

Corrections to FDA In Vitro Abuse Deterrent Open Session Backgrounder

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Office of New Drug Products (ONDP)

Office of Pharmaceutical Quality (OPQ)

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

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

Troxyca

June 8, 2016

Document/Page	FDA text	Correction
Open BB P.52 Errata	Section 1B, first paragraph, second sentence: “The formulation was defeated in the following solvents, when extracted for 12 hours or longer using intact pellets (Common Solvents A, G, K and N).”	Delete ‘K’ from the sentence: i.e. : “The formulation was defeated in the following solvents, when extracted for 12 hours or longer using intact pellets (Common Solvents A, G, and N)”.
Open BB P.52 Errata	Section 1B, first paragraph, 3rd sentence: “When Common Solvent K was used, 90% of oxycodone was extracted in 3 hours or more,”	Change to: “When Common Solvent K was used, 90% of oxycodone was extracted in 6 hours or more,”
Open BB P.53 Errata	Section 1B second paragraph “When crushed pellets were used for extraction study, no oxycodone could be extracted in common solvents A and G.”	Delete sentence “ When crushed pellets were used for extraction study, no oxycodone could be extracted in common solvents A and G. “
Open BB P.53	Section 1B second paragraph: “When common solvents I were used, about 40% to 50% of oxycodone, in 30 minutes or less was isolated.”	Change to: “When common solvent O was used, about 40% to 50% of oxycodone, in 30 minutes or less was isolated.”

Document/Page	FDA text	Correction
Open BB P.52	Section 1B second paragraph: “Under stress conditions 80% to 90% of the oxycodone was isolated within 1-4 hours of extraction time using intact pellets. With <u>crushed</u> pellets no oxycodone was isolated.”	Delete sentence: “With crushed pellets no oxycodone was isolated.”
Open BB P.53	Section 1B paragraph four: “Common solvents L to N are particularly effective at selectively extracting oxycodone from intact pellets.”	Change to: “Common solvents K to M are particularly effective at selectively extracting oxycodone from intact pellets.”
Open BB Errata and Conclusion in Open BB P.54	Part 1D second paragraph: “Common solvents B to E appear to be capable of removing naltrexone selectively from crushed ALO-02.”	Delete sentence: “Common solvents B to E appear to be capable of removing naltrexone selectively from crushed ALO-02.”

NDA 207621

Troxyca ER (oxycodone hydrochloride [HCL] and
naltrexone hydrochloride [HCL])
Extended-Release Capsules for Oral Use
Labeling Section 9: Drug Abuse

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Center for Drug Evaluation and Research, FDA

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

June 8, 2016

Outline

- Drug Abuse: Class-wide Abuse Language
- Risks Specific to Abuse of Troxyca ER
- Abuse Deterrence Testing
 - In vitro testing
 - Clinical human abuse potential studies
- Abuse Potential Endpoints
 - Take Drug Again and Drug Liking
- Types of Studies: Oral and Intranasal Abuse Potential Studies; Simulated IV Abuse Potential Study
- Summary

Section 9.2 Class-Wide Abuse Language

- Troxyca ER contains oxycodone, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, morphine, and oxymorphone.
- Troxyca ER can be abused and is subject to misuse, addiction, and criminal diversion.
- The high drug content in the extended-release formulations adds to the risk of adverse outcomes from abuse and misuse.
- All patients treated with opioids require careful monitoring for signs of abuse and addiction.

Section 9.2 Abuse - Risks Specific to Abuse of Troxyca ER

- Taking chewed, crushed, or dissolved Troxyca ER enhances drug release and increases the risk of overdose and death.
- If the capsules are crushed or chewed, up to 100% of the sequestered naltrexone HCl dose could be released.
- In opioid-tolerant individuals, the absorption of naltrexone HCl may increase the risk of precipitating withdrawal.
- Due to the presence of talc excipient, parenteral abuse can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury.

Abuse Deterrence Studies

- In vitro laboratory tests were performed to evaluate the effect of different physical and chemical conditions intended to defeat the extended-release formulation.
- When Troxyca ER is crushed and mixed in a variety of solvents, both oxycodone HCl and naltrexone HCl are simultaneously extracted.

