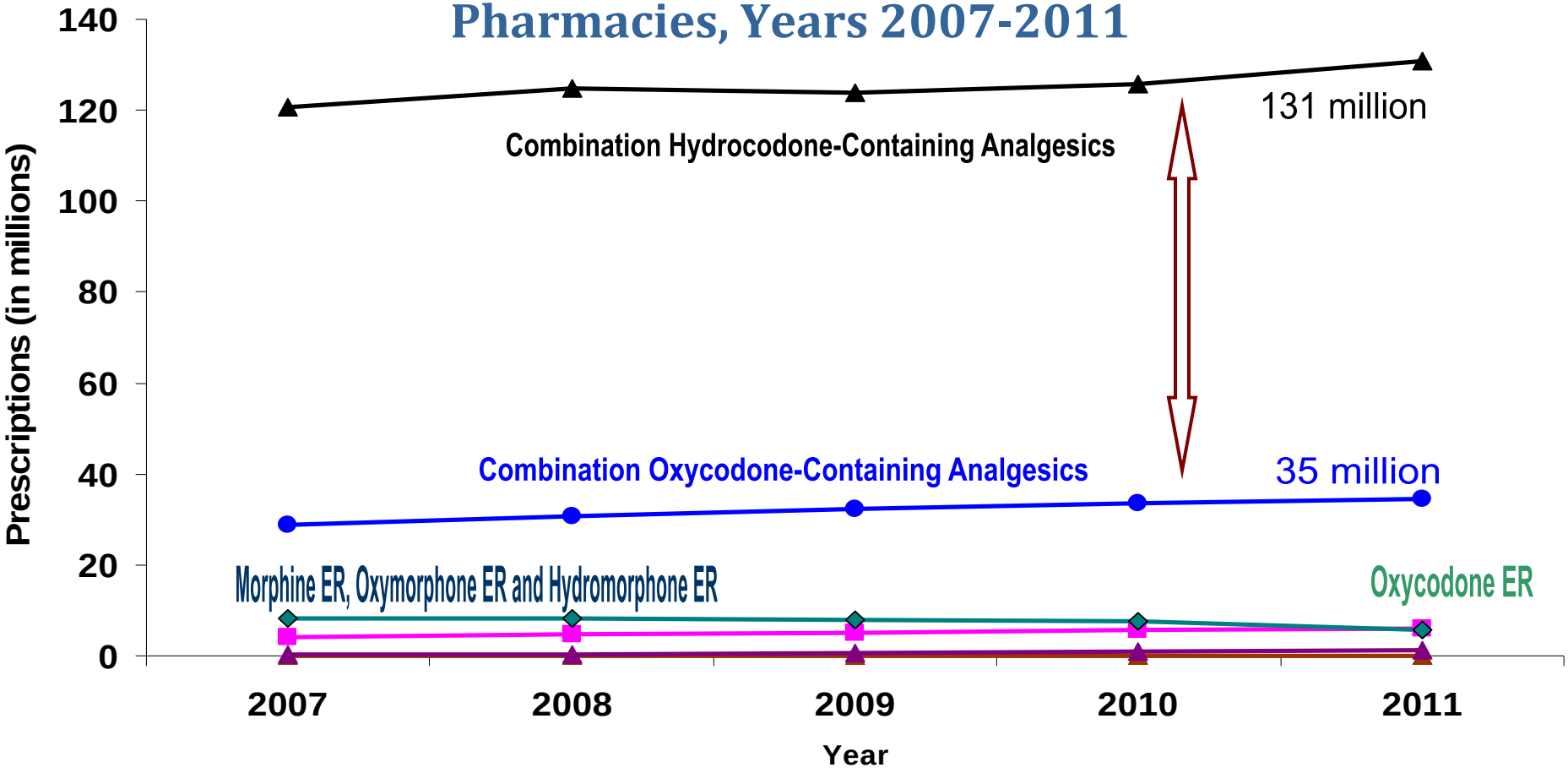
IMS Health, Vector One®: National (VONA) and Total Patient Tracker (TPT)

IMS Health, Vector One®: National (VONA) and Total Patient Tracker (TPT)

Measures dispensing of prescriptions *out of retail pharmacies into the hands of consumers*

