Exalgo Hydromorphone ER

Efficacy and Safety Review

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ALSDAC/DSaRM
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Presentation Overview

- **Background Hydromorphone**
  - Hydromorphone Immediate Release (HMIR)
  - Hydromorphone Extended Release (HMER)
- **Exalgo**
  - Regulatory history
  - Clinical Development
  - Efficacy Findings
  - Safety Findings
- **Specific Safety Issues**
- **Conclusions**

Hydromorphone

- Semi-synthetic, hydrogenated ketone of morphine
- Opioid agonist acting on μ-opioid receptors
- 1st synthesized Germany 1921
- Clinical analgesic use since 1926

Hydromorphone Immediate-Release
Dilaudid

- 1st FDA-approved HMIR (1984)
- **Formulations**: Injectable; Oral Solution and Tablets (2, 4, 8 mg)
- **Indication**: Management of pain in patients where an opioid analgesic is appropriate
- **Schedule II drug**
  - Highest potential for abuse and risk of producing respiratory depression

Opioid Equianalgesic Potency

Nonproprietary (Trade) Name	IM or SC Dose	ORAL Dose
Morphine sulfate	10 mg	40-60 mg
Hydromorphone HCl (DILAUDID)	1.3-2 mg	6.5-7.5 mg
Oxymorphone HCl (Numorphan)	1-1.1 mg	6.6 mg
Levorphanol tartrate (Levo-Dromoran)	2-2.3 mg	4 mg
Meperidine, pethidine HCl (Demerol)	75-100 mg	300-400 mg
Methadone HCl (Dolophine)	10 mg	10-20 mg

* Dosages, and ranges of dosages represented, are a compilation of estimated equipotent dosages from published references comparing opioid analgesics in cancer and severe pain.

(Source: Dilaudid label)

Hydromorphone Extended-Release
Palladone

- 1st FDA-approved HMER
- **Indication**: Management of persistent, moderate to severe pain in patients requiring continuous, ATC analgesia with a high potency opioid for an extended period of time
- **Regulatory history**
  - **December 1998:** NDA submitted; multiple review cycles
  - **September 2003:** AC meeting (Abuse/Misuse Risk)
  - **September 2004:** Palladone approved

Advisory Committee Recommendations

Palladone (2003) Risk Management

- **Phased Rollout**
  - Promote appropriate and safe use of drug
  - Reduce abuse
  - Minimize diversion
- **Surveillance System**
  - Collect and analyze data in timely manner
  - Use of prespecified outcomes and interventions
- **Education Component**
  - Educate physicians regarding risks of opioids in general and Palladone in particular

Approved Risk Management Program
Palladone

- **Labeling**
  - Package Insert
  - MedGuide
- **Education**
  - Healthcare Professional Education
  - Patient and Caregiver Education
- **Surveillance**
  - Regular Monitoring with specific interventions
  - Evaluation metrics (surveillance outcomes)
- **Limited Rollout**

Palladone Limited Roll Out

- Rolled out over 18 months
- Promotional detailing by sales representatives directed at single entity opioid prescribers
- First 6 months limited marketing to prescribers most likely to treat patients requiring Palladone use
  - (Anesthesiology, Neurology, Oncology, Pain Medicine, PMR, Psychiatry)
- Months 7-18 added Primary Care, Surgeons, Other Specialties in 6 month intervals
- Limited and targeted sales force
- Evaluated metrics at months 6, 12, and 18

Abuse Liability Assessment

Palladone (2004)

- In vitro dissolution in alcohol study
  - 89% hydromorphone dose was dumped into 10 mL of 40% ethanol after 15 minutes

- In vivo Alcohol Interaction Study
  - OL, 4 arm PK cross over study
  - Co-ingestion Palladone (12 mg capsule) + 240 mL of 40%, 20%, 4% ethanol or water

Palladone Alcohol Interaction Study
Findings

- The average peak HM concentration was up to 6X greater with 40% alcohol than water.
- The integrity of the extended release profile of Palladone was defeated in the presence of alcohol.
- There was a potential for dose dumping.

Palladone Alcohol Interaction Study

Outcome

Purdue voluntarily suspended sales and marketing of Palladone in July 2005.

Hydromorphone Extended Release
Exalgo

Proposed:

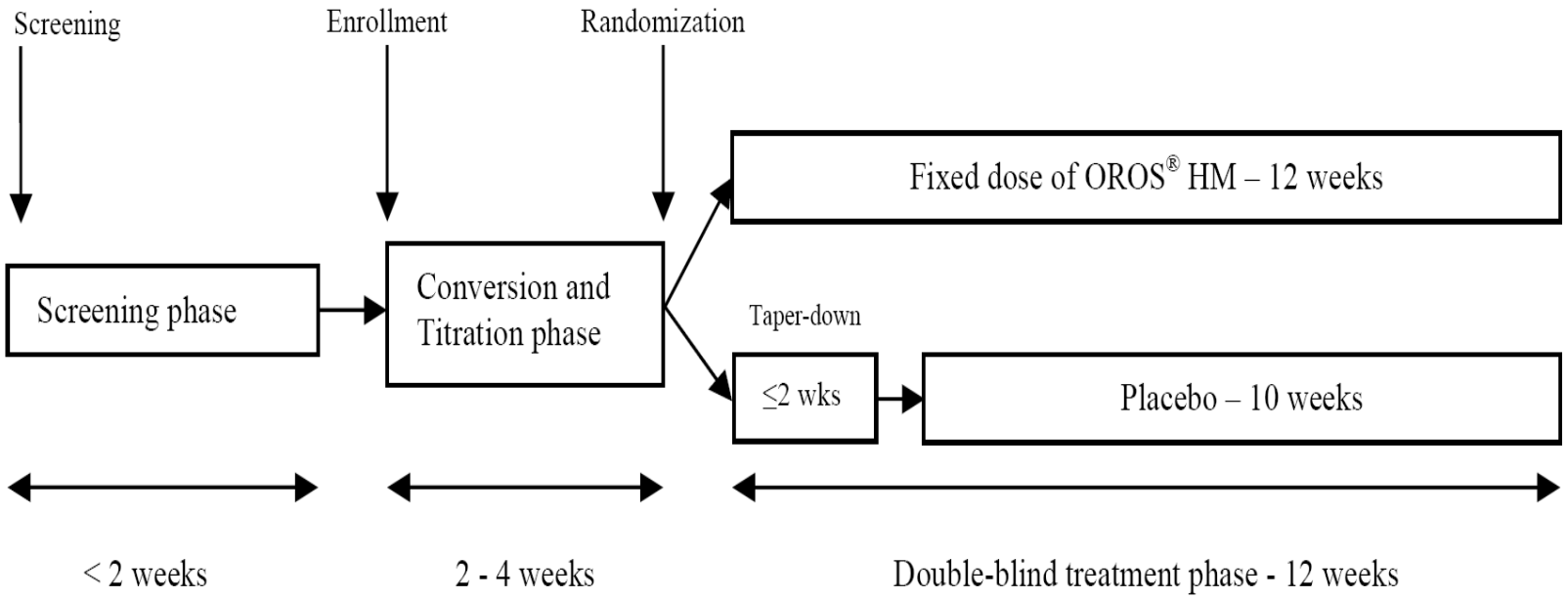
- **Usage**: Once daily
- **Dosage**: Oral tablets 8,12,16 and 32 mg
- **Indication :** Management of moderate to severe pain in opioid-tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time

