History of "Abuse-Deterrent" Combination Opioids

Frank Pucino, PharmD, MPH
Clinical Reviewer
Division of Anesthesia and Analgesia Products
CDER/FDA/DHHS

Overview of Presentation

- Approved abuse-deterrent combination opioid products
- Postmarketing assessment on their potential for abuse

Public Health Concern

- Prevalence of opioid abuse
- Economic burden
- Morbidity
- Mortality

"Abuse-Deterrent" Combination Opioid Products

- Combination drugs developed with the intent to limit the abuse potential of the opioid component

Combination Rule: 21CFR300.50(a)

"Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effect…"

- A special case of this rule is where a component is added…to minimize the potential for abuse of the principal active ingredient

Approved "Abuse-Deterrent" Combination Opioids

- **TALWIN NX™ (CIV)**
  - Pentazocine/naloxone
- **SUBOXONE™ (CIII)**
  - Buprenorphine/naloxone
- **EMBEDA™ (CII)**
  - Morphine/naltrexone

Naloxone and naltrexone were added to deter intravenous or oral abuse of these opioids

Naloxone

- Pure opioid antagonist
- Causes partial or complete reversal of opioid effects
- Administered IV
  - Very limited systemic bioavailability by non-parenteral routes of administration
    - Added to limit parenteral abuse

TALWIN NX™

- TALWIN™ (pentazocine) was approved in 1967 for the relief of moderate-to-severe pain
  - No known potential for abuse
  - Not scheduled
- 1968: First reports of dependence, limited
- Late 1970's: Increasing frequency of cases of abuse, diversion, overdose and death
  - T's and Blues
    - TALWIN™ and tripelennamine HCl (antihistamine, blue tablet)
  - Intravenous abuse of crushed tablets
    - Substitute for heroin

Efforts to Mitigate Abuse

- 1979: Schedule IV controlled substance
  - Labeling changed to include postmarketing events of addiction
- 1982: Reformulated with naloxone
  - Pentazocine 50mg/naloxone 0.5mg
  - Marketed as TALWIN NX™ starting April 1983
- January 1983: TALWIN™ withdrawn from market
  - Reports of abuse declined during the two years following withdrawal from the market

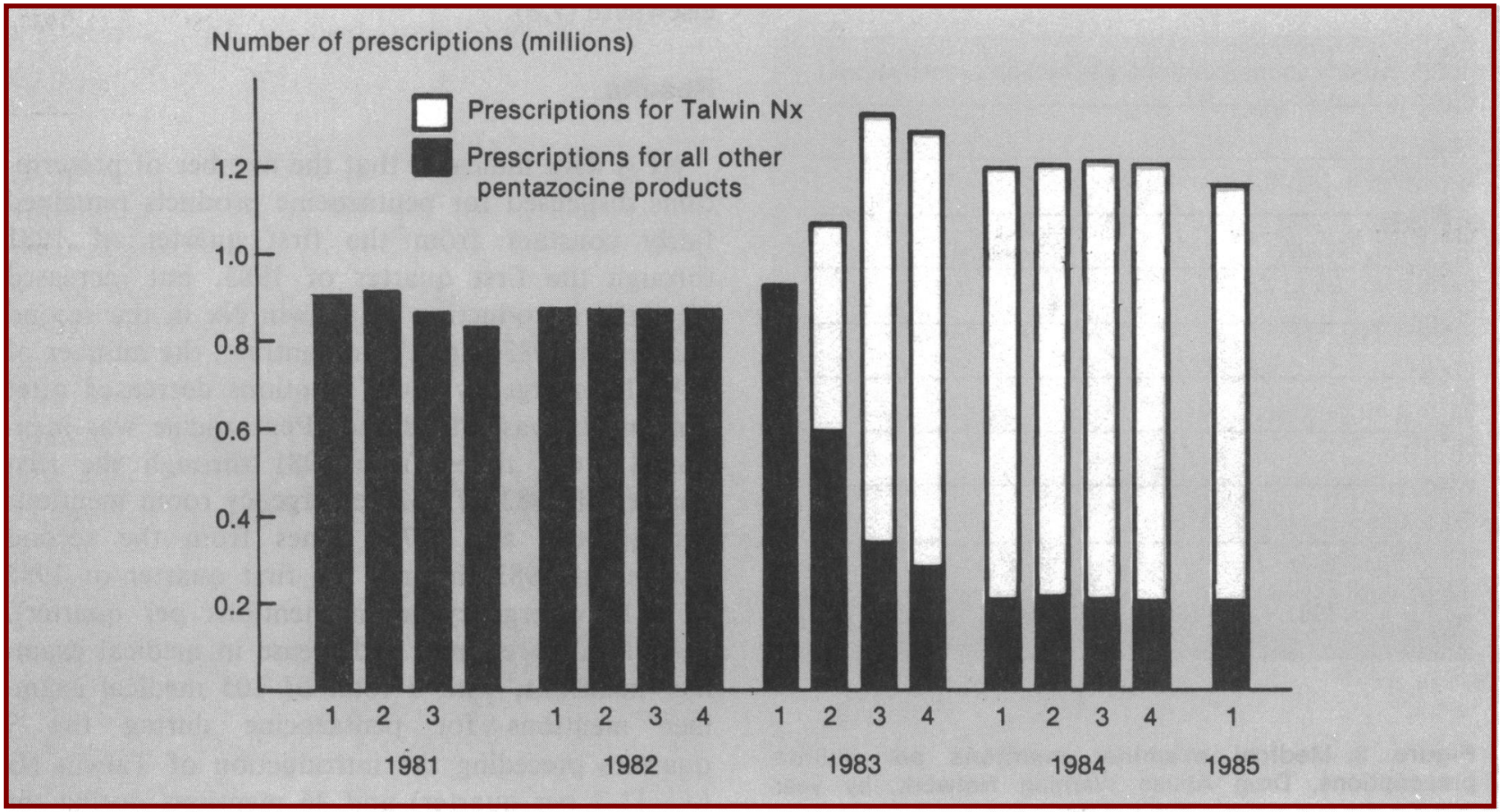
Impact of Addition of Naloxone on Use and Abuse of Pentazocine

Baum B, Hsu JP, Nelson RC.

Public Health Reports

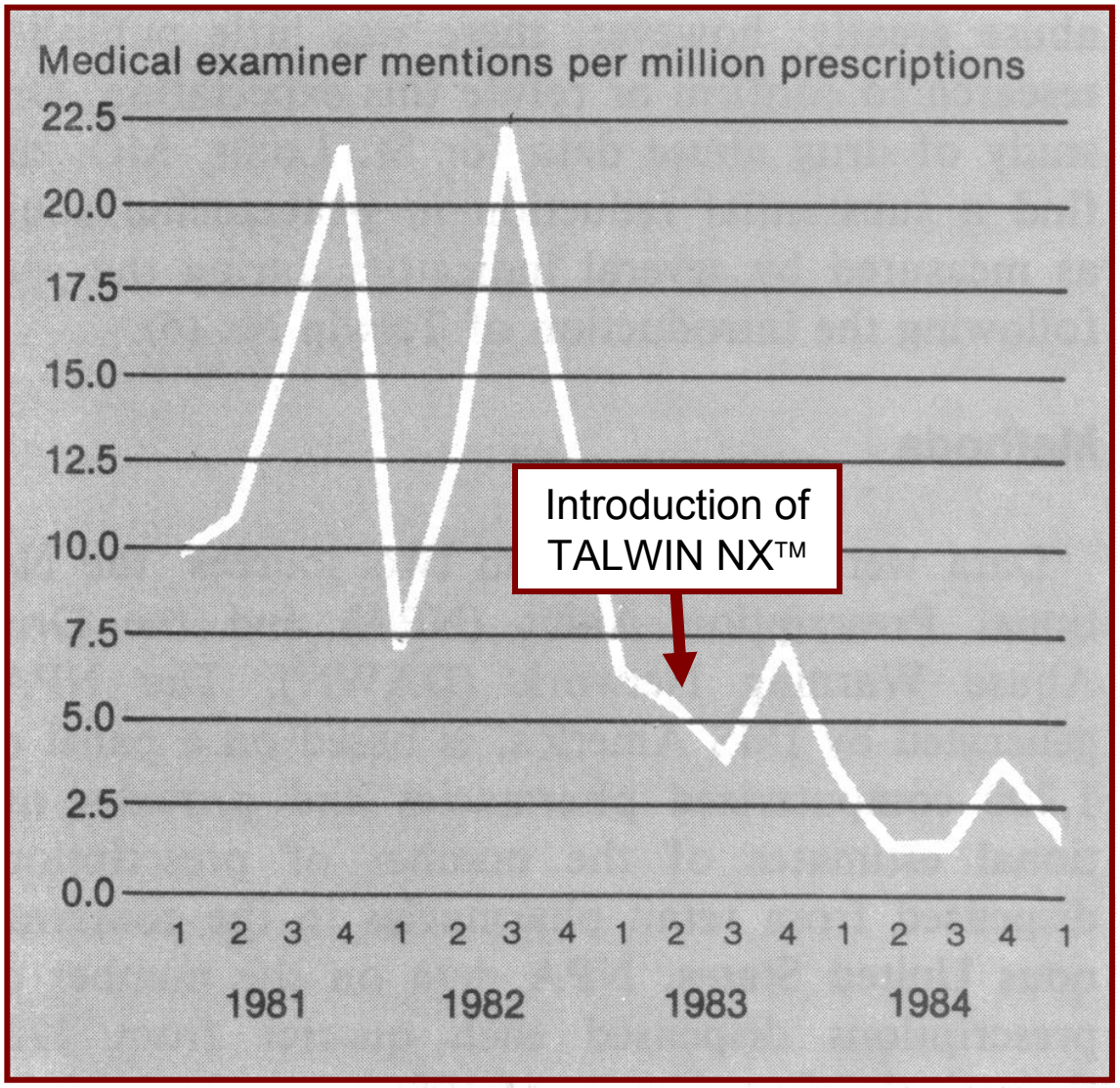
July-August 1987;102 (No.4)

Pentazocine Rx's Dispensed from Retail Pharmacies*



*Intercontinental Marketing Service (IMS) Prescription Audit

DAWN Medical Examiner Mentions per Million Rx's



Possible Factors Contributing to the Decrease in Abuse of TALWIN™

- Change in the availability of heroin
- Scheduling of TALWIN™
- Removal of single entity TALWIN™ from the market
- Introduction of TALWIN NX™

SUBOXONE™

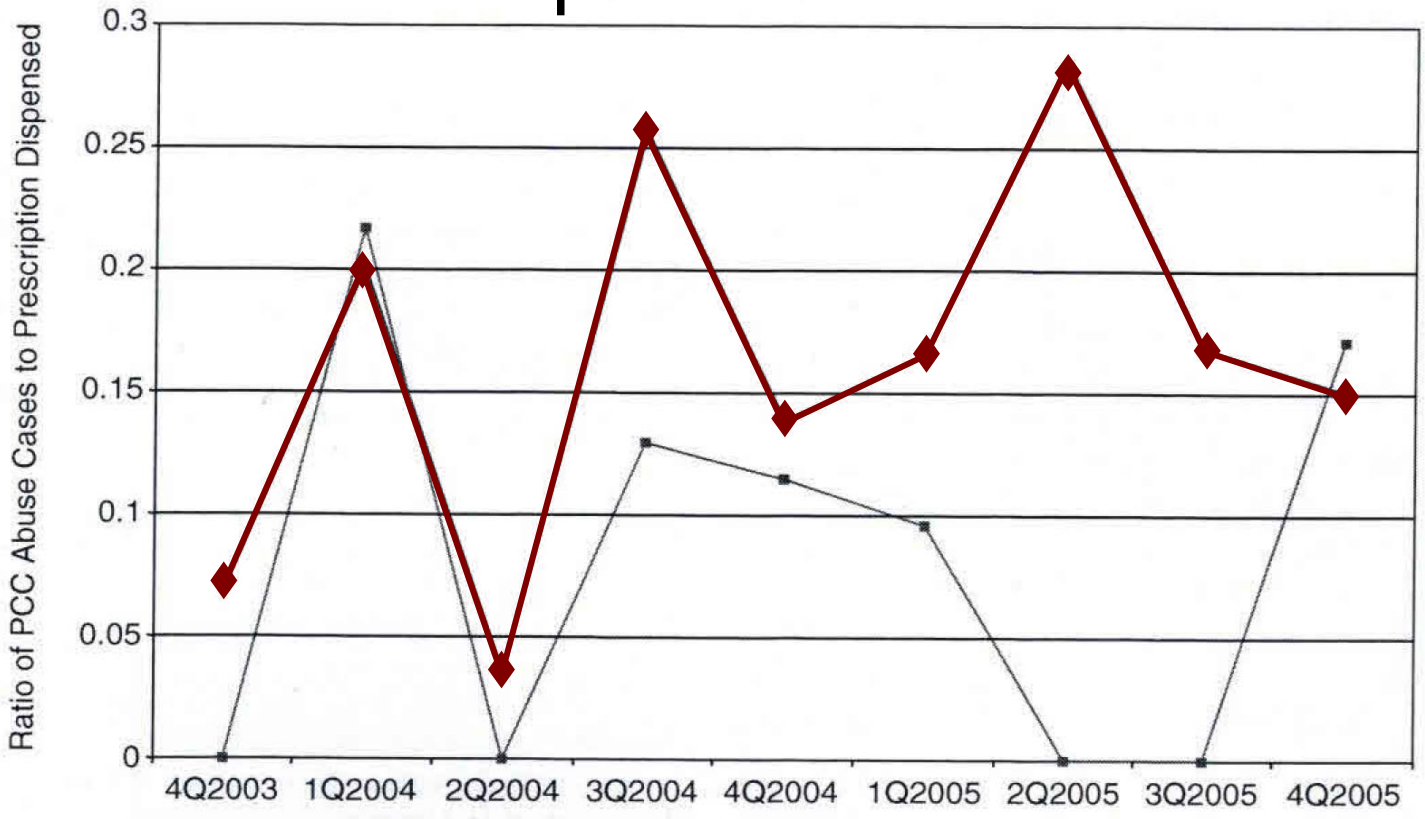
- Combination of buprenorphine HCl (partial mu opioid agonist) plus naloxone HCl (full opioid antagonist)
  - Buprenorphine/naloxone: 2 mg/0.5 mg, 8 mg/2 mg
- Approved in October, 2002 for the treatment of opioid dependence, along with SUBUTEX™, which is buprenorphine HCl without the addition of naloxone
  - Both products are interchangeable in terms of the pharmacokinetics of buprenorphine

- SUBOXONE™ was designed for sublingual administration
  - Absorption of the naloxone component caused no clinically significant effect
    - Plasma concentrations measurable
- If administered intravenously, the naloxone component would become available
  - Blocking the euphoric effects of the opioid component or precipitate opioid withdrawal
- Limited formal studies conducted to assess the impact of SUBOXONE™ on abuse liability

SUBOXONE™ Abuse

- Reports of abuse
  - Sublingual, nasal inhalation, injection
- Baltimore Sun, December 2007
  - “The Bupe Fix” - Naloxone does not always deter abuse
  - Maine health department reported that misuse spread rapidly as more SUBOXONE™ was prescribed. Abusers of the drug "have figured out how to separate out the naloxone" to inject the buprenorphine….
  - In Massachusetts, a police detective, said, "A lot of people are injecting it. They're getting hooked on it.“

Ratio of SUBOXONE™ & SUBUTEX™ Abuse Cases per 1000 Rx's in 18 PCs



-♦- SUBOXONE™ (Ratio 0.16 cases/1000 Rx's) -■- SUBUTEX™ (Ratio 0.08 cases/1000 Rx's)

Smith MY, et al. J Addict Dis. 2007;26(3):107-11

Diversion & Injection - Opioid Substitution

Australian Postmarketing Surveillance Studies 2006-08

- Compared to buprenorphine (adjusting for availability) buprenorphine/naloxone was associated with:
  - Less removal from the dosing site (22% vs 35% ≥ 1 dose in 2008)
    - Stockpile (54%) / help a friend (27%)
  - Less injection of doses (13% vs. 28%)
    - 38% vs. 18% reported “no liking”
  - Less injection of diverted medication by out of treatment injection drug users
    - 5% vs. 14% within last 6 mos
  - Less market demand
    - 17% vs 9% as of September 2008 (same street price as buprenorphine)

Larance B, et al. National Drug and Alcohol Research Centre Technical Report No. 302, 2009

EMBEDA™

- Combination of morphine sulfate (mu agonist) and naltrexone HCl (oral full opioid antagonist)
  - Morphine/naltrexone: 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, 100 mg/4 mg
- Approved in August 2009 for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time
- The morphine component is bioequivalent to KADIAN™ (extended-release morphine sulfate)

EMBEDA™

- Designed to be administered as intact capsules or intact pellets sprinkled over applesauce
  - Administered in this way, the absorption of naltrexone is negligible
- In non-dependent recreational opioid users, if EMBEDA™ was crushed (120 mg of morphine) and administered, 87.5% of subjects had some degree of decreased drug liking vs. 31% of subjects receiving immediate-release morphine
- No formal postmarketing studies have been conducted to assess the impact of EMBEDA™ on abuse liability

Summary

- Three approved "abuse-deterrent" combination opioid products
  - TALWIN NX™ (pentazocine/naloxone)
    - Appeared to decrease pentazocine abuse
      - Various contributing factors
  - SUBOXONE™ (buprenorphine/naloxone)
    - Multiple reports of IV and intranasal abuse
    - The limited postmarketing assessments of abuse liability are inconclusive
  - EMBEDA™ (morphine/naltrexone)
    - No formal postmarketing assessment of abuse liability

Outpatient Drug Utilization Patterns for Oxycodone Containing Products in the U.S., Years 2005-2009

Hina Mehta, PharmD
Drug Utilization Analyst
Division of Epidemiology
Office of Surveillance and Epidemiology
FDA/CDER
Acurox AC, April 2010

Outline

- Objective
  - To describe the extent of use for combination and single-ingredient Oxycodone product usage in terms of sales and prescription data in the U.S. population by form
- Methods
  - IMS, Health
  - SDI
    - VONA/TPT
    - PDDA
  - Products Examined
    - Single ingredient oxycodone (i.e. OxyIR®/Oxycontin®)
    - Combination oxycodone (i.e. Percocet®/Percodan®)
- Results
- Summary

Methods: Database Descriptions

- IMS Health, IMS National Sales Perspectives™
  - Sales data used to determine pattern of distribution
    - Measures sales data from manufacturer to retail and non-retail channels of distribution
    - **Eaches** are the number of bottles, packets of pills, syringes, vials, etc. of a product shipped in each unit
    - 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 (began 1998), HMOs, miscellaneous channels (began 1999; prisons, universities, other)