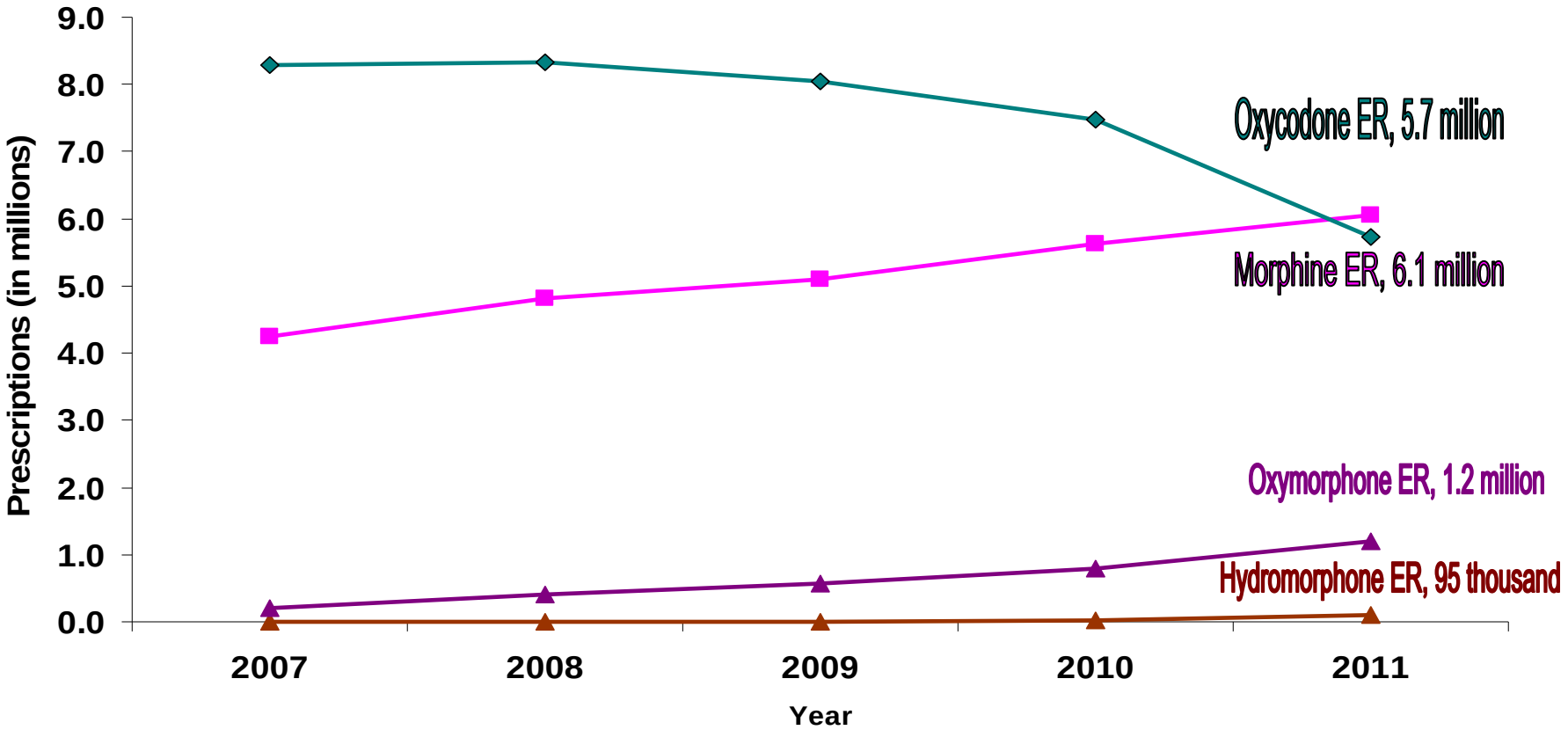
- National-level projected prescription and patient-centric tracking service
- 59,000 U.S. retail pharmacies

Number of Prescriptions Dispensed for Selected Opioid Analgesics Dispensed Through U.S. Outpatient Retail Pharmacies, Years 2007-2011



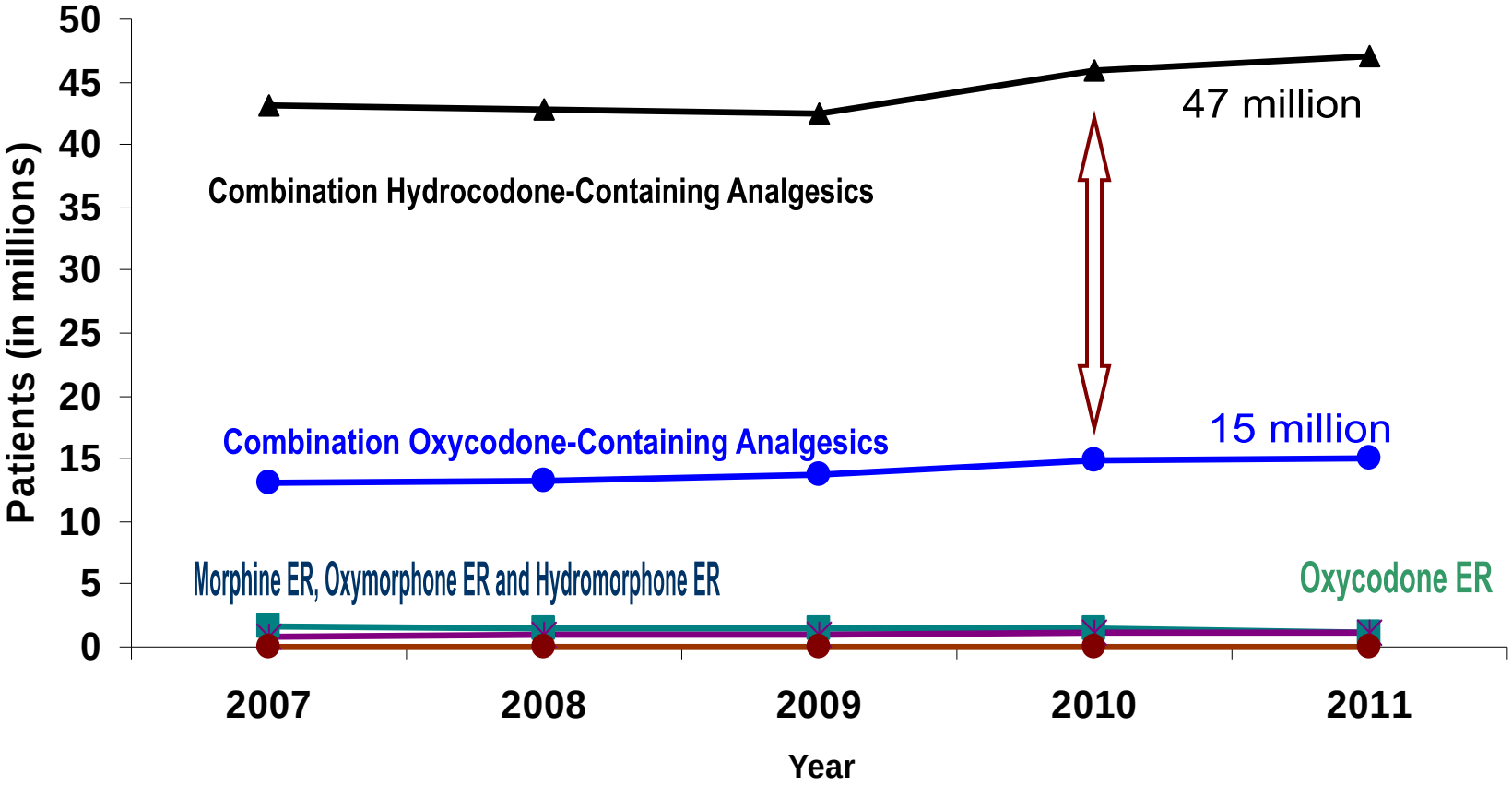
IMS Health, Vector One®: National (VONA). Extracted September, November 2012