Clinical Abuse Potential Studies

- The abuse potential of Troxyca ER when crushed was examined by the oral and intranasal routes. A third study was conducted with IV administration of simulated crushed Troxyca ER.
- **Take Drug Again** was measured on a bipolar 100-point Visual Analog Scale (VAS) where 0 represents strongest negative response (definitely would not take drug again), 50 represents a neutral response, and 100 represents the strongest positive response (definitely would take drug again).
- **Drug Liking** was measured on a bipolar 100- point Visual Analog Scale (VAS) where 0 represents maximum disliking, 50 represents a neutral response (neither like nor dislike), and 100 represents maximum liking.

Oral Abuse Potential Study Design and Results

- In a randomized, double-blind, active- and placebo-controlled study, 31 non-dependent, recreational opioid abusers received all six of the following treatments by the oral route:
 - crushed 40 mg Troxyca ER in solution, crushed 40 mg immediate-release (IR) oxycodone HCl in solution, intact 60 mg Troxyca ER, crushed 60 mg Troxyca ER in solution, crushed 60 mg IR oxycodone HCl in solution, and placebo.
- Oral administration of crushed 40 mg Troxyca ER was associated with statistically significantly lower means and medians for Drug Liking and Take Drug Again compared with crushed 40 mg IR oxycodone HCL and statistically significantly lower means and medians for Drug Liking of Troxyca ER 60 mg compared to crushed 60 mg IR. The Summary Statistics are shown in the following table:

Summary Statistics of Abuse Potential Measures

Table 6. Summary Statistics of Abuse Potential Measures of Drug Liking (E_{max}) and Take Drug Again (E_{max}) following Oral Administration

Bipolar VAS Scale (100 point)		Placebo	TROXYCA ER 40 mg/4.8 mg Crushed	IR Oxycodone 40 mg Crushed	TROXYCA ER 60 mg/7.2 mg Intact	TROXYCA ER 60 mg/7.2 mg Crushed	IR Oxycodone 60 mg Crushed
		N=31	N=31	N=31	N=31	N=31	N=31
Drug Liking (E_{max}) [*]	Mean (SE)	51.6 (0.68)	69.5 (3.45)	85.6 (2.94)	59.3 (2.75)	74.3 (3.30)	90.0 (2.46)
	Median (range)	51.0 (50,68)	64.0 (50,100)	94.0 (50,100)	51.0 (50,100)	73.0 (50,100)	100.0 (57,100)
Take Drug Again (E_{max}) [*]	Mean (SE)	45.5 (3.47)	56.7 (6.00)	82.9 (3.66)	47.7 (5.12)	71.1 (5.08)	80.6 (4.56)
	Median (range)	50.0 (0,92)	58.0 (0,100)	90.0 (30,100)	50.0 (0,100)	77.0 (0,100)	90.0 (0,100)