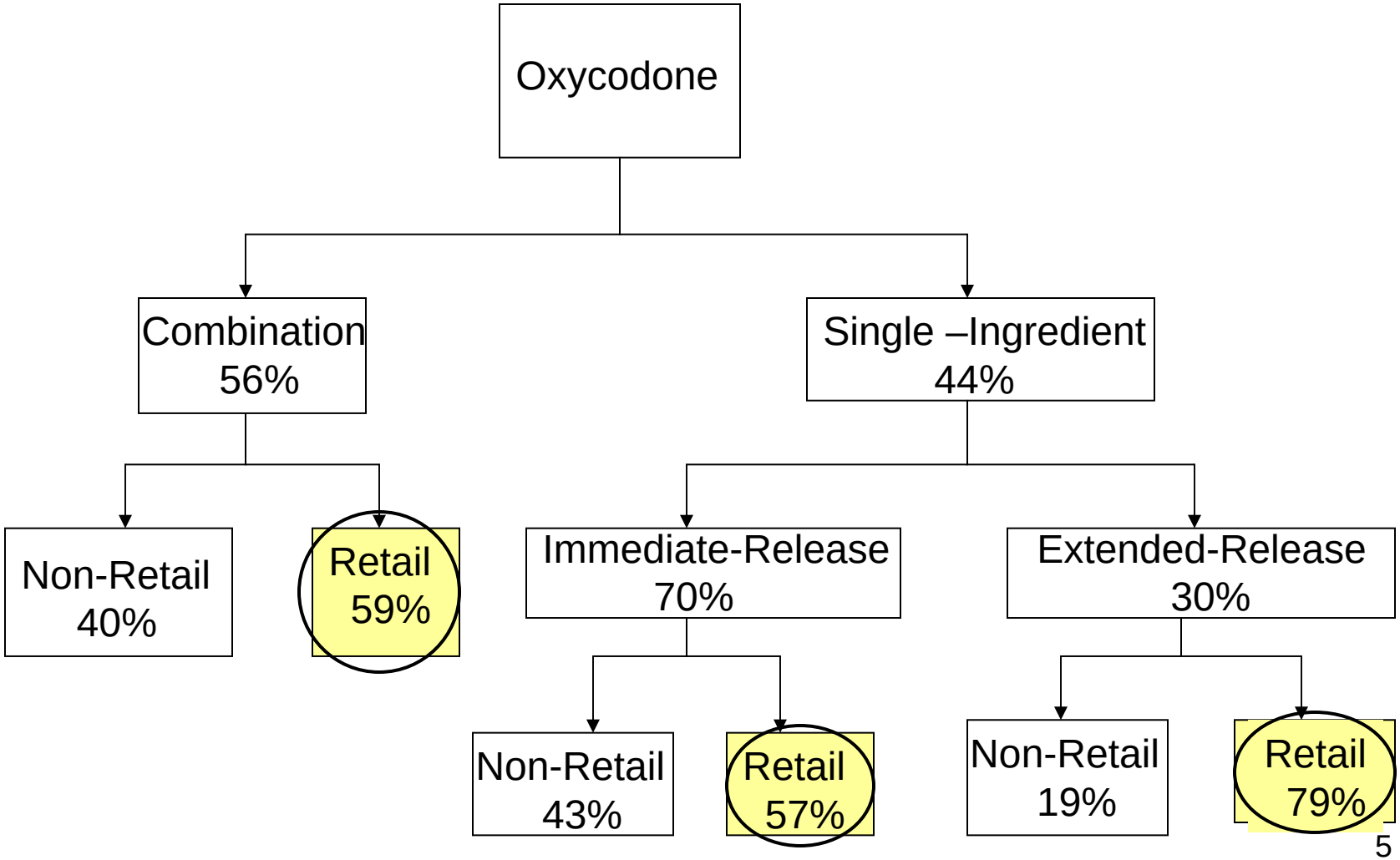
Sales Data

IMS HEALTH, IMS National Sales PerspectiveTM, Extracted March 2010

- Year 2009
  - 56% of sales as combination oxycodone
    - 59% to retail pharmacy settings
    - 40% to non-retail pharmacy settings
  - 44% of sales as single ingredient oxycodone
    - 87% of sales as immediate release (IR) oxycodone
      - 64% to retail and 35% to non-retail pharmacy settings
    - 13% of sales as extended release (ER) oxycodone
      - 83% to retail and 15% to non-retail pharmacy settings

Sales Data, Y2009

IMS HEALTH, IMS National Sales PerspectiveTM, Extracted March 2010



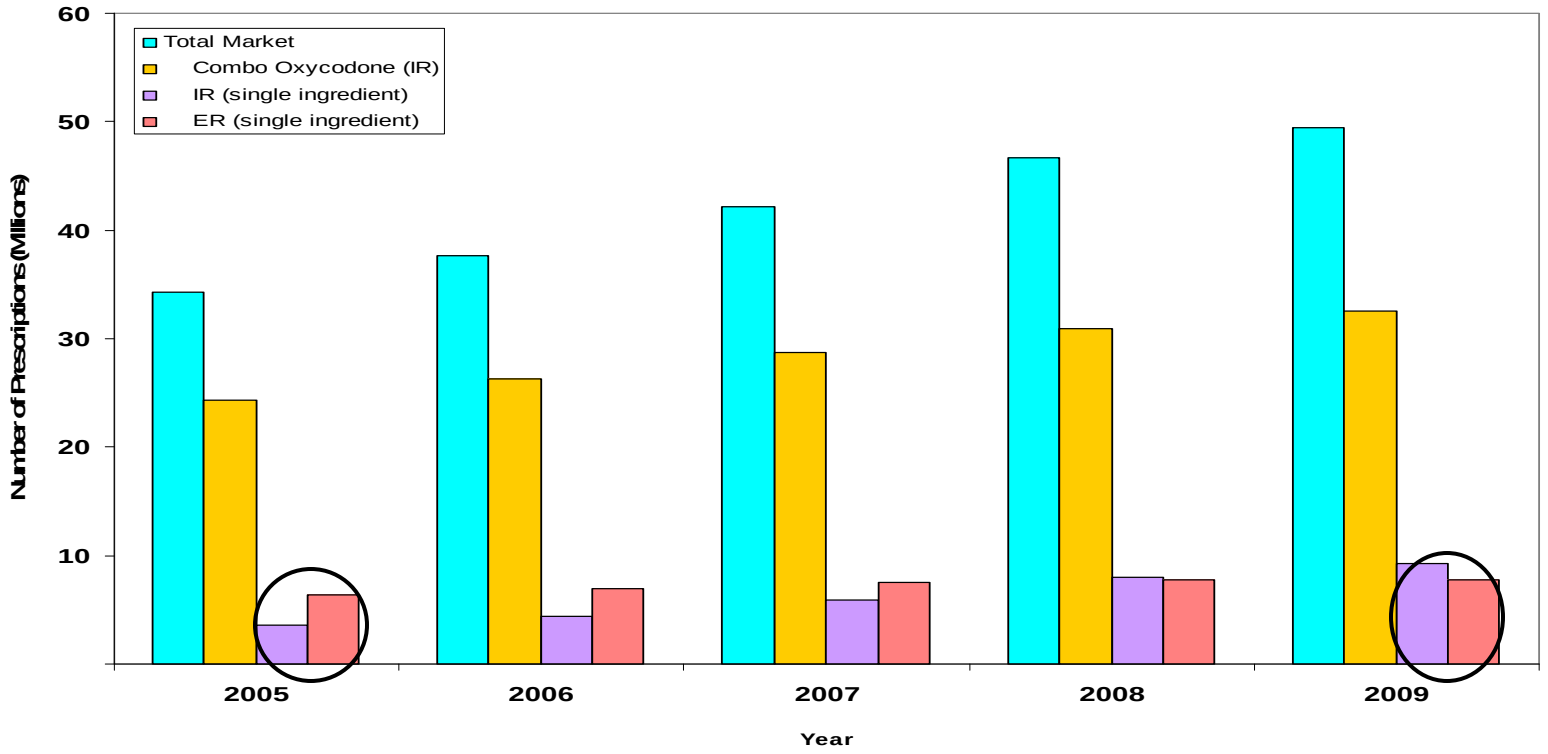
Results: Prescription and Patient Level Data

Outpatient Utilization Data Sources

- SDI Vector One®: National (VONA) & Total Patient Tracker (TPT)
  - National-level projected prescription and patient-centric tracking service
  - 59,000 U.S. retail pharmacies
  - >2.0 billion prescription claims per year
  - >160 million unique patients
- SDI Physician Drug and Diagnosis Audit (PDDA)
  - Monthly survey that monitors disease states and physician intended prescribing habits on a national-level
  - 3,200 panelists, 30 specialists
  - Includes diagnoses, patients characteristics, and treatment patterns

Total Number of Prescriptions Dispensed for Single-Ingredient and Combination Oxycodone Through U.S. Outpatient Retail Pharmacies, Years 2005-2009

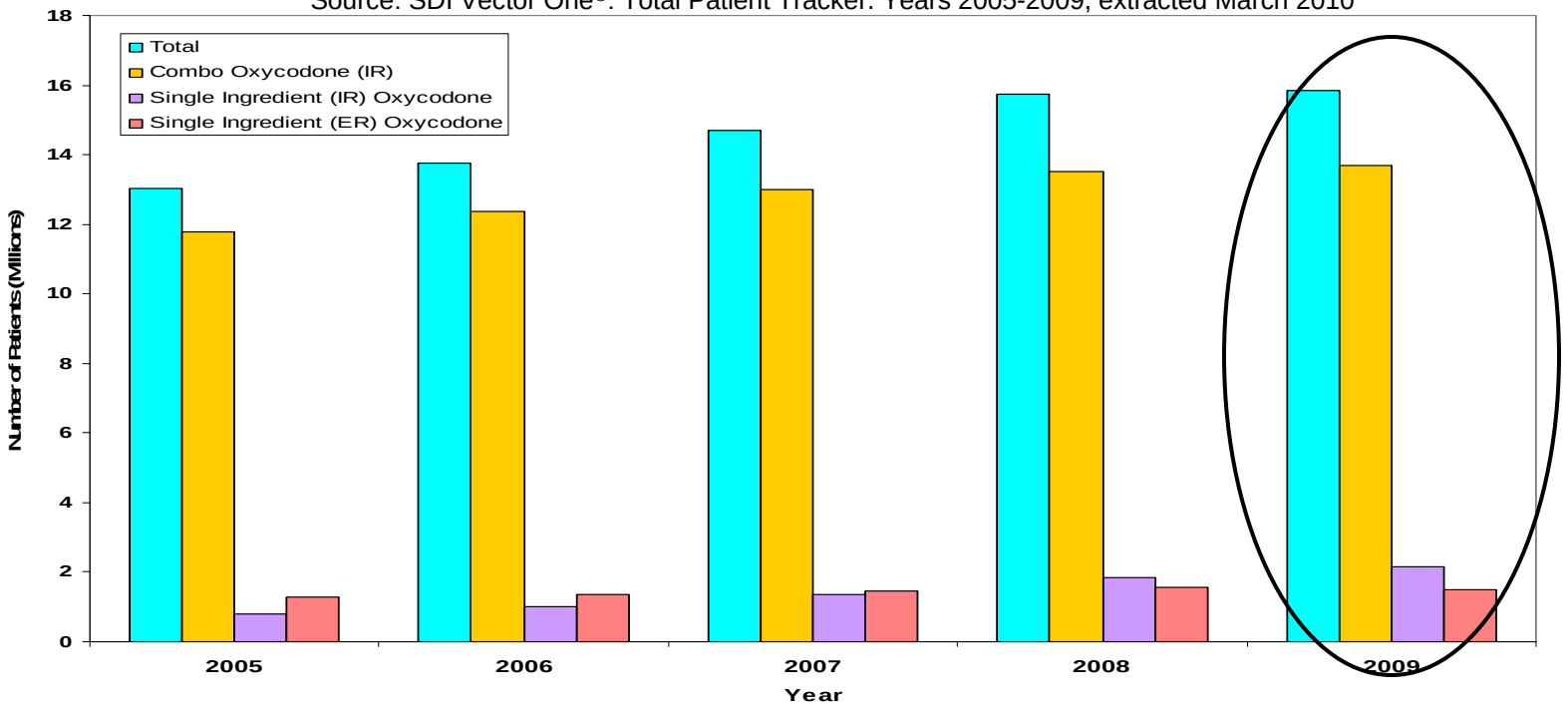
Source: SDI Vector One®: National. Years 2005-2009, extracted March 2010



- Combination oxycodone products accounted for 66% of oxycodone market in Y2009
- Shift from majority of use of single ingredient oxycodone as ER (64%) in Y2005 to majority of use as IR (54%) in Y2009

Number of Patients Receiving a Prescription for Single Ingredient and Combination Oxycodone Through U.S. Outpatient Retail Pharmacies, 2005-2009

Source: SDI Vector One®: Total Patient Tracker. Years 2005-2009, extracted March 2010



- Total number of patients receiving a prescription for an oxycodone containing product: 15.8 million
- 86% of patients received a prescription for combination oxycodone product in Y2009 while 21% received a prescription for single ingredient oxycodone
- Shift from majority of patients receiving a prescription for single ingredient oxycodone as ER (61%) in Y2005 to majority of use as IR (63%) in Y2009

Directions for Use, Signa, for Single Ingredient Oxycodone Products as Reported by Office-Based Physicians, 2005-2009 cumulative

Source: SDI Physician Drug and Diagnosis Audit. Years 2005-2009, extracted March 2010

- 63% of mentions for single ingredient oxycodone were for the ER products
  - 54% of mentions were for BID dosing
  - Nearly 25% were for frequency greater than BID
  - 7% of mentions were for QD dosing schedule
  - 14% of mentions were other/unspecified
- 37% of mentions for single ingredient oxycodone were for the IR products
  - 28% of mentions were for QID dosing
  - 20% of mentions were for frequency greater than QID
  - 22% of mentions were for frequency less than QID
  - 30% of mentions were other/unspecified

Directions for Use, Signa, for Combination Oxycodone Products by Form as Reported by Office-Based Physicians, 2005-2009 cumulative

Source: SDI Physician Drug and Diagnosis Audit. Years 2005-2009, extracted March 2010

- 99% of mentions for combination oxycodone products were for oxycodone/acetaminophen
  - 50% of mentions were for frequencies greater than QID
  - 27% of mentions were for QID dosing
  - 11% of mentions were for frequencies less than QID
  - 11% of mentions were other/unspecified

Dispensed Prescription for Single Ingredient and Combination Oxycodone by Prescriber Specialty Through U.S. Outpatient Retail Pharmacies, 2005-2009

Source: SDI Vector One®: National. Years 2005-2009, extracted March 2010

- Top 5 prescribing specialties:
  - General Practice/Family Medicine and Internal Medicine for all formulations
  - Combination oxycodone products: Orthopedic Surgery, Emergency Medicine, and Dentists
  - Single-ingredient immediate and extended release products: Anesthesiologists, Pulmonary Medicine and Rehab, and Nurse Practitioners

Strengths and Limitations

- Analysis was representative of national outpatient retail pharmacy usage patterns
- Inpatient (40% for combination, 43% for IR and 19% for ER) use was not captured in this analysis
- Sales distribution analyzed
  - Combination oxycodone: 59%
  - Single Ingredient IR: 57%
  - Single Ingredient ER: 79%

Summary

- Use of oxycodone containing products has gradually increased over the last 5 years
- Majority of oxycodone use is combination products
- A shift in majority use of single-ingredient ER products in Y2005 to IR products in Y2009
- Not uncommon for dosing schedule of ER and IR oxycodone containing products to exceed QID schedule

Misuse / Abuse of Opioid Analgesics: Findings from The Drug Abuse Warning Network (DAWN)

Catherine Dormitzer, PhD, MPH
Division of Epidemiology (DEPI)
Office of Surveillance and Epidemiology (OSE)

Overview

- Background
  - DAWN
  - Comparator Drugs
- Methods
- Summary of Calculations
- Conclusions

Drug Abuse Warning Network (DAWN)

- Nationally Representative, Stratified probability sample of short-term, non Federal hospitals with 24-hour emergency departments (EDs)
  - Administered by SAMHSA
- Type of case
  - Suicide Attempt
  - Adverse Reaction
  - Accidental Ingestion
  - **Overmedication**
  - **Seeking Detox**
  - **Other**

Selection of Comparator Drugs

- **Oxycodone C-II**
  - **Immediate Release/Single Ingredient (IR-S)**
  - Immediate Release/Combination Product (IR-C)
  - Extended Release/Single Ingredient (ER-S)
- **Hydrocodone C-III (IR-C)**
- **Hydromorphone C-II (IR-S)**

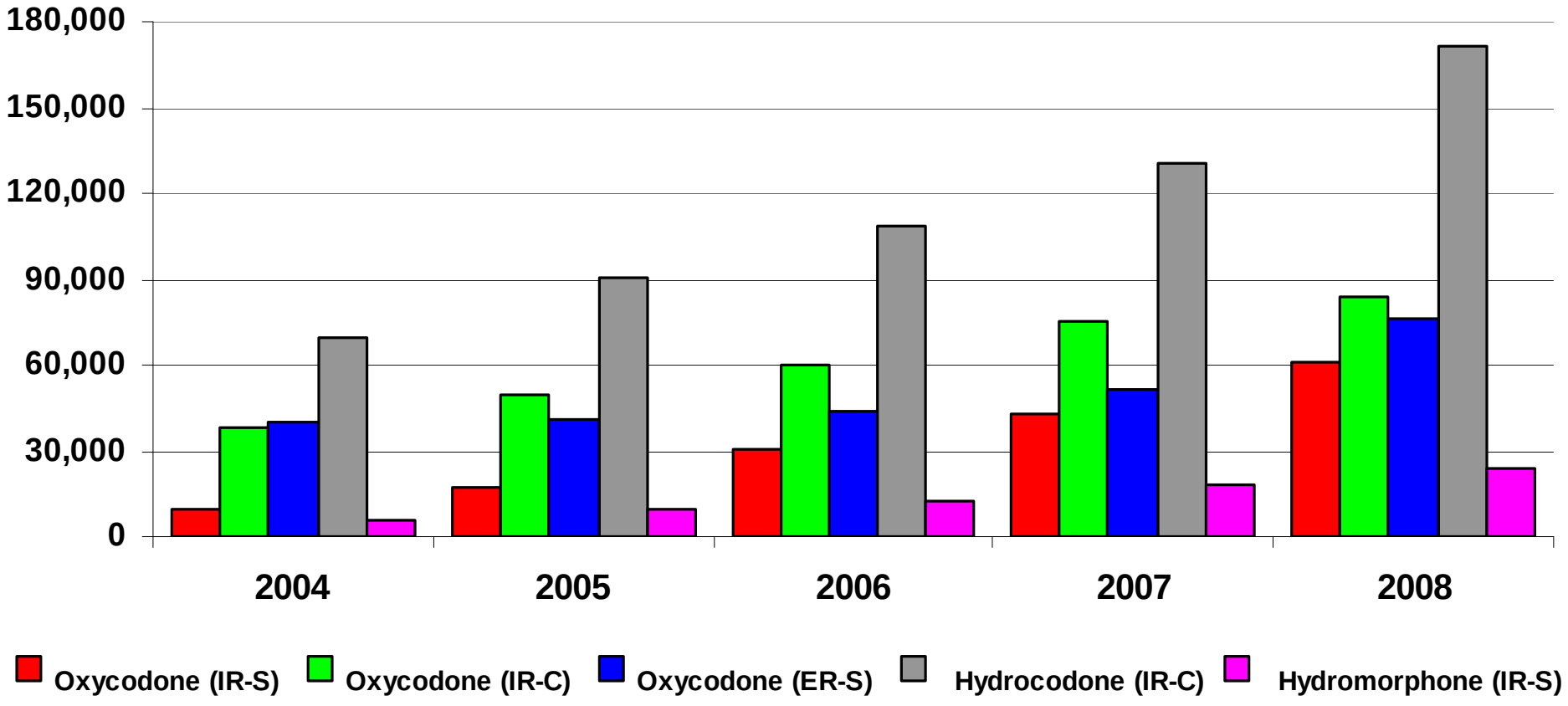
NMUP & ALLMA Case Constructs

- **NMUP** – non-medical use of pharmaceuticals: overmedication, seeking detox, "other"
- **ALLMA** – all misuse/abuse: includes all NMUP cases plus ED visits where illegal drugs or alcohol present