Number of Prescriptions for Selected Extended-Release/Long-Acting Opioid Analgesics Dispensed Through U.S. Outpatient Retail Pharmacies, Years 2007-2011



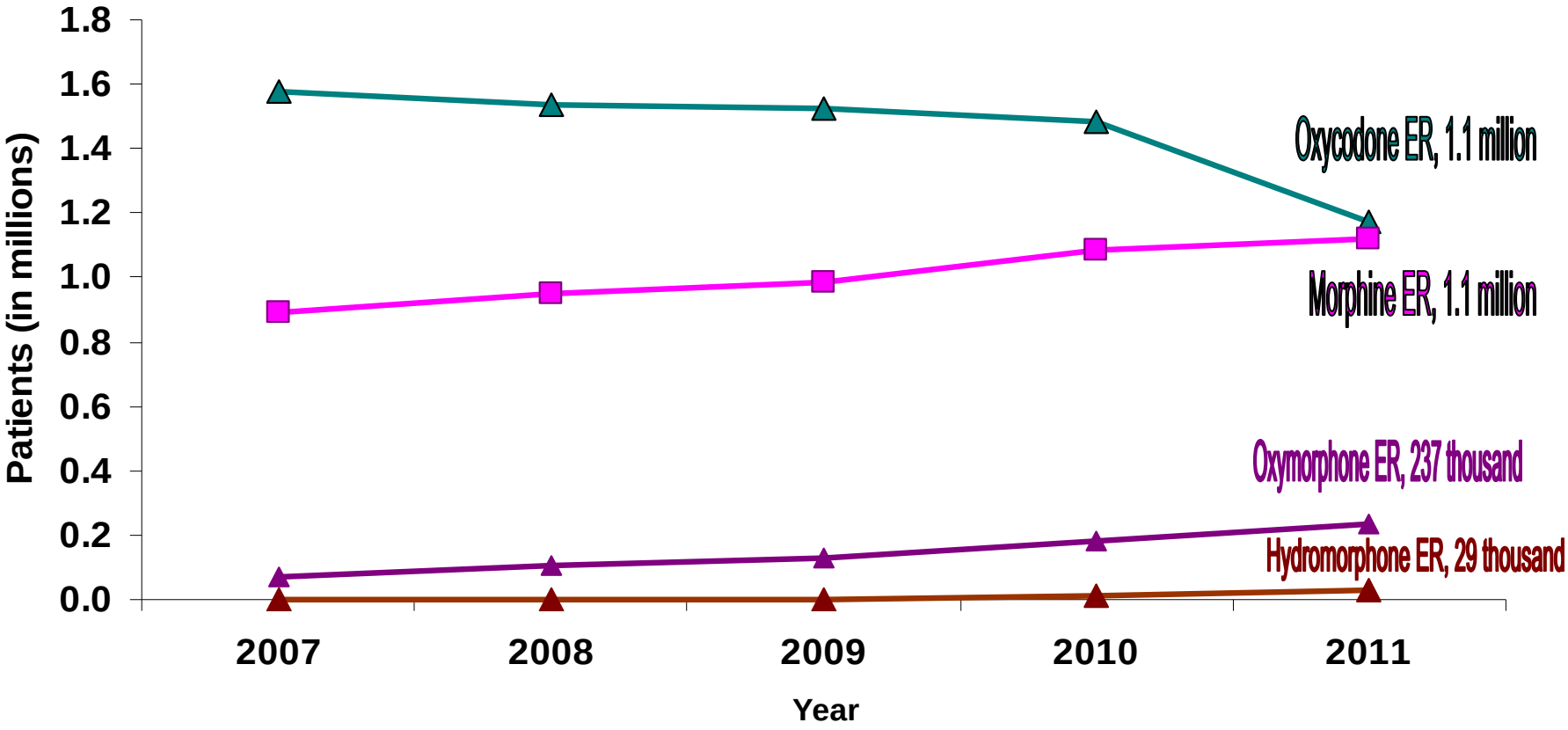
IMS Health, Vector One®: National (VONA). Extracted September, November 2012

Number of Patients Receiving a Dispensed Prescription for Selected Opioid Analgesics through U.S. Outpatient Retail Pharmacies, Years 2007-2011



IMS Health, Total Patient Tracker (TPT). Extracted September, November 2012

Number of Unique Patients Receiving Prescriptions for Selected Extended-Release/Long-Acting Opioid Analgesics Dispensed Through U.S. Outpatient Retail Pharmacies, Years 2007-2011



IMS Health, Total Patient Tracker (TPT). Extracted September, November 2012

Prescriber Specialty Data
Outpatient Retail Pharmacies

Years 2007-2011

IMS Health, Vector One®: National (VONA)

Percentage of Prescriptions Dispensed for Selected Opioid Analgesics by Prescriber Specialty Through U.S. Outpatient Retail Pharmacies, Years 2007-2011, Cumulative

	Hydrocodone Combination	Oxycodone Combination	Oxycodone ER	Oxymorphone ER	Morphine ER	Hydromorphone ER
	Share %	Share %	Share %	Share %	Share %	Share %
General Practice/Family Practice/Osteopathy	25.6	18.7	26.8	17.1	24.7	9.5
Internal Medicine	14.0	12.5	16.9	9.6	14.9	5.1
Dentist	10.4	5.3	0.1	0.1	0.1	0.1
Orthopedic Surgery	8.3	8.9	4.1	0.9	1.2	1.2
Unspecified	5.6	5.9	6.2	7.9	7.2	9.5
Physician Assistant	3.8	5.0	3.8	6.5	4.6	6.2
Nurse Practitioner	3.3	3.6	5.0	8.0	6.7	5.4
Anesthesiologists	2.6	4.3	10.3	21.0	15.3	29.3
Physical Medicine/Rehab	2.4	3.6	9.1	18.0	10.9	23.3
All Others	24.0	32.2	17.9	10.9	14.4	10.5