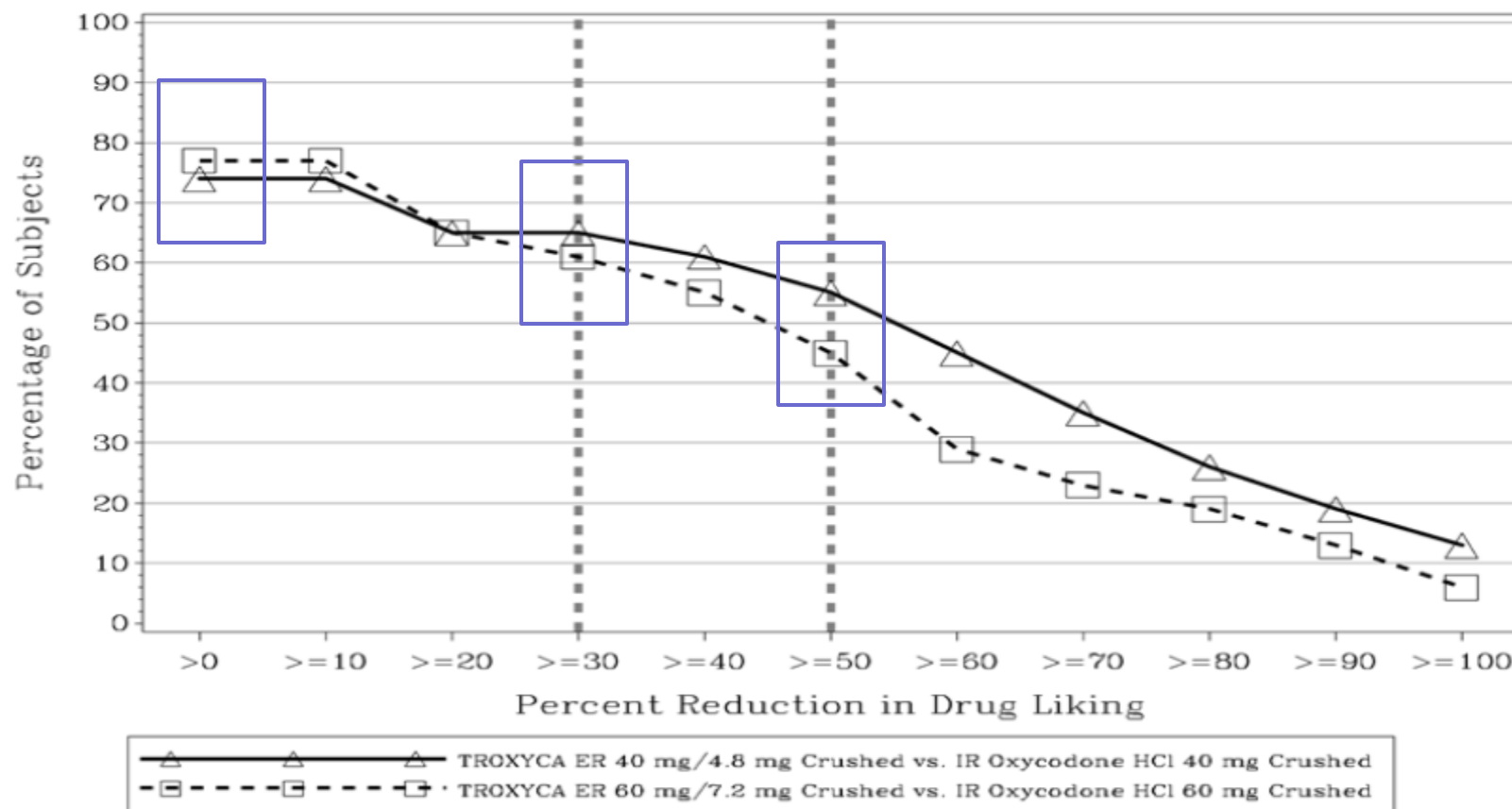
^{*} Presented on bipolar 100-point Visual Analog Scales (VAS) (0=maximum negative response, 50=neutral response, 100=maximum positive response).

E_{max} = maximal response for Drug Liking and Take Drug Again; ER = extended-release; IR = immediate-release; SE = standard error

Source: Proposed Troxyca ER label. Note: Boxes added here for emphasis and will not appear in labeling.

Percent Reduction Profile for Oral Abuse Potential Study

Figure 1. Percent Reduction Profiles for E_{max} of Drug Liking VAS for Oral Administration of Crushed TROXYCA ER vs. Crushed IR Oxycodone HCl



Source: Proposed Troxyca ER label. Note: Boxes added here for emphasis and will not appear in labeling.

Intranasal Abuse Potential Study Design and Results

- In a randomized, double-blind, active-and placebo-controlled study, 27 non-dependent, recreational opioid abusers with experience with intranasal administration of opioids received all four of the following treatments by the intranasal route:
 - crushed 30 mg Troxyca ER, crushed 30 mg IR oxycodone HCl, crushed placebo sugar spheres, and crushed placebo lactose tablets.
- Intranasal administration of crushed Troxyca ER was associated with statistically significantly lower means and medians for Drug Liking and Take Drug Again compared with crushed IR oxycodone HCL. The Summary Statistics are shown in the following table.