Key Regulatory History

- 1999 - NDA was submitted by Knoll Pharmaceuticals
- 2000 - Approvable Letter was issued
    - Clinical deficiency: lack of efficacy in key study
    - Would require one AWC study with multiple dosing of the to-be-marketed formulation in the setting of moderate to severe pain to establish efficacy
- 2000 - NDA was transferred to ALZA corporation
- 2007 - NDA was transferred to Neuromed
- 2009 - Neuromed submitted the complete response to address the deficiencies

Efficacy

Key Efficacy Study Design



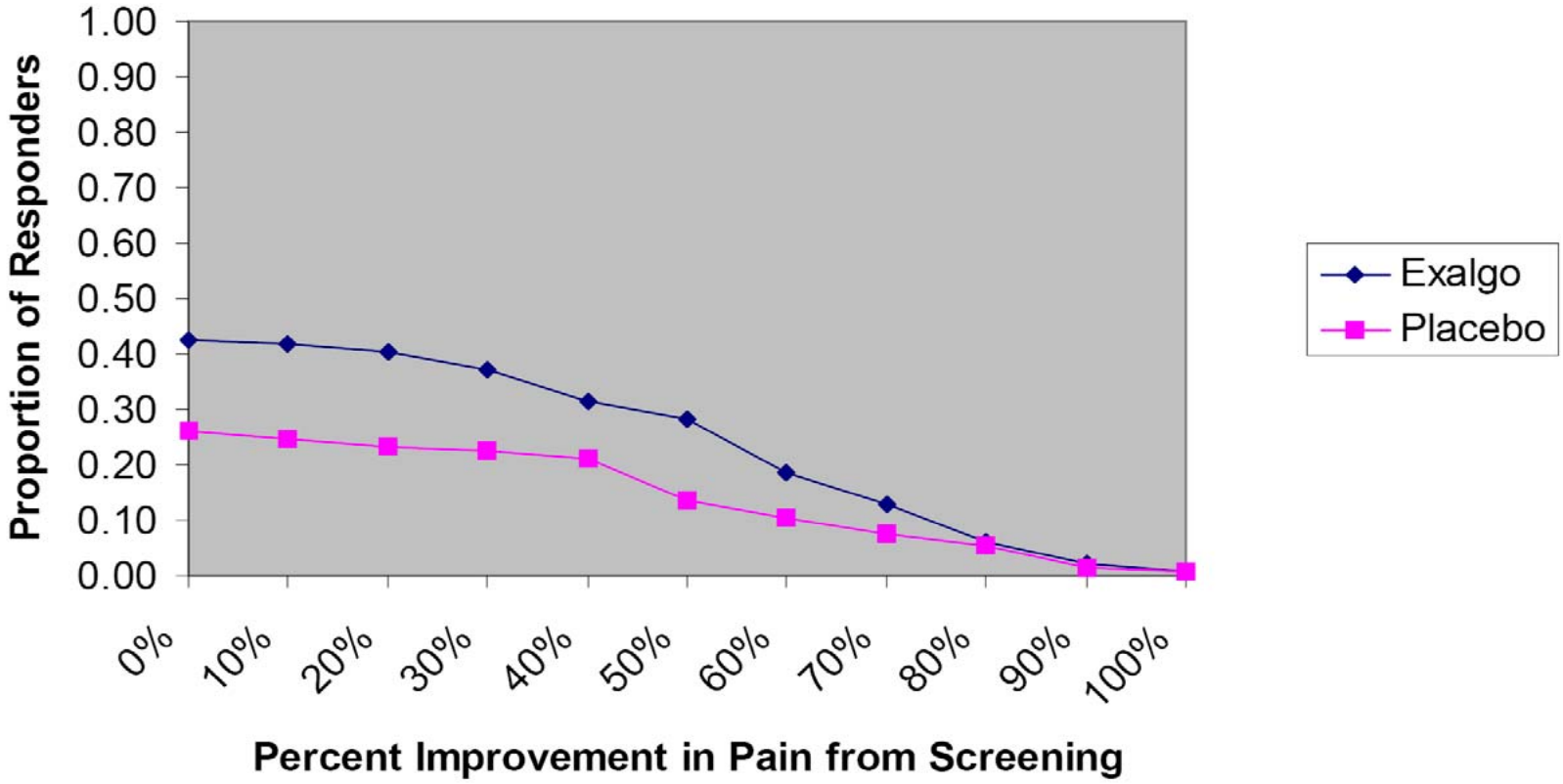
Multicenter, DB, PC study with a randomized withdrawal design in patients with Chronic Low Back Pain

Primary Analysis

Primary Endpoint: Change from Baseline to Week 12/Final Visit in weekly mean pain intensity scores

Statistic	Hydromorphone	Placebo	p-value
Baseline			
N	133	133	
Mean	3.2	3.1	
Median	3.3	3.3	
Range (min, max)	0, 6	0, 6	
Visit 11/Final visit (Week 12)			
N	133	133	
Mean	3.8	4.8	
Median	3.6	4.8	
Range (min, max)	0, 9	0, 9	
Change from Baseline			<0.001
N	133	133	
Mean	0.6	1.7	
Median	0.2	1.6	
Range	-5, 5	-3, 7	

Cumulative Proportion of Responders



SAFETY

(preliminary results)

Exalgo Exposure

- 3,075 patients in pooled analysis (chronic pain)
- 2,335 patients received at least one dose
  - 2,264 in primary studies
  - 569 in extended studies
- Duration
  - > 6 months = 420
  - >12 months = 141
- Daily doses ranged from 6 mg to 1984 mg/day

Deaths

Phase 2/3 Studies	Exalgo (N=2335)	Placebo (N=466)
Controlled studies	2	0
Uncontrolled studies	62	-
Total	**64**	**0**

- No deaths definitely or probably related to study drug
- Majority of deaths occurred in cancer patients and appeared to be related to cancer disease progression

Selected Death Narratives

Diagnosis	Brief Narrative	Causality
Respiratory Failure	68 yo male, **metastatic** squamous cell **lung cancer**; multiple concomitant medications; no autopsy	Unrelated
Asthenia, delirium	70 yo male, **metastatic cancer** (unknown primary); multiple concomitant medications; no autopsy	Unrelated

Serious Adverse Events

MedDRA Term	Exalgo (N=240/2335)	Placebo (N=8/466)
GI disorders	49	3
Infections and infestations	44	2
General disorders and administration site conditions	43	1
Neoplasms (benign, malignant and unspecified)	31	1
Nervous System Disorders	29	1

MedDRA = Medical Dictionary for Regulatory Activities

Common Adverse Events

MedDRA Preferred Term	Exalgo (%)	Placebo (%)
Any Adverse Event	80	61
Constipation	30	9
Nausea	27	9
Vomiting	14	3
Somnolence	14	3

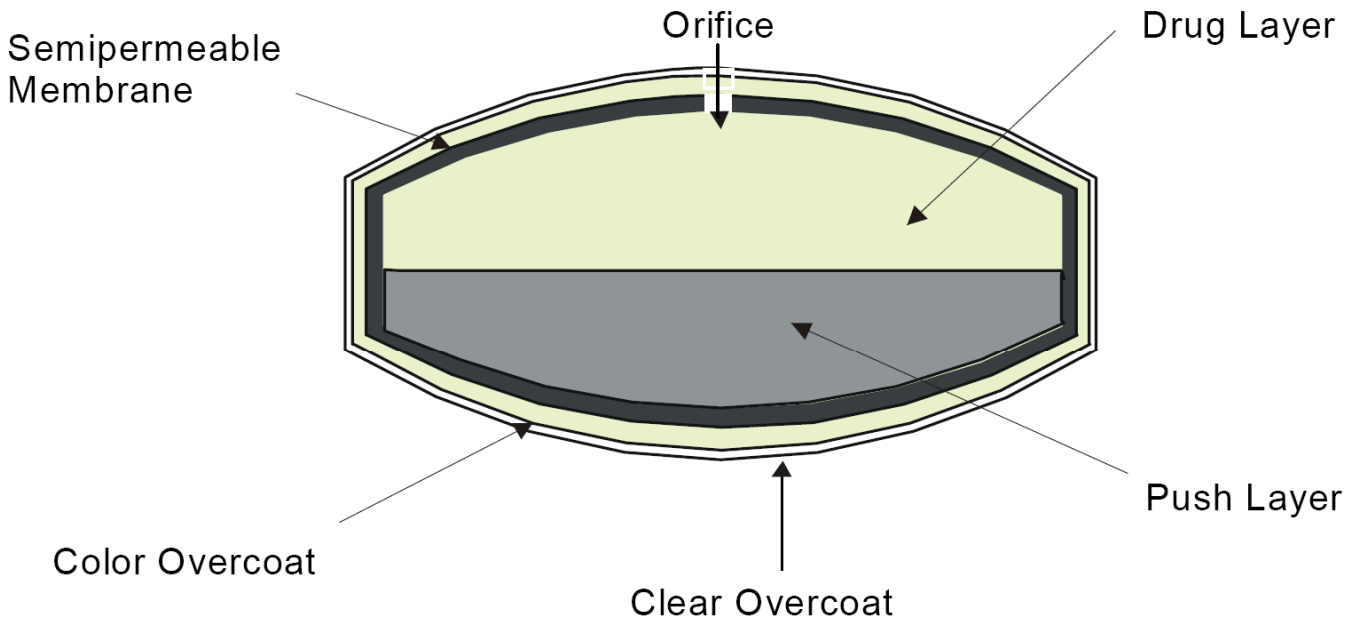
Adverse Events Leading to Discontinuation

MedDRA Preferred Term	Exalgo N=2335 (%)
Any Adverse Event	23
Nausea	6
Constipation	4
Vomiting	3
Somnolence	2

Specific Safety Issues

- OROS Technology
- Exalgo-Alcohol Interaction
- Abuse and Misuse

OROS Technology



OROS Technology and GI Events

- Literature reports of formation of medication bezoars with associated GI obstruction in some OROS products
- Other reported GI complications include
  - Ulceration
  - Hemorrhage
  - Gastritis
  - Perforation

Source: 1) Prisant, LM, et al. Arch Intern Med, V.151, Sept. 1991, p.1868-1869
2) Taylor JR, et al. The Annals of Pharmacotherapy, V. 32 Sept.1998, p. 940-946

Exalgo Treatment-Related GI Events

GI Obstruction (6)	
Small bowel obstruction	2
Gastric outlet obstruction	1
Intestinal obstruction	1
Fecaloma	1
Bezoar of stomach	1
GI perforation (4)	
Perforated sigmoid colon	1
Perforated large intestine	1
Perforated bowel	1
Diverticulitis w/ perforated colon	1
Other (9)	
GI disorder (1); Severe Nausea/Vomiting (3)	4
Constipation	3
Diverticulitis w/o perforation	1
Abdominal pain (upper)	1

Exalgo GI Summary

- All GI obstructive events occurred in the uncontrolled studies.
- All patients with GI obstructive events had significant pre-existing GI history.
- Nausea, vomiting, and constipation were the usual clinical presentation.

Exalgo Alcohol Interaction

Exalgo Alcohol Interaction

- In vitro and in vivo data showed that in the presence of alcohol, the extended release profile is maintained.

- Overall, there is no significant potential for dose dumping.

Abuse and Misuse

- Abuse Liability study will be discussed by Dr. JianPing Gong of Controlled Substance Staff (CSS)

Conclusions

Exalgo (Oros Hydromorphone ER)

- Appears efficacious in population studied
- Has similar adverse event profile to other high potency opioids
- Does not dose dump in alcohol
- May have similar risks in terms of GI obstruction and bezoar formation as other marketed OROS formulations

Outpatient Drug Utilization Trends for Hydromorphone

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Division of Epidemiology
Office of Surveillance and Epidemiology
September 23, 2009

Outline

- Sales distribution analysis
- Dispensed prescription and Patient-level analysis, Years 2006-2008
  - Hydromorphone products compared to select opioid pain products
  - Prescriber specialty
- Diagnoses associated with use
- Summary

Hydromorphone products* included

- **<u>Immediate-release (IR) hydromorphone products</u>:**
  - **Tablet: Dilaudid®**
  - **Oral Liquid: Dilaudid-5®**

Includes marketed brand and generic oral formulations

Select Potent Opioid pain products* included

- **Immediate-release (IR) opioid pain products:**
  - **Oxycodone hydrochloride, Oxycodone/APAP, Oxycodone/ASA, Methadone hydrochloride, Morphine sulfate, Fentanyl, and Oxymorphone hydrochloride**

- **Extended-release (ER) opioid pain products:**
  - **Oxycodone hydrochloride, Fentanyl transdermal patch, Morphine sulfate and Oxymorphone hydrochloride**

Includes marketed brand and generic C-II formulations

Sales distribution data
Year 2008

IMS Health, IMS National Sales Perspectives™ Retail and Non-Retail

IMS Health, IMS National Sales Perspectives™

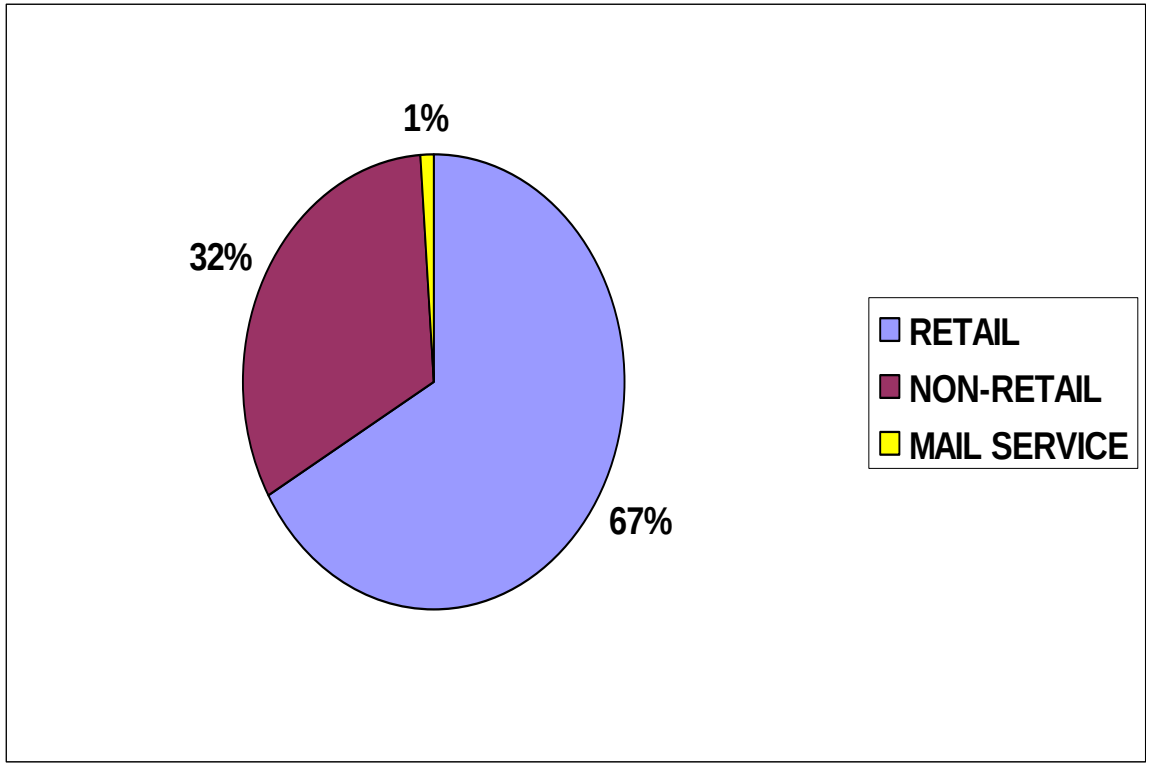
- **Measures the volume of products, in units and dollars, moving from manufacturers to retail and non-retail channels of distribution**
  - **Eaches are the number of bottles, packets of pills, syringes, vials, etc. of a product shipped in each unit**

- **Retail Channels - chain, independent, mass merchandisers, food stores with pharmacies, and mail-order 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)**

Wholesale channels of distribution for hydromorphone in the U.S., Year 2008

Source: IMS Health, IMS National Sales Perspectives™, Year 2008. Extracted 8/09



- **Retail sales distribution, 67%**
- **Non-retail sales distribution, 32%**
- **Mail order, 1%**

Prescription-Level Data

Years 2006-2008

SDI Vector One®: National (VONA)

Surveillance Data, Inc.
Vector One®: National (VONA)

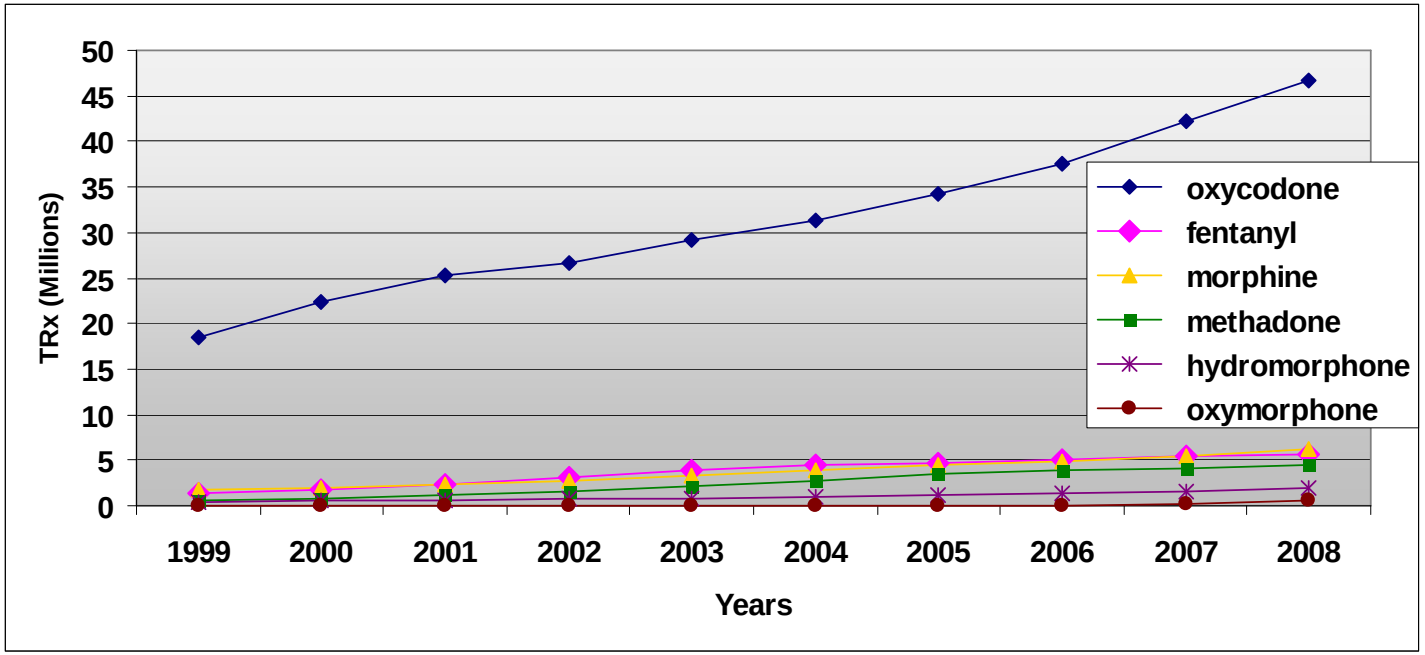
- **SDI's Vector One®: National (VONA) is a national-level projected prescription and patient-centric tracking service.**
  - **Receives over 2.0 billion prescription claims per year, representing over 160 million unique patients.**

- **The number of dispensed prescriptions is obtained from a sample of approximately 59,000 pharmacies throughout the U.S., accounting for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide.**

- **Retail pharmacies include:**
  - **national retail chains**
  - **mass merchandisers**
  - **pharmacy benefits managers and their data systems**
  - **provider groups**

Total number of prescriptions dispensed for selected potent opioids from U.S. outpatient retail pharmacies, Years 1999-2008

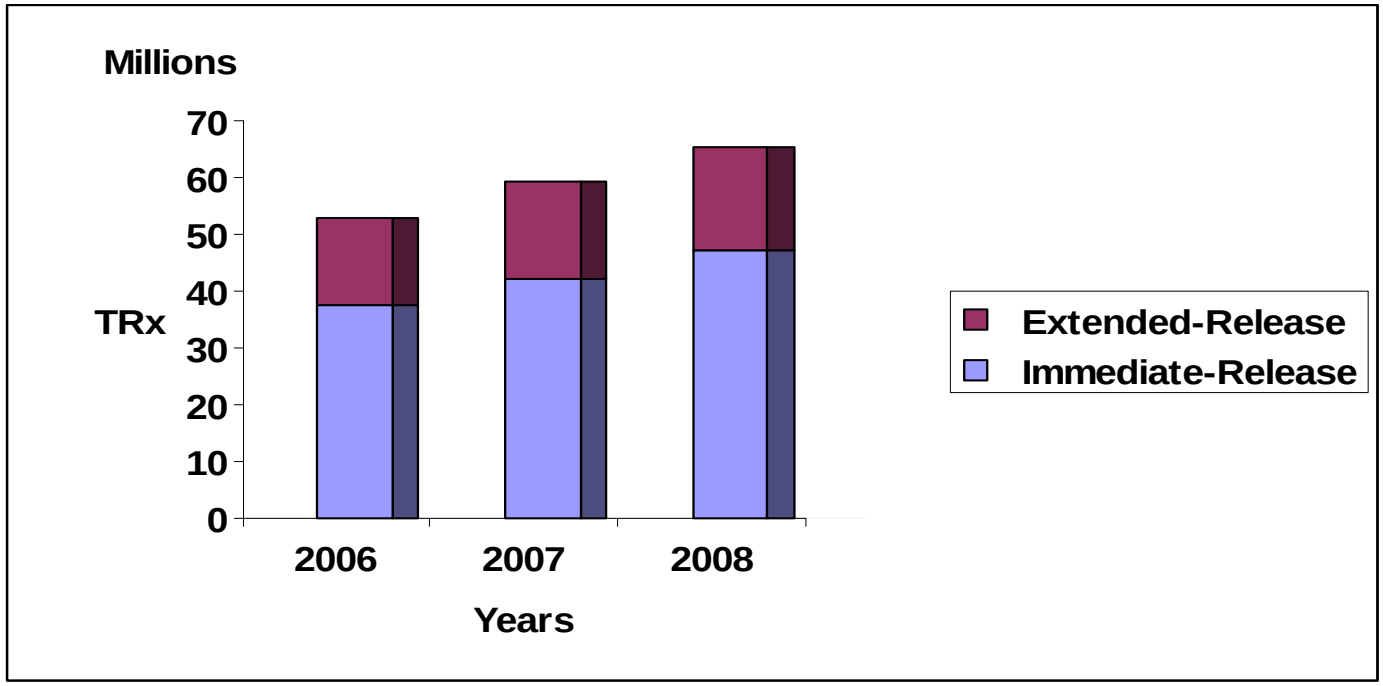
SDI Vector One®: National (VONA). Extracted Aug 2009



- Includes both immediate and extended-release formulations

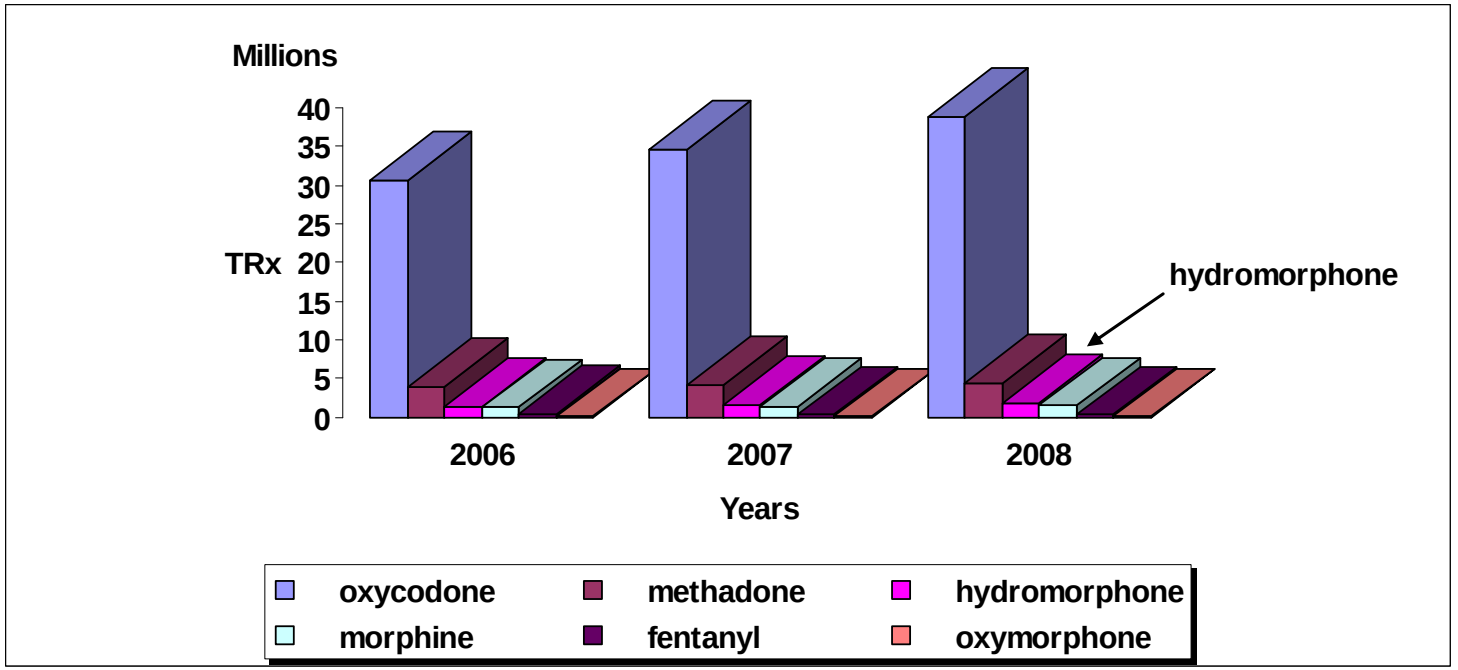
Total number of dispensed prescriptions for selected potent opioid pain products by product form from U.S. outpatient retail pharmacies , Years 2006 – 2008

Source: SDI Vector One®: National, Data Extracted 8-2009



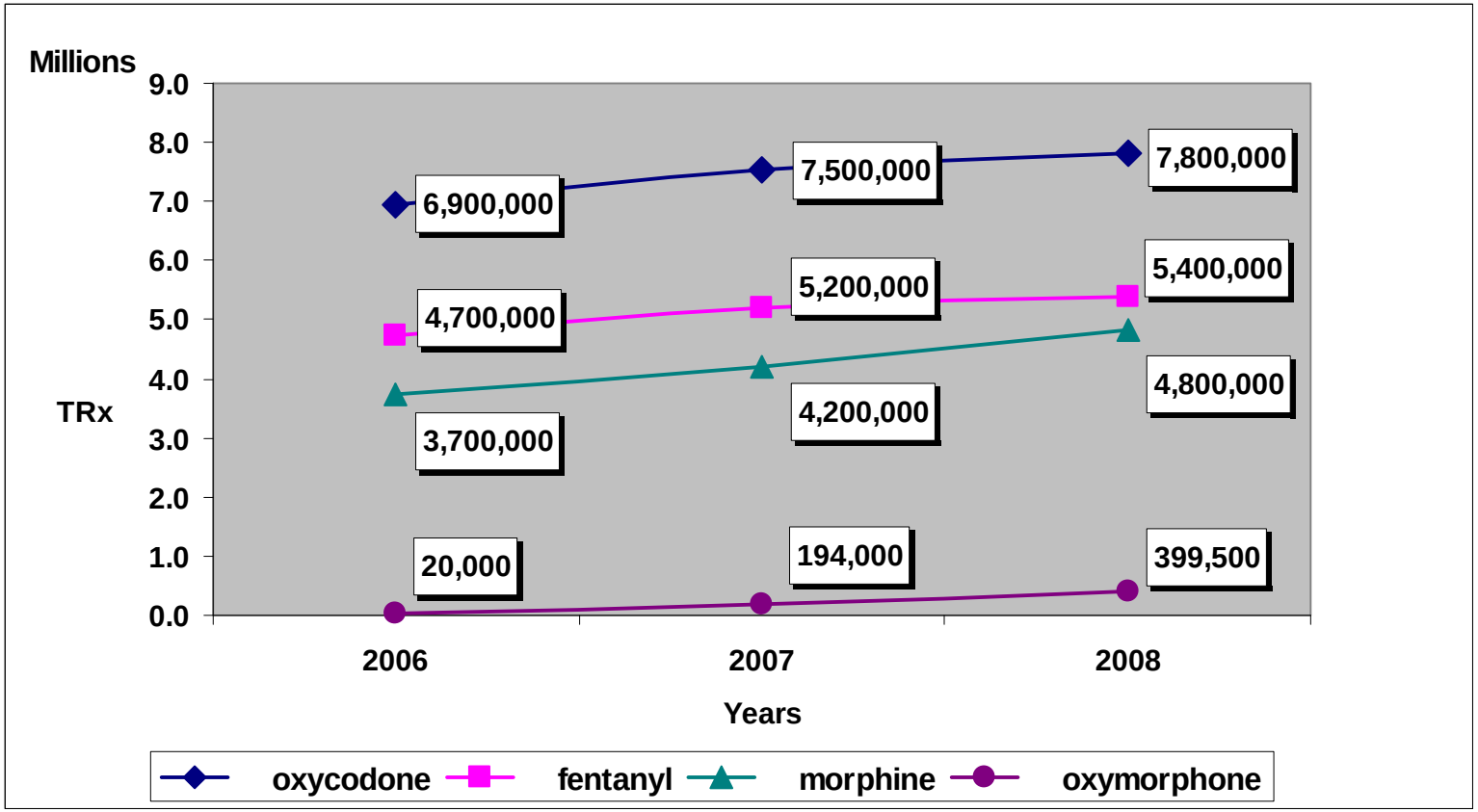
Total number of dispensed prescriptions for potent immediate-release opioid pain products and hydromorphone from U.S. outpatient retail pharmacies, Years 2006 – 2008

Source: SDI Vector One®: National, Data Extracted 6-2009



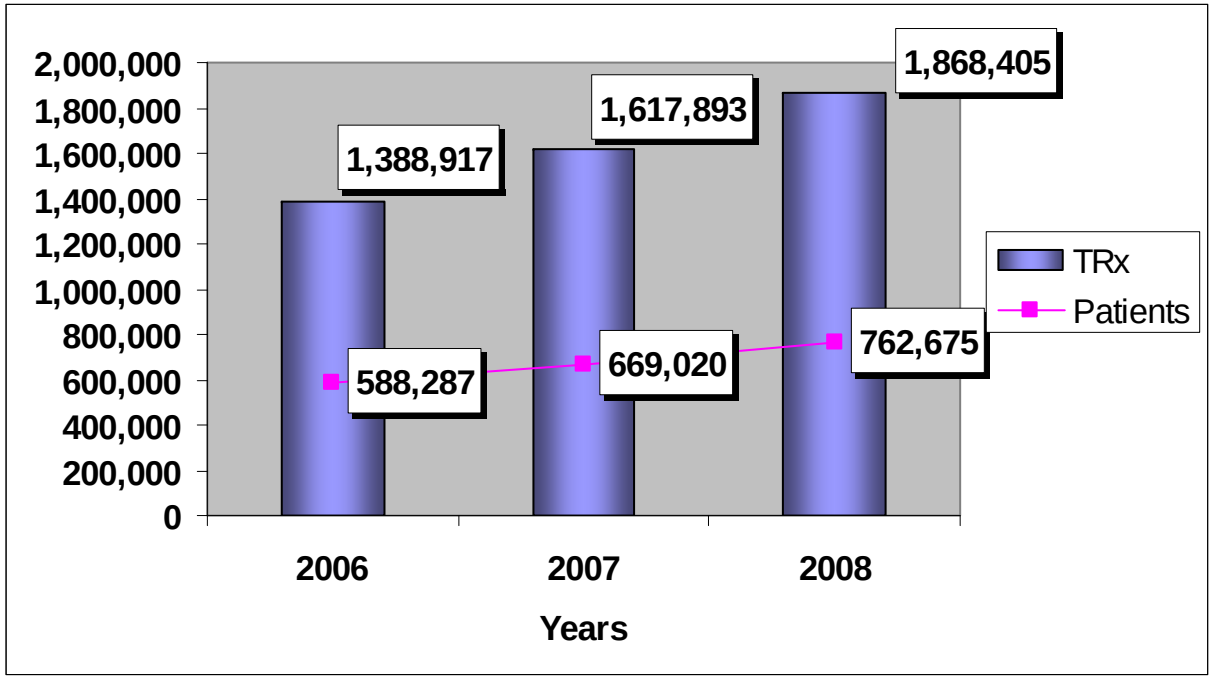
Total number of dispensed prescriptions for selected potent extended-release opioid pain products from U.S. outpatient retail pharmacies, Years 2006 – 2008

Source: SDI Vector One®: National, Data Extracted 6-2009



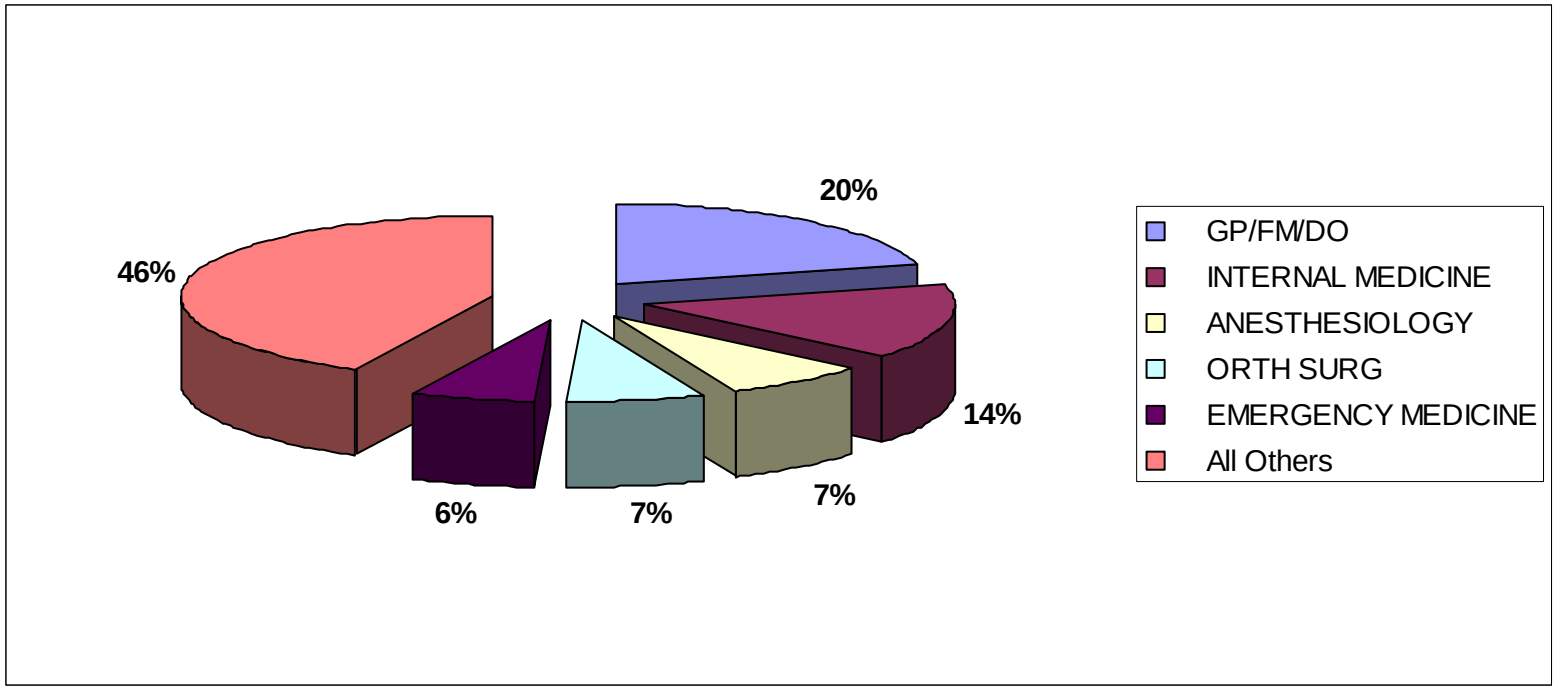
Total number of projected patients and dispensed prescriptions for all potent immediate-release hydromorphone products from U.S. outpatient retail pharmacies, Years 2006 – 2008

Source: SDI Vector One®: National, Data Extracted 6-2009
SDI Total Patient Tracker, Extracted 8-2009



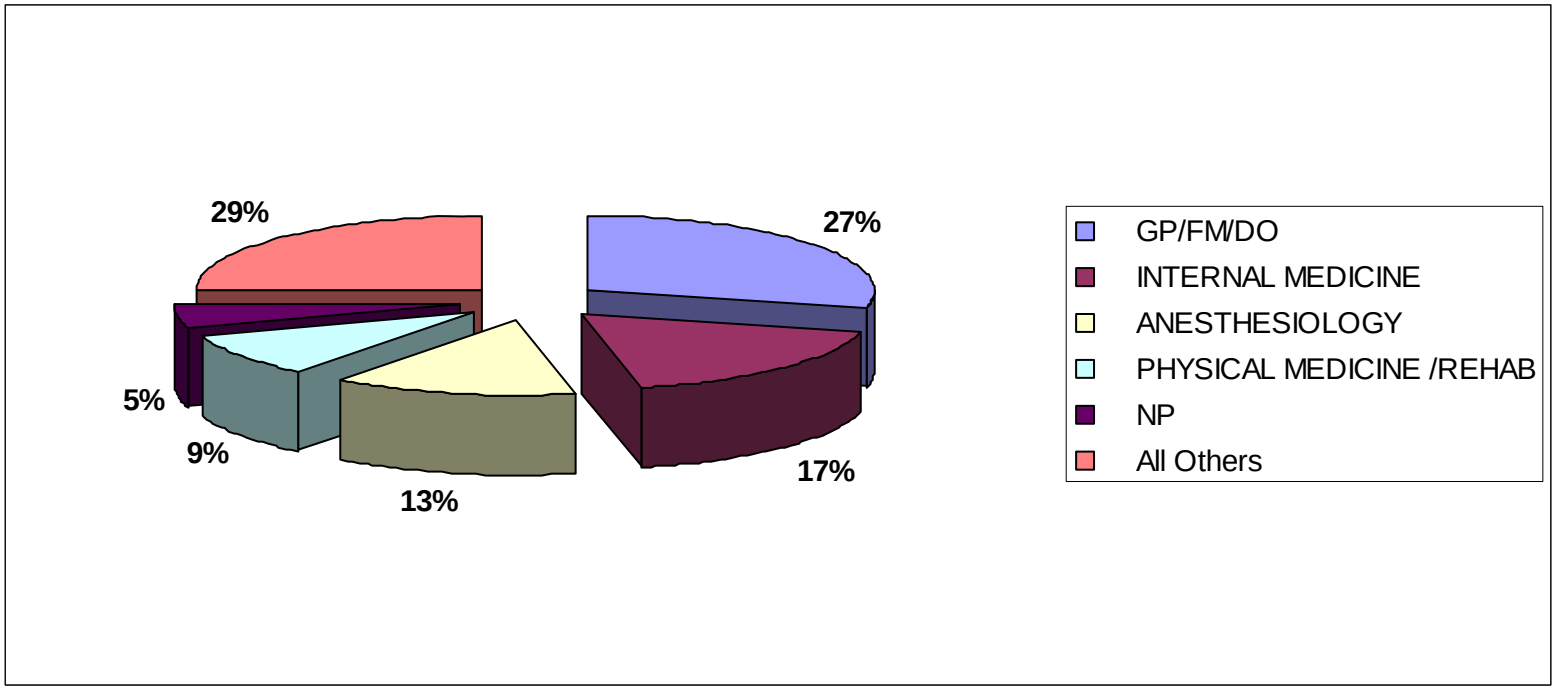
Percentage of dispensed prescriptions for selected potent immediate-release opioid products by top 5 prescribing specialties from U.S. outpatient retail pharmacies, Years 2008

Source: SDI Vector One®: National, Data Extracted 6-2009



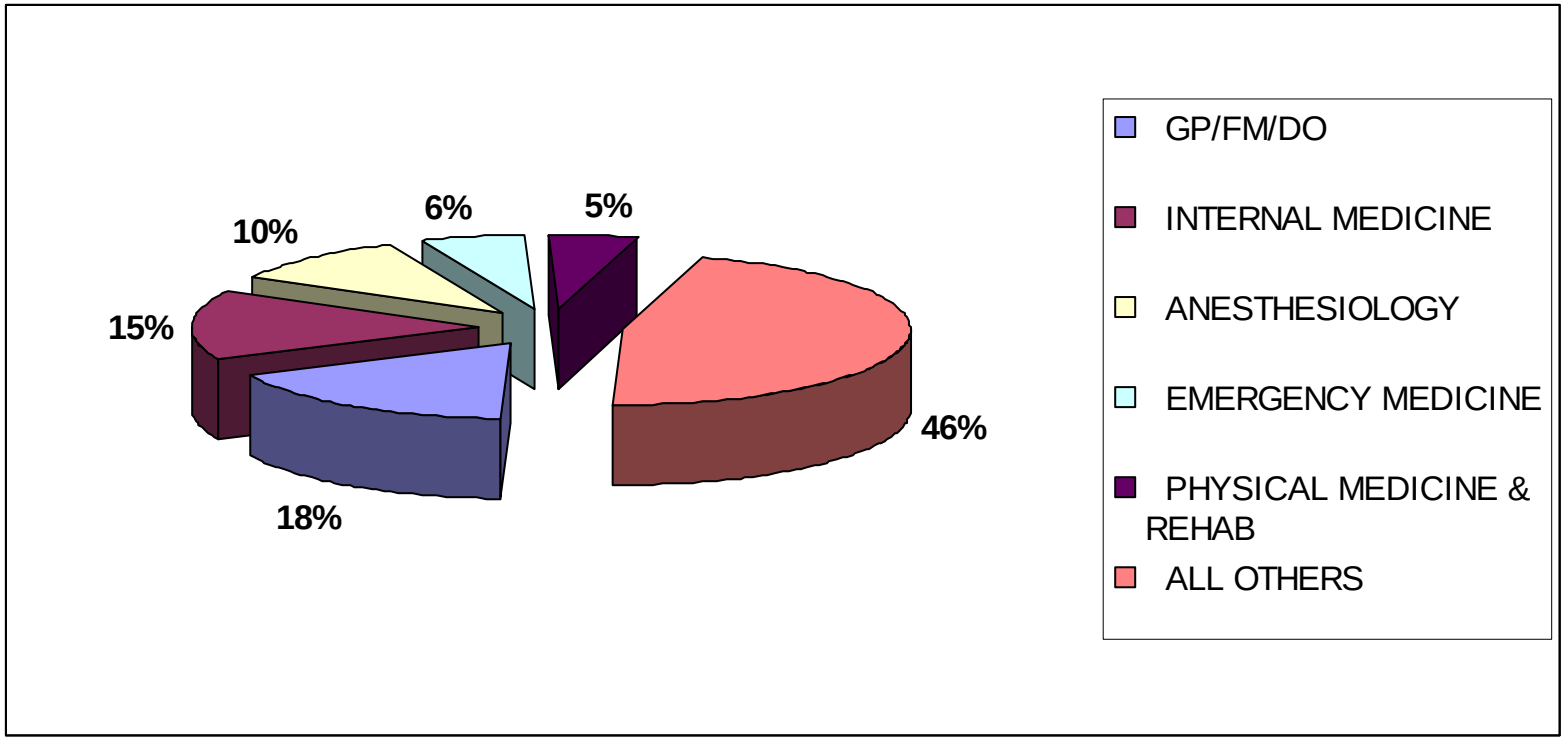
Percentage of dispensed prescriptions for selected potent extended-release opioid products by top 5 prescribing specialties from U.S. outpatient retail pharmacies, Year 2008

Source: SDI Vector One®: National, Data Extracted 6-2009



Percentage of dispensed prescriptions for hydromorphone products by top 5 prescribing specialties from U.S. outpatient retail pharmacies, Year 2008

Source: SDI Vector One®: National, Data Extracted 8-2009

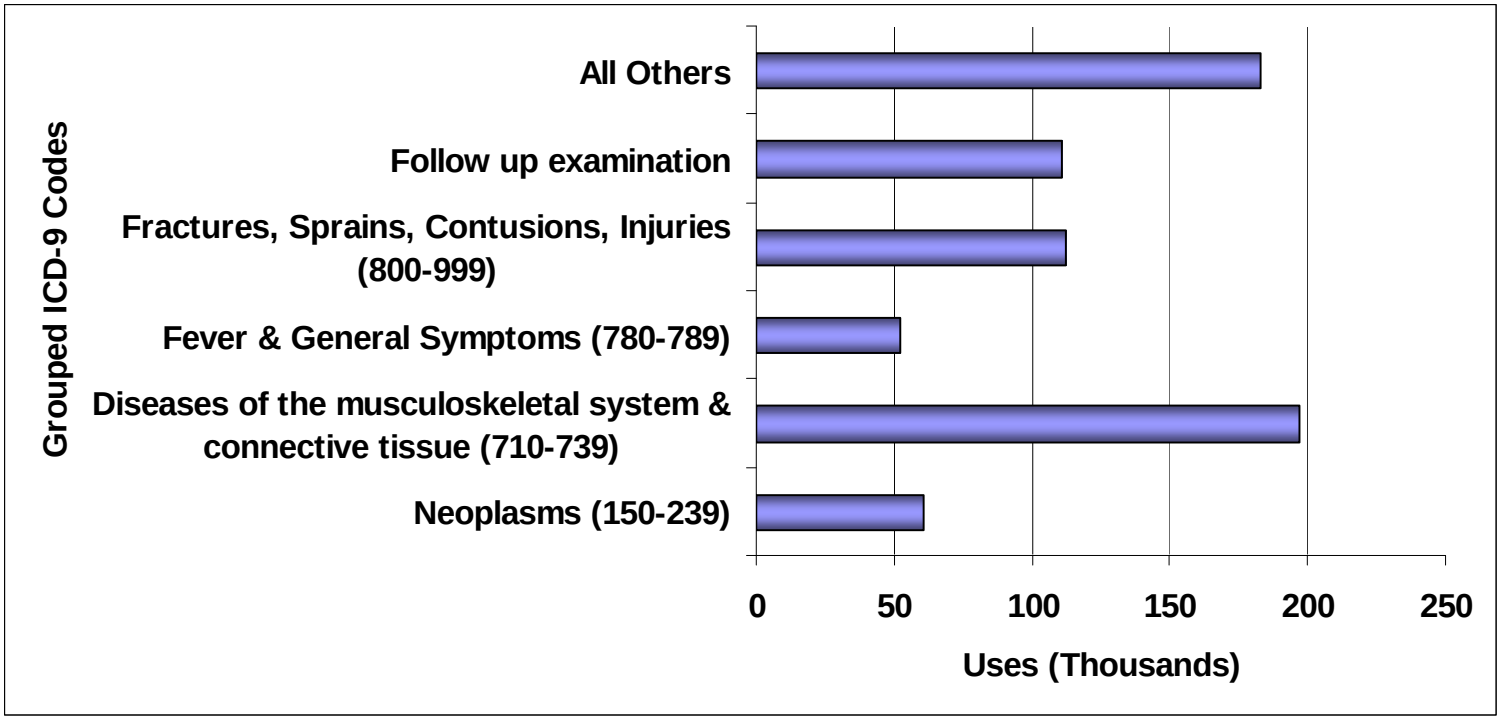


Office-based physician survey data
Years 2006-2008

SDI Physician Drug and Diagnosis Audit™ (PDDA™)

Diagnoses Associated with the Use of Hydromorphone products, Year 2008

Source: SDI Physician Drug and Diagnosis Audit, Extracted June 2009



Summary

- **For years 2006-2008, approximately 4.9 million hydromorphone prescriptions were dispensed to 1.7 million patients in the outpatient retail pharmacy setting**

- **Total dispensed prescriptions for hydromorphone products increased 34% between years 2006 and 2008, however these products accounted for only 1% of the selected opioid market share in Year 2008**

- **Top 5 prescribing specialties for hydromorphone: GP/FM/DO, IM, Anesthesiology, EM, and PM&R**

Summary

- **Top three grouped ICD-9 diagnoses codes associated with the use of hydromorphone:**

1. **Musculoskeletal system & connective tissue (27.2%)**
2. **Fractures, Sprains, Contusions, and Injuries (15.5%)**
3. **Follow up examination (15.4%)**

Back-up Slides

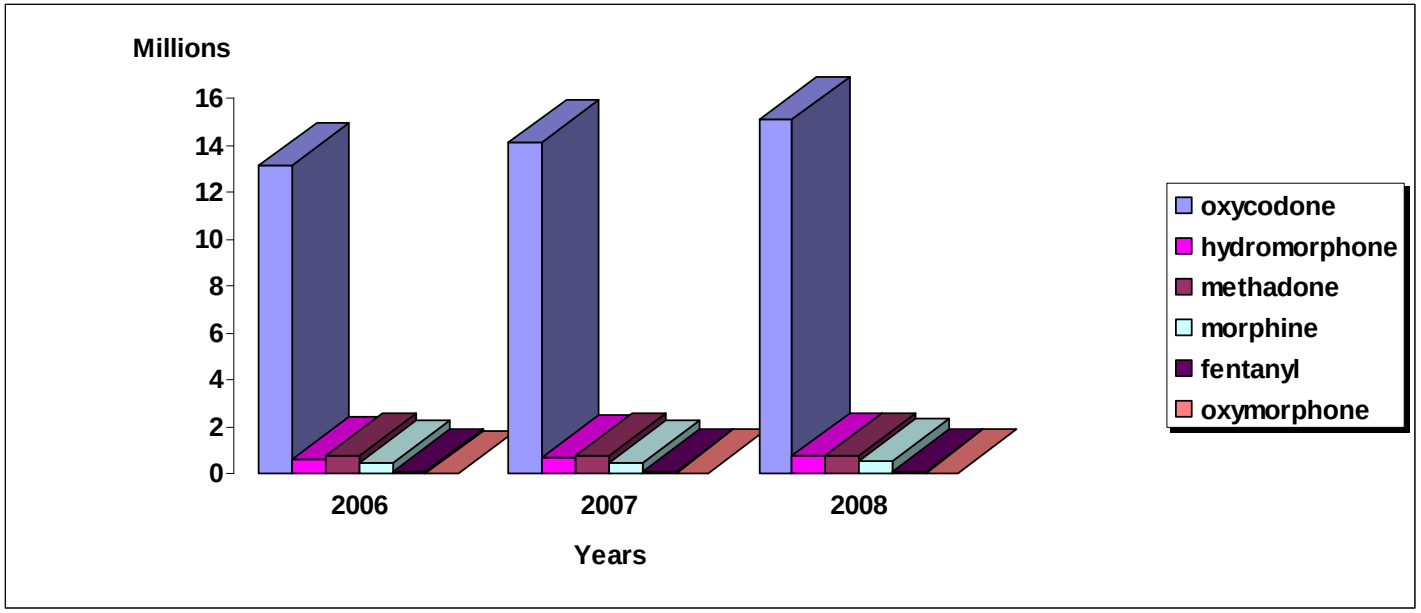
Patient-Level Data

Years 2006-2008

SDI Vector One®: Total Patient Tracker (TPT)