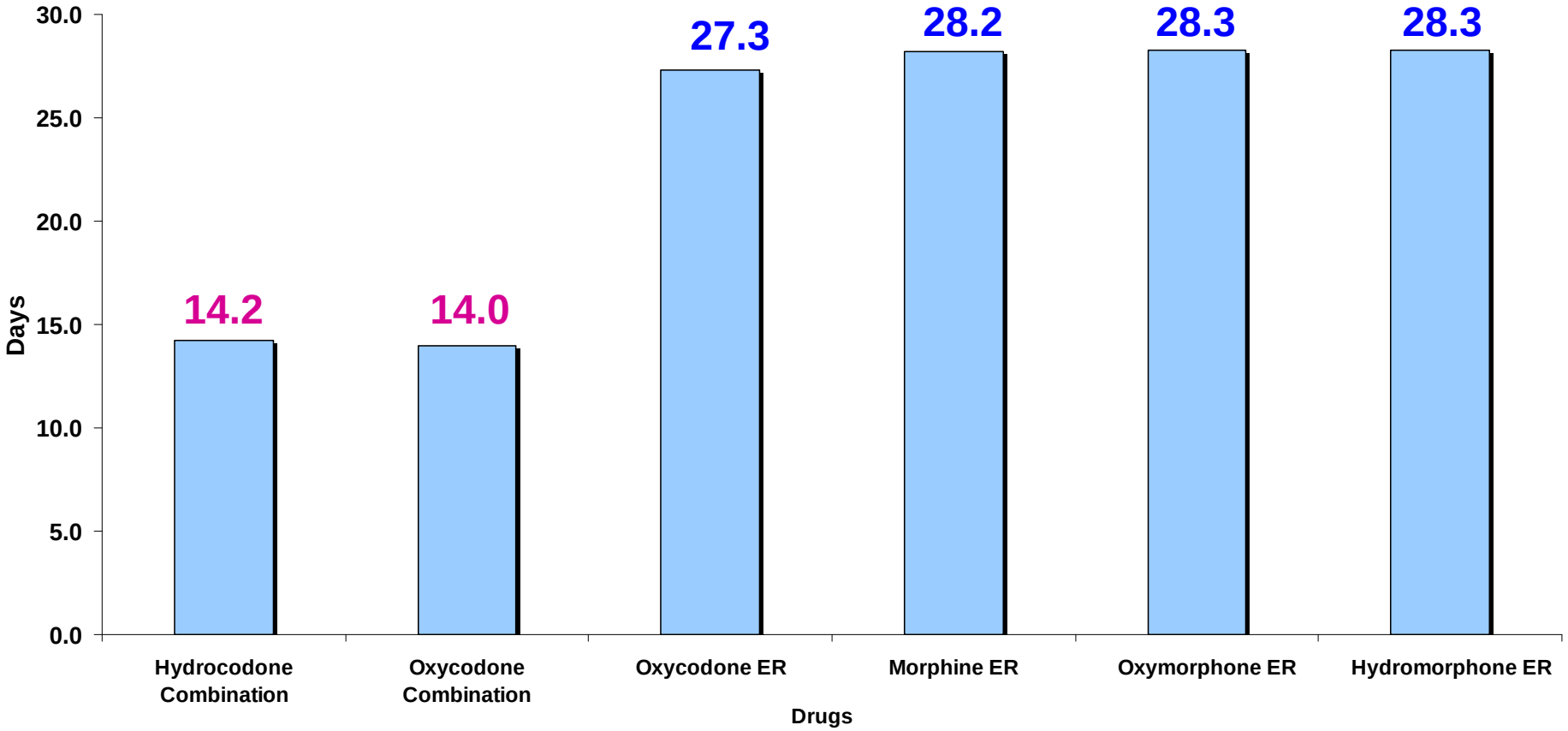
Source: IMS, Vector One®: National (VONA) Extracted September and November 2012.

Average Days of Therapy Dispensed Per Prescription
Outpatient Retail Pharmacies

Year 2011

IMS Health, Vector One®: National (VONA)

Average Number of Days of Therapy Dispensed Per Prescription for Selected Opioid Analgesics Through U.S. Outpatient Retail Pharmacies, Year 2011



IMS Health, Vector One®: National (VONA). Extracted September, November 2012

Distribution of Days of Therapy

Year 2010-2011

Source Healthcare Analytics Prometis Lx®

Source Healthcare Analytics Prometis Lx®

- **Measures *longitudinal* product use based on medical and prescription claims**
  - Commercial plans
  - Medicare Part D plans
  - Medicaid claims
  - Cash

Crude Days of Therapy for Selected Opioid Analgesics in a Sample of Patients, Years 2010-2011, cumulative

Source Healthcare Analytics ProMetis Lx®, Extracted January, 2012

Regimen	Number of Sample Patients	Days of Therapy			
		Median	Average	Min	Max
Combination Hydrocodone-Containing Analgesics	16,281,353	8	45.1	2	730
Combination Oxycodone-Containing Analgesics	5,497,455	6	30.0	2	730
Oxycodone ER	70,654	31	42.6	2	664

Diagnosis Data

January 2007 – November 2011

Encuity Research TreatmentAnswers™

Diagnosis Data

Encuity Research, TreatmentAnswers™

- Monthly survey that monitors disease states and physician-intended prescribing habits on a national level
- 3,200 panelists, 30 specialties, 115 pain specialists
- Includes diagnoses, patients characteristics, and treatment patterns