Summary Statistics of Abuse Potential Measures

Table 7. Summary Statistics of Abuse Potential Measures for Drug Liking and Take Drug Again with Intranasal Administration of Crushed TROXYCA ER Compared to Crushed IR Oxycodone HCl

VAS Scale (100 point)		Placebo for TROXYCA ER	TROXYCA ER 30 mg/3.6 mg Crushed	Placebo for IR Oxycodone	IR Oxycodone 30 mg Crushed
		N=27	N=27	N=27	N=27
Drug Liking (E_{max}) [‡]	Mean (SE)	51.0 (0.23)	60.3 (2.36)	51.3 (0.65)	93.7 (2.11)
	Median (range)	51.0 (50,56)	55.0 (50,100)	51.0 (50,68)	100.0 (50,100)
Take Drug Again (E_{max}) [‡]	Mean (SE)	47.9 (2.92)	58.1 (6.27)	46.5 (3.67)	88.5 (5.18)
	Median (range)	50.0 (0,83)	51.0 (0,100)	50.0 (0,98)	100.0 (0,100)

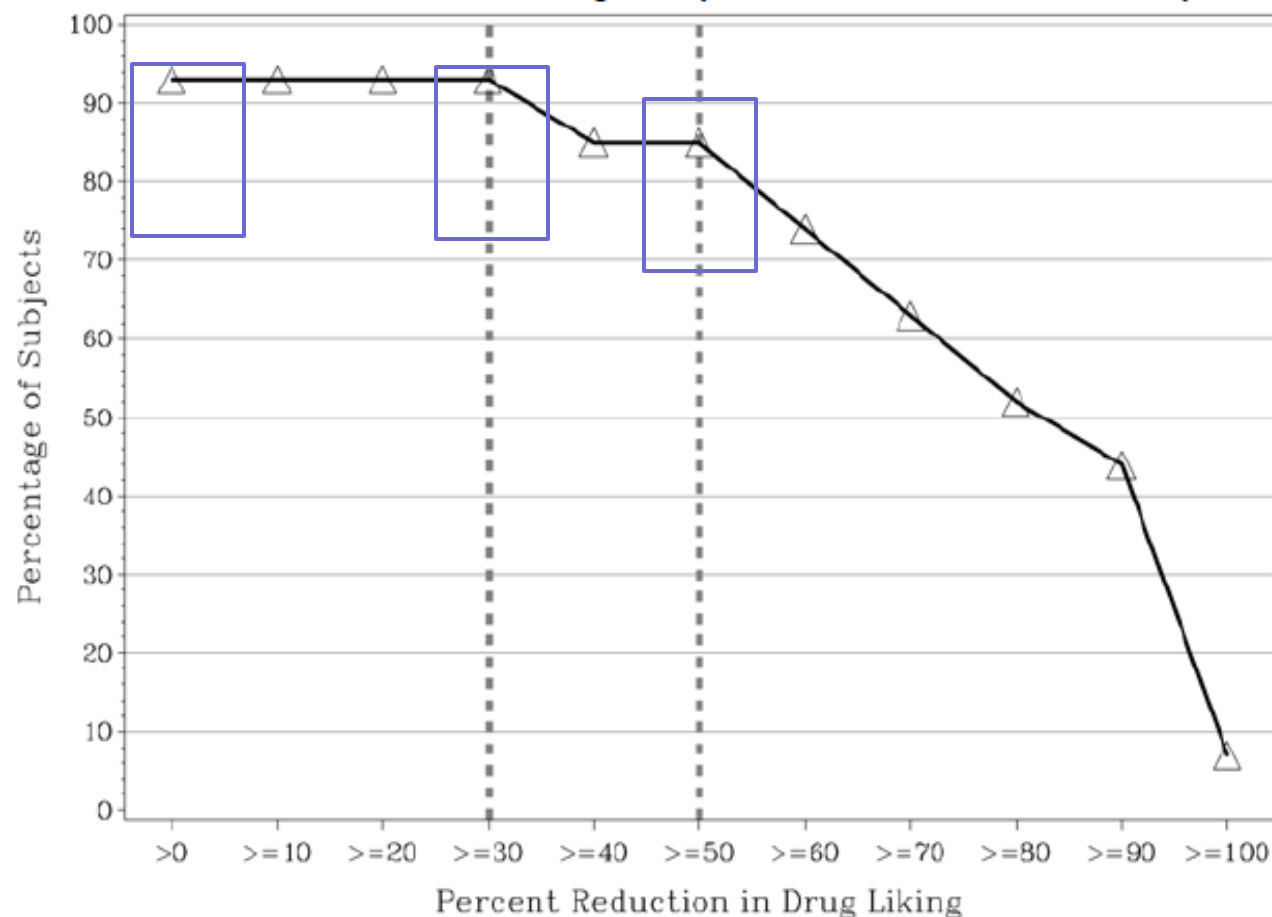
* Presented on bipolar 100-point Visual Analog Scales (VAS) (0=maximum negative response, 50=neutral response, 100=maximum positive response).

