

MNK-812

Introduction and Overview

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Joint Meeting Anesthetic and Analgesic

Drug Products Advisory Committee (AADPAC) and the Drug Safety
and Risk Management Advisory Committee (DSaRM)

NDA 209774 Oxycodone IR Tablets

November 14, 2018

FDA Presentations

- **Introduction and Overview**
 - Jennifer L. Nadel, MD
- **In Vitro Category 1 Abuse-Deterrent Studies of MNK-812**
 - Valerie Amspacher, PharmD
- **Nonclinical Safety Assessment of MNK-812 Excipients**
 - R. Daniel Mellon, PhD
- **Examination of Intranasal Human Abuse Potential Study MNK48121013**
 - James M. Tolliver, PhD
- **Review of Recent Epidemiologic Data on Use, Misuse and Abuse of Oxycodone**
 - Tamra Meyer, PhD, MPH
- **MNK-812 Clinical Summary of Abuse Deterrence**
 - Jennifer L. Nadel, MD

MNK-812 Background

- Oxycodone immediate release (IR) with abuse-deterrence (AD) for the intranasal (IN) and intravenous (IV) routes
 - Indication: Pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate
 - Doses: 5, 10, 15, 20, and 30 mg
- Efficacy and safety established by demonstration of bioequivalence to Roxycodone
 - Therefore, efficacy and safety studies were not conducted or required

MNK-812 Clinical Development Program

- 2 Pharmacokinetic (PK) Studies
 - To demonstrate bioequivalence to Roxicodone
 - Safety findings consistent with opioid IR class
- 1 Human Abuse Potential (HAP) Study
 - To evaluate the effect of the abuse deterrent properties on the potential for intranasal abuse

MNK-812 HAP Study- Adverse Events

System Organ Class Preferred Term, N (%)	Intact Oral MNK-812 N=41	Intranasal MNK-812 N=40	Intranasal Oxycodone (IR) N=42	Placebo N=42
Subjects at least 1 AE	32 (78)	29 (72.5)	24 (57.1)	12 (28.6)
Respiratory, Thoracic, Mediastinal Disorders				
Cough	6 (14.6)	21 (52.5)	4 (9.5)	6 (14.3)
Nasal Discomfort	3 (7.3)	11 (27.5)	1 (2.4)	3 (7.1)
Nasal Congestion	0	10 (25.0)	0	1 (2.4)
Hiccups	1 (2.4)	2 (5.0)	1 (2.4)	0
Oropharyngeal Pain	2 (4.9)	1 (2.5)	1 (2.4)	0
Paranasal Sinus Discomfort	1 (2.4)	1 (2.5)	0	1 (2.4)
Epistaxis	0	1 (2.5)	1 (2.4)	0
Hypoxia	0	0	0	1 (2.4)
Nasal Pruritus	0	0	0	0
Pulmonary Congestion	0	0	0	1 (2.4)
Gastrointestinal Disorders				
Nausea	11 (26.8)	10 (25)	6 (14.3)	2 (4.8)
Vomiting	7 (17.1)	2 (5)	3 (7.1)	0
Constipation	4 (9.8)	3 (7.5)	3 (7.1)	0
Retching	0	3 (7.5)	1 (2.4)	1 (2.4)
Dry mouth	0	4 (10)	0	0
Abdominal distension	2 (4.9)	0	0	0
Abdominal pain upper	0	0	1 (2.4)	0
Diarrhea	1 (2.4)	0	0	0
	0	0	0	1 (2.4)



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In Vitro Category 1 Abuse-Deterrent Studies of MNK-812

Valerie Amspacher, PharmD

Chemistry, Manufacturing and Controls (CMC) Reviewer

Division of New Drug Products II

Office of New Drug Products (ONDP)

Office of Pharmaceutical Quality (OPQ)

CDER, FDA

Joint AADPAC/DSARM Meeting

November 14, 2018

MNK-812

- Immediate release oxycodone tablet with abuse-deterrent features
- 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg strengths
- Tested according to “Abuse-deterrent Opioids – Evaluation and Labeling”

Category 1 Studies

- Physical Manipulation
 - Manual
 - Mechanical

Category 1 Studies

- Small Volume Extraction (5-10 mL)
 - Pre-treatment
- Large Volume Extraction (≥ 30 mL)

Category 1 Studies

- 30 mg MNK-812 - immediate release oxycodone with abuse-deterrent features – NDA 209774

VS

- 30 mg Roxicodone – immediate release oxycodone product currently marketed

Reproducibility

- FDA labs repeated a select fraction of the studies performed by SpecGx LLC
- Our lab results are in general agreement with those of SpecGx LLC but we differ in our interpretation of those results

Physical Manipulation

- No pre-treatment
- Manual tools
 - Maximum of about 10% of particles <500 microns for MNK-812 15 and 30 mg tablets
 - Maximum of about 94% of particles <500 microns for Roxycodone 15 and 30 mg tablets

Physical Manipulation

- No pre-treatment
- Mechanical tools
 - Maximum of about 90% of particles <500 microns for MNK-812 15 and 30 mg tablets
 - Roxicodone not tested
- Generally particle sizes of <500 microns are considered to be insufflatable

Small Volume Extraction

- Looked at the following conditions with 30 mg tablets:
- Pre-treatment/ no pre-treatment
- Intact and Ground tablets
- Temperature of extraction with and without agitation
- Extraction time
- Solvents tested are those frequently used by individuals who abuse
- Needle size

Small Volume Extraction

- Both pre-treated and non-pre-treated tablets
- MNK-812 - Syringeability hindered by gel-like consistency of extract with small volumes of liquid
- MNK-812 - Many conditions yielded recoveries of 10% or less

Conditions Varied

- Intact or Ground tablet
- Needle gauge
- Temperature of extraction
- Still or agitated solution
- Extraction time
- Solvent frequently used by individuals who abuse

Solvent	% recovery in 5 mL (extraction volume)
A	51.9
A	49.5
A	50.6
A	60.4
A	50.2

Small Volume Extraction

- MNK-812 - With pre-treatment, physical manipulation and elevated extraction temperatures, up to **60%** of the oxycodone dose can be recovered with a specific ingestible/injectable household solvent for a syringeable dose in about 1 hour
- Roxycodone – generally 70-80% of dose could be recovered with manual manipulation and extraction and syringed in 10-15 minutes

Large Volume Extraction

- Looked at the following conditions with 30 mg tablets:
 - No pre-treatment
 - Intact and Ground tablets
 - Temperature of extraction with and without agitation
 - Solvents tested are those frequently used for abuse

Large Volume Extraction

- 30mL
- 14 solvents of varying pH, polarity, and ionic strength were tested

Large Volume Extraction

- The abuse-deterrent features are defeated in 30 mL of the most frequently-used solvent for IV abuse in 2 hours with no pre-treatment of tablets
- Recoveries greater than 80% are regularly achieved in solvents of low, neutral and high pH
- Intact or ground tablets at any temperature

MNK-812 Conclusions

- Up to 60% of oxycodone can be extracted and syringed with 5 mL of solvent from MNK-812 30 mg pre-treated tablets with a solvent frequently used for abuse under specific conditions
- Greater than 80% of oxycodone can be extracted in 30mL with solvents frequently used for abuse from MNK-812 30 mg non-pre-treated tablets

Nonclinical Safety Assessment of MNK-812 Excipients

R. Daniel Mellon, PhD
Pharmacology Toxicology Supervisor
DAAAP, ODE-II, OND, CDER, FDA

Preview

- The Agency has no nonclinical safety concerns with the excipients used in MNK-812 when the product is used as intended (oral).
- The Agency generally agrees with the Applicant's assessment of the toxicology study results conducted to date to assess the risk of misuse of the product via intravenous (IV) route of administration.
- The existing data, although limited, suggest that intravenous injection of extracts of MNK-812 did not result in clear evidence of thrombotic microangiopathy, unlike the published nonclinical study that tested excipients present in the reformulated Opana ER.
- However, there are limitations to existing data.
- ***FDA cannot rule out the possibility that adverse effects could occur with more frequent and/or prolonged administration of manipulated MNK-812 for IV use.***

Safety Assessment of Excipients

- FDA evaluates the safety of excipients for the intended route of administration in accordance with the FDA guidance to industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf>.
- Intended reformulations of oral products to an IV drug product requires IV toxicology studies (local and systemic) and blood compatibility studies in accordance with the FDA guidance for industry: *Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternative Route*, available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079245.pdf>.
- In the past, the Agency did not require an assessment of oral drug product excipient safety via IV or other unintended routes.
- However...

Postmarketing Experience with Opana ER Reformulation

Unanticipated outcomes with the introduction of an abuse-deterrent (AD) opioid formulation to the market (Opana ER):

- Adverse events resulting from manipulation of the formulation for use by the unintended IV route of administration
 - Anemia, thrombocytopenia, thrombotic microangiopathy (TMA), acute kidney injury, retinal damage, cardiac involvement
- Data also support a shift from intranasal route of abuse to the more dangerous intravenous route of abuse
 - Increase in outbreaks of HIV and Hepatitis C in drug users who were sharing manipulated reformulated Opana ER

Current Agency Approach to Excipient Safety

- The Agency approach to AD-opioid excipient safety changed:
 - We require sponsors to provide a risk assessment of the potential adverse effects and risks associated with abuse of the final drug product, ideally based on results of Category 1 studies.
 - Should consist of in vitro assessments, analysis of the Category 1 data with literature-based assessment of risk, and/or nonclinical studies
 - An adequate assessment of the potential risks associated with non-oral abuse of the final drug product formulation is needed to determine the complete risk: benefit profile of the drug product.
- We include potential excipient-related adverse events from abuse of opioid drug products in Section 9.2 of the prescribing information.