Diagnoses Associated with Selected Opioid Analgesics, January 2007-November 2011, Cumulative

	Hydrocodone Combination	Oxycodone Combination	Oxycodone ER	Morphine ER	Oxymorphone ER	Hydromorphone ER
	N= 2,850,000	N= 1,406,000	N= 13,385,000	N= 2,618,000	N= 1,410,000	N= 183,000
Diseases of the Musculoskeletal System and Connective Tissue (710-739)	25%	20%	59%	68%	63%	64%
Disease of Respiratory System (462-493)	21%	2%	0%	0%	0%	0%
Fractures, Sprains, Contusions, Injuries (800-999)	19%	26%	6%	3%	5%	9%
Follow up examinations	10%	14%	6%	4%	6%	5%
Headaches and Nerve Pain (337-359)	3%	4%	17%	15%	14%	4%
Fever and General Symptoms (780-789)	3%	4%	2%	2%	5%	7%
Neoplasms (140-239)	2%	0%	7%	4%	4%	8%
Disease of Genitourinary System (592-626)	2%	22%	0%	0%	1%	0%
Bacterial, Viral and Parasitic Infections (001-138)	1%	0%	1%	0%	1%	0%
All others	13%	7%	2%	2%	3%	3%

Source: Encuity Research TreatmentAnswers™ , Extracted January, November 2012

Limitations

- Only outpatient opioid use assessed; inpatient, emergency department and other non-outpatient settings not included
- No statistical tests were performed to determine statistically significant changes over time

Summary

- The utilization of combination hydrocodone containing analgesics far exceeded all other opioid analgesics analyzed
- Primary care practitioners prescribed about 40% of total IR combination opioid analgesic prescriptions
  - Shorter mean days of therapy per prescription
  - Appear to be used more often to treat acute pain conditions
- As compared to IR combination opioid analgesics, ER/LA opioid analgesics were prescribed more often by Anesthesiologist and Physical Medicine and Rehabilitation
  - Longer mean days of therapy per prescription
  - Appear to be used more often to treat chronic pain conditions

Misuse / Abuse of Hydrocodone and Oxycodone Products by Composition and Formulation:

Findings from the Drug Abuse Warning Network (DAWN)

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Office of Pharmacovigilance and Epidemiology (OPE)
Office of Surveillance and Epidemiology (OSE)
CDER, FDA

Question of Interest

- How much abuse can we anticipate might be associated with a single-ingredient extended-release hydrocodone product?
  - No such product currently on the U.S. market

Rationale for this Analysis

- **Hydrocodone:** combination immediate-release product
- **Oxycodone:** combination immediate-release product
  - **Oxycodone** also available as single-ingredient, extended-release product
- Compare abuse patterns for two formulations of **oxycodone**
- We may learn what abuse patterns are possible for single-ingredient, extended- release **hydrocodone** product

Oxycodone – Is it Similar to Hydrocodone?

- Opioid analgesic
- Long marketing history
- Large market share

BUT

- Oxycodone products (combination and single-ingredient) are schedule II
- Hydrocodone combination products are schedule III, single-ingredient is schedule II

Drug Abuse Warning Network (DAWN)

- Nationally representative, stratified probability sample of short-term, non-federal hospitals with 24-hour emergency departments (EDs)
- National estimates of drug-related emergency department visits
- Provides estimates that are specific to:
  - Substance
  - Composition
  - Formulation

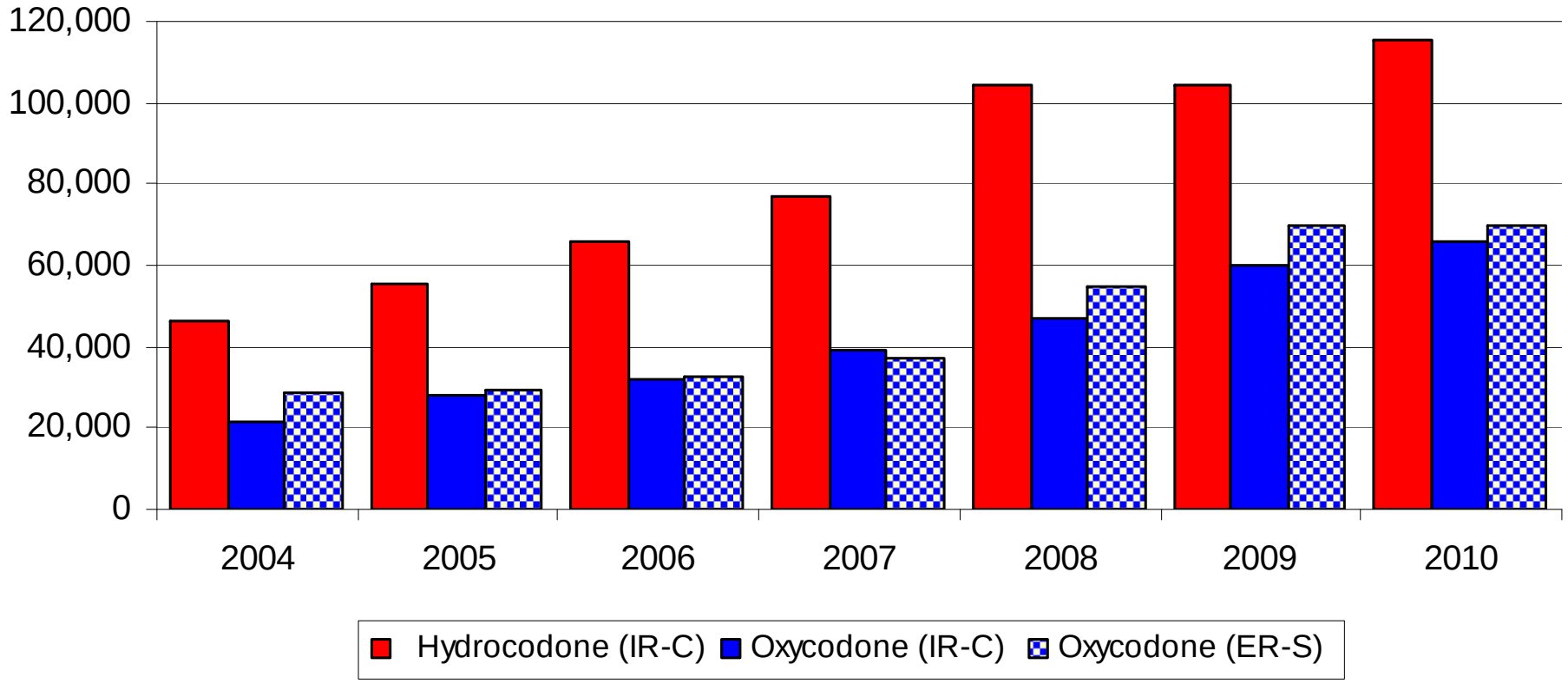
All Misuse and Abuse (AllMA) Case Construct