E_{max} = maximal response for Drug Liking and Take Drug Again; ER = extended-release; IR = immediate-release; SE = standard error

Source: Proposed Troxyca ER label. Note: Boxes added here for emphasis and will not appear in labeling.

Percent Reduction Profile for Intranasal Study

Figure 2. Percent Reduction Profile for E_{max} of Drug Liking VAS for Intranasal Administration of Crushed 30 mg/3.6 mg TROXYCA ER vs. Crushed 30 mg IR Oxycodone HCl in the Intranasal Study



Source: Proposed Troxyca ER label. Note: Boxes added here for emphasis and will not appear in labeling.

Simulated IV Abuse Potential Study Design

- This study compared 20 mg IV oxycodone HCl in combination with 2.4 mg IV naltrexone HCl (to simulate parenteral use of crushed Troxyca ER) to 20 mg of IV oxycodone HCl and placebo in 29 non-dependent recreational opioid abusers
- Intravenous administration of oxycodone and naltrexone showed statistically significantly lower mean and median Drug Liking and Take Drug Again Emax scores.
 - Drug Liking median score was 51 for Troxyca ER compared to oxycodone alone median score of 97.
 - Take Drug Again median score was 50 for Troxyca ER compared to oxycodone alone median score of 81.
 - 90% experienced some reduction in Emax of Drug Liking with simulated parenteral use of crushed Troxyca ER compared to IV oxycodone.

Summary

- The in vitro and pharmacokinetic data demonstrate that crushing Troxyca ER pellets results in the simultaneous release and absorption of oxycodone HCl and naltrexone HCl. These data along with results from the oral and intranasal human abuse potential studies indicate that Troxyca ER has properties that are expected to reduce abuse via the oral and intranasal routes. However, abuse of Troxyca ER by these routes is still possible.
- Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of Troxyca ER on the abuse liability of the drug.
- A human abuse potential study of intravenous oxycodone HCl and naltrexone HCl to simulate crushed Troxyca ER demonstrated lower Drug Liking and Take Drug Again Emax compared with oxycodone HCl alone. However, it is unknown whether these results with simulated crushed TROXYCA ER predict a reduction in abuse by the IV route until additional postmarketing data are available.



Drug Utilization Patterns for Oxycodone ER and Other ER/LA Opioid Analgesics 2011-2015

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Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and
the Drug Safety and Risk Management Advisory Committee (DSaRM) Joint
Meeting

June 8, 2016

Outline

- Sales Distribution
- Prescription Utilization
- Prescriber Specialty
- Limitations
- Summary

Extended Release (ER)/ Long Acting (LA) Opioid Analgesics

- **Oral-dosage Forms:**

- Oxycodone
- Methadone
- Morphine
- Hydromorphone
- Oxymorphone
- Tapentadol
- Hydrocodone