Reformulated Opana ER Investigation (Hunt et al., 2017)

- Injected guinea pigs with PEO+ powder (polyethylene oxide 7,000,000 Da plus smaller amounts of hypromellose, macrogol, a-tocopherol, and citric acid) supplied by ENDO at doses that were predicted to mimic dosing in humans who manipulate oral drug products for intravenous use
 - Material tested was not subjected to heat curing or other manufacturing processes
- Administered bolus doses of PEO+ at 0.1 or 0.3 mg/kg either once or 5 times at 1.5 hour intervals. This resulted in plasma levels of PEO of 3 and 5 mcg/mL after single injections and 15 and 40 mcg/mL after repeated injections.
 - Estimated levels individuals may administer via manipulated reformulated Opana ER.
- Reproduced anemia, thrombotic microangiopathy, acute kidney injury
 - Not due to lack of blood compatibility directly, but likely indirect via increased sheer stress in microvasculature and deposition of free hemoglobin in tissues

Does MNK-812 have the same risk for TMA as the Opana ER reformulation?

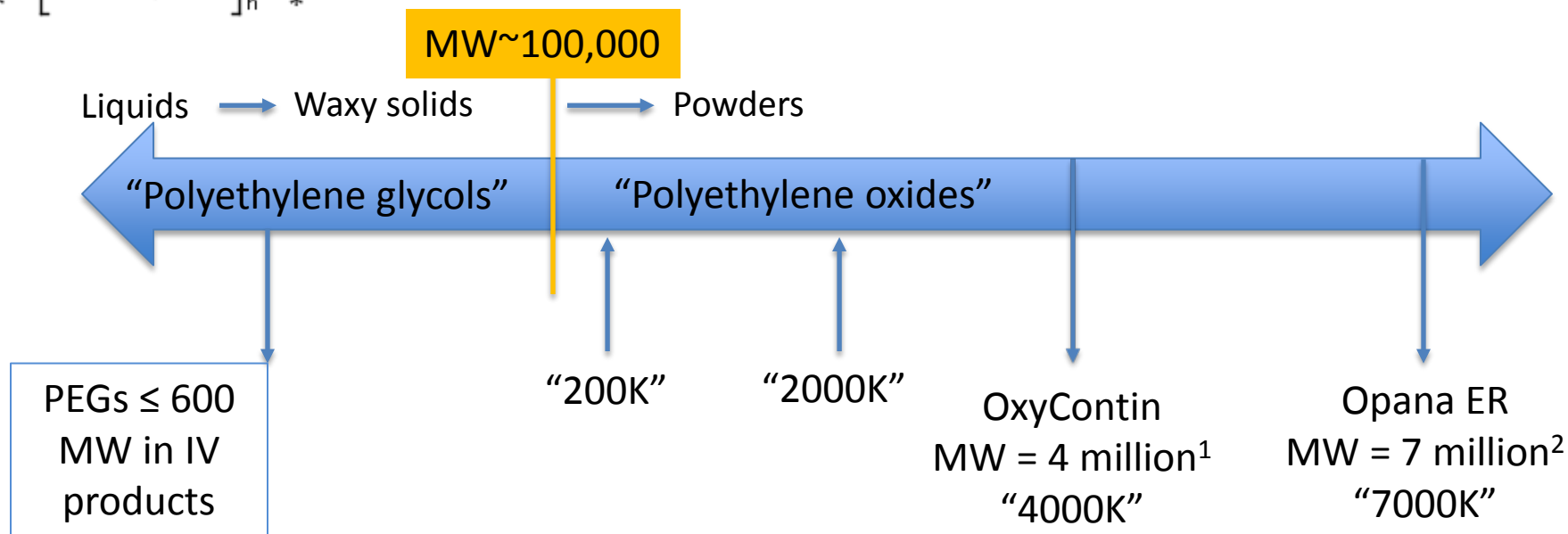
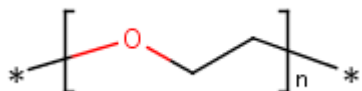
Toxicology Study of Syringeable Material from Category 1 Manipulations of MNK-812

- No adverse effects in in vitro blood compatibility studies
 - Similar to data from Hunt et al. with PEO+
- Rabbits (4 females/group) were injected IV once a day for three days with syringeable material from two different Category 1 conditions and sacrificed on Day 4.
 - IV administrations resulted in oxycodone-related clinical signs
 - 50% increase in spleen weight on treatment
 - Increased incidence of **minimal mixed cell infiltrates eye**, minimal to slight mixed cell infiltrates lung, spleen congestion
 - **No clear evidence of thrombotic microangiopathy or acute kidney injury under the conditions tested**

Single-dose and 14-day Rat IV Toxicology Data: PEO 200K and PEO 2000K

- Rat IV toxicology studies with PEO 200K and PEO 2000K (not in MNK-812) but smaller mean molecular weight (MW) than the 7000K material in reformulated OPANA ER and tested by Hunt et al. (2017)
 - Material was not subjected to heat curing or other manufacturing processes
- **Animals dose with 200K PEO:** No deaths, predominantly vacuolation of tissues, lymphocyte/macrophage infiltrates in the heart, but no strong evidence of anemia or microangiopathy (one HD 14 day animal with minimal necrosis in heart at recovery)
- **Animals dose with 2000K PEO:** Deaths, renal injury, anemia, myocardial degeneration/necrosis, consistent with microangiopathy
 - Collectively, higher molecular weight PEO appears to produce greater and/or faster onset toxicity

Polyethylene Oxide Polymers in AD Opioids



¹Purdue Pharma (2009) FDA Advisory Committee Meeting Open Public Session

²Hunt et al. (2017)

Conclusions and Limitations

- Uncured higher molecular weight PEO (HMW PEO), if injected IV, can be expected to result in thrombotic microangiopathy, acute kidney injury, cardiac damage, retinal damage, etc.
- If manipulation of an AD-opioid for IV use can extract higher molecular weight PEO, we expect similar toxicities would occur (in a dose- and duration-dependent manner, possibly MW dependent).
- IV toxicology data to date in rabbits with manipulated MNK-812 did not demonstrate same degree of damage as reported by Hunt et al. 2017 with PEO+ in guinea pigs, however...
- **Key Limitations:**
 - Content of syringeable material tested in MNK-812 IV toxicology studies is not known
 - MNK-812 studies dosed only once a day for three days only with single product manipulations and may not reflect human patterns of abuse

Key Points

- Other FDA-approved opioids also contain PEO (e.g., OxyContin, Hysingla, Arymo, Zohydro)
 - To date, these products do not appear to carry same risk for TMA as reformulated Opana ER
 - Three published reports of TMA with IV OxyContin from overseas
- Not all PEO-based AD-opioid drug products are the same, differential risk could theoretically be based on:
 - Differences in manufacturing processes, curing methods, heat, additives, etc.
 - Differences in MW of PEO used
 - Differences in methods used to prepare these products for abuse via IV route
 - Differential patterns of abuse of the drug substances and/or drug products

Overall Assessment

- In terms of TMA risk, the risk of the PEO in various AD-opioid drug products cannot be simply extrapolated across the class based on reformulated Opana ER.
- Injecting any manipulated oral drug can result in significant toxicity (e.g., granulomas, thrombotic microangiopathy, risk of spread of infectious disease).
- FDA cannot rule out the possibility that adverse effects could occur with more frequent and/or prolonged administration of manipulated MNK-812 for IV use. However, if the PEO in this product is able to be extracted into an IV syringe and injected, we would expect similar results as noted with reformulated Opana ER (dose- and duration-dependent toxicity due to PEO accumulation).
- This product, if approved, would likely have similar warnings in labeling regarding risk of IV injection of manipulated drug products as other opioids.

Examination of Intranasal Human Abuse Potential Study MNK48121013

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Controlled Substance Staff (CSS)
CDER/FDA

November 14, 2018
FDA Joint Meeting of the AADPAC/DSaRM

MNK-812 Tablets

- Are being developed as an abuse deterrent formulation under NDA 209774.
- Contain excipients which, according to Sponsor, cause nasal irritation expected to deter intranasal abuse.
- Human abuse potential study MNK48121013 in support of a possible intranasal abuse deterrent claim.
 - Randomized, placebo-controlled, double-blind, double dummy, 4-period crossover study utilizing 38 recreational opioid users.
- This presentation will briefly examine the evidence for MNK-812 tablets having a potential intranasal abuse-deterrent effect via an aversive mechanism
 - Primary Comparison: Insufflated manipulated MNK-812 30 mg vs Insufflated manipulated Oxycodone HCl IR 30 mg.

Definitions

Pharmacokinetic (PK) Terms

- C_{max} = maximum oxycodone plasma level achieved.
- T_{max} = Time to achieve C_{max}
- AUC = Area under the oxycodone plasma concentration vs. time curve - indication of oxycodone exposure at selected time intervals.

Pharmacodynamic (PD) Terms

- VAS = Visual Analogue Scale – 0 to 100 points
- E_{max} = Maximum or peak effect, as measured on VAS
- TE_{max} = Time to achieve peak effect
- AUE = Area under the effect vs. time curve – indication of the cumulative experience for each effect at selected time intervals.

Data to Assess Aversive Effects

- Percentage of manipulated (powdered) dose insufflated.
- Pharmacokinetics of Plasma Oxycodone
- 0 – 100 mm Visual Analog Scales for the following subjective measures
 - Ease of Snorting
 - Bipolar Drug Liking
 - Unipolar High
 - Bipolar Take Drug Again
 - Bipolar Overall Drug Liking
 - Unipolar Bad Effects
- Subject Rated Nasal Tolerability

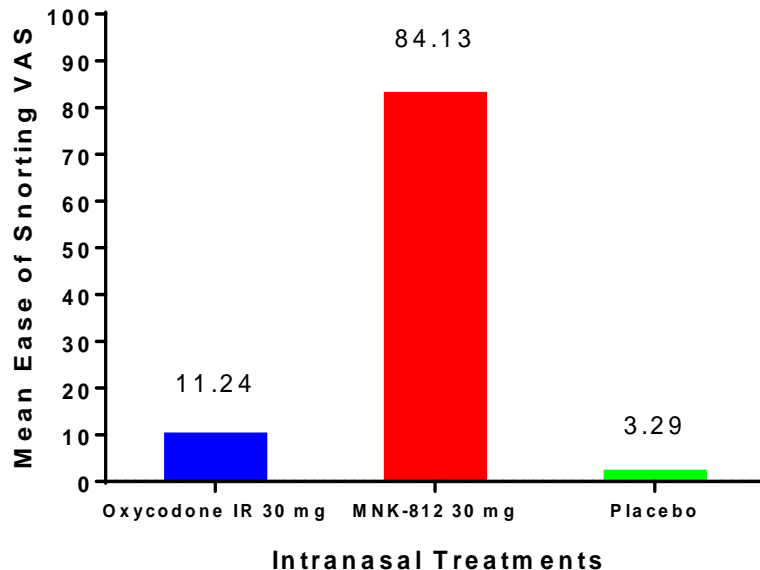
Percentage of Dose Insufflated

Statistic	Intranasal Treatments in Completer Population (N = 38) Percentage of Dose Insufflated		
	30 mg Manipulated MNK-812	30 mg Manipulated Oxycodone IR	Placebo
Mean	98.18	99.91	100.00
Standard Deviation	7.01	0.56	0
Median	100.00	100.00	100.00
Minimum	62	97	100
Maximum	100	100	100

Most of the subjects were able to insufflate the entire dose for each intranasal treatment. Three subjects insufflated 85%, 84%, and 62% of the MNK-812 dose.

Unipolar Ease of Snorting VAS

(5 minutes post-insufflation)



Statement: “Snorting the drug was...”

Anchors:

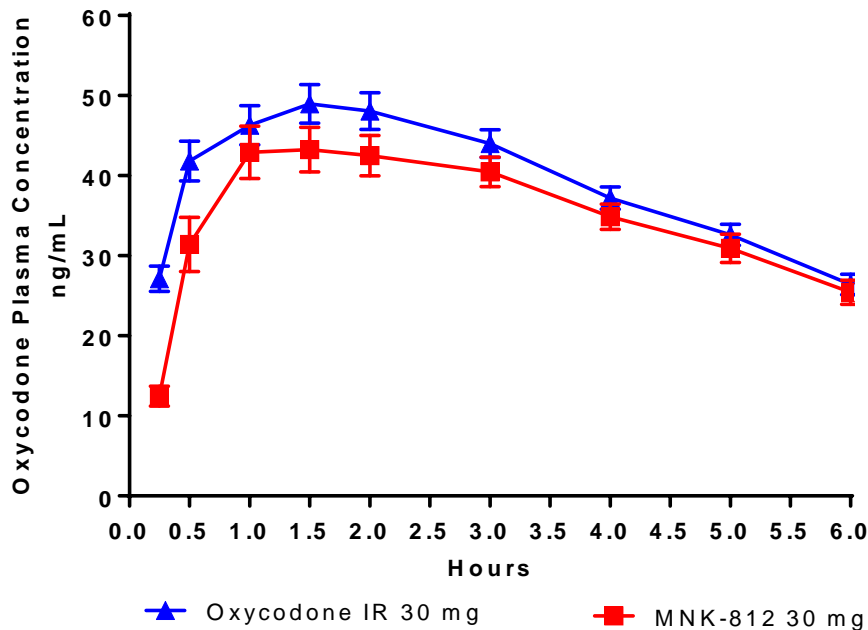
0 = “very easy”

100 = “very difficult”

Overall, subjects reported it to be more difficult to insufflate manipulated MNK-812 tablets than manipulated Oxycodone IR tablets.

Pharmacokinetics for Insufflated Treatments

Mean (SEM) Oxycodone Plasma Concentration vs Time for Insufflated Treatments



Insufflated MNK-812 30 mg

- C_{max} = 55.0 ng/mL
- T_{max} = 2.44 hours
- AUC_{0-1hour} = 22.32

Insufflated Oxycodone IR 30 mg

- C_{max} = 55.7 ng/mL
- T_{max} = 2.06 hours
- AUC_{0-1hour} = 31.29

Any differences in oxycodone exposure may be of limited importance in explaining differences in subjective measures.

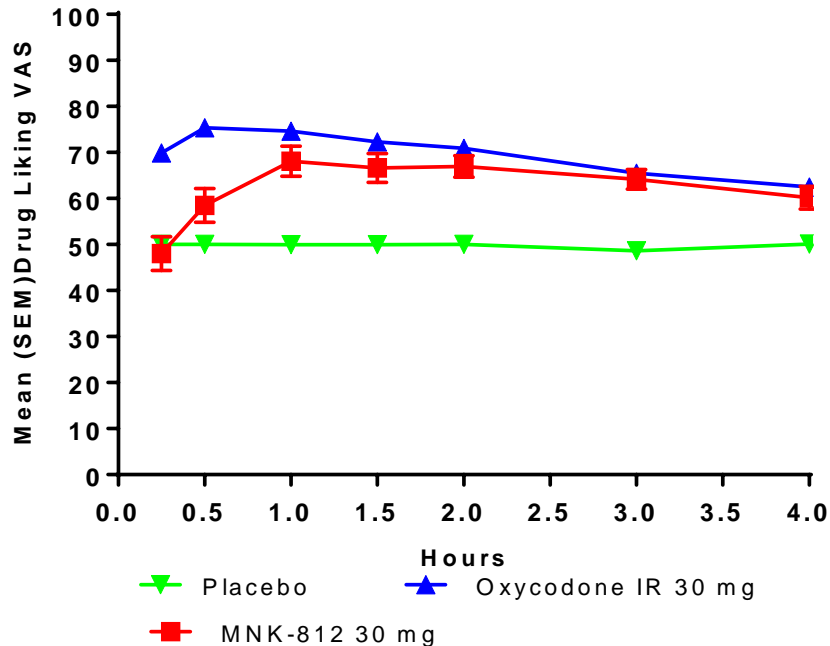
Drug Liking VAS and High VAS

("At the Moment")

- **Bipolar Drug Liking VAS (Primary Measure)**
 - Taken at various times post-dosing from 0.25 hours to 12 hours.
 - Question: "Do you like the drug effect you are feeling now?"
 - Anchors: 0 = "Strong disliking"; 50 = "Neither like nor dislike"; 100 = "Strong liking"
- **Unipolar High VAS (Secondary)**
 - Taken at various times post-dosing from 0.25 hours to 12 hours
 - Subjects respond to question: "Do you feel high?"
 - Anchors: 0 = "None" and 100 = "Extremely"

Bipolar Drug Liking VAS

Mean Drug Liking as a Function of Time Post-Insufflation.



Insufflated MNK-812

- LSmean Emax = 77.4
- Median Tmax = 1.49 hours
- LSmean AUE0-0.5 hours= 0.52

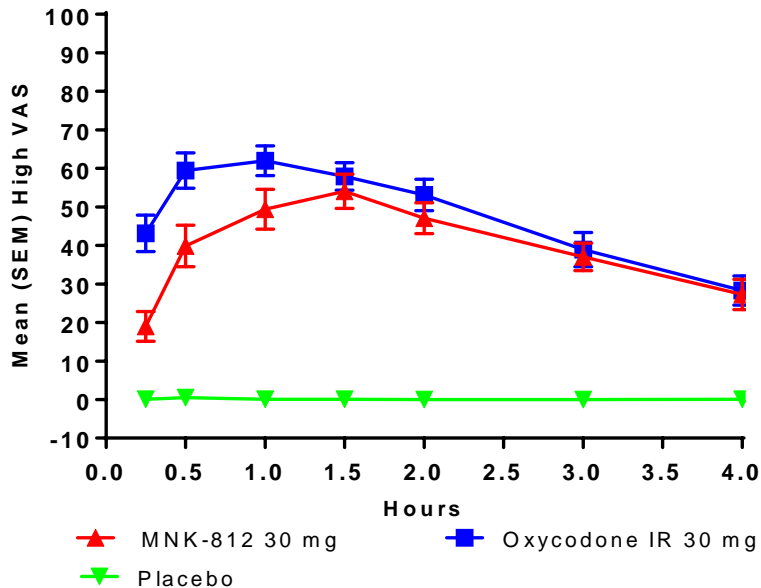
Insufflated Oxycodone HCl IR

- LSmean Emax = 82.7
- Median Tmax = 1.0 hours
- LSmean AUE0-0.5 hours= 8.16

Compared to insufflated Oxycodone IR, insufflation of MNK812 was associated with a reduced drug liking experience over the first 30 minutes, but no meaningful clinically relevant reduction in Emax of Drug Liking as reflected in at least a 10% reduction ($p = 0.1409$).

Unipolar High VAS

Mean High VAS as a Function of Time Post-Insufflation



Insufflated MNK-812

- LSmean Emax = 68.0
- Median Tmax= 1.5 hours
- AUE0-1 hours = 32.09

Insufflated Oxycodone HCl IR

- LSmean Emax = 72.6
- Median Tmax = 1.0 hours
- AUE0-1 hours = 48.67

Emax values for High following insufflated Oxycodone HCl IR and MNK-812 were not statistically significantly difference ($p= 0.356$)

Over the first hour, cumulative High experience was lower following insufflation of MNK-812 compared to Oxycodone HCl IR ($p<0.001$)



Bipolar Take Drug Again VAS

(Global Assessment)

Insufflated Treatments	LSmean Emax	Standard Error	95% Confidence Interval (CI)	
			Lower bound	Upper bound
MNK-812 30 mg	46.4	3.5	39.5	53.3
Oxycodone HCl IR 30 mg	77.0	3.5	70.1	83.9
Placebo	50.1	3.5	43.2	57.0

Question: *“Would you want to take the drug you just received again, if given the opportunity?”*

Anchors:
0 = “Definitely would not”
50 = “Do not care” 100 = “definitely would”

When compared to insufflated Oxycodone HCl IR, insufflated MNK-812 30 mg was associated with a statistically significant reduction ($p < 0.0001$) in maximum Take Drug Again.

Bipolar Overall Drug Liking VAS

(Global Assessment)

Insufflated Treatments	LSmean Emax	Standard Error	95% Confidence Interval	
			Lower bound	Upper bound
MNK-812 30 mg	49.8	3.3	43.3	56.2
Oxycodone HCl IR 30 mg	77.5	3.3	71.0	83.9
Placebo	48.6	3.3	42.2	55.1

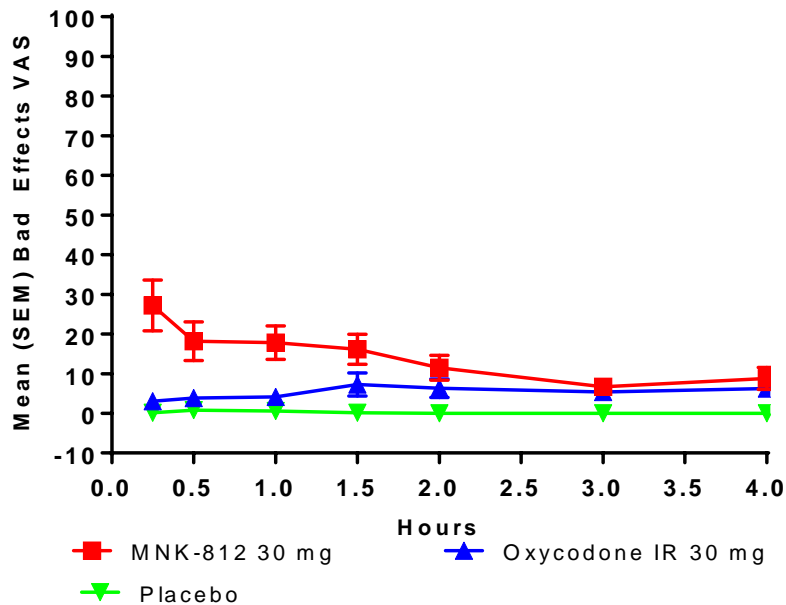
Statement: “Overall, my liking for this drug is...”

Anchors:
 0 = “Strong disliking”
 50 = “Neither like or dislike”
 100 = “Strong liking”

When compared to insufflated Oxycodone HCl IR, insufflated MNK-812 30 mg was associated with a statistically significant reduction ($p < 0.0001$) in maximum Overall Drug Liking.

Unipolar Bad Effects VAS

Mean Bad Effects Scores as function of Time Post-Insufflation.



Question "Does the drug have any bad effects?"

Anchors: 0 = "None"; 100 = "Extremely"

The LSmean Emax for Bad Effects produced by insufflated MNK-812 30 mg and insufflated Oxycodone HCl IR 30 mg, were 38.567 and 18.462 mm and statistically significant ($p < 0.001$).

Data overall suggest a limited adverse nasal tolerability associated with insufflated MNK-812.

Nasal Tolerability for Insufflated MNK-812

Nasal Symptom	Hours Post-Dose	Nasal Symptom Ratings Percentage of Subjects (N = 38)			
		None	Mild	Moderate	Severe
Intranasal Irritation	0.25	12.5	30.0	27.5	30.0
	0.5	25	37.5	25.0	12.5
	1.0	42.5	47.5	7.5	2.5
Nasal Burning	0.25	15	20.0	30.0	35.0
	0.5	35	25.0	27.5	12.5
	1.0	50	37.5	10.0	2.5
Runny Nose/Nasal Discharge	0.25	15	32.5	30.0	22.5
	0.5	15	52.5	30.0	2.5
	1.0	42.5	50.0	7.5	0
Facial Pain/Pressure	0.25	30	22.5	32.5	15.0
	0.5	32.5	35.0	22.5	10.0
	1.0	57.5	35.0	5.0	2.5
Nasal Congestion	0.25	15	35.0	35.0	15.0
	0.5	32.5	42.5	30.0	5.0
	1.0	45	42.5	12.5	0
Need to Blow Nose	0.25	15	27.5	37.5	20.0
	0.5	15	52.5	30.0	2.5
	1.0	42.5	50.0	7.5	0

4-Point Scale Rating for Six Nasal Symptoms:

0 = No effect

1 = Mild

2 = Moderate

3 = Severe

Adverse nasal symptoms are most prominent at 0.25 hours and decline substantially by 1 hour post-insufflation.

Conclusions from Study MNK48121013

1. The overall findings suggest that MNK-812 30 mg tablets, in contrast to Oxycodone HCl IR 30 mg tablets, may provide a deterrent effect to intranasal abuse via an aversive effect aimed at limiting nasal tolerability. This deterrent effect is not likely due to differences of oxycodone exposure. An alternative explanation would be that insufflation of MNK-812 is associated with a limited degree of nasal irritation that is most intense at the earliest time point of 0.25 hours and subsides substantially by one hour.
2. The slow rise in Drug Liking and High observed over the first hour post-insufflation of MNK-812 may reflect in part the decline in the severity of the adverse nasal symptoms documented by subjects over this same period. Following the delay, subjects did experience both Drug Liking and High.

Conclusions from Study MNK48121013

3. Significant reductions in Take Drug Again VAS and Overall Drug Liking VAS following insufflation of MNK-812 compared to Oxycodone HCL IR are consistent with a possible aversive effect associated with MNK-812. The fact that for both measures these reductions did not extend substantially into the negative region of the bipolar scales may reflected the limited extent of the adverse nasal effects and/or the fact that following a delay subjects did experience significant levels of drug liking and high.

Review of Recent Epidemiologic Data on Use, Misuse and Abuse of Oxycodone

Tamra Meyer, PhD, MPH

Team Lead

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Division of Epidemiology II

Office of Pharmacovigilance and Epidemiology

Office of Surveillance and Epidemiology

CDER, FDA

MNK-812, Joint AADPAC/DSaRM Meeting

November 14, 2018

Considering Public Health Impact in Opioid Drug Approvals

- FDA is presenting trends in misuse, abuse, and related outcomes for similar marketed opioids to help the committee assess potential public health risks and benefits of new opioid approvals
- Consistent with NASEM, 2017: “Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use”
 - “Integrating public health considerations into [FDA’s] regulation of opioids—including its approval decisions on new opioids—would be consistent with both its past practice and a generally accepted understanding of its statutory authority.”
 - “Public health considerations may include how the availability or use of the product will affect an unintended population or the broad public health impact resulting from the aggregated effects on patients taking the drug.”

Objectives of Epidemiology Review

1. Review data on **utilization** of oxycodone-containing products and comparator drugs
 2. Review epidemiologic data on **misuse and abuse** of oxycodone-containing products and comparator drugs to inform public health risk/benefit assessment
- * We will not describe published studies of associations between AD formulations of opioids and reductions in misuse, abuse, and related outcomes, as the FDA awaits complete submission of postmarket data under PMRs to demonstrate meaningful effects on misuse, abuse, or related adverse clinical outcomes in the community

AD, abuse-deterrent; PMR, postmarket requirement

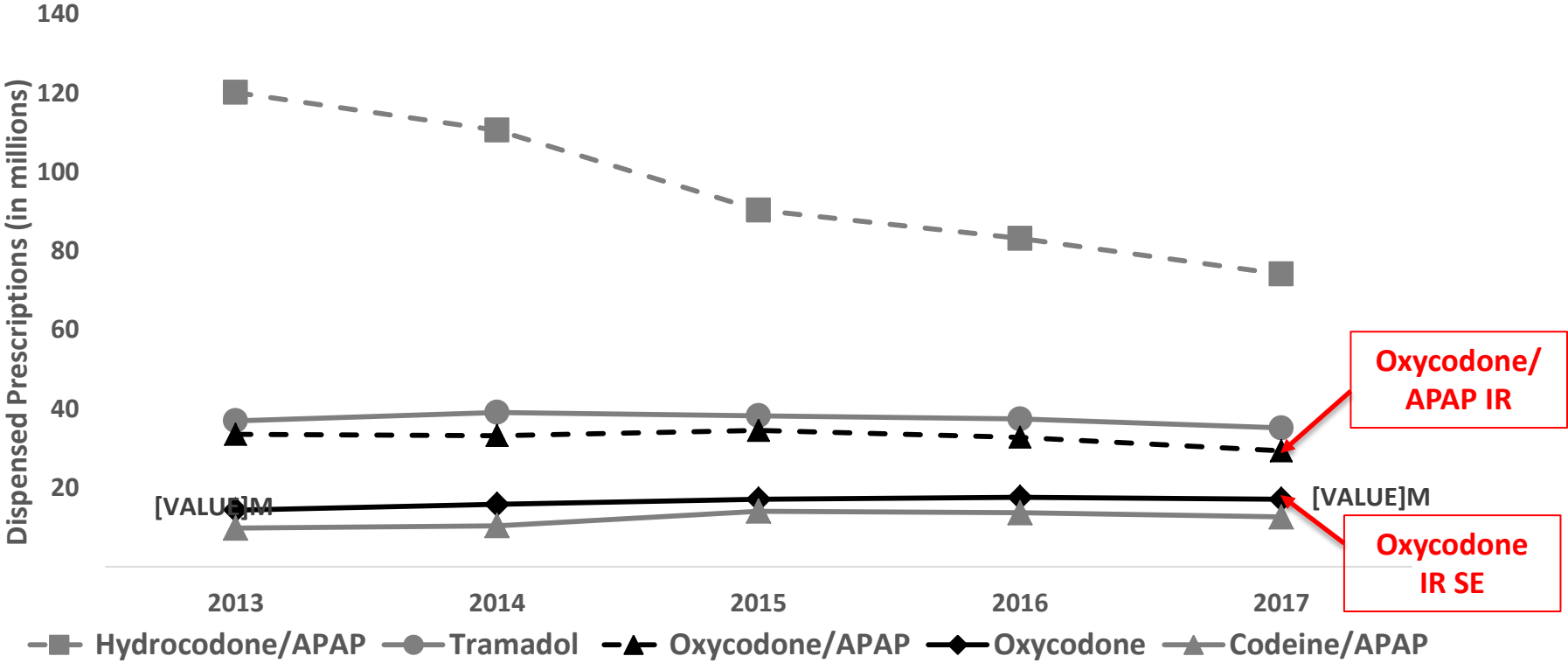
Objectives of Epidemiology Review

1. Review data on **utilization** of oxycodone-containing products and comparator drugs
 - Which are the most frequently dispensed IR opioid analgesics?
 - How frequently are specific oxycodone products dispensed in the US?
 - Among products intended to deter abuse, which are the most frequently dispensed?

IR, immediate-release

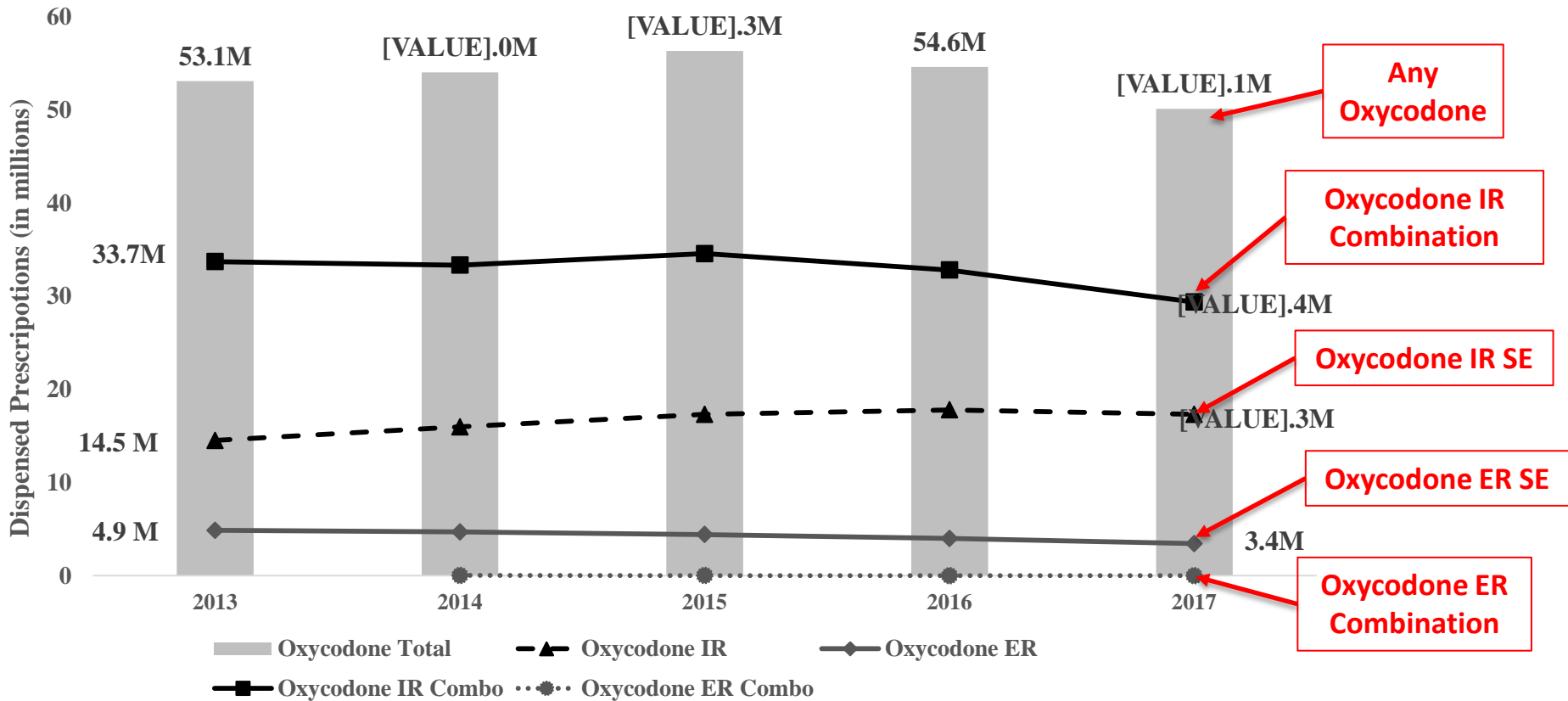


17 Million Oxycodone Immediate-Release (IR) Single-Entity (SE) Prescriptions Dispensed in 2017



Nationally Estimated Number of Dispensed Prescriptions for Oral Immediate Release Opioid Analgesics from U.S. Outpatient Retail Pharmacies, Source: IQVIA, National Prescription Audit™, Years 2013-2017. Data Extracted October 2018. APAP, Acetaminophen

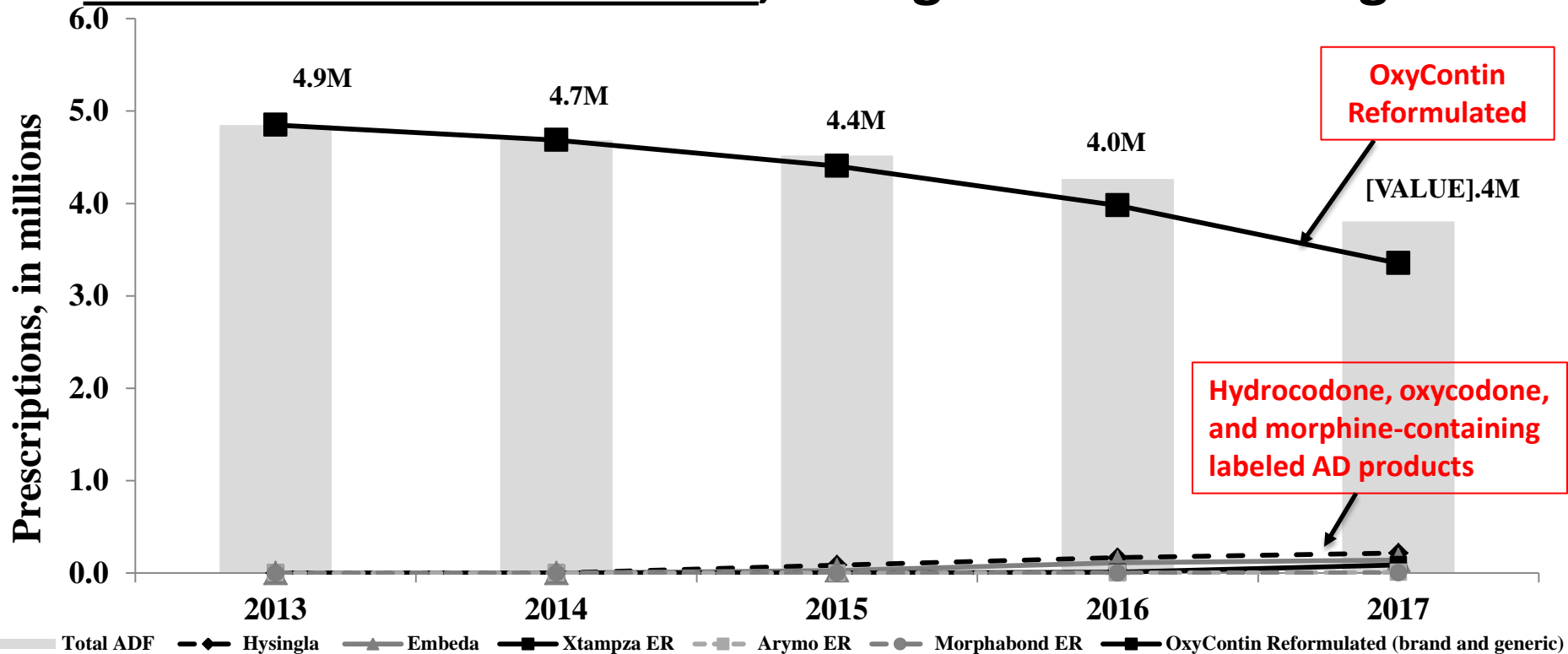
50 Million Oxycodone Prescriptions in 2017, IR >>>ER



Data Source: IQVIA, National Prescription Audit™, Years 2013-2017. Data Extracted April 2018.

IR, Immediate-Release formulations include oral solid tablets/capsules and oral liquids; ER Extended-Release, SE, single entity

Reformulated OxyContin Majority of Dispensed Abuse-deterrent Products, though Use Decreasing



Source: IQVIA, National Prescription Audit™, Years 2009-2017. Data Extracted February 2018.

*ADF Products not marketed during study period: RoxyBond (Oxycodone IR) - Approved 04/2017; Targiniq ER (oxycodone/naloxone ER) Approved 07/2014; Troxyca ER (Oxycodone/naltrexone ER) - Approved 08/2016; Vantrela ER (Hydrocodone ER) - Approved 01/2017
 AD, abuse-deterrent; ER, extended-release; IR, immediate-release

Objectives of Epidemiology Review

2. Misuse and Abuse

- What is the current scale of misuse and abuse of prescription opioids?
- Which are the most frequently abused opioids?
- What are common routes of abuse for oxycodone-containing products, including available abuse-deterrent formulations?
- What is the magnitude of morbidity and mortality associated with oxycodone-containing products versus comparator drugs?

Definitions of Misuse/Abuse

- **Misuse:** the intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse
- **Abuse:** the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect

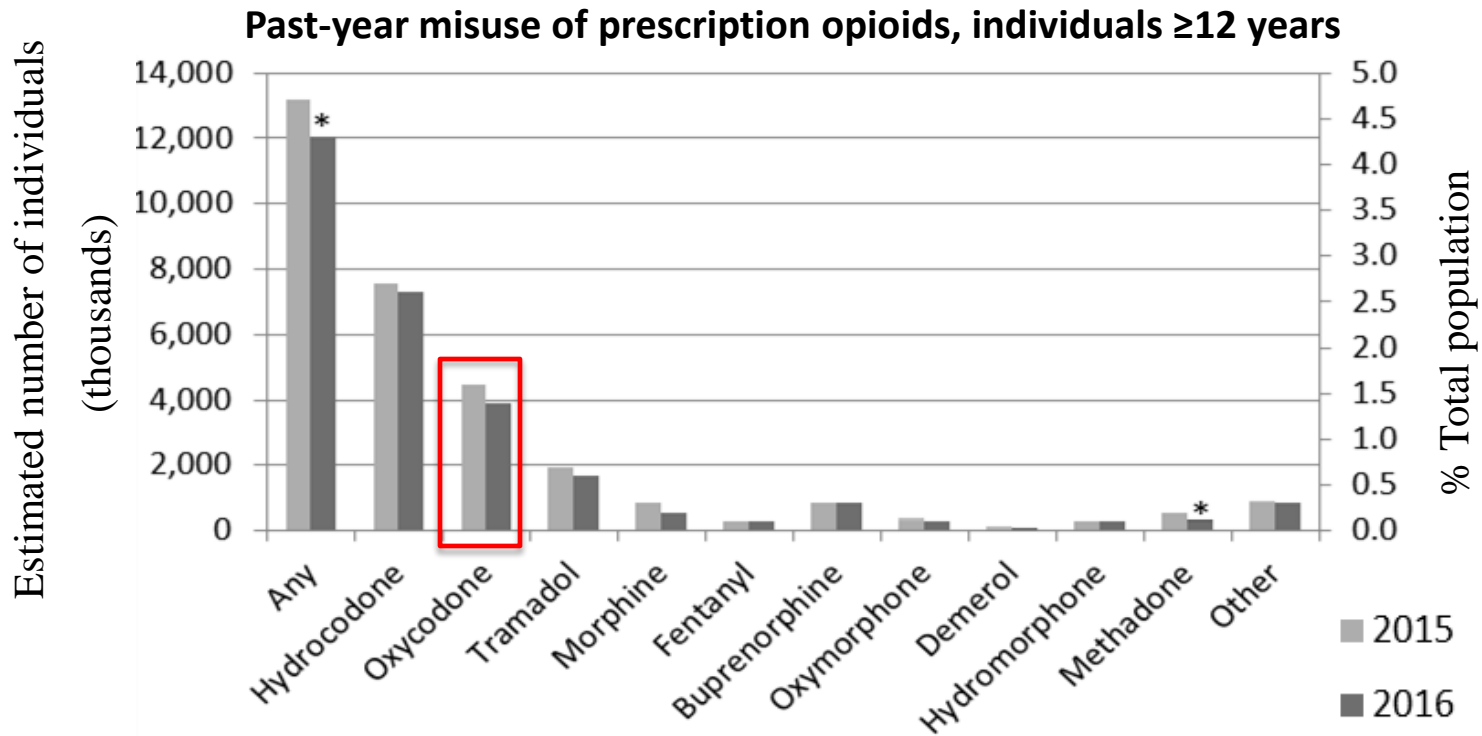
Food and Drug Administration [Internet]. "Abuse-Deterrent Opioids—Evaluation and Labeling: Guidance for Industry" [updated 2015 Apr; cited 2018 May 10.] Available from: <https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf>.

Data Sources Included

- NSDUH- National Survey on Drug Use and Health, 2016
- NEISS-CADES- National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance, 2016
- AAPCC NPDS- American Association of Poison Control Centers, National Poison Data System, 2012-2015
- RADARS[®] TCP- Researched Abuse, Diversion and Addiction-Related Surveillance Treatment Center Program, 2016
- LITERATURE/NAVIPPRO[™]- National Addictions Vigilance Intervention and Prevention Program, 2012-2015
- NVSS-M and DIM- National Vital Statistics System-Mortality and Drug Involved Mortality Data for Overdose Deaths, 2010-2015

Scale of Misuse and Abuse

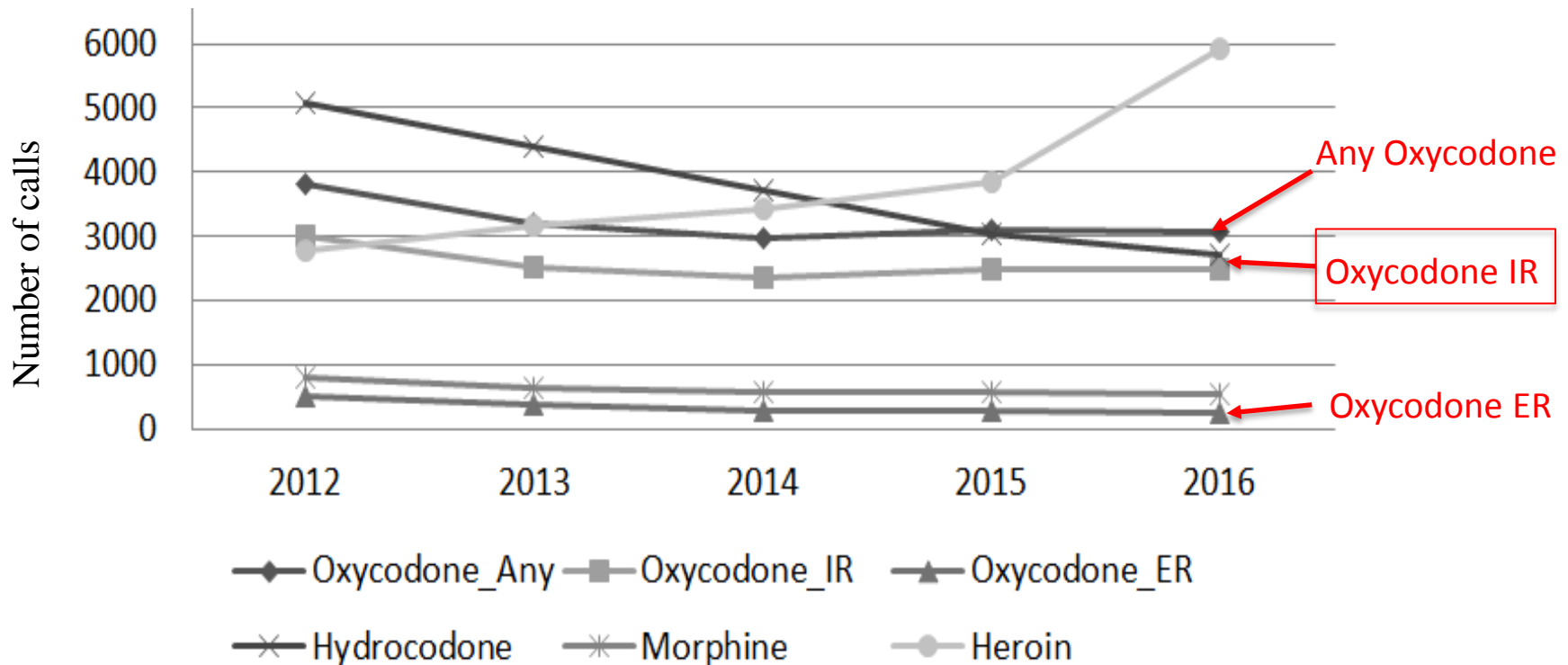
Oxycodone was Misused* by ~3.9 Million Individuals in the US During the Year 2016 (NSDUH)



Data Source: National Survey on Drug Use and Health (NSDUH), 2016

*NSDUH definition of “misuse” encompasses use of a drug in any mode other than as medically directed, including but not limited to abuse

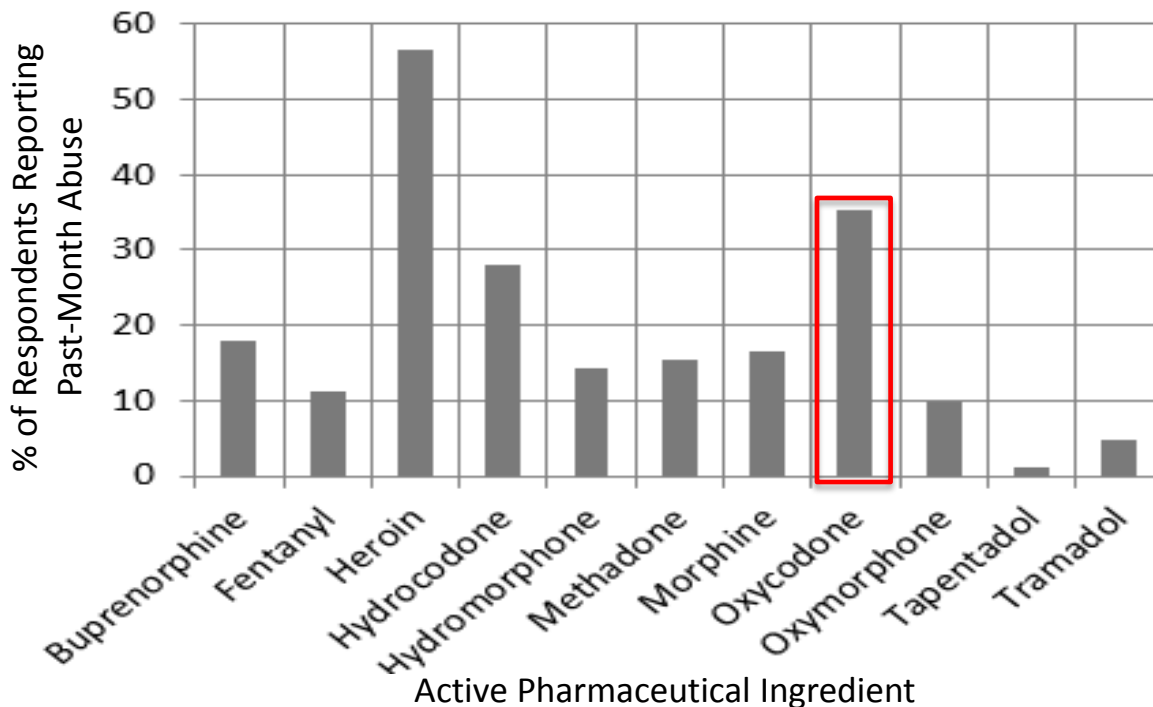
Over the Period 2012-2016, Intentional Exposure Calls* to PCCs Involving Oxycodone > 3000/yr (NPDS)



Data Source: American Association of Poison Control Centers (AAPCC)/National Poison Data System (NPDS); IR, Immediate-Release; ER, Extended-Release; PCCs, Poison Control Centers *restricted to individuals ≥12 years

Relative Frequency of Abuse, Specific Products

35% of Individuals Entering Treatment for OUD in 2016 Reported Past-Month Abuse of Oxycodone; IR > ER (RADARS[®] TCP)

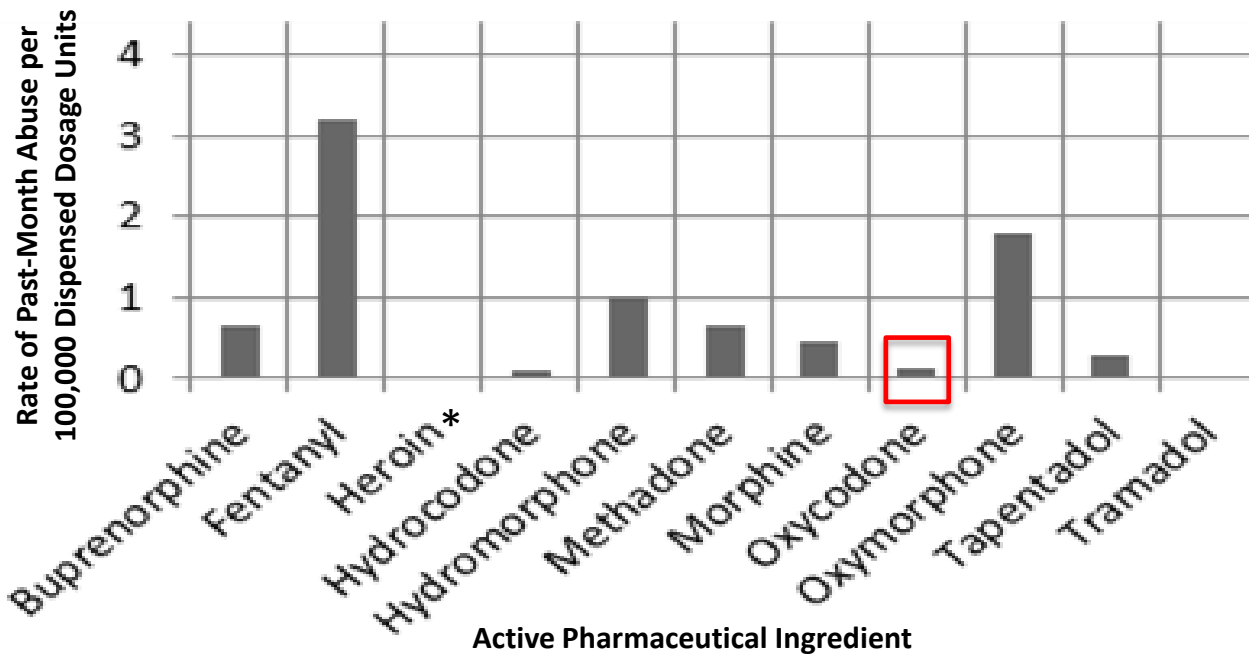


Oxycodone IR:
22% reported past-month abuse

Oxycodone ER:
15% reported past-month abuse

Data Source: Researched Abuse, Diversion and Addiction-Related Surveillance Treatment Center Program (RADARS[®] TCP); OUD, opioid use disorder

The Relative Frequency of Oxycodone Abuse Versus Other Products Changes After Adjusting for Utilization (RADARS[®] TCP)



Oxycodone IR:
 abuse rate- **0.09** individuals endorsing past-month abuse per 100,000 dosage units dispensed

Oxycodone ER:
 abuse rate- **0.89** individuals endorsing past-month abuse per 100,000 dosage units dispensed

Data Source: Researched Abuse, Diversion and Addiction-Related Surveillance Treatment Center Program (RADARS[®] TCP); IR, immediate-release; ER, extended-release

*Heroin could not be adjusted for prescription volume, but is retained on graph for consistency



Routes of Abuse

Most Common Route of Oxycodone Abuse is Oral (NPDS)

Percentage (%) of single-substance abuse exposure calls reporting specific exposure routes, among individuals 12 years and older, NPDS, 2012-2016

Route	Specific Oxycodone Products		
	Extended-release (N=497)	Immediate-release, single-entity (N=1,358)	Immediate-release, Combination Ingredient (N=1,242)
Ingestion	74.3	74.3	88.4
Inhalation/nasal	12.7	13.6	7.2
Parenteral (injection)	12.3	12.6	5.4

Data Source: American Association of Poison Control Centers (AAPCC)/National Poison Data System (NPDS);

Non-Oral Routes of Abuse are More Common in Treatment Center Populations

Routes of abuse reported in the past 30 days among patients entering or being assessed for treatment of substance use disorder, NAVIPPRO™, Jan 2012-June 2015

Opioid Category	Oral	Snort	Inject
Oxycodone IR-Combination	70%	40%	10%
Oxycodone IR- Single-Entity	40%	60%	40%
ADF ER/LA (includes oxycodone and other opioid moieties)	60%	20-30%	30%

← IR

← ER/LA (ADF)

Cassidy TA, Oyedele N, Mickle TC, Guenther S, Budman SH. Patterns of abuse and routes of administration for immediate-release hydrocodone combination products. *Pharmacoepidemiol Drug Saf.* 2017 Sep;26(9):1071-1082. doi: 10.1002/pds.4249. Epub 2017 Aug 3.

ADF, Abuse-deterrent formulation; ER/LA, Extended Release/Long-Acting; IR, Immediate-Release

Morbidity and Mortality

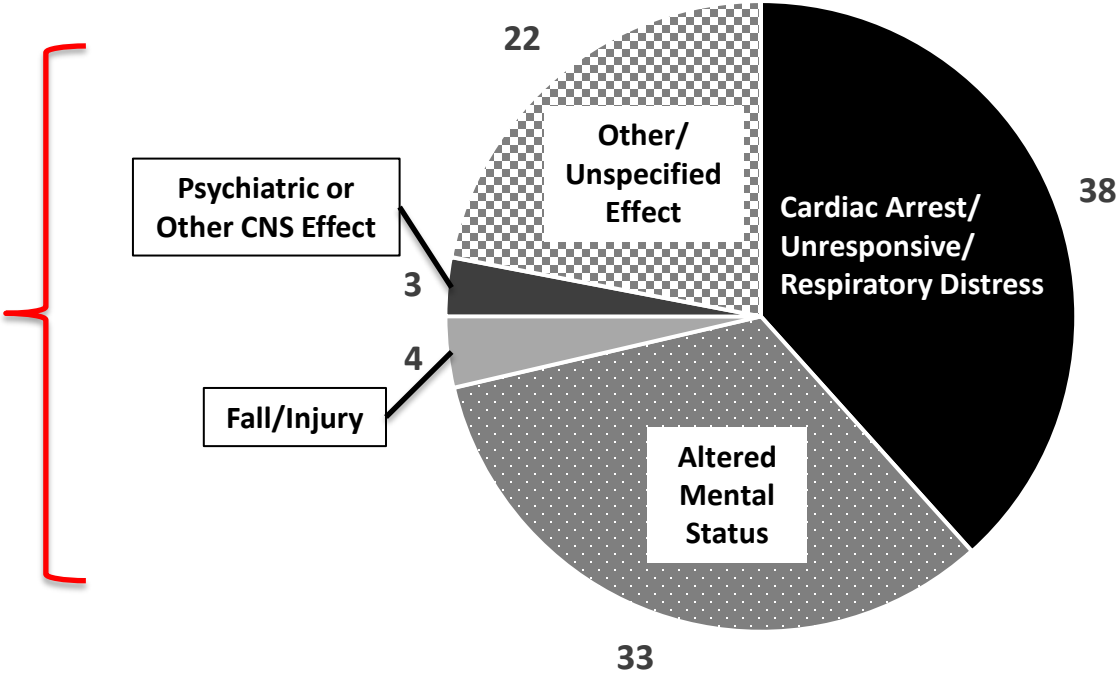
During 2016, an Estimated 105,771 ED Visits in the US Involved Harms from Oxycodone (NEISS-CADES)

- In 2016, 274,940 estimated ED visits for harms attributed to use of prescription opioids in the US
 - 105,771 (38%) of visits for harms attributed to prescription opioids were for oxycodone-containing products
 - 38,396 (36%) were attributed to therapeutic use
 - 16,171 (15%) were attributed to self-harm attempts
 - 51,204 (48%) were attributed to non-medical use
 - Concurrent substance use was common (15% >1 Rx opioid, 32% benzodiazepine, 48% illicit drug(s) or alcohol)

ED, emergency department; Rx, prescription

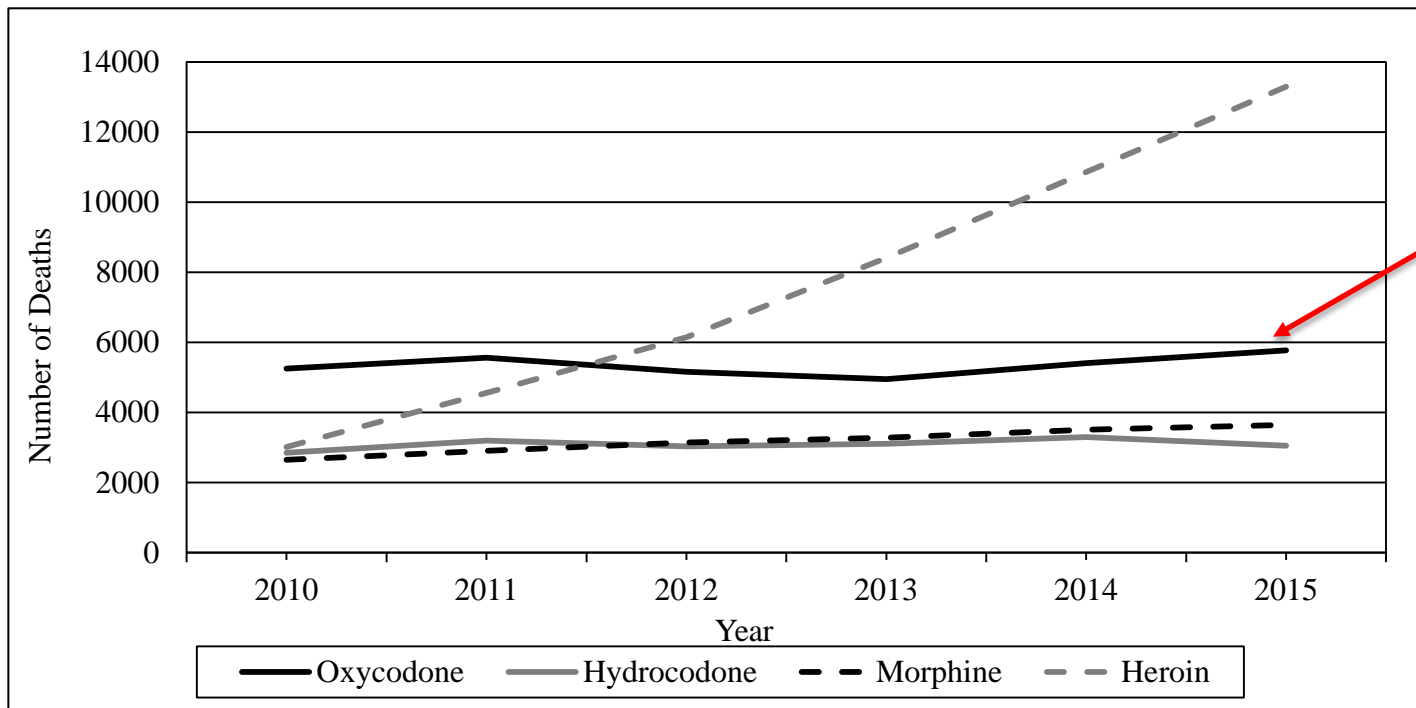
~19,600 ED Visits in the US with Non-Medical Use of Oxycodone Resulted in Cardiac Arrest, Respiratory Failure/Distress or Non-Responsiveness (NEISS-CADES)

Non-medical use of oxycodone
N= 51,204 ED visits in the US



Data Source: NEISS-CADES 2016;
CNS, Central Nervous System; ED, Emergency Department

Over the Period 2010-2015, Oxycodone-Involved Deaths Totaled 32,128; > 5000 Deaths/year (NVSS-M/DIM)



Oxycodone-involved deaths have not declined

Data Source: National Vital Statistics System-Mortality (NVSS-M) /Drug Involved Mortality (DIM)

Key Limitations of Data Sources (1)

- NSDUH
 - Survey biases: recall, response, social desirability
- NPDS
 - Presumed under-capture, particularly overdoses resulting in out-of-hospital death
 - The proportion of cases captured may vary over time and across drugs
- RADARS[®] TCP/NAVIPPRO[™]
 - Findings from the treatment centers may not be broadly generalizable or nationally representative
 - Product misclassification may occur (self-report)

Key Limitations of Data Sources (2)

- NEISS-CADES
 - Does not include cases that result in death before or during ED evaluation
 - Potential for misclassification of products (e.g., oxycodone single entity vs. oxycodone combination)
 - Only includes acute opioid harms resulting in an ED visit; does not include visits for opioid withdrawal, seeking treatment/detoxification, or inadequate therapy
- NVSS-M/DIM
 - Reliance on literal text of death certificate likely to miss proportion of opioid-related deaths that do not contain include information on specific drugs, and this proportion with an identified drug changes over time

ED, emergency department

Conclusions

- Oxycodone-containing products frequently dispensed in the US, and combination-ingredient IR formulations constitute the majority of dispensed oxycodone prescriptions
- Oxycodone-containing products are among the most frequently misused and abused prescription opioid products per population but not after taking into account the prescription volume
- We had no data on routes of abuse of RoxyBond™, the currently approved oxycodone IR product with AD labeling, but other available AD products are known to be abused by non-oral routes
- Despite the growing popularity of illicit opioids, oxycodone-containing products continue to be involved with morbidity and mortality in the US

AD, abuse-deterrent; IR, immediate-release

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- Judy Staffa, PhD, RPh - OSE

MNK-812

Clinical Summary of Abuse Deterrence

Jennifer L. Nadel, MD

Outline

- Abuse-Deterrent Opioid Formulations (ADFs):
Goals and Experience
- MNK-812: Abuse-Deterrence (AD) Results
 - MNK-812: Clinical Summary of Category 1 Testing
 - MNK-812: Clinical Summary of Excipient Safety
- Risk vs. Benefit of AD products

Abuse-Deterrent Formulations



- FDA abuse-deterrence guidance developed in response to serious public health concern of opioid abuse and misuse
- Relevant Definitions
 - Abuse:
 - The intentional, non-therapeutic use of a drug product or substance to achieve a desirable psychological or physiological effect
 - Abuse-Deterrent Properties:
 - Properties shown to meaningfully **DETER** abuse

Common AD Technologies

- Physical/chemical barriers
- Aversion
- Agonist/antagonist combinations

Goals For ADFs

A successful ADF does the following:

- Delivers a consistent and effective dose of opioid analgesic when used as labeled
- Can be expected to, or actually does, result in a reduction in abuse by making it more difficult to abuse by one or more relevant routes

Experience with ADFs

- ADFs are NOT abuse proof and do NOT prevent addiction
- We have approved 10* opioid analgesic products labeled with AD properties in accordance with the FDA Guidance.
- AD labeling is based on data from premarket studies
 - Category 1 (In vitro studies)
 - Category 2 (Pharmacokinetic studies)
 - Category 3 (Clinical abuse potential studies)

*Of the 10 approved products, only 6 have marketing status, as listed in the Orange Book. These products include: OxyContin, Embeda, Hysingla ER, MorphaBond ER, Xtampza ER, and RoxyBond.

Experience with ADFs

- All FDA approved ADFs have postmarket requirements to conduct additional studies (Category 4 studies) to evaluate whether the postmarket data support a meaningful effect of ADFs on reductions in abuse, misuse, or related adverse clinical outcomes in the community
- To date, none of the sponsors of ADF opioid analgesics have completed and submitted all the required postmarketing studies

MNK-812 AD Properties

- Aversive Characteristics:
 - Designed to cause nasal irritation
 - Intended to deter IN abuse
- Physical/Chemical Characteristics:
 - Forms a viscous solution potentially making it more difficult to draw up in to a syringe and to inject
 - Intended to deter IV abuse
 - Designed to be more difficult to crush into a fine powder
 - Intended to deter IN abuse

MNK-812 AD Results

- Intranasal (IN) route:
 - HAP study demonstrates that subjects experienced less overall drug liking and less willingness to take drug again with use of MNK-812 under the conditions tested.
- Intravenous (IV) route:
 - Under certain conditions 50-60% and 80-90% of oxycodone present in a tablet could be isolated and potentially injected with small volume and large volume extraction, respectively
- Smoking route :
 - This route generally not currently a relevant route of abuse for oxycodone.

Clinical Summary

MNK-812 Category 1 Testing

- Oxycodone can be extracted from MNK-812 for IV use
- Extracted oxycodone may potentially be shared among persons who inject drugs
- Sharing may lead to associated public health risks, such as blood-borne illnesses

Clinical Summary

MNK-812 Excipient Safety

- Unanticipated outcomes have occurred with the introduction of ADFs to the market (reformulated Opana ER):
 - Data supporting a shift from one route of abuse to another more dangerous route of abuse - from IN to IV
 - Excipient-related adverse events associated with ADF abuse by unintended routes of administration, i.e., thrombotic microangiopathy with IV use of manipulated reformulated Opana ER
 - HIV and Hepatitis C in individuals who were sharing manipulated reformulated Opana ER
- At this point, no clear evidence of thrombotic microangiopathy
 - FDA cannot rule out an increased risk with more frequent and/or prolonged exposure or manipulation

ADF Risks vs. Benefits

Risks

- Postmarketing experience with OxyContin has shown there are potential GI risks from swelling and hydrogelling when taken by the intended oral route
- Potential for excipient-related adverse events when abused by unintended routes
- Possible shift from IN to more dangerous IV abuse
- Possibility of substitution of more dangerous, illicit opioids

Benefits

- None to the individual patient, when used as directed
- Potential for improved product safety through reduced abuse, however, societal benefits are theoretical and are not yet supported by data

Concluding Remarks

- The safety and efficacy of MNK-812 is based on demonstration of bioequivalence to Roxycodone
- The AD data for MNK-812 show that there is some abuse deterrence by the IN route
- Category 1 data demonstrate that oxycodone suitable for IV use can be extracted from MNK-812 under certain conditions
- Large volumes can be extracted and potentially result in solution sharing
- If the PEO in this product is extracted and injected, we may have similar consequences as reformulated OPANA ER