- **AllMA –** all misuse/abuse:
  - Overmedication
  - Seeking detox
  - "Other"
  - ED visits where illegal drugs or alcohol present and contributed to visit

Analysis – "Abuse Ratios"

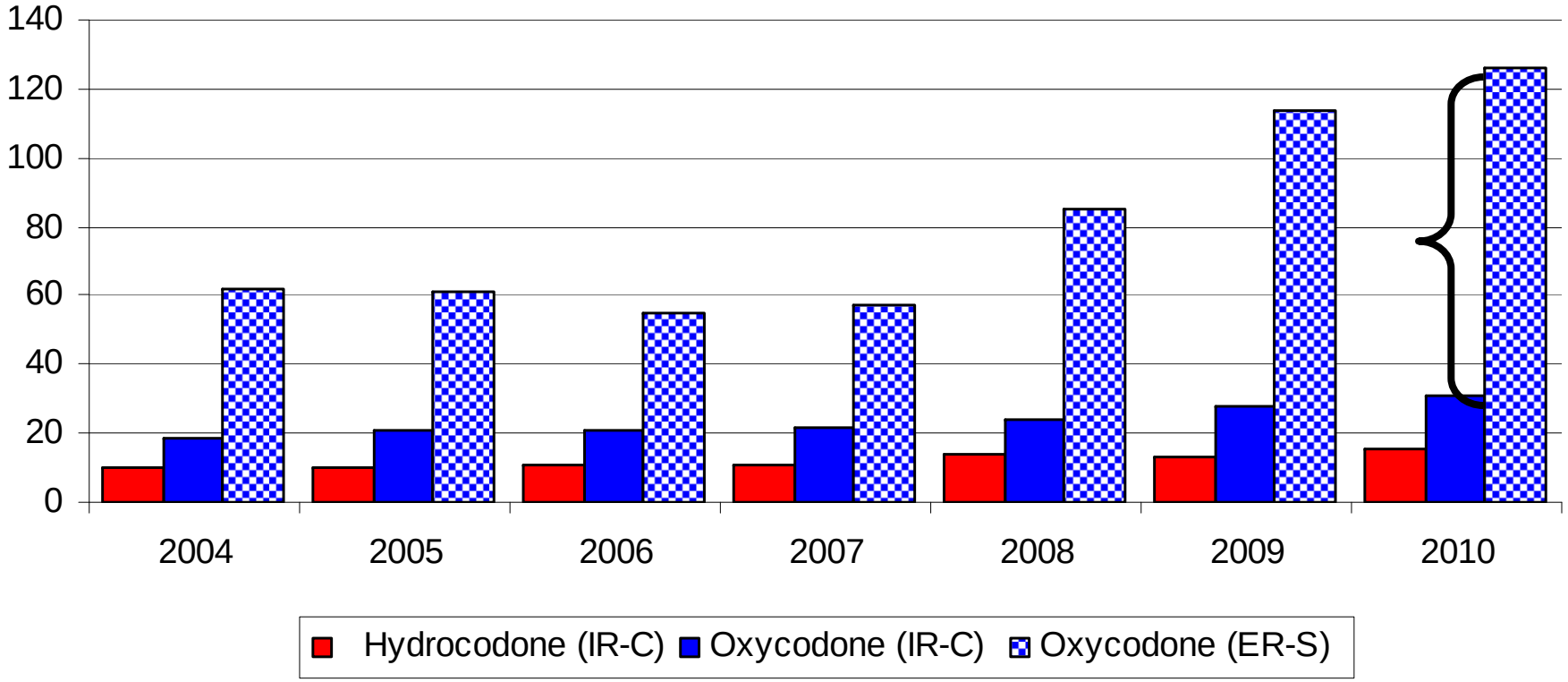
- **Numerator data**
  - Number of AllMA related ED visits (DAWN)
- **Denominator data**
  - Million tablets dispensed: used as proxy for drug availability
- **Abuse ratios**
  - Number of AllMA ED visits /million tablets dispensed

National Estimates of AllMA ED Visits by Drug Formulation: DAWN 2004-2010



Source: DAWN 2004-2010; SAMHSA

Abuse Ratios -- National Estimates of AllMA ED Visits per Million Tablets Dispensed: 2004–2010



Sources: DAWN 2004-2010; SAMHSA; IMS Health

Limitations

- Abuse ratios use numerator and denominator data from different sources
  - Data are not linked
  - Different sampling methodologies
  - Different populations
- Focuses only on abuse-related ED visits as a measure of abuse

Summary

- The abuse ratio (for ED visits) for single-ingredient ER oxycodone products is 3-4 fold higher than combination IR oxycodone products
- May be useful in anticipating abuse patterns for single-ingredient ER hydrocodone products, if approved
  - Magnitude of abuse ratios is higher for oxycodone than hydrocodone, but abuse patterns between formulations may be similar

Extended-Release/Long-Acting Opioid Analgesics REMS An Overview

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Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research, FDA

Outline

- What is a REMS
- Goals of the Extended Release/Long Acting (ER/LA) opioid analgesics REMS
- Components of the ER/LA Opioid Analgesics REMS
- ER/LA REMS would apply to hydrocodone-ER (Zohydro ER)

What is a "REMS"?