- **Transdermal Delivery (TD) Systems:**

- Fentanyl
- Buprenorphine

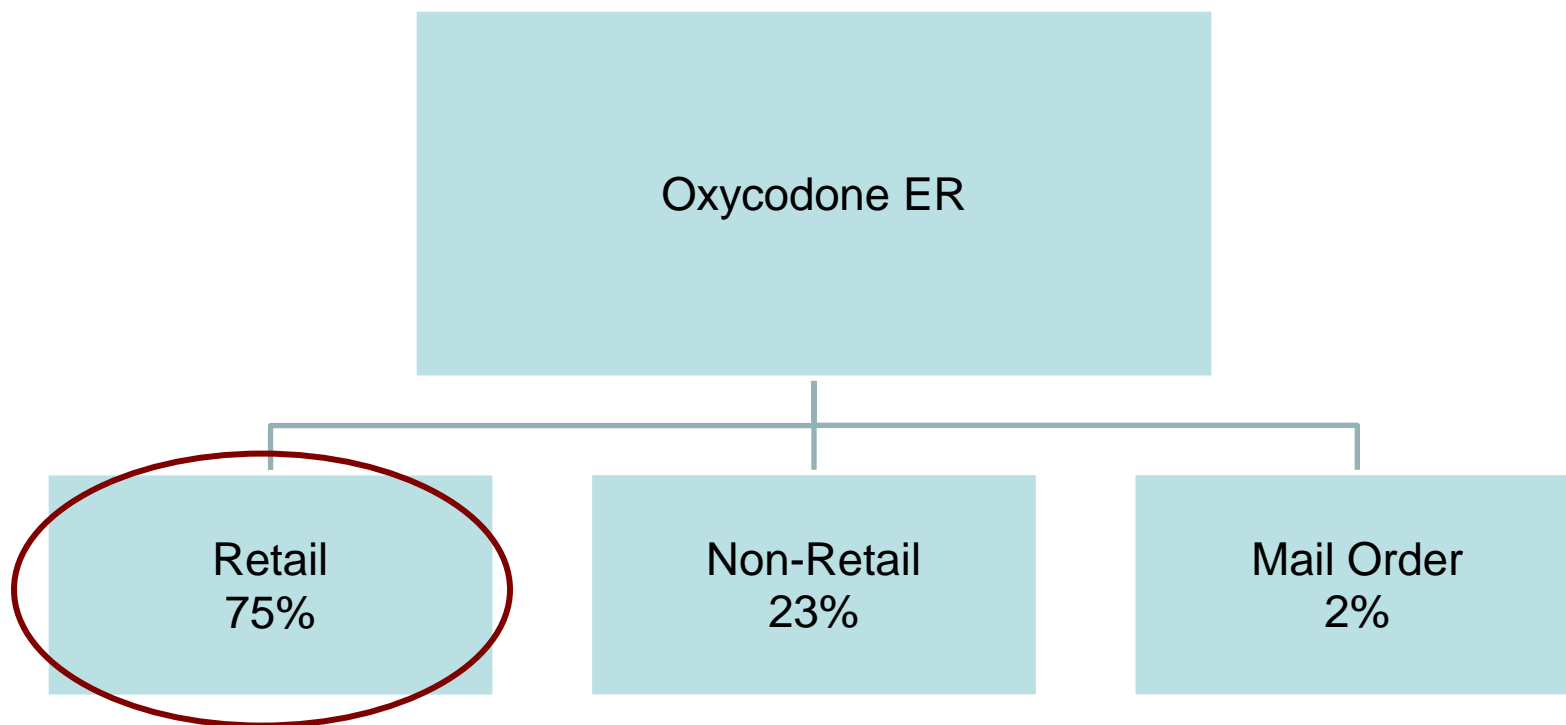
Sales Distribution Data

- IMS National Sales Perspectives Database™
- Captures sales of drug products from manufacturers to all retail and non-retail settings
 - Retail chain pharmacies, mail-order pharmacies, hospitals, etc.
- Data are nationally projected
- Does not represent actual patient use