Analysis – Abuse Ratios

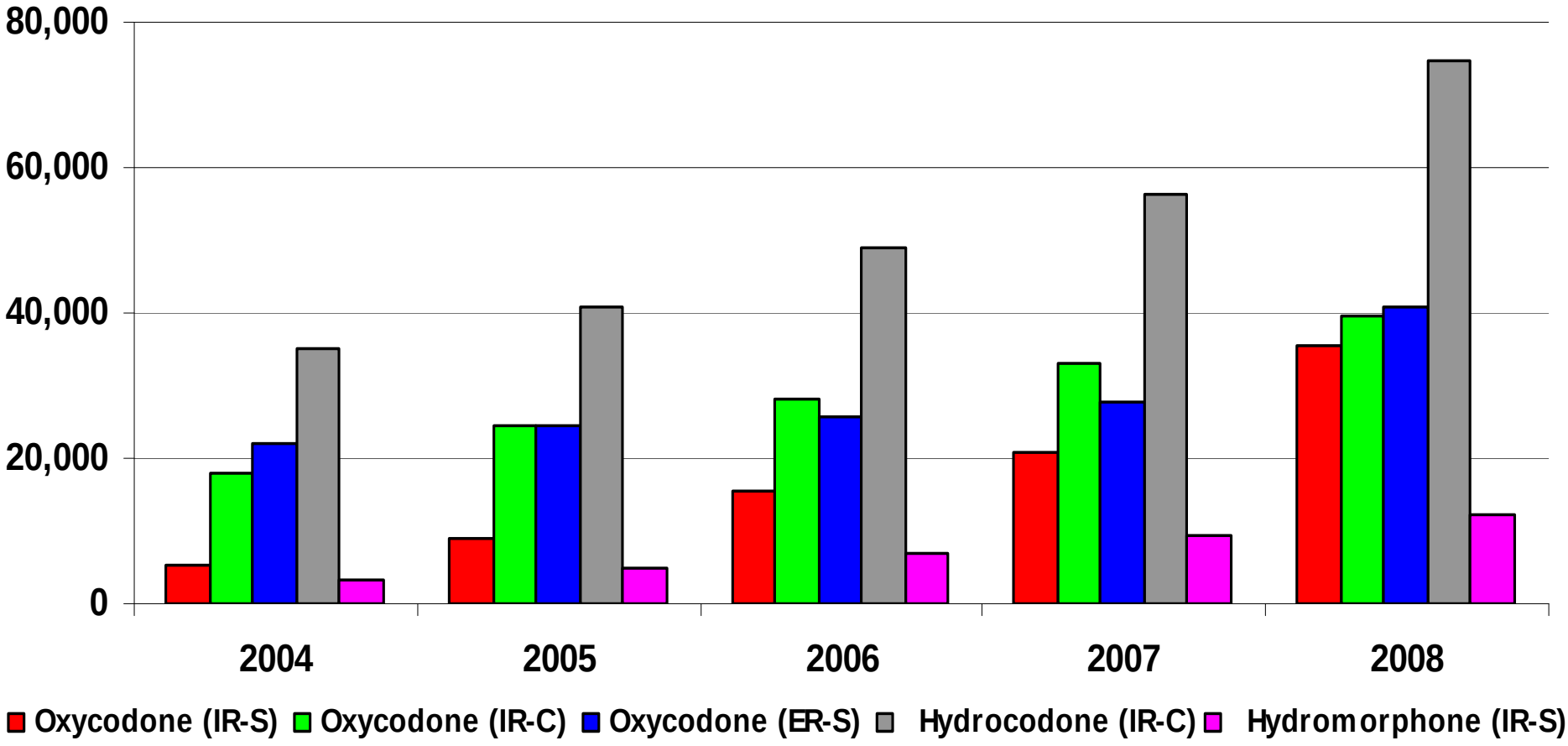
- **Numerator data**
  - Number of NMUP & ALLMA related ED Visits (DAWN)
- **Denominator data**
  - Retail prescriptions used as proxy for drug availability
- **Abuse ratios**
  - number of NMUP ED visits /10,000 retail prescriptions
  - number of ALLMA ED visits /10,000 retail prescriptions

DAWN: National Estimates of All Drug Related ED Visits by Drug Type, 2004-2008



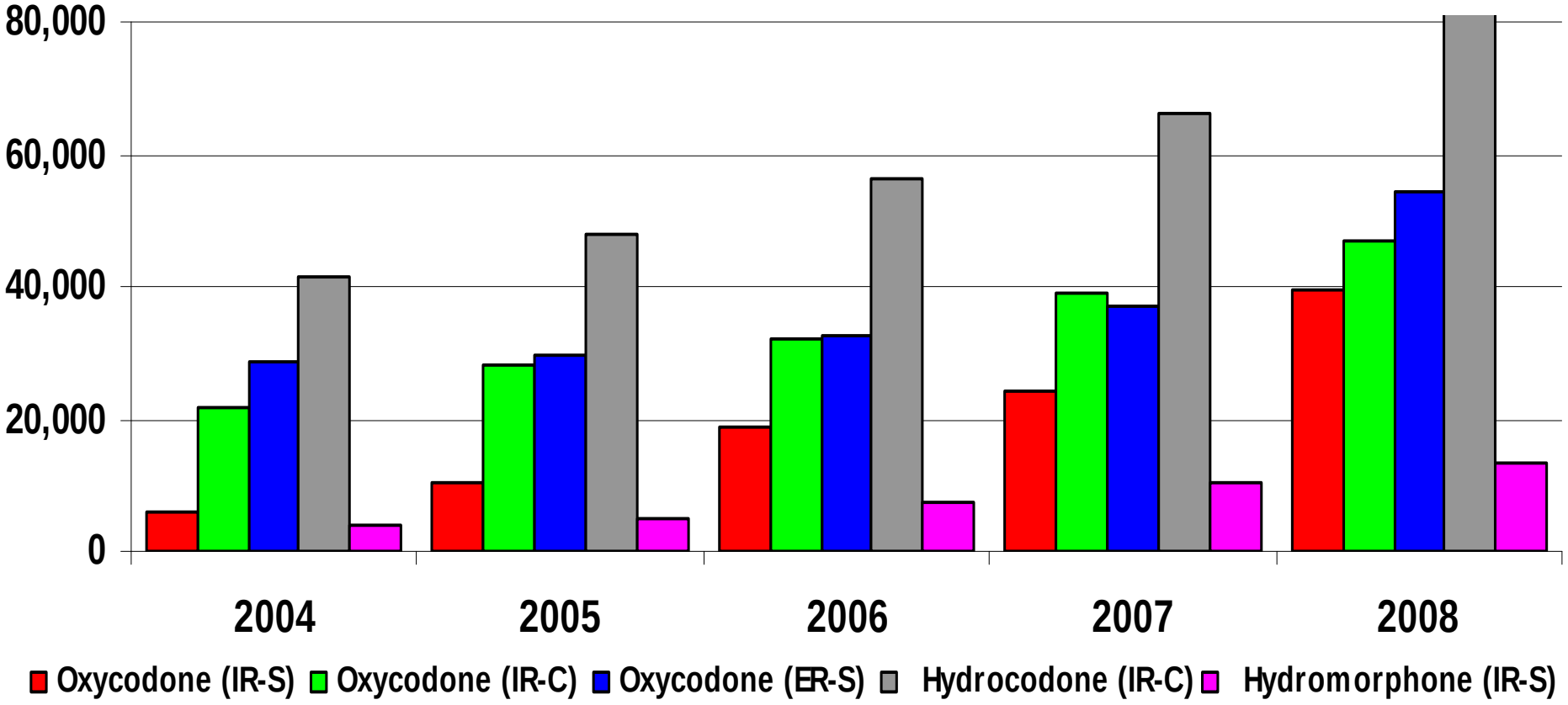
Source: DAWN 2004-2008; SAMHSA

DAWN: Nonmedical Use ED Visits (NMUP) by Drug Type, 2004-2008



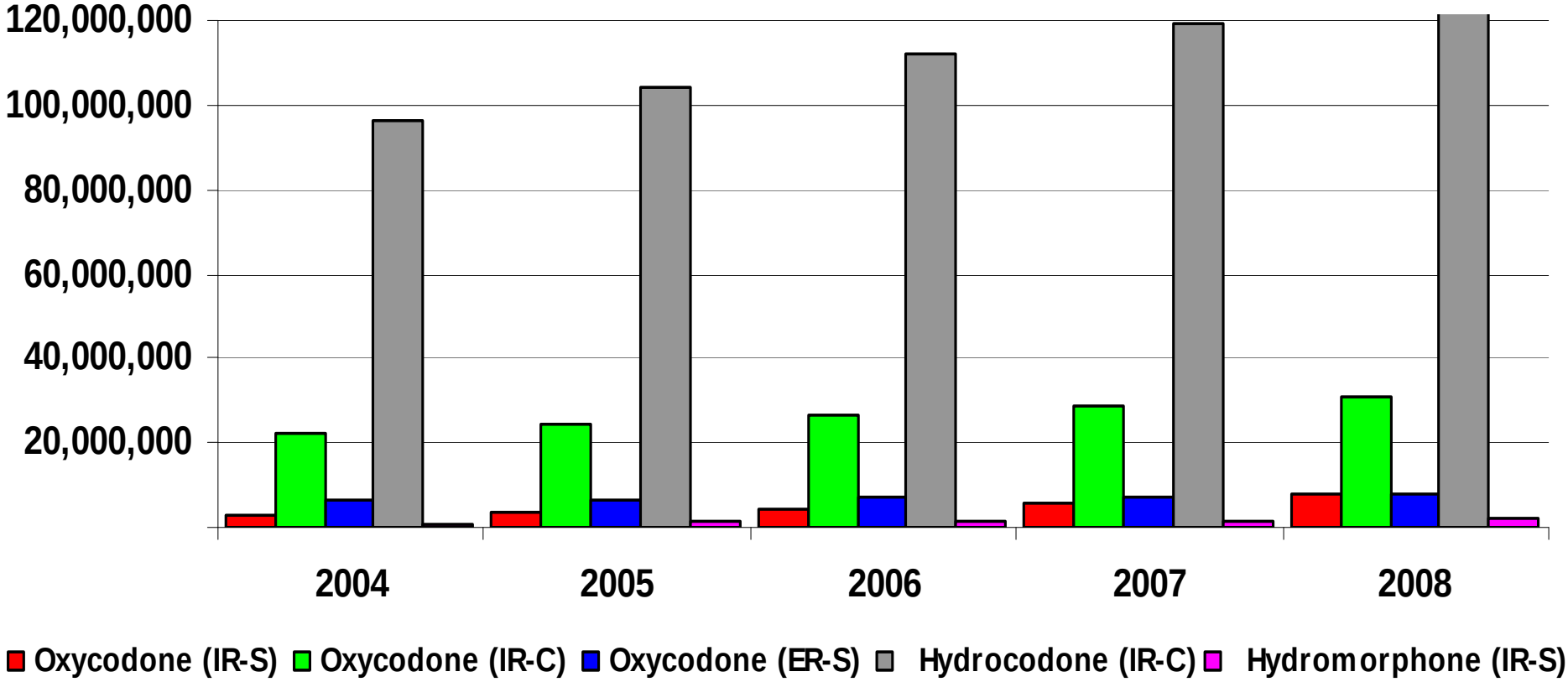
Source: DAWN 2004-2008; SAMHSA

DAWN: All Misuse/Abuse ED Visits (ALLMA) by Drug Type, 2004-2008



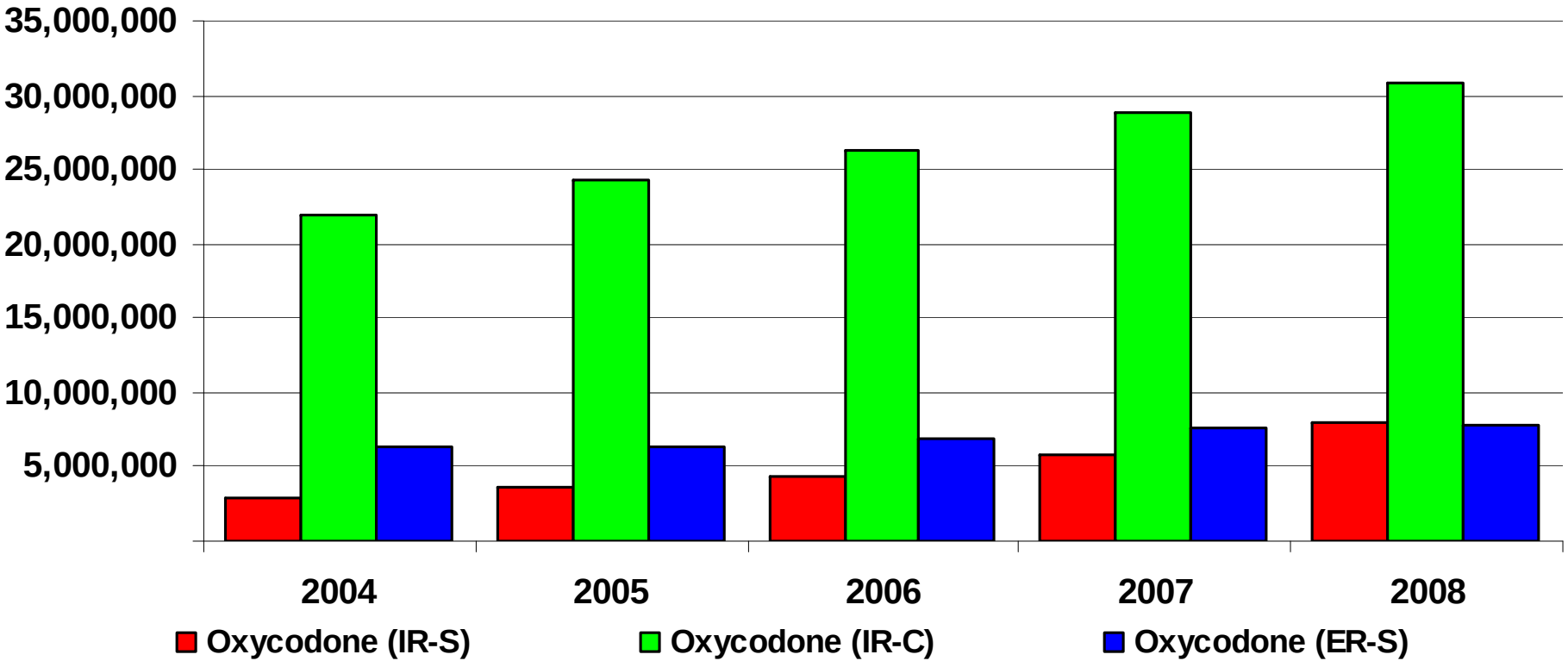
Source: DAWN 2004-2008; SAMHSA

Nationally Projected Retail Prescriptions for Selected Opioids, 2004-2008



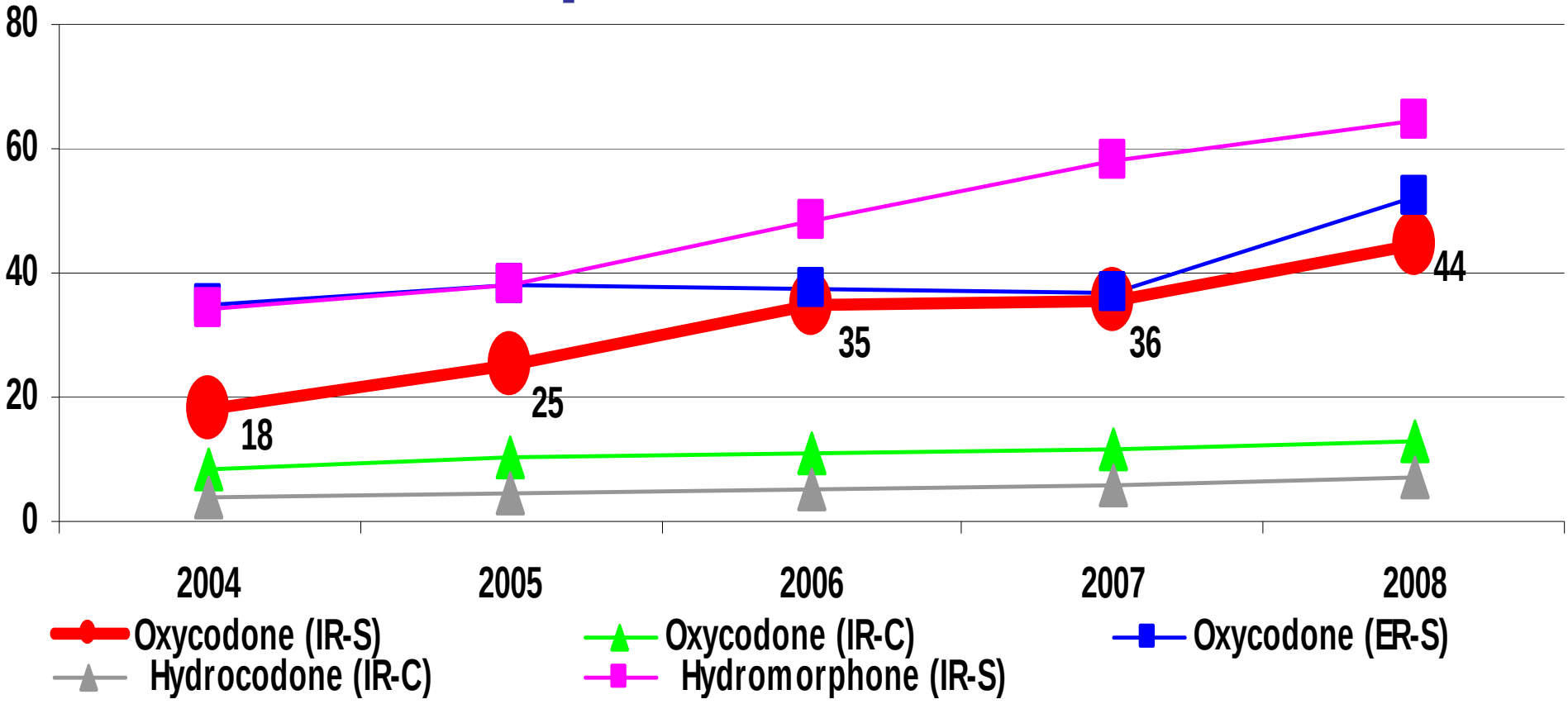
Source: SDI Vector One®: National. Years 2004-2008, extracted March 2010