- Risk Evaluation and Mitigation Strategies (REMS) are intended for drugs with serious risks that would outweigh the benefits absent some special risk management tools
- A REMS is a risk management plan that uses risk minimization strategies beyond approved professional labeling to manage serious risks associated with a drug
- Can be required at the time of drug approval or during the postmarket period when "new safety information" becomes available

REMS Elements

- Potential components
  - A Medication Guide or Patient Package Insert
  - Communication plan
  - Elements to assure safe use (ETASU)
    - (a) Health care providers who prescribe the drug have particular training or experience, or are specially certified
    - (b) Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
    - (c) The drug is dispensed to patients only in certain health care settings
    - (d) The drug is dispensed to patients with evidence or other documentation of safe use conditions
    - (e) Patient is subject to certain monitoring
    - (f) Patient is enrolled in a registry
  - Implementation system
- REMS are required to have a timetable for submission of assessments of the REMS

ER/LA Opioid Analgesics REMS Goals

- Help address the significant increase in inappropriate prescribing, misuse and abuse of these products over the past decade.
- Minimize the burden on the healthcare system of having all these products with a different REMS.
  - Any new member of the ER/LA opioid analgesic class will be required to participate in the ER/LA REMS

ER/LA Opioid Analgesics Included in REMS

AVINZA (morphine sulfate) extended-release capsules

BUTRANS (buprenorphine) Transdermal System for transdermal administration

DOLOPHINE (methadone hydrochloride) tablets and its generic equivalents

METHADONE ORAL SOLUTION and its generic equivalents

METHADONE ORAL CONCENTRATE

DURAGESIC (Fentanyl Transdermal System) for transdermal administration and its generic equivalents

EMBEDA (morphine sulfate and naltrexone hydrochloride) extended-release capsules

EXALGO (hydromorphone HCL) extended-release tablets

KADIAN (morphine sulfate) extended-release capsules and its generic equivalent

MS CONTIN (morphine sulfate) controlled release tablets and its generic equivalents

NUCYNTA ER (tapentadol) extended-release oral tablets

OPANA ER (oxymorphone hydrochloride) extended-release tablets and its generic equivalents

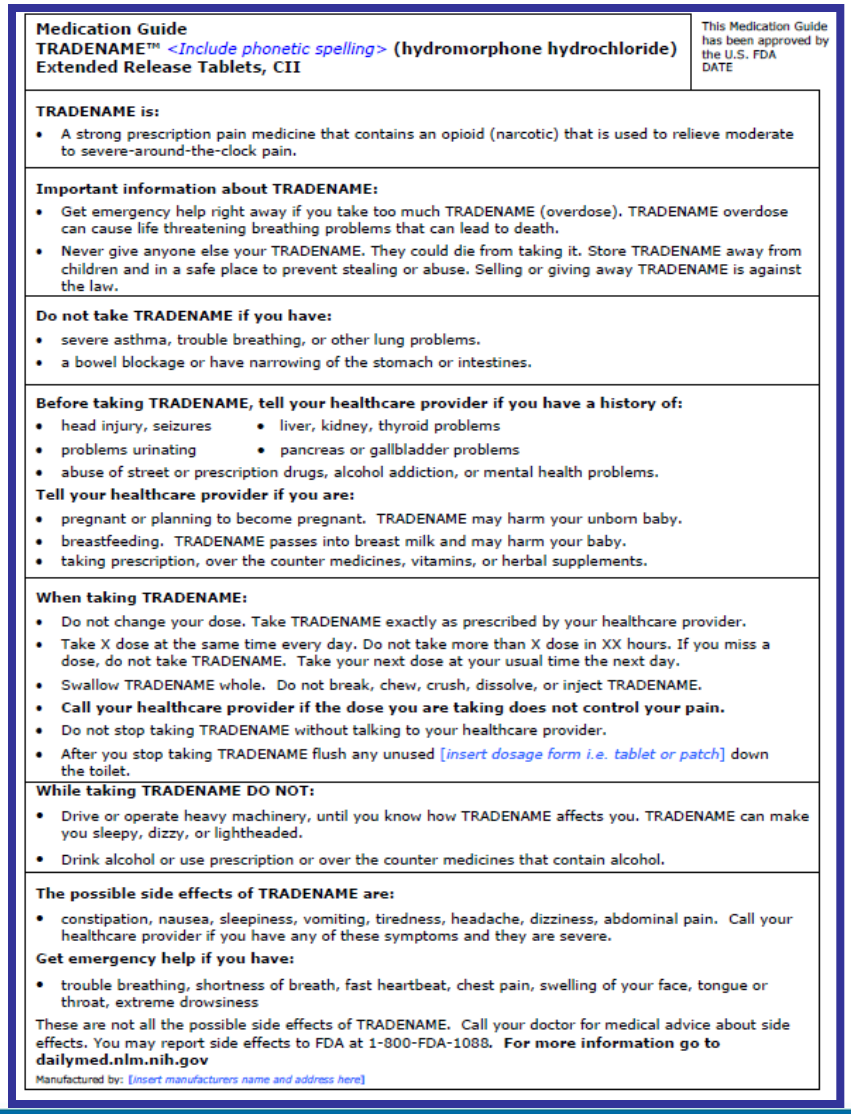
OXYCONTIN (oxycodone hydrochloride controlled-release) tablets

ER/LA REMS Elements

- Medication Guide
- Elements to Assure Safe Use
  - Patient Counseling Document
  - Training for healthcare providers who prescribe ER/LA opioid analgesics
- Timetable for Submission of Assessments

ER/LA Opioid Analgesics REMS Medication Guide

- Communicates essential information to patients
- Not intended to replace patient counseling
- Aids patients in use of medication at home
- Has both common content applicable to all ER/LA opioids and product specific information necessary for safe and effective use of the drug



Medication Guide
TRADENAME™ *<Include phonetic spelling>* **(hydromorphone hydrochloride) Extended Release Tablets, CII**

This Medication Guide has been approved by the U.S. FDA
DATE

TRADENAME is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to relieve moderate to severe-around-the-clock pain.