Sales Distribution Data

Year 2015

IMS Health, IMS National Sales Perspective™, Extracted March 2016



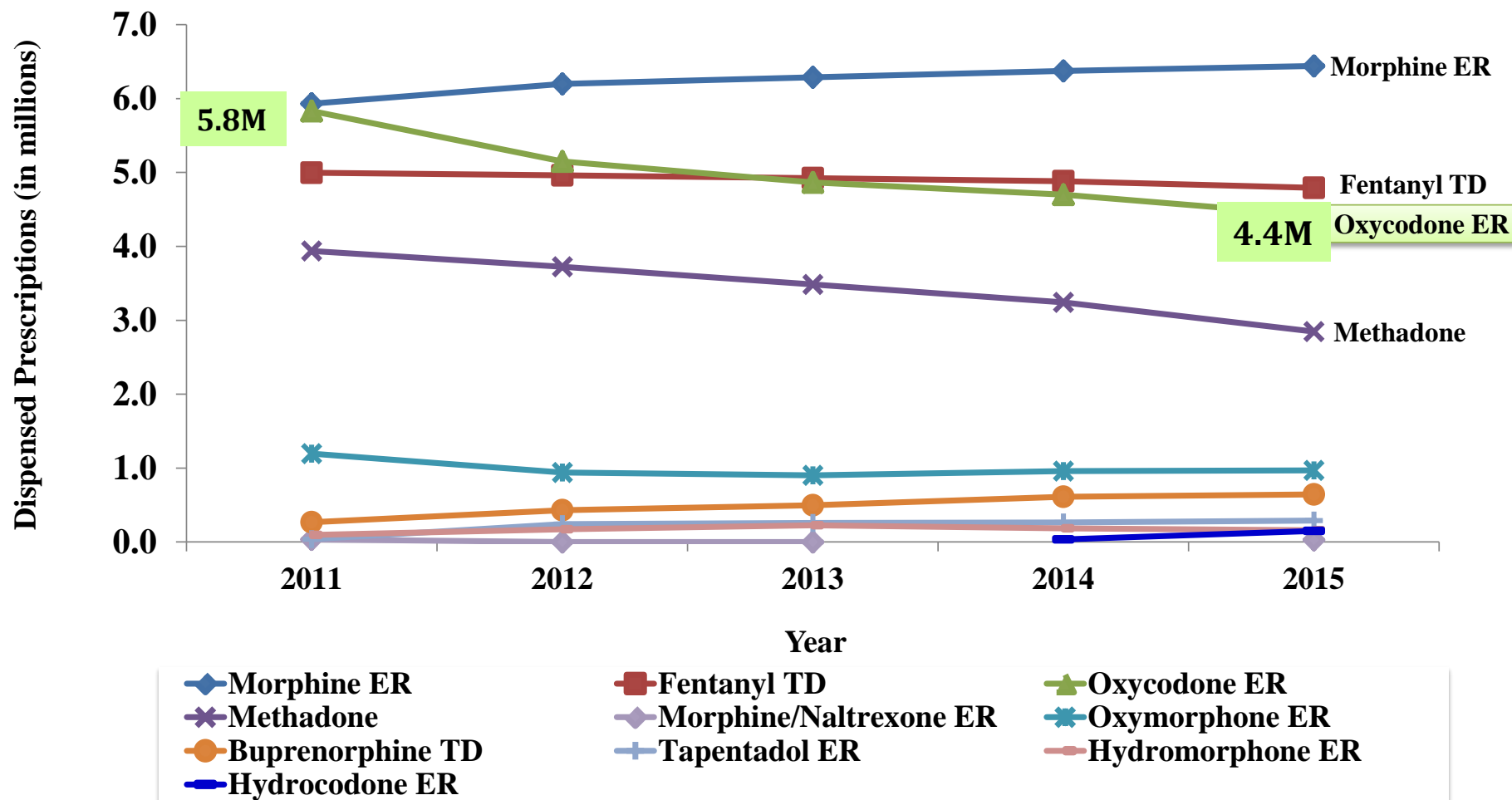
Database Descriptions

Prescription Utilization and Prescriber Specialty Data :

- IMS Health, National Prescription Audit™ (NPA) Database
- Measures dispensing of prescriptions out of retail pharmacies into the hands of consumers
- Data can be stratified by prescriber specialty

Prescription Drug Utilization:

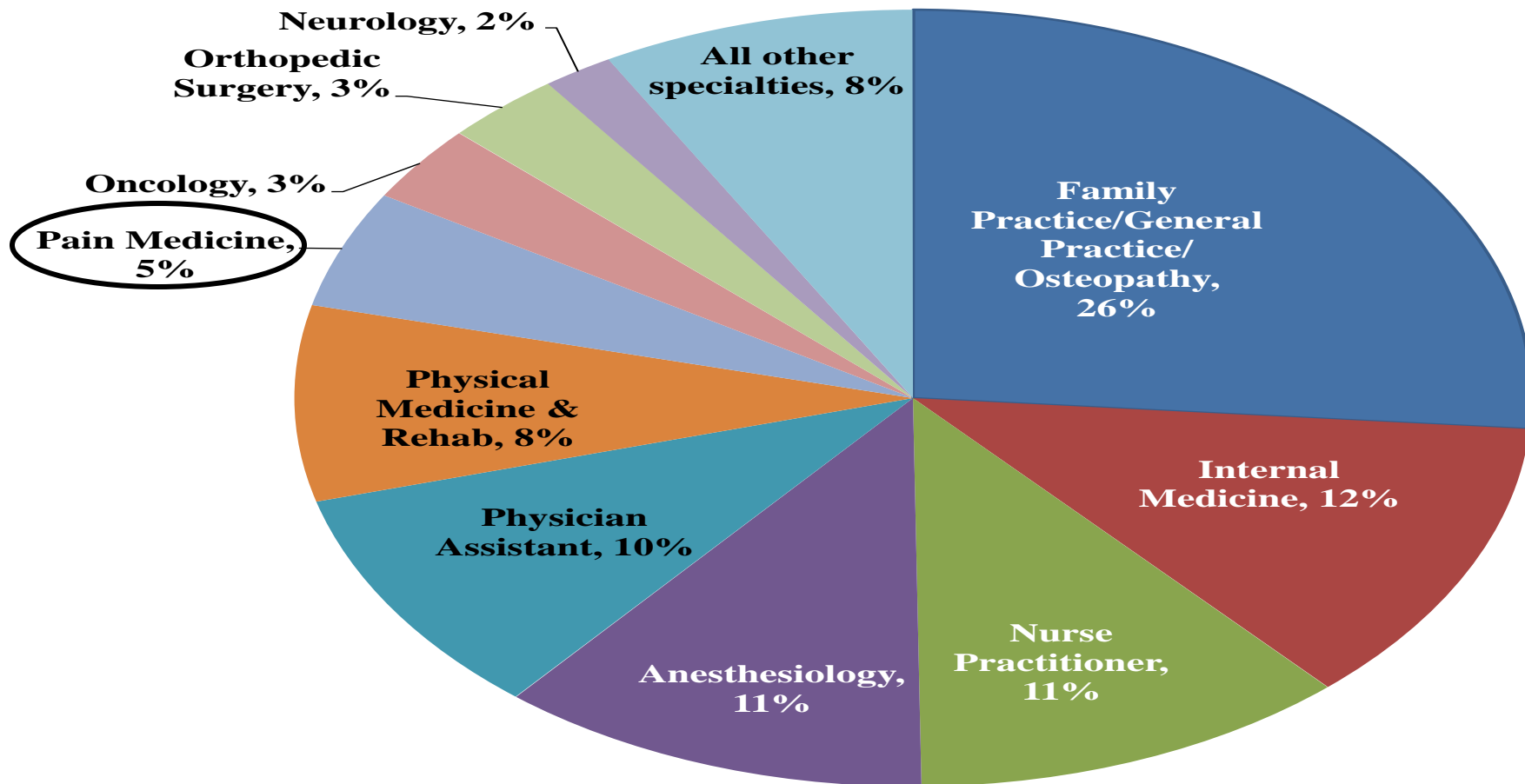
Nationally estimated number of prescriptions dispensed for ER/LA opioid analgesics from U.S. outpatient retail pharmacies, 2011-2015



Source: IMS, National Prescription Audits (NPA). Data extracted March 2016.

Top Prescriber Specialty: 2015

Top 10 prescriber specialties by the nationally estimated number of prescriptions dispensed for oxycodone ER from U.S. outpatient retail pharmacies



Source: IMS Health, National Prescription Audit (NPA). Year 2015. Extracted March 2016

Limitations:

- Only outpatient retail pharmacy use was assessed
- Top specialties captured as reported by the prescription data

Summary:

- Decreased utilization of oxycodone ER from 2011-2015
- Third most frequently dispensed ER/LA opioid with 4.4 million prescriptions
- One-quarter of oxycodone ER prescriptions written by family practice/general practice/osteopathy