Projected Retail Prescriptions for Oxycodone Products, 2004-2008



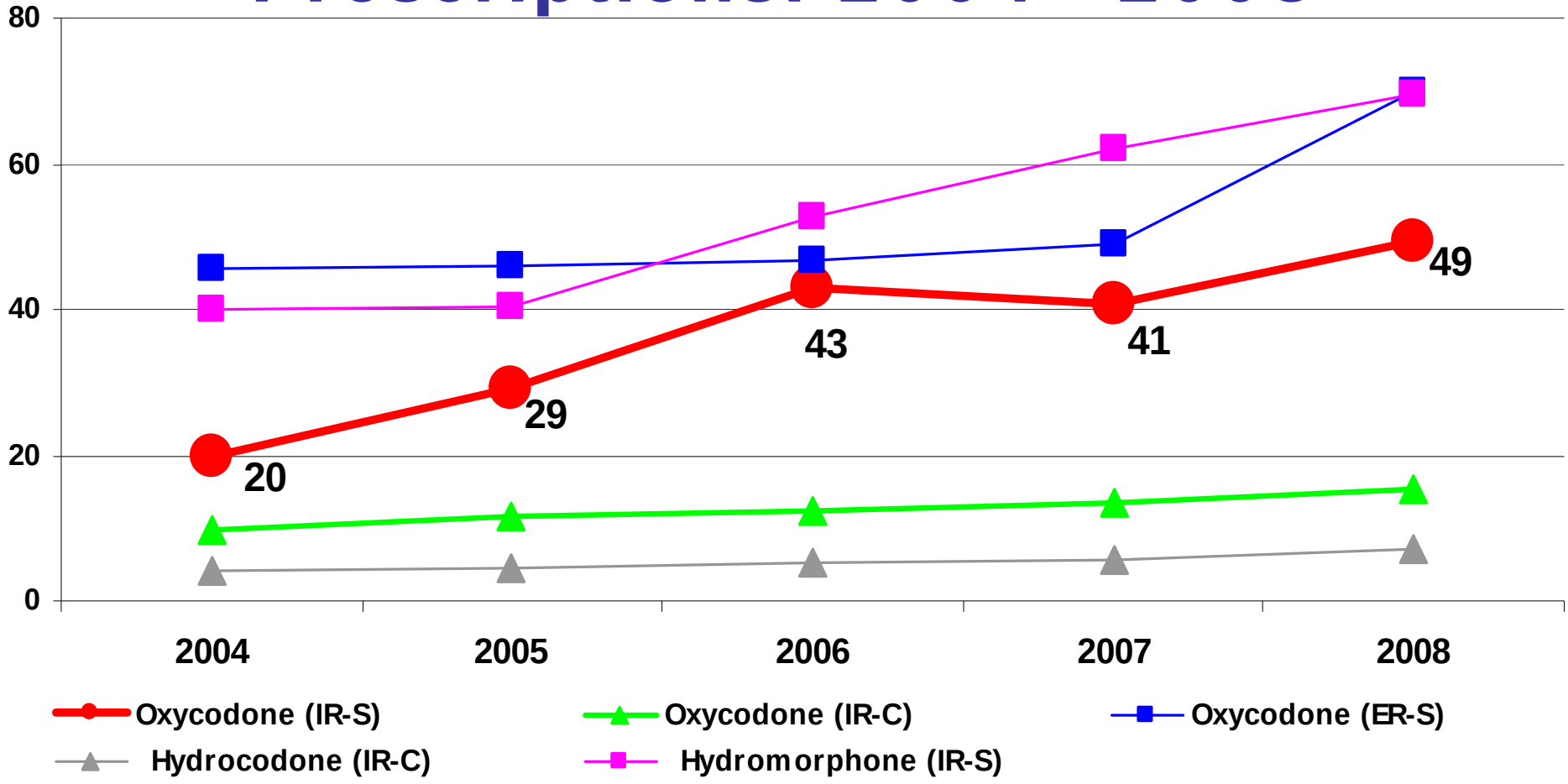
Source: SDI Vector One®: National. Years 2004-2008, extracted March 2010

Number of NMUP ED Visits per 10,000 Prescriptions: 2004 –2008



Sources: DAWN 2004-2008; SAMHSA; SDI. VONA

Number of ALLMA ED Visits per 10,000 Prescriptions: 2004 –2008



Sources: DAWN 2004-2008; SAMHSA; SDI. VONA

Limitations

- Calculating estimates using data from different sources
  - Data are not linked
  - Different Sampling Methodologies
  - Different Populations

Summary

- The non-medical use of pain relievers derived from DAWN can help to quantify the public health burden of non-medical use of opioids.
  - Prescription data can serve as a proxy for drug availability and provides context for non-medical use.
- Non-medical or misuse/abuse ED visits associated with opioid analgesics derived from DAWN continue to increase from 2004 through 2008.
  - Prescription drug use of opioid analgesics also continues to rise

Conclusion

- Over the last five years, the number of ED visits associated with single-ingredient, immediate-release oxycodone products have increased.
- The ratios of non-medical use and abuse of single-ingredient oxycodone products appear to be increasing more rapidly compared to combination oxycodone products.

Reported Manipulation of Oxycodone Immediate-Release Products

L. Shenee' Toombs, Pharm.D.
Safety Evaluator
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology

Overview

- AERS search
- Methods of manipulation
  - Oxycodone Immediate-Release Products
- Summary

Adverse Event Reporting System:
Spontaneous Adverse Event Reporting

- Voluntary, “spontaneous” reporting
- Facilitated by the FDA MedWatch Program
- Reports are stored and retrieved via Adverse Event Reporting System (AERS) database

AERS Strengths

- Includes all U.S. marketed products
- Detection of events not seen in clinical trials
- Especially good for events with rare background rate, short latency

AERS Limitations

- Extensive underreporting
- Quality of reports is variable
- Reporting biases
- Actual numerator & denominator not known
- Causality of drug-event association often in question

AERS Search

- Search limited to active ingredients:
  - Single and Combination Products
  - Oxycodone and oxycodone HCl
  - High Level Group Term: Medication Error
- 6368 reports retrieved
- Narrative search for terms:
  - **crush, chew, inhale, dissolve, inject, snort, cut, grind, melt, crack, boiling, and heating**

Results of Narrative Search

Total number of reports evaluated	439
Reports excluded – did not involve manipulation of oxycodone immediate-release products	406
Cases further evaluated – to determine cases involving improper methods of manipulation and/or routes of administration	33

Oxycodone Immediate-Release Cases (n=33)

- Medication errors (n=1)
  - Accidental exposure
- Ease of administration (n=2)
- Manipulation unclear (n=4)
- Abuse (n=26)

Cases Describing Abuse (n=26)

Methods of manipulation (n=23)	
crush	19
dissolving	1
ground (grind)	1
boiled	1
cooked	1
Methods of administration (n=24)	
nasal inhalation	15
injected	9

Note: Not all of the cases indicated both the method of manipulation and how the product was administered.

Limitations

- Limited amount of cases evaluated
  - Underreporting
  - Inability to extract all relevant cases from AERS database
  - Limited information presented within case
- Spontaneous reporting does not represent all abuse in the US

Summary

- Manipulation associated with abuse
  - Manipulation is not completely representative of all abuse
- Crushing most prevalent method of manipulation reported.
- Nasal Inhalation and injection were the only methods of administration reported.

Acknowledgements

Lubna N. Najam, Pharm.D.

Alice Tu, Pharm.D.

Division of Medication Error Prevention and Analysis

Office of Surveillance and Epidemiology

Back-up Slide

Outcome Data for Abuse Cases (n=26)

Death	15
Hospitalization	2
Non-serious	1
Unknown	8

Note: Causality of these events could not be established because most cases involved the abuse of multiple medications and could not be solely attributed to the oxycodone-containing product.

NDA 22-451
Acurox (oxycodone/niacin) IR tabs
Efficacy and Safety Review

Igor Cerny, PharmD
Clinical Reviewer
Division of Anesthesia and Analgesia Products
CDER/FDA/DHHS

Oxycodone

- A semi-synthetic opioid with an agonist activity on mu (primarily), kappa and delta receptors
- C-II drug available Rx as:
  - IR single-entity tab/cap
  - IR combination tab/cap with acetaminophen (Tylox®, Percocet, e.g.), aspirin (Percodan®), or ibuprofen (Combunox®)
  - ER single-entity tablet (OxyContin®, e.g.)
- Well-known history of abuse

Niacin

- **Vitamin B3** or **nicotinic acid**
- Found in variety of foods including liver, chicken, beef, fish, cereal, peanuts and legumes.
- U.S. ***DRI***: 16 mg/day for men, 14 mg/day for women.
- Found in many multivitamins (Centrum, e.g.); however, many other multivitamins (Theragran, e.g.) contain either niacin/niacinamide combinations or just niacinamide.
- Niacin and niacinamide are similar in their activity as vitamins; however, niacinamide does not appear to reduce cholesterol or cause flushing.
- Marketed OTC in doses up to 500 mg

Prescription Niacin

- Available as SR (Niacor, e.g.) and ER (Niaspan, e.g.) tabs/caps
- Dose range: 500 mg to 2000 mg once daily
- Indications:
  - to reduce elevated TC, LDL-C, Apo B and TG, and increase HDL-C in patients with primary hyperlipidemia and mixed dyslipidemia.
  - adjunctive therapy for treatment of adult patients with severe hypertriglyceridemia who present a risk of pancreatitis

Acurox Formulation Details

- Immediate-release combination oxycodone + niacin tablet designed to discourage abuse
  - **niacin** to induce flushing, etc. when taken in excess
  - **sodium laurel sulfate**, a surfactant that may cause irritation of the nasal mucosa
  - **polyethylene oxide**, a substance that polymerizes upon wetting, forming a gel

Efficacy

Pivotal Study 105

- **Design:** Randomized, double-blind, placebo-controlled, parallel-group, multicenter, repeat-dose (48-hour duration: Q6H for 8 doses)
- **Treatment groups:**
  - 2 x Placebo Tabs (N=136)
  - 2 x Acurox 5/30 Tabs (N=135)
  - 2 x Acurox 7.5/30 Tabs (N=134)
- **Population**: bunionectomy in 405 healthy adults (89% female, 75% white, 75% ASA I, 24% ASA II; 4% ≥65y)
- **Rescue**: ketorolac injection (not for 1st 60 mins)

Study 105 Primary Efficacy Endpoint: SPID48

	Placebo (N=136)	Acurox™ 2 × 5/30 mg (N=135)	Acurox™ 2 × 7.5/30 mg (N=134)
$SPID_{48}$: Mean ± SD	604.48 ± 1124.857	998.46 ± 1102.164	1224.97 ± 1128.569
P-value vs. placebo	-	0.0001	<0.0001

Secondary endpoints followed suit

Safety

NDA Safety Data

- NDA studies fell into four basic categories:
  - Efficacy study (105)
  - Dose-ranging studies for niacin in healthy volunteers
  - Abuse liability studies in opioid-experienced, non-dependent volunteers (CSS presentation)
  - Pharmacokinetic studies
- No deaths or SAEs reported in the NDA
- **In Study 105**:
  - >95 % completed
  - Most common reasons for study discontinuation: withdrawal of consent and AEs (hypotension, vomiting)

Safety Database

- Total # of subjects exposed to Acurox tablets (containing *oxycodone & niacin in the Acurox matrix*) = **407** (269 [66%] from 105).
- The longest duration of exposure to Acurox: PK Study 109: **26** subjects received Acurox 5/30 and Acurox 10/60 Q6h for 15 doses at each dosage level over **7 days**

Concerns Regarding Added Niacin

- Niacin, added to cause **noxious flushing effects** in abusers, caused effects that were tolerable in *normal volunteers,* calling into question niacin's "efficacy"
- Sponsor studies indicate that **Food** greatly blunts the flushing reaction; presumably, **NSAIDs** also blunt flushing.
- Niacin's noxious effects do occur in subjects taking Acurox at typical acute analgesic doses for legitimate reasons
- Is it justifiable to subject patients in acute pain to additional AEs in exchange for the *possibility* that niacin may deter some abusers?

What is the "Niacin Flush" Reaction?

- Vaso-cutaneous; typically see skin warmth, redness, itching, and/or tingling
- May also be experienced as skin stinging or burning, with increased sebaceous gland activity
- (not as common) Can be accompanied by dizziness, tachycardia, palpitations, shortness of breath, sweating, chills, and/or edema, can result in syncope (rare)
- Occurs within 20 minutes or 2-4 hours after IR or ER niacin, respectively; generally persists for 0.5-1.5 hours
- Reportedly occurs in approximately 53-91% of patients at cholesterol lowering doses
- Glycine conjugates of niacin such as nicotinuric acid have been associated with the flushing reaction which appears to result from the cutaneous production of prostanoids, including prostaglandins D2/E2

Oxycodone can also cause Flushing

- From the Roxicodone label:
  - "*Oxycodone, in therapeutic doses, produces peripheral vasodilatation…Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, **flushing**, red eyes, sweating, and/or orthostatic hypotension*."
- *Caveat*: no oxycodone-only arm in 105; can't tell with 100% certainty which active ingredient is responsible for the flushing reaction

Select AEs: Study 105

System Organ Class Preferred Term	Number of Subjects, n (%)		
	Placebo (N=136)	Acurox® 10/60 mg (N=135)	Acurox® 15/60 mg (N=134)
Nausea	14 (10.3)	68 (50.4)	83 (61.9)
Vomiting	5 (3.7)	46 (34.1)	67 (50.0)
Constipation	1 (0.7)	4 (3.0)	6 (4.5)
Dizziness	6 (4.4)	22 (16.3)	32 (23.9)
Somnolence	2 (1.5)	8 (5.9)	6 (4.5)
Pruritus	1 (0.7)	17 (12.6)	13 (9.7)
Pruritus generalized	1 (0.7)	9 (6.7)	10 (7.5)
Flushing	**2 (1.5)**	**22 (16.3)**	**15 (11.2)**
Feeling hot	**1 (0.7)**	**6 (4.4)**	**5 (3.7)**
Erythema	**0 (0.0)**	**2 (1.5)**	**2 (1.5)**
Burning sensation	**0 (0.0)**	**2 (1.5)**	**2 (1.5)**

Flushing AEs: Study 103

System Organ Class Preferred Term	Number of Subjects, n (%)		
	Acurox® 5/0 mg (N=22)	Acurox® 5/30 mg (N=22)	Acurox® 5/60 mg (N=22)
Flushing	**3 (13.6)**	**7 (31.8)**	**9 (40.9)**
Feeling hot	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Erythema	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Burning sensation	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**

(Phase 2 Multi-dose Study for 5 days of oxycodone and up to 10 days for niacin)

Select Adverse Events for IR Oxycodone from a recent NDA

Preferred term	placebo N=619 N(%)	Oxycodone IR 10-15 mg N=675 N(%)
Nausea	80 (13)	298 (44)
Vomiting	26 (4)	208 (31)
Dizziness	48 (8)	168 (25)
Pruritus	8 (1)	73 (11)
Hot Flush	**3 (0.5)**	**8 (1)**
Feeling Hot	**4 (1)**	**11 (2)**

Acurox-associated Flushing

- The data support the conclusion that the high rates of flushing and related adverse events are related to niacin, not oxycodone.
- We believe that the Sponsor's niacin dose-ranging data foretold problems with a 60 mg niacin dose (2 Acurox tablets).

Sponsor Conducted Niacin Trial: Study 101

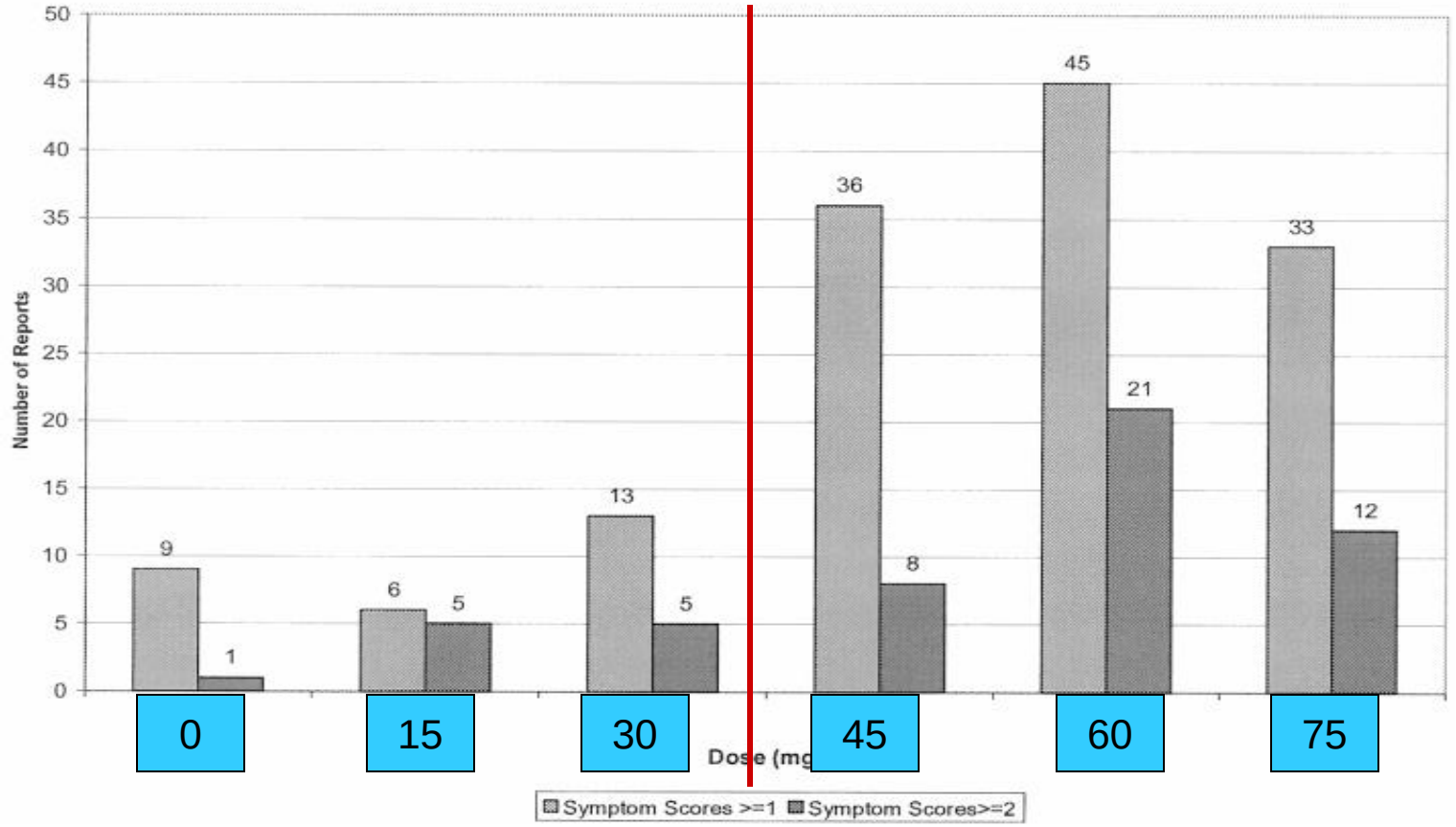
- Purpose: "*to determine* ***an appropriate strength of niacin*** *to use in an Aversion Technology formulation of oxycodone*."
- 49 healthy adults received niacin (0-75 mg) or placebo in random order.

Study 101: Vasodilatory AEs

	Fasted	
Niacin (mg)	N	**Vasodilatory N**
0	25	**3**
15	25	**2**
30	25	**5**
45	25	**13**
60	25	**11**
75	25	**11**

Study 101: Severity of AEs

Number of Reports of Symptom Scores in Fasting Subjects: All Reports (≥1) and Moderate and Severe Reports (≥2)



Combination Drug Regulation: 21 CFR 300.50 (a)(2)

- Reads in part:
  - "*Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects…*
  - *Special cases of this general rule are when a component is added:…To minimize the potential for abuse of the principal active component…*"
- Is Niacin "efficacious"?

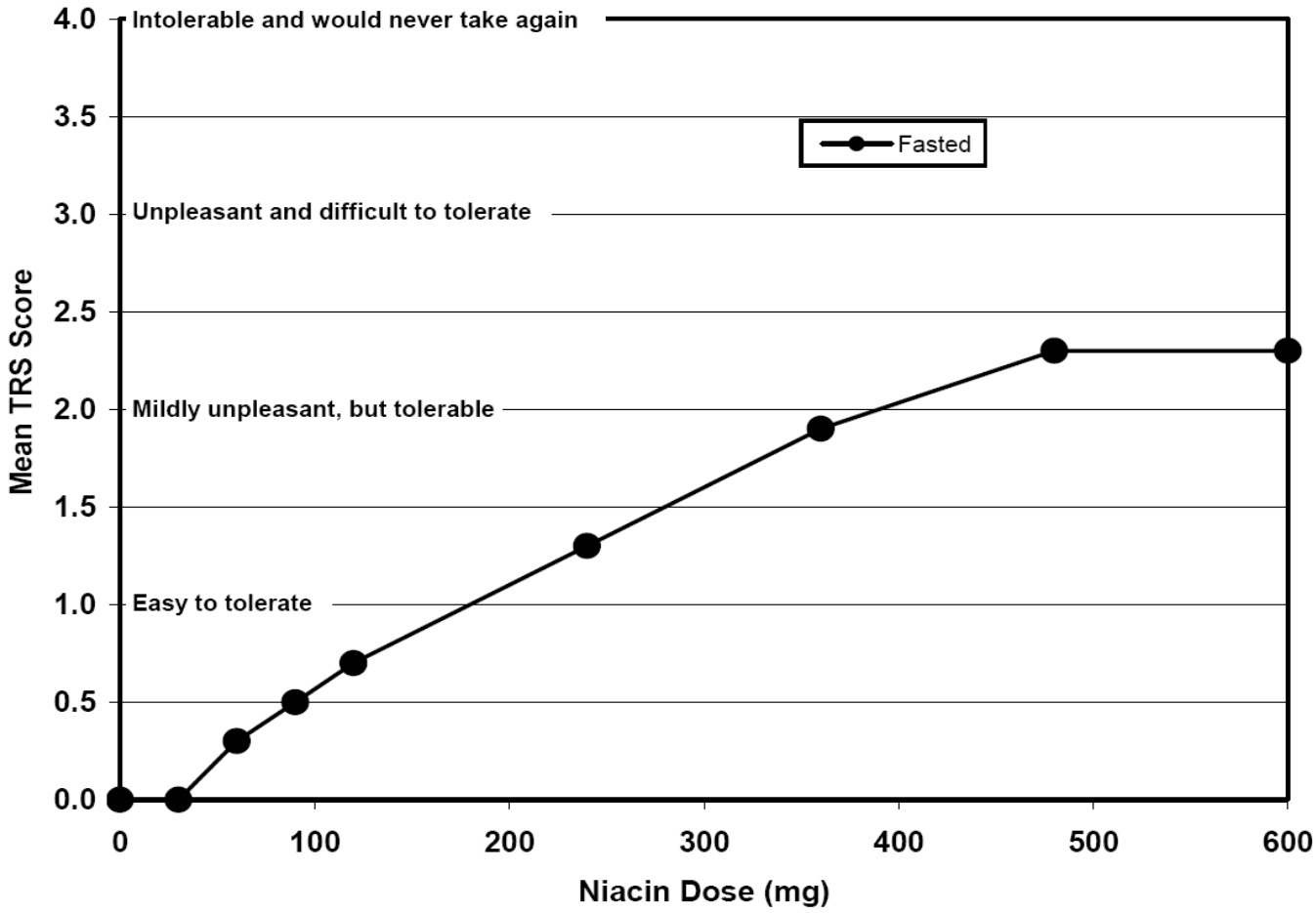
Study 101: Noxious Effects of Niacin greatly blunted by food

	Fasted		Fed	
Niacin (mg)	N	**Vasodilatory N**	N	**Vasodilatory N**
0	25	**3**	25	**5**
15	25	**2**	25	**4**
30	25	**5**	24	**3**
45	25	**13**	24	**5**
60	25	**11**	24	**5**
75	25	**11**	25	**4**

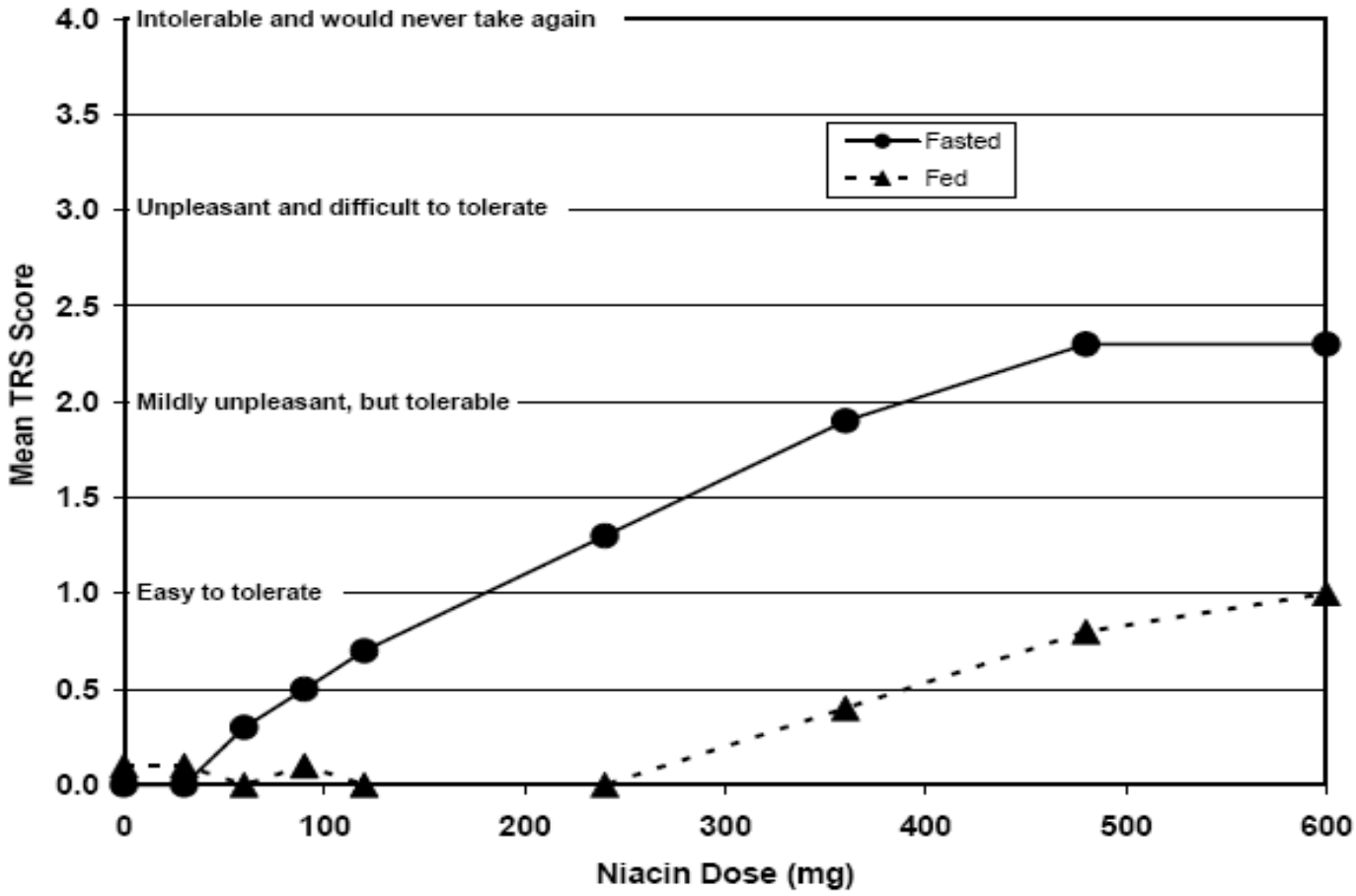
Sponsor Conducted Niacin Trial: Study 107

- 50 healthy adults received niacin (30, 60, 90, 120, 240, 360, 480, and 600 mg) in Acurox matrix (excluding oxycodone) and placebo in random sequence.
- 25 subjects took study drug following a standardized high-fat breakfast while the other half fasted.
- Tolerability was assessed using an unvalidated Tolerability Rating Scale (TRS), where:
  - 0 = “no effect”;
  - 1= “easy to tolerate”;
  - 2 = “mildly unpleasant, but tolerable”;
  - 3 = “unpleasant and difficult to tolerate”; and
  - 4 = “intolerable and would never take again.”

Tolerability of Niacin in 107



Tolerability improved in Fed State



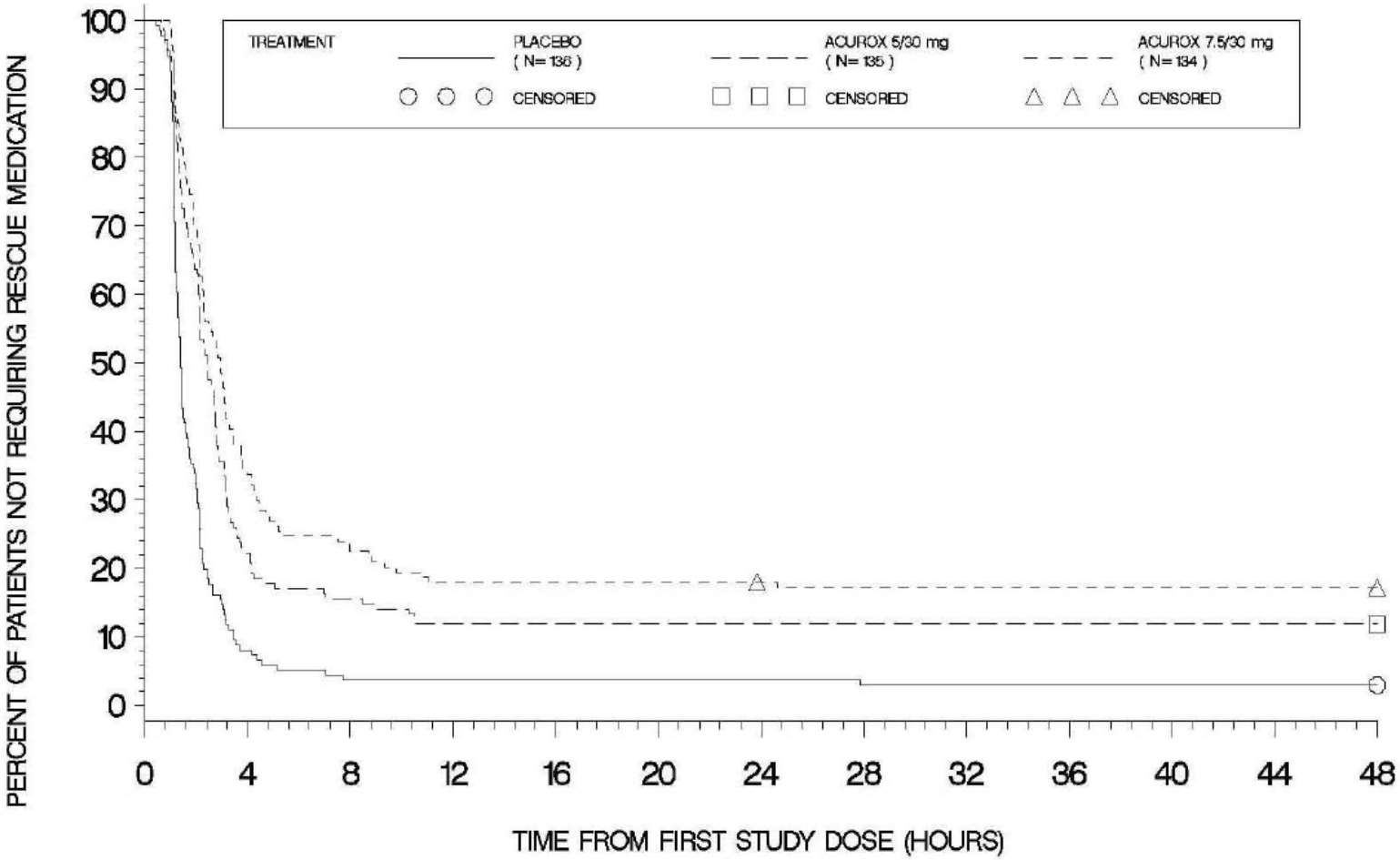
Conclusions from Niacin Studies 101 and 107

- The Sponsor's decision to formulate Acurox with 30 mg of niacin/tablet, with instructions that permit 2 tablets per dose (60 mg total dose of niacin), will likely result in symptoms of flushing
- Noxious effects in *normal volunteers* appear quite tolerable
- Studies confirm what is known in the literature and from product labeling: food greatly blunts the noxious effects of niacin
- This fairly easy way to circumvent the potential abuse deterrent properties of Acurox calls into serious question the efficacy of the added niacin.

Another Easy Way to Blunt Niacin

- As per literature reports/studies and per product labels, **flushing** can be reduced in frequency or severity by pretreatment with **aspirin** (325 mg) or an **NSAID** taken 30 minutes prior to dosing.
- Also brings up questions about the use of ketorolac (an NSAID) for rescue in Study 105.

Study 105: % of Subjects NOT Needing Rescue



Did Ketorolac Mask Reports of Flushing?

- Most subjects received rescue medication within the first 6 hours of the trial – before 2nd Acurox dose.
- Given the assumption that an NSAID is likely to mitigate flushing, it is likely that the incidence and/or severity of flushing in Study 105 was *underestimated* because of the high rate of ketorolac use.

Overall Conclusions:

- Sponsor's stated goal in the development of Acurox:
  - "*The overall goal was to develop a product that when used as prescribed would have a* ***safety and efficacy profile indistinguishable from currently marketed commercial formulations of opioid products****, but when used inappropriately (i.e. abused) the product could produce undesirable and reversible effects, thus resulting in* ***reduced potential for abuse****."*

Conclusions, continued

- Acurox appears to be an effective analgesic when compared to placebo.
- Study 105 indicates that patients treated with Acurox experience vasodilatory AEs at a rate higher than our experience with oxycodone would predict if the oxycodone were causative.
  - Unlike Study 105 with a very healthy (99% ASA I or 2) relatively young population, the actual use population may often be older with comorbidities.

Conclusions, continued

- The Applicant has failed to justify the addition of niacin because:
  - Niacin's noxious effects appear to be tolerable in normal volunteers; and
  - These noxious effects are greatly offset by food and, presumably, NSAID premedication.
- Given niacin's questionable efficacy as an abuse deterrent, patients taking Acurox for pain would be needlessly put at risk for additional niacin AEs (flushing).
- Sponsor has not met their primary goal of a product with a **safety** profile similar to oxycodone alone that also deters abuse.

Abuse Liability of Acurox (Oxycodone/Niacin) Immediate Release Tablets

Jovita Randall-Thompson, Ph.D., Pharmacologist
Controlled Substance Staff

Center for Drug Evaluation and Research
Food and Drug Administration

Anesthetic and Life Support Drugs Advisory Committee
April 22, 2010

Acurox: Human Abuse Liability Studies

Two clinical studies evaluating the abuse potential of the oral administration of Acurox® were conducted:

Study AP-ADF-102

-Double blind crossover study
-Clinical Phase II

Study AP-ADF-111

-Double blind crossover study
-Clinical Phase II
-Study is divided into two parts

Study: AP-ADF-102

Sponsor's Objectives:

- To determine the dose-response for niacin-induced flushing
- To evaluate the safety and tolerability of niacin-induced flushing
- To confirm the appropriate strength of niacin to use in their Aversion® Technology formulation of oxycodone HCl
- To determine whether the flushing induced by niacin is of sufficient intensity to deter abuse in a population of subjects with a history of opioid abuse
- To evaluate the effect of food on niacin-induced flushing

Study: AP-ADF-102

Participants:

-25 participants (3 females and 22 males); 18 to 55 years of age

-with a history of drug abuse

-exposed to food restricted (fasting) conditions or fed a high calorie meal

-breakfast consisting of two fried eggs, hash browns, two fried bacon strips, toast, butter and whole milk

Treatments:

-Niacin (240, 480, and 600 mg) with 40 mg of oxycodone (kept constant)

-40 mg of oxycodone alone

Study AP-ADF-102: Method

Day -30 to -2	Day -1	Treatment Phase: Day 1, 3, 5, 7 and 9	
Pre-Screening Phase	***Baseline-Screening Phase***	***Treatment Administration***	***Treatment Assessment Time: 0.5, 1, 1.5, 2, 3, 4, 5, 6 & 12 hrs***
Eligibility Interview		**Groups:** **a. Oxy40** **b. Niacin240/Oxy40** **c. Niacin480/Oxy40** **d. Niacin600/Oxy40** **e. Niacin600/Oxy40 -fed meal** *5 treatments, 5 periods, Williams Squares*	**1. Drug Rating Questionnaire - Subject (DRQS)** **-No drug pre-discrimination testing was performed nor were there pre-testing qualifications used to establish liking of the positive control.** **2. Addiction Research Center Inventory (ARCI)** **-Baseline not collected**
Urine Drug Screen	**X**		
Naloxone Challenge	**Food restricted (Fasted)** ↑		
Physical Exam	**X**		
Vital Signs	**X**		

Study AP-ADF-102: Subjective Measures:

Drug Rating Questionnaire – Subject (DRQS)

Visual Analogue Scale (VAS)

Do you like the drug effect you are feeling now?

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29

not at all O O O O O O O O O O O O O O O O O O O O O O O O O O O O O O O **an awful lot**

Addiction Research Center Inventory (ARCI)

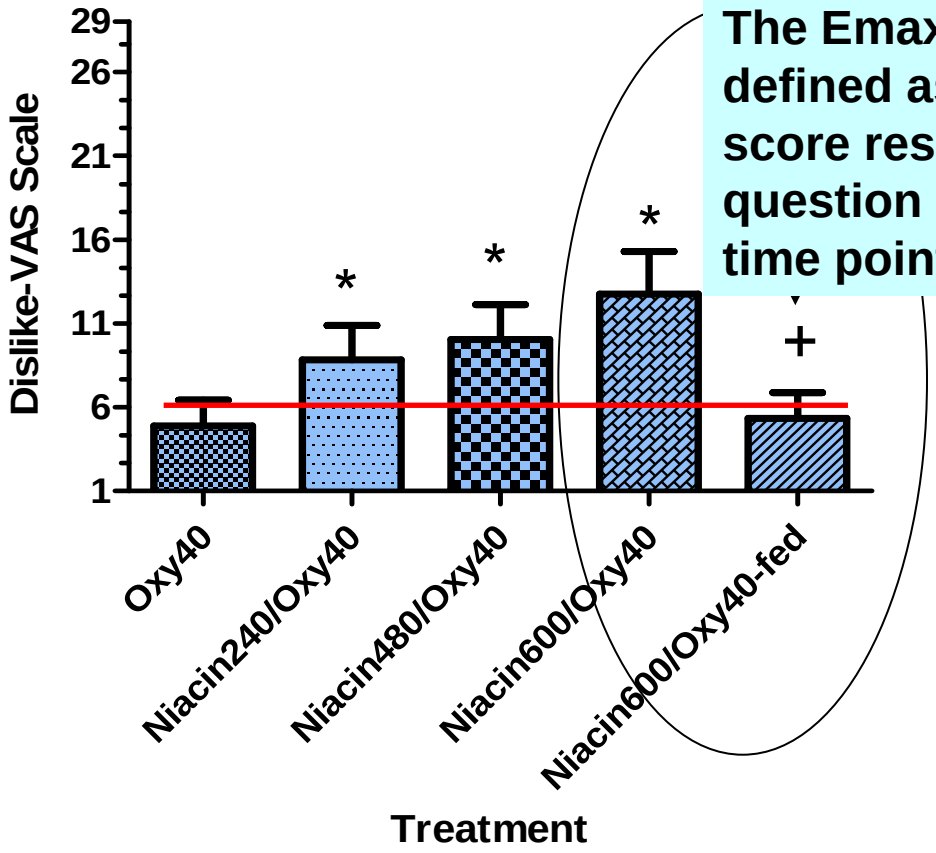
a. Morphine-Benzedrine Group Scale (MBG) (euphoria)

b. LSD Specific Scale (dysphoria)

c. Pentobarbital-Chlorpromazine-Alcohol Group Scale (PCAG) (sedation)

Study AP-ADF-102: Findings

Primary Endpoint: Dislike Scale - Mean Emax VAS Scores



The Emax VAS Score is defined as the maximum VAS score response to the DRQS question recorded over the 9 time points.

Summary:

e mean Emax
rted with
sus Oxy alone,
s **abolished**
consumed.

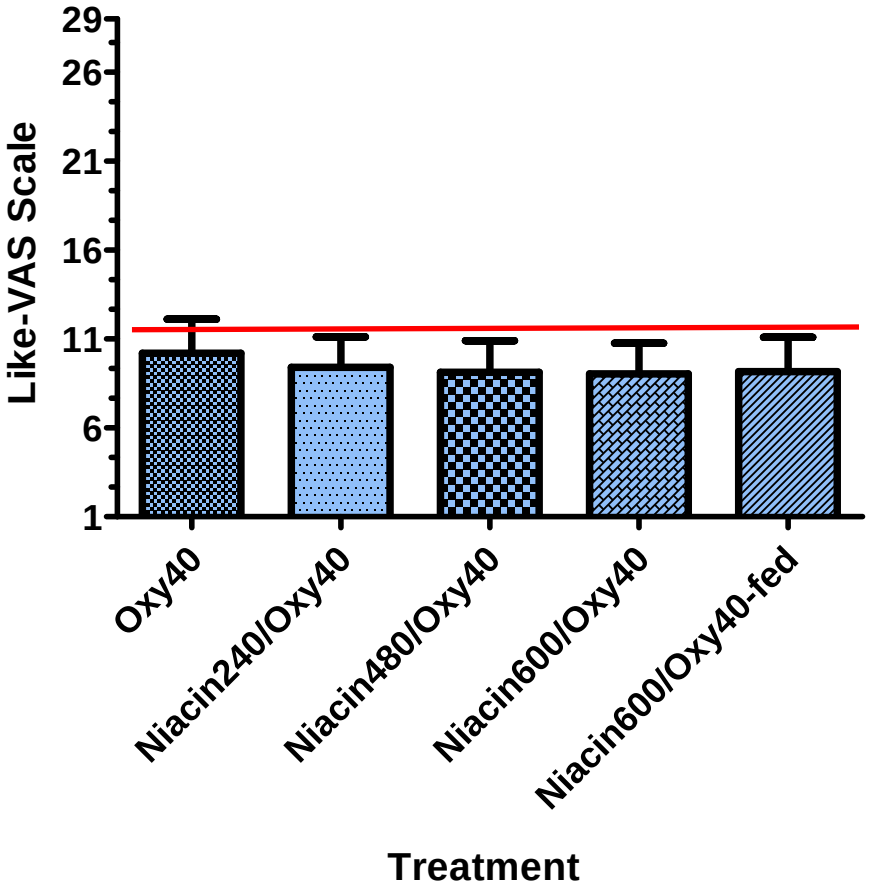
-The scientific literature shows that Food, Aspirin and other NSAIDs and tolerance attenuate niacin-induced flushing (AEs).

-The Sponsor did not test Aspirin or other NSAIDs or tolerance.

** = Significant Differences from Oxy40; + = Significant Differences from Niacin600/Oxy40 (Fed effect)*

Study AP-ADF-102: Findings cont.

Secondary Endpoint: Like Scale - Mean Emax VAS Scores



Summary:

-Participants' like mean Emax scores **did not differ** over treatments.

-Also, participants' MBG and LSD mean Emax scores **did not differ** over treatments (not shown)

Study: AP-ADF-111

Two part assessment

Part I

Sponsor's Objective: To assess the effect of oxycodone HCl on niacin-induced dysphoric effects

Part II

Sponsor's Objective: To assess the abuse liability and abuse deterrent potential of 4 times the usual recommended dose of Acurox®

Study: AP-ADF-111

Participants:

-30 participants (4 females and 26 males); 18 to 55 years of age

- history of drug abuse

-all exposed to food restricted conditions

-Drug was administered after subjects fasted for at least 10 hours. Participants were not permitted to eat until 4 hours post-dose.

Treatments:

Part I: placebo, 240 mg of niacin only and 240 mg of niacin with 40 mg of oxycodone

Part II: 240 mg of niacin with 40 mg of oxycodone (Niacin240/Oxy40 as in Study 102) and 40 mg oxycodone alone

Study AP-ADF-111: Method

Day -30 to -2	Day -1	Treatment Phase: Day 1, 3, 5, 7 & 9	
Pre-Screening Phase	***Baseline-Screening Phase***	***Treatment Administration***	***Treatment Assessment Time: 0.5, 1, 1.5, 2, 3, 4, 5, 6 & 12 hrs***
Eligibility Interview		**Part I** **a. Niacin240** **b. Niacin240/Oxy40** **c. Placebo** **Part II** **d. Niacin240/Oxy40** **e. Oxy40** *3 treatments, 3 periods, Williams Squares; followed by 2 treatments, 2 periods, crossover*	**1. Drug Rating Questionnaire - Subject (DRQS)** **- No drug pre-discrimination testing was performed nor were there pre-testing qualifications used to establish liking of the positive control.** **2. Addiction Research Center Inventory (ARCI)** **-Baseline not collected**
Urine Drug Screen	**X** ****All subjects were Food restricted**		
Naloxone Challenge			
Physical Exam	**X**		
Vital Signs	**X**		

Study AP-ADF-111: Subjective Measures

Drug Rating Questionnaire – Subject (DRQS)

Visual Analogue Scale (VAS)

Do you feel a drug effect now?

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29

not at all O O O O O O O O O O O O O O O O O O O O O O O O O O O O O **an awful lot** **or**

Bipolar - Visual Analogue Scale (VAS)

Do you dislike or like the drug effect you are feeling now?

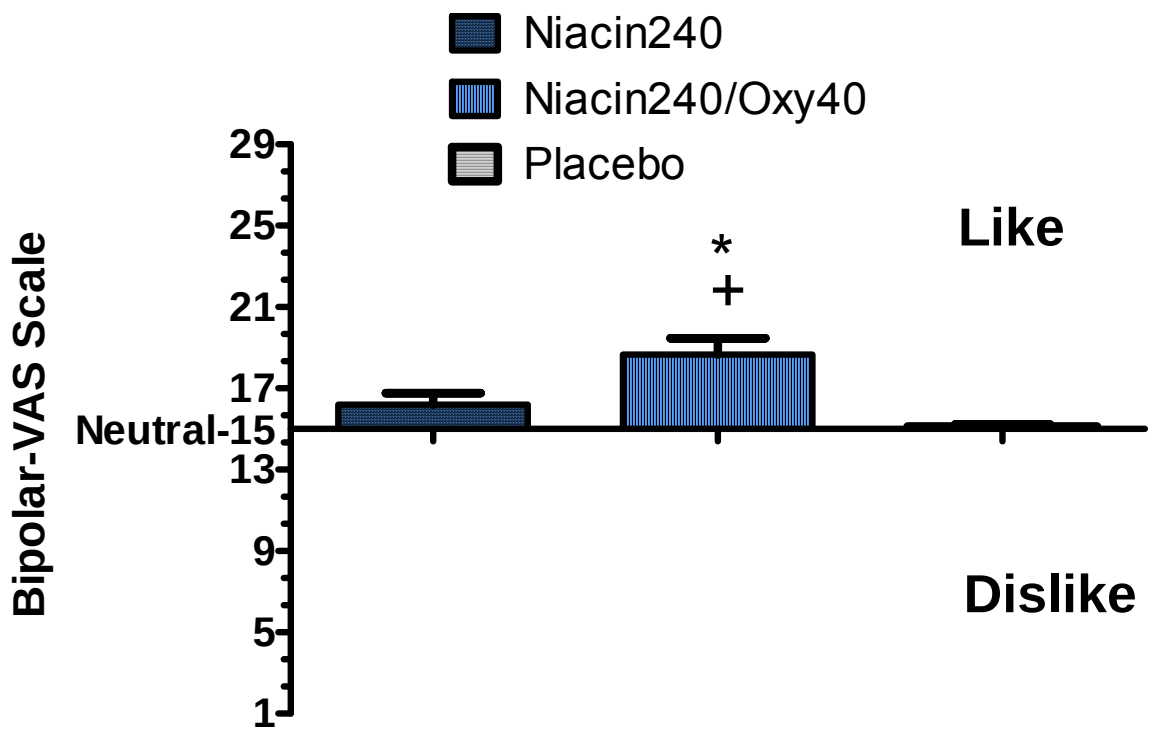
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29

dislike an awful lot O O O O O O O O O O O O O O O O O O O O O O O O O O O O O **like an awful lot**

neutral

Study AP-ADF-111/Part I: Findings

Primary Endpoint: Bipolar Scale - Mean Emax VAS Scores



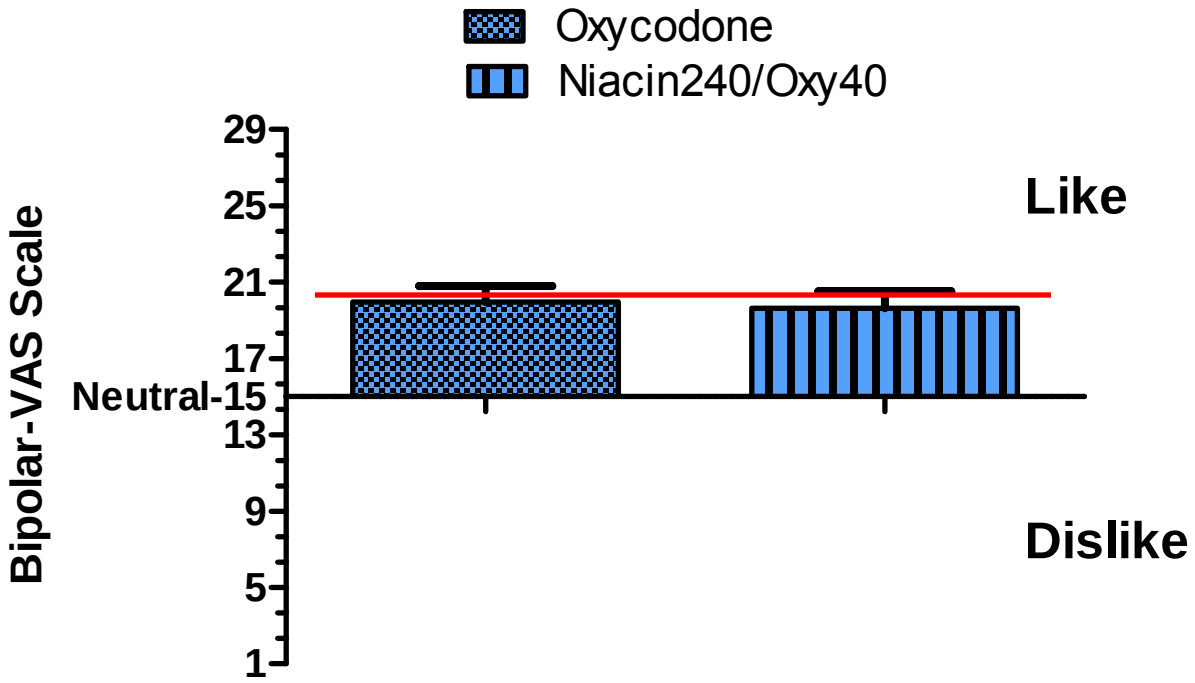
Summary:

-Combining oxycodone with niacin produces a higher mean Emax score, thus **oxycodone appears to attenuate niacin-induced aversive effects**.

** = Significant Differences from Placebo; + = Significant Differences from Niacin 240*

Study AP-ADF-111/Part II: Findings

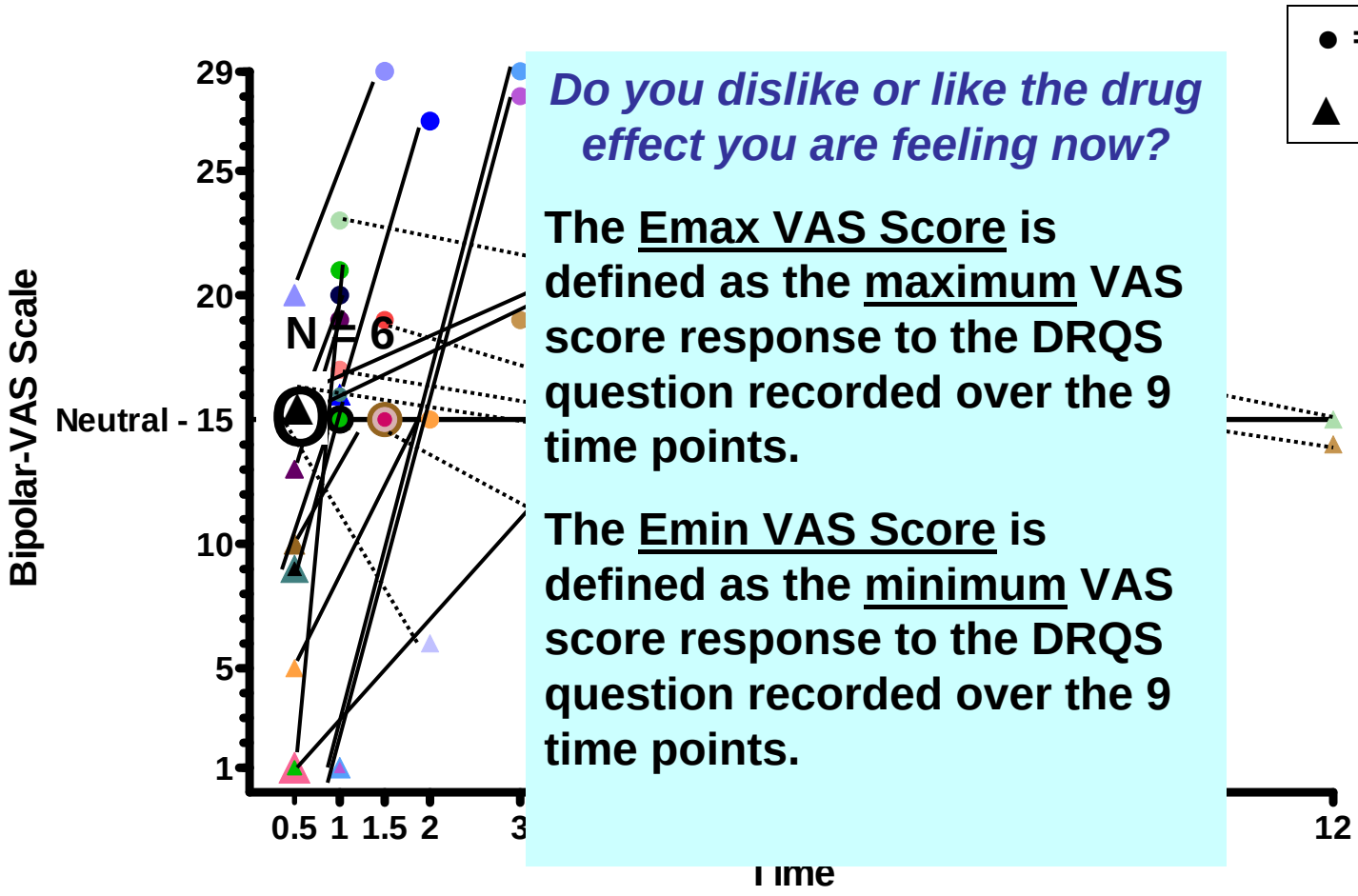
Primary Endpoint: Bipolar Scale - Mean Emax VAS Scores



Summary:

-Participants' bipolar mean Emax scores **did not differ** between the niacin/oxycodone combination and oxycodone alone treatments.

Study AP-ADF-111/Part II: Distribution of Emax & Emin for Niacin240/Oxy40

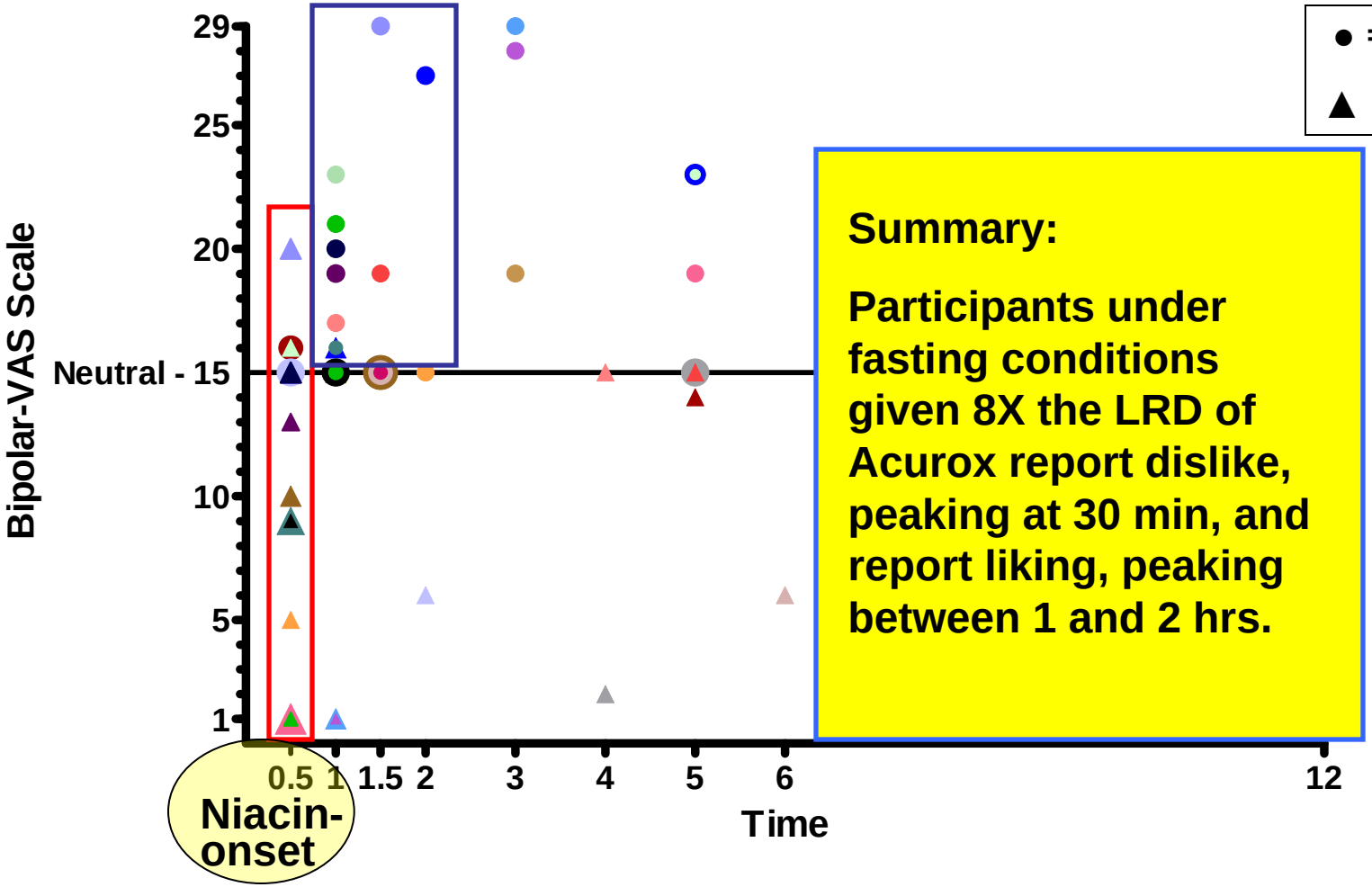


Do you dislike or like the drug effect you are feeling now?

The <u>Emax VAS Score</u> is defined as the <u>maximum</u> VAS score response to the DRQS question recorded over the 9 time points.

The <u>Emin VAS Score</u> is defined as the <u>minimum</u> VAS score response to the DRQS question recorded over the 9 time points.

Study AP-ADF-111/Part II: Distribution of Emax & Emin for Niacin240/Oxy40



Summary:

Participants under fasting conditions given 8X the LRD of Acurox report dislike, peaking at 30 min, and report liking, peaking between 1 and 2 hrs.

Overall Summary

1. **The consumption of food prior to Acurox administration abolishes the aversive pharmacological effects of niacin (Study 102).**

2. **Data appears to show that oxycodone diminishes aversive effects produced by niacin (Study 111).**

3. **The quick onset /offset of niacin's pharmacological effects illustrates a transient and short-lived dislike/aversive effect when tested under food fasting conditions (Study 111).**

4. **The data do not demonstrate that the initial "dislike" mediated by niacin within the first 30 min decreases the peak liking of oxycodone over all.**

Conclusions

- **The findings do not substantiate the Sponsor's claim that niacin decreases the potential for abuse of oxycodone when taken by oral route.**

- **Niacin's aversive effects are abolished with eating a meal and have little affect on oxycodone's euphoric properties.**

- **Data addressing the attenuation of niacin's flushing by pre-dosing with Aspirin, or other NSAIDs or due to tolerance was not submitted by the Sponsor.**

- **A degree of effort is required to bypass abuse deterrent mechanisms. At this time it is undetermined whether Acurox contains oral abuse deterrent mechanisms that are difficult to bypass.**

Thank you

Statistical Evaluations of Human Abuse Potential Studies for Acurox®

Ling Chen, Ph.D.
Mathematical Statistician
Center for Drug Evaluation and Research
Food and Drug Administration

Anesthetic and Life Support Drugs Advisory Committee
April 22, 2010

Primary Abuse Potential Measure of Interest

- Primary measure of Interest:

  Study 102: Like Effect (Scale: 1 – 29)

  Study 111: Like Effect from Like/Dislike Effect
  (Bipolar Scale: 1-29)

- Other Measures of Interest – Dislike Effect and ARCI MBG

  The Sponsor and the FDA reported that no significant difference was found on ARCI MBG between 40 mg oxycodone and the combination drug.

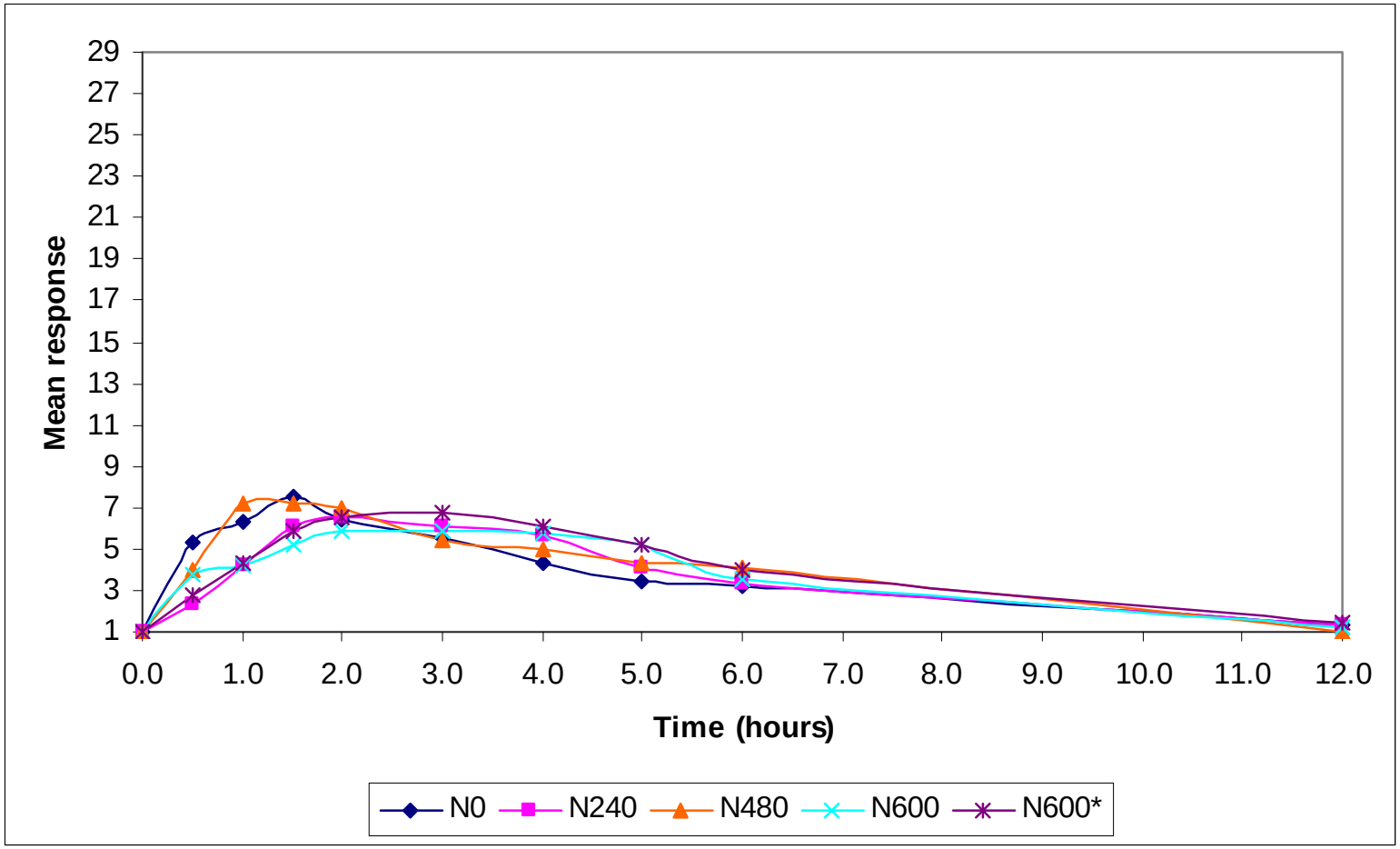
Primary Endpoint of Interest

- Drug Liking VAS is the main abuse potential measure of interest in the human abuse potential studies. In studies 102 and 111, Like Effect VAS would capture the reinforcing effects of oxycodone. Thus, responses on the liking scale will allow evaluation of the proposed deterrent effects of niacin in the combination drug 40 mg oxycodone + various doses of niacin.

- Because study subjects may reach the drug liking peak effects at different time points, the primary endpoint of interest is Emax of Like Effect, the maximum response in liking that occurs any time over the 8 hour period after dosing. (Most drugs will show the Emax during this timeframe.) However, the Sponsor did not collect data at hours 7 and 8; Emax during 6 hours after dosing was used in my statistical analysis.

- Notice that if a subject does not respond to 40 mg oxycodone, any response to the combination drug (Liking or Disliking) is due to the niacin only.

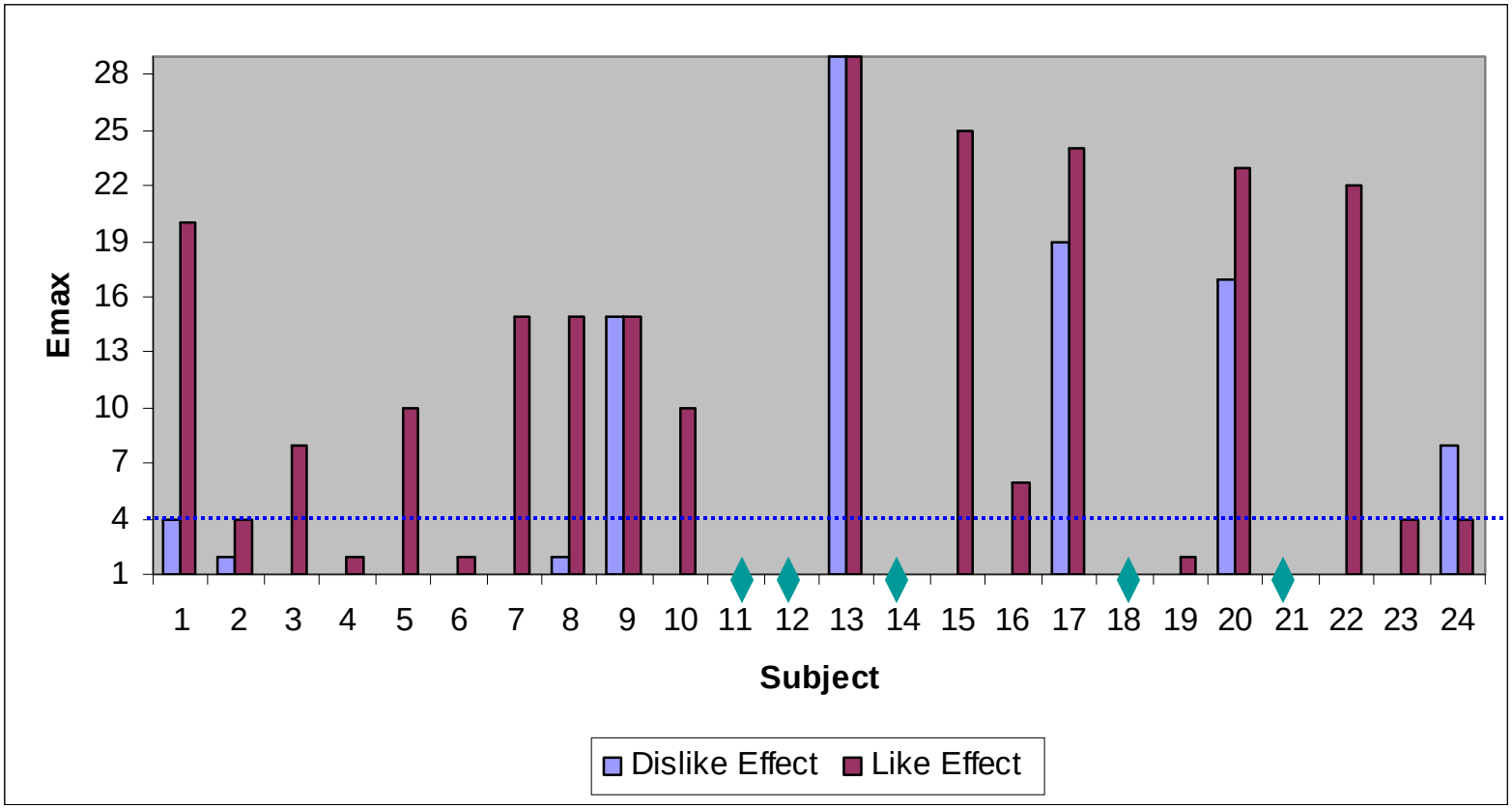
Mean Time Course Profiles for Like Effect (Study 102, N=24)



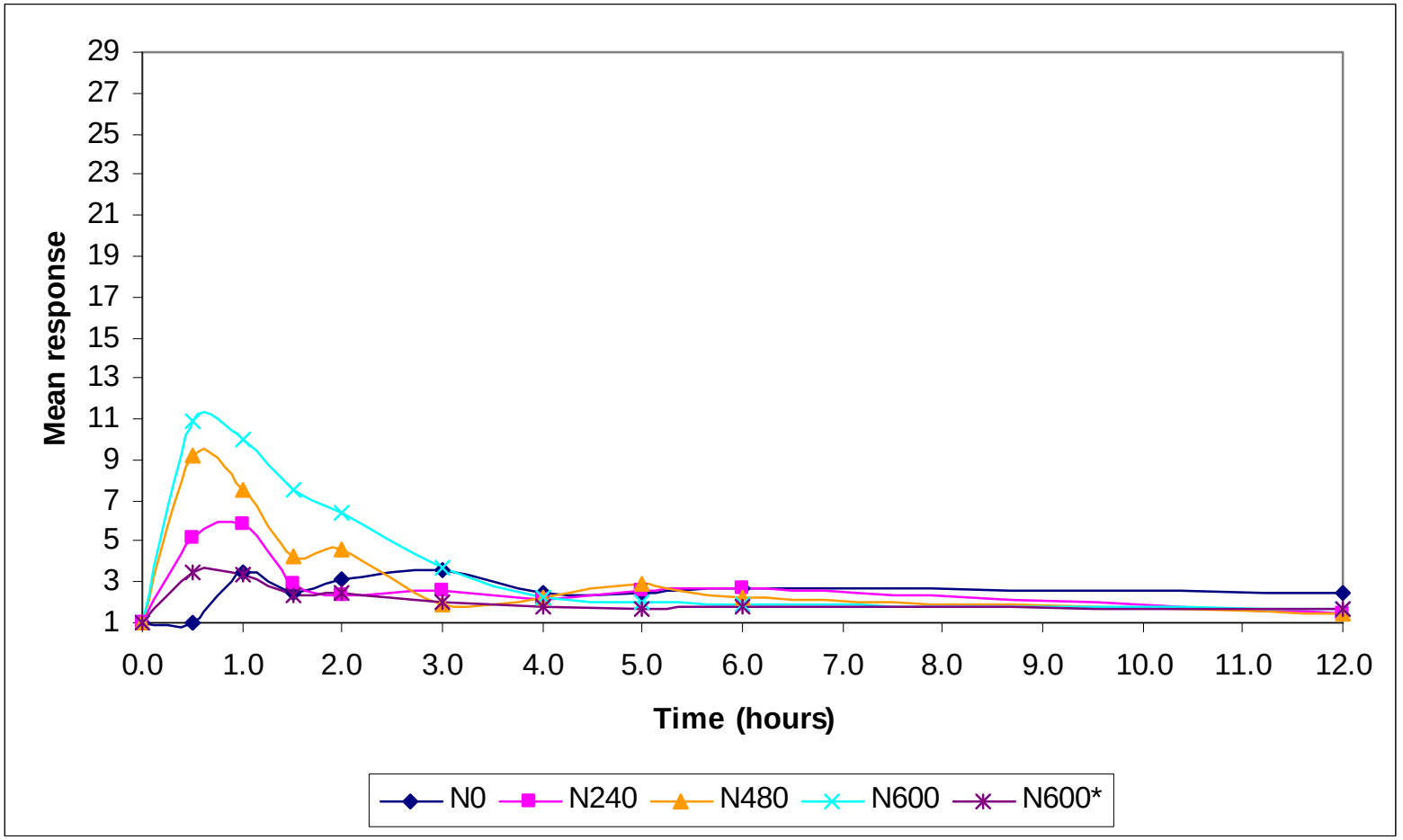
Non-responders to 40 mg Oxycodone (Study 102)

Treatment \Usubjid	1011	1012	1014	1018	1021	
O40	1	1	1	1	1	Emax of Like
O40+N240	2	1	1	5	22	
O40+N480	1	1	1	4	25	
O40+N600	1	20	1	4	26	
O40+N600*	1	1	1	1	19	
O40	1	1	1	1	1	Emax of Dislike
O40+N240	2	29	1	1	6	
O40+N480	1	1	1	1	23	
O40+N600	2	10	1	1	29	
O40+N600*	1	1	1	1	20	

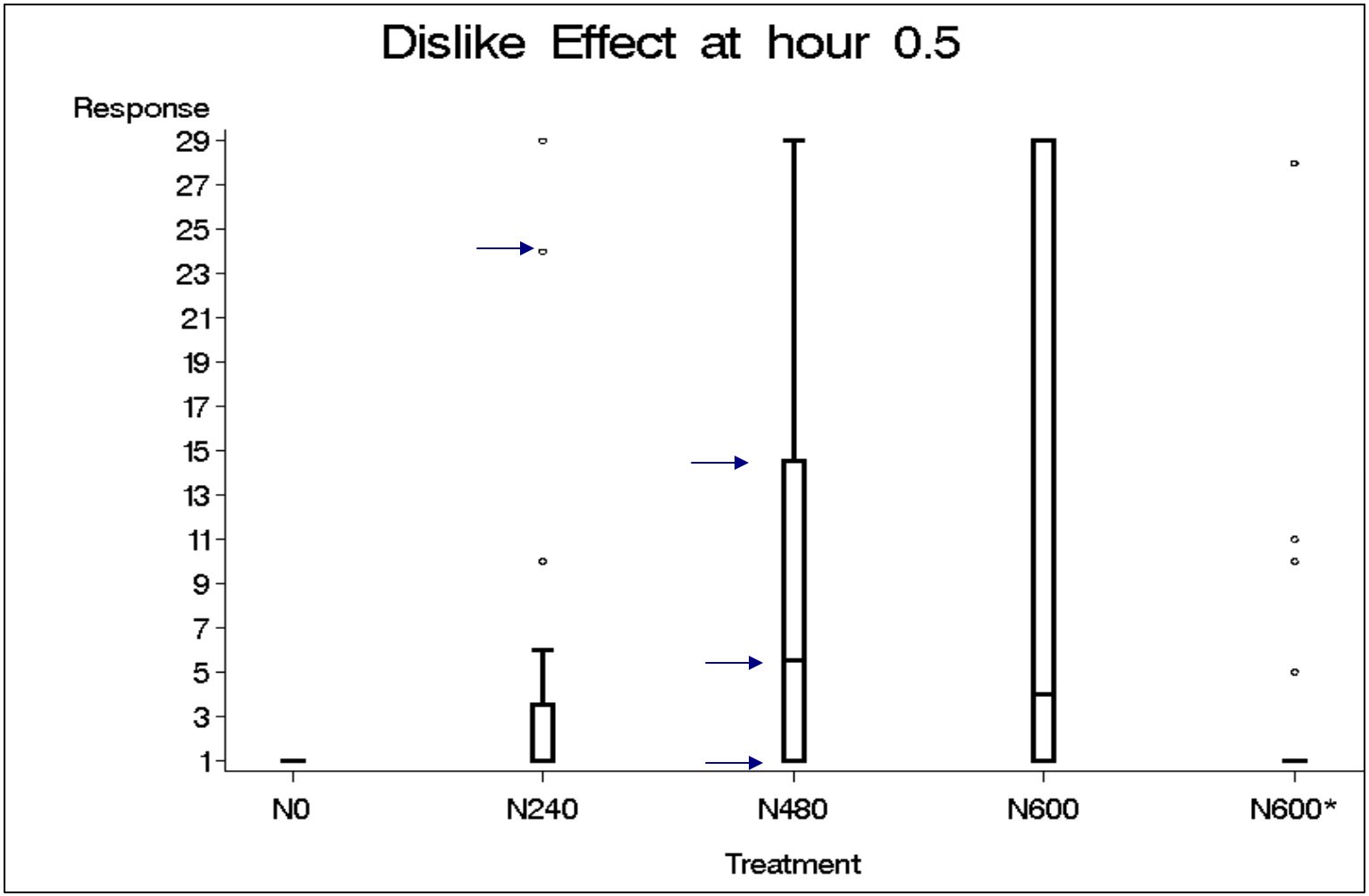
Emax of Like (or Dislike) Effect from Individual Subjects to 40 mg Oxycodone Treatment (Study 102)



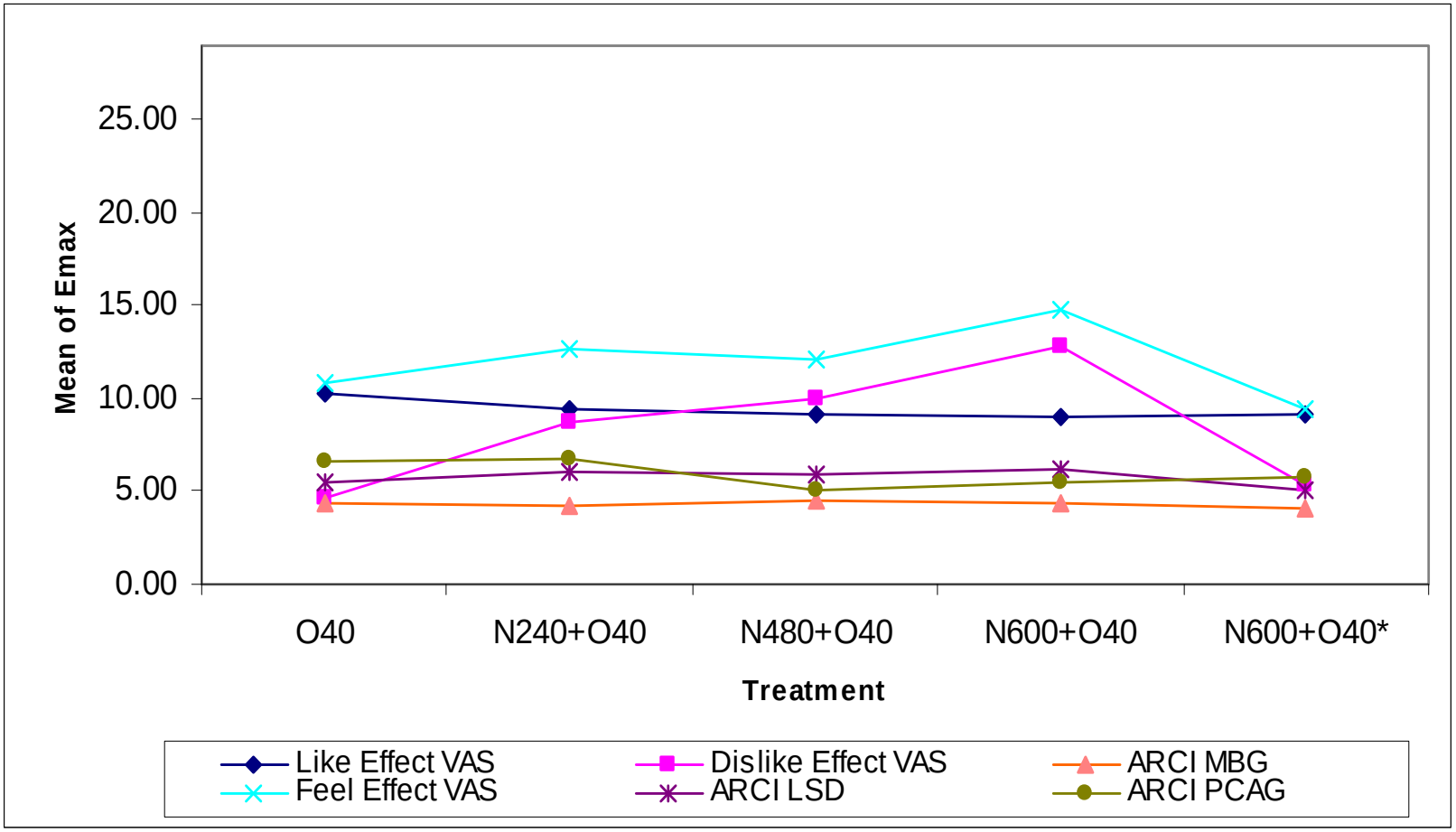
Mean Time Course Profiles for Dislike Effect (Study 102, N=24)



Boxplots of Dislike Effect (Study 102, N=24)



Mean Dose Responses of Treatments (Study 102, N=24)



Two Parts of the Treatment Phase in Study 111

- There are two parts of the treatment phase:

  Part I:

  N240 alone – niacin 240 mg alone
  N240 + O40 – niacin 240 mg + oxycodone 40 mg
  P – placebo

  Part II:

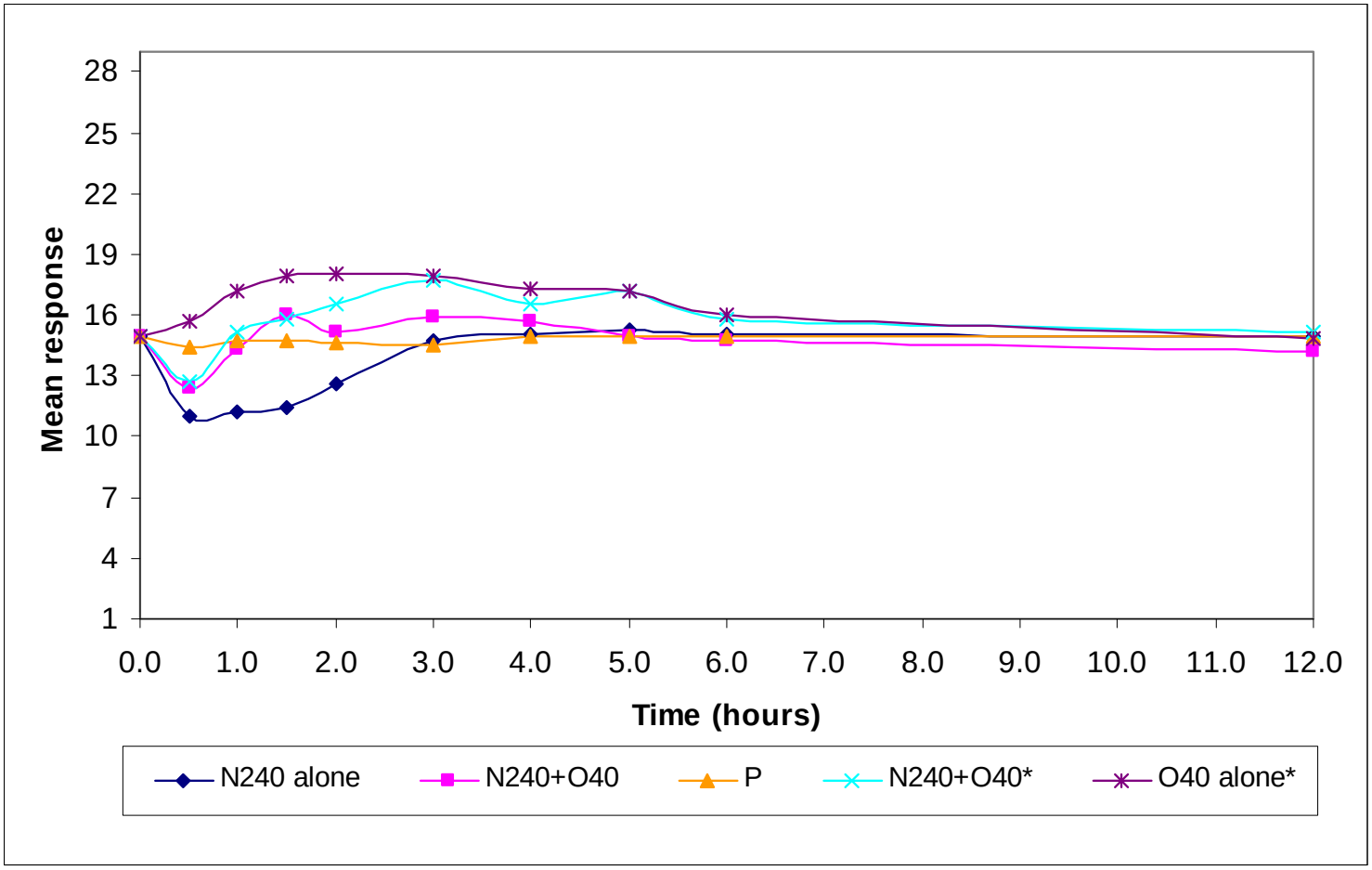
  N240 + O40* – niacin 240 mg +oxycodone 40 mg
  O40 alone* - oxycodone 40 mg alone

- Bipolar scale for Like/Dislike Effect (1 – 29)
  1 – 14 Dislike Effect, 15 neutral, and 16 – 29 Like Effect

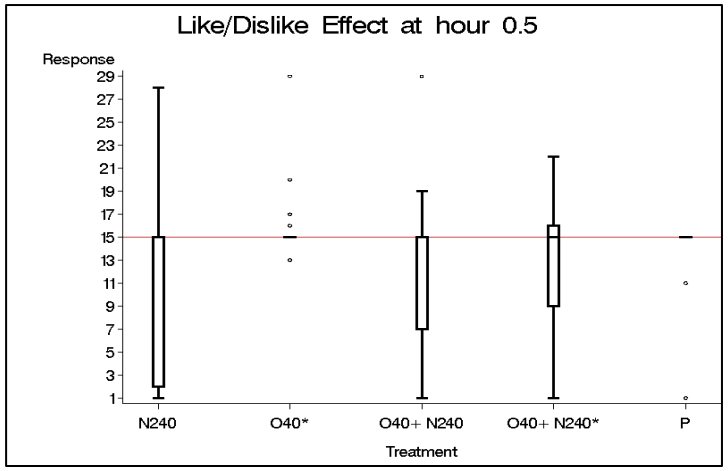
Non-responders to 40 mg Oxycodone for Like/Dislike Effect (Study 111, N=30)

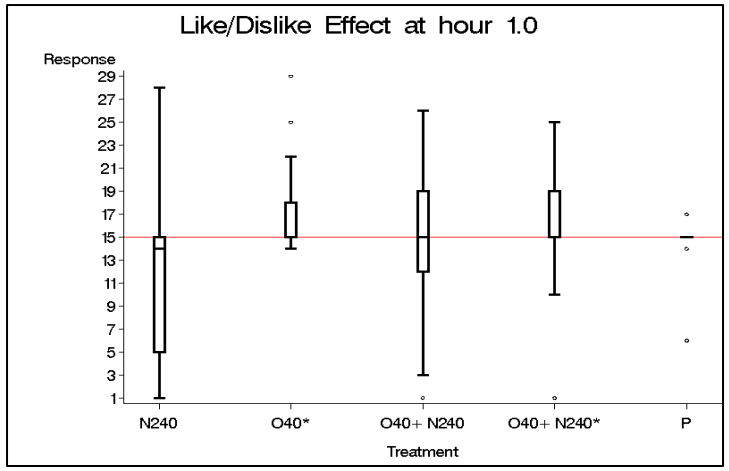
Treatment \Usubjid	005	010	019	021	029	
N240 alone	15	16	15	15	15	Emax of Like/Dislike
O40+N240	15	15	15	23	15	
placebo	15	15	16	15	15	
O40+N240*	15	15	15	19	15	
O40 alone*	15	15	15	15	15	
N240 alone	11	5	6	1	1	Emin of Like/Dislike
O40+N240	10	6	9	1	1	
placebo	15	15	15	15	15	
O40+N240*	10	5	15	1	1	
O40 alone*	15	15	15	15	15	

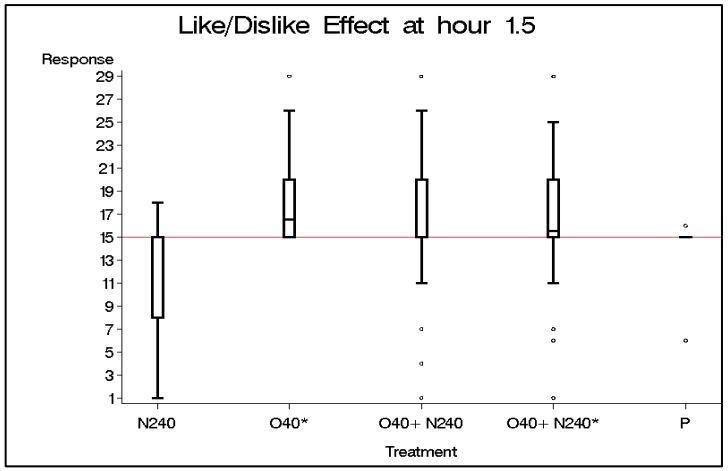
Mean Time Course Profiles for Like/Dislike Effect (Study 111, N=30)

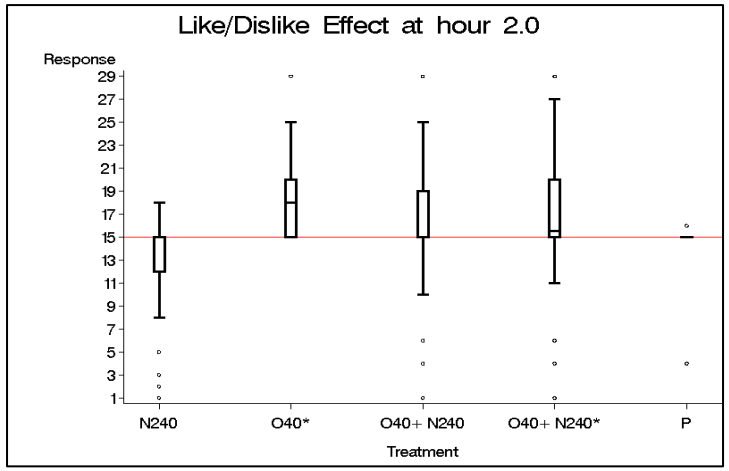


Boxplots of Like/Dislike Effect (Study 111, N=30)

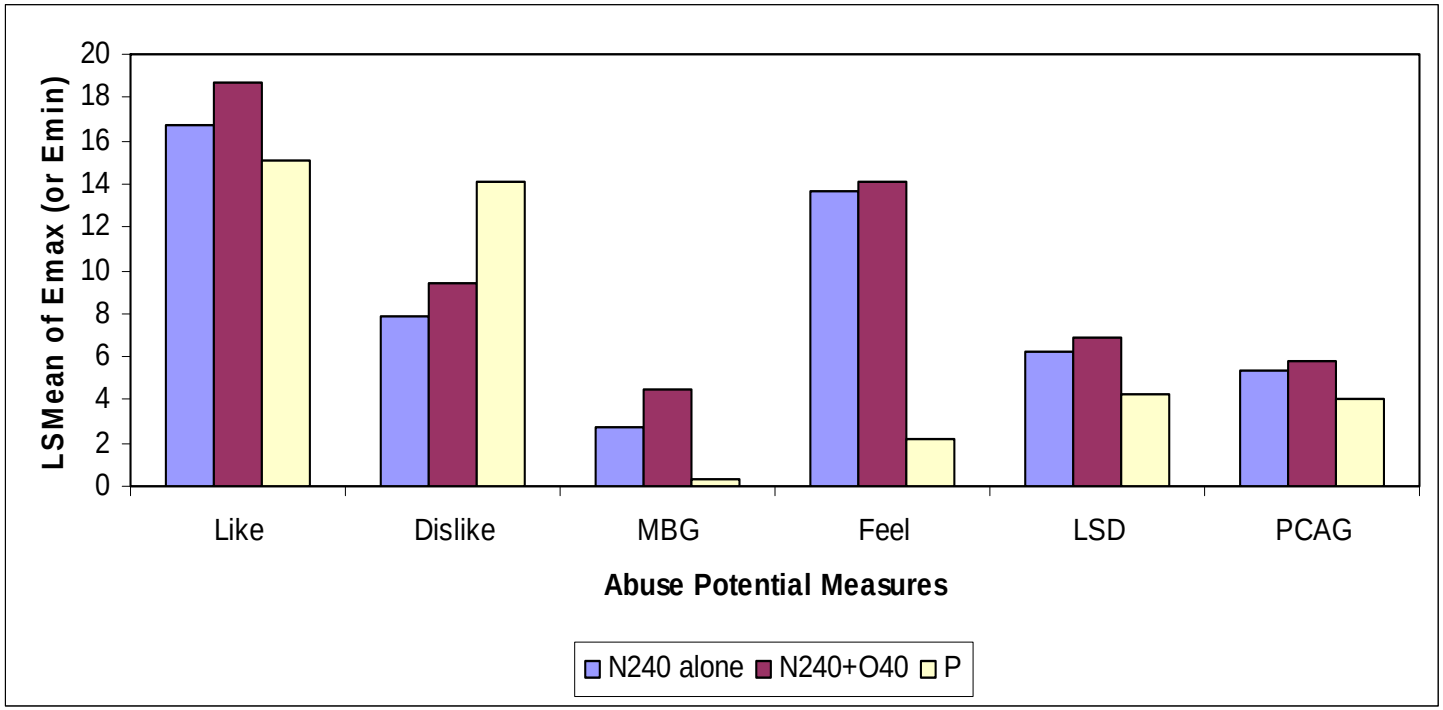






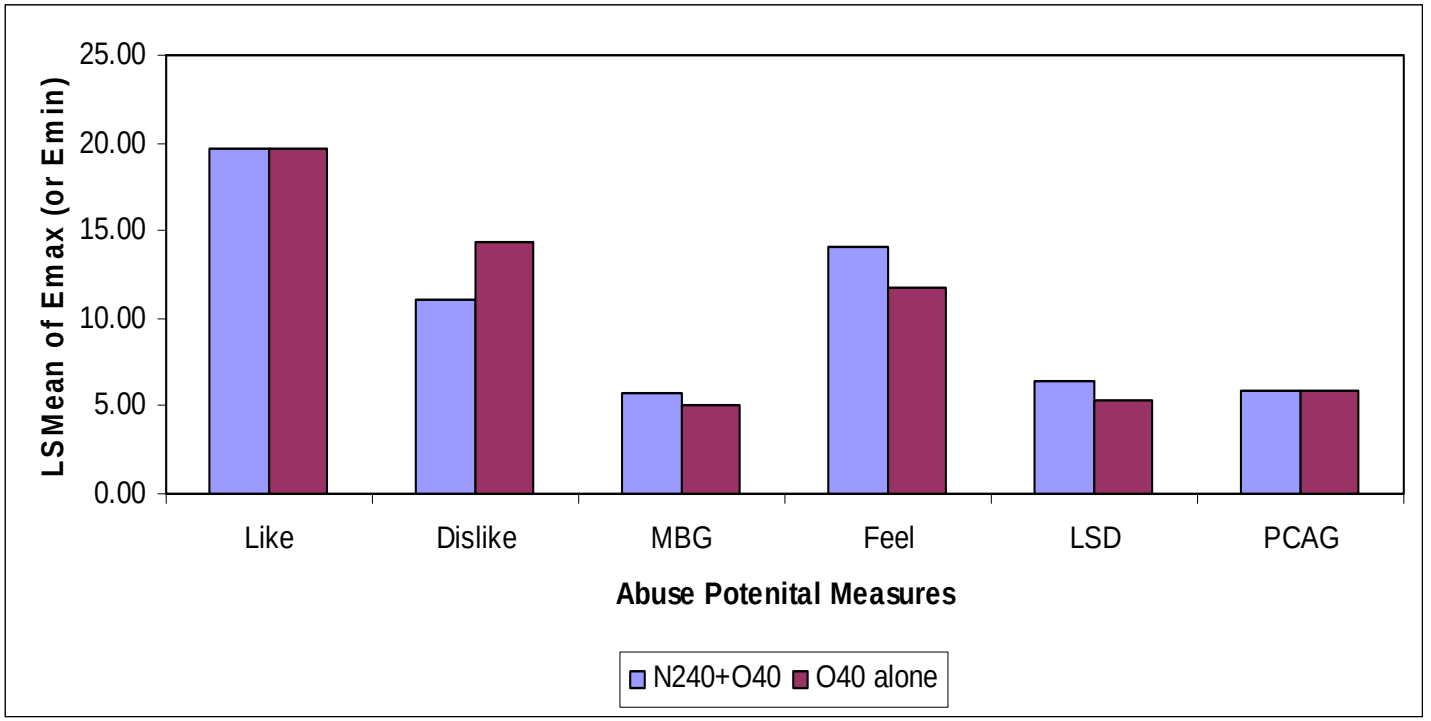


Summary of Statistical Analysis for Part 1 (Study 111)



Comparison	Like	Dislike	MBG	Feel	LSD	PCAG
N240 vs N240+O40	S	NS	NS	NS	NS	NS
N240 vs P	NS	S	S	S	S	S
N240+ O40 vs P	S	S	S	S	S	S

Summary of Statistical Analysis for Part 2 (Study 111)



Comparison	Like	Dislike	MBG	Feel	LSD	PCAG
N240+O40 vs O40	NS	NS	NS	NS	NS	NS

Summary of Findings

- Both human abuse potential studies (102 and 111) had some subjects with no or very low responses to 40 mg oxycodone alone, the positive control.
- No significant differences were found in mean of Emax between 40 mg oxycodone and 40 mg oxycodone + various doses of niacin treatments on Like Effect VAS and ARCI MBG.
- The mean of Emax in 40 mg oxycodone with various doses of niacin on Dislike Effect were statistically significantly higher than that to 40 mg oxycodone alone in Study 102. However, the dislike effect was moderate to the combination drug, and some of the dislike effect from the combination drug may be due to non-responders and mild responders to 40 mg oxycodone.
- A fatty meal completely abolished the disliking effects of niacin in the combination drug.

Conclusion

- Any niacin deterrent effects are abolished by a fatty meal.
- The addition of niacin to 40 mg oxycodone did not result in significant deterrent effects on abuse potential measures of interest, even under fasting conditions.