Important information about TRADENAME:

- Get emergency help right away if you take too much TRADENAME (overdose). TRADENAME overdose can cause life threatening breathing problems that can lead to death.
- Never give anyone else your TRADENAME. They could die from taking it. Store TRADENAME away from children and in a safe place to prevent stealing or abuse. Selling or giving away TRADENAME is against the law.

Do not take TRADENAME if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking TRADENAME, tell your healthcare provider if you have a history of:

- head injury, seizures
- liver, kidney, thyroid problems
- problems urinating
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.

Tell your healthcare provider if you are:

- pregnant or planning to become pregnant. TRADENAME may harm your unborn baby.
- breastfeeding. TRADENAME passes into breast milk and may harm your baby.
- taking prescription, over the counter medicines, vitamins, or herbal supplements.

When taking TRADENAME:

- Do not change your dose. Take TRADENAME exactly as prescribed by your healthcare provider.
- Take X dose at the same time every day. Do not take more than X dose in XX hours. If you miss a dose, do not take TRADENAME. Take your next dose at your usual time the next day.
- Swallow TRADENAME whole. Do not break, chew, crush, dissolve, or inject TRADENAME.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- Do not stop taking TRADENAME without talking to your healthcare provider.
- After you stop taking TRADENAME flush any unused *[insert dosage form i.e. tablet or patch]* down the toilet.

While taking TRADENAME DO NOT:

- Drive or operate heavy machinery, until you know how TRADENAME affects you. TRADENAME can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over the counter medicines that contain alcohol.

The possible side effects of TRADENAME are:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue or throat, extreme drowsiness

These are not all the possible side effects of TRADENAME. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**

Manufactured by: *[insert manufacturers name and address here]*

ER/LA Opioid Analgesics Patient Counseling Document

- One page document
- Allows specific patient information to be included

Patient Counseling Document on Extended-Release / Long-Acting Opioid Analgesics

Patient Name:

The DOs and DON'Ts of Extended-Release / Long - Acting Opioid Analgesics

DO:

- Read the **Medication Guide**
- Take your medicine exactly as prescribed
- Store your medicine away from children and in a safe place
- Flush unused medicine down the toilet
- Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Call 911 or your local emergency service right away if:

- You take too much medicine
- You have trouble breathing, or shortness of breath
- A child has taken this medicine

Talk to your healthcare provider:

- If the dose you are taking does not control your pain
- About any side effects you may be having
- About all the medicines you take, including over-the-counter medicines, vitamins, and dietary supplements

DON'T:

- **Do not** give your medicine to others
- **Do not** take medicine unless it was prescribed for you
- **Do not** stop taking your medicine without talking to your healthcare provider
- **Do not** break, chew, crush, dissolve, or inject your medicine. If you cannot swallow your medicine whole, talk to your healthcare provider.
- **Do not** drink alcohol while taking this medicine

For additional information on your medicine go to: **dailymed.nlm.nih.gov**

Patient Counseling Document on Extended-Release / Long-Acting Opioid Analgesics

Patient Name:

Patient Specific Information

Patient information

Take this card with you every time you see your healthcare provider and tell him/her:

- Your complete medical and family history, including any history of substance abuse or mental illness
- The cause, severity, and nature of your pain
- Your treatment goals
- All the medicines you take, including over-the-counter (non-prescription) medicines, vitamins, and dietary supplements
- Any side effects you may be having

Take your opioid pain medicine exactly as prescribed by your healthcare provider.

ER/LA Opioid Analgesics REMS Prescriber Education

- Continuing Education (CE) training will be provided through accredited CE activities supported by independent educational grants from ER/LA opioid analgesic manufacturers
- FDA developed the core messages (FDA Blueprint) to be communicated to prescribers
- The prescriber training program is voluntary
- The core REMS prescriber education to be about three hours in length
- Content is not exhaustive nor a substitute for a more comprehensive pain management course
- A list of REMS-compliant CE courses offered by accredited CE providers will be posted at www.ER-LA-opioidREMS.com when the list becomes available

FDA Blueprint* for Prescriber Education for ER/LA Opioid Analgesics

- Why Prescriber Education is Important
- Assessing Patients for Treatment with ER/LA Opioid Analgesic Therapy
- Initiating Therapy, Modifying Dosing, and Discontinuing Use of ER/LA Opioid Analgesics
- Managing Therapy with ER/LA Opioid Analgesics
- Counseling Patients and Caregivers about the Safe Use of ER/LA Opioid Analgesics
- General Drug Information for ER/LA Opioid Analgesics
- Specific Drug Information for ER/LA Opioid Analgesics

* http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM277916.pdf

ER/LA Opioid Analgesics REMS Assessment

- REMS assessments are required on a pre-established schedule
- FDA may modify the REMS based on information learned through the REMS assessment
- Assessment, among other metrics, includes:
  - Healthcare providers' awareness and understanding of the serious risks associated with these products
  - Patients' understanding of the serious risks of these products
  - Surveillance for adverse events

ER/LA Opioid Analgesics REMS-Milestones

- ER/LA REMS approved July 9, 2012
- REMS-compliant CE courses offered by accredited CE providers available no later than March 1, 2013

Conclusion

- FDA aims to balance ensuring appropriate access to needed medications with minimizing undue risk
- REMS programs enable FDA to make products available that require additional risk management tools to ensure that the product's benefits outweigh its risks
- If approved, Zohydro-ER would fall under the ER/LA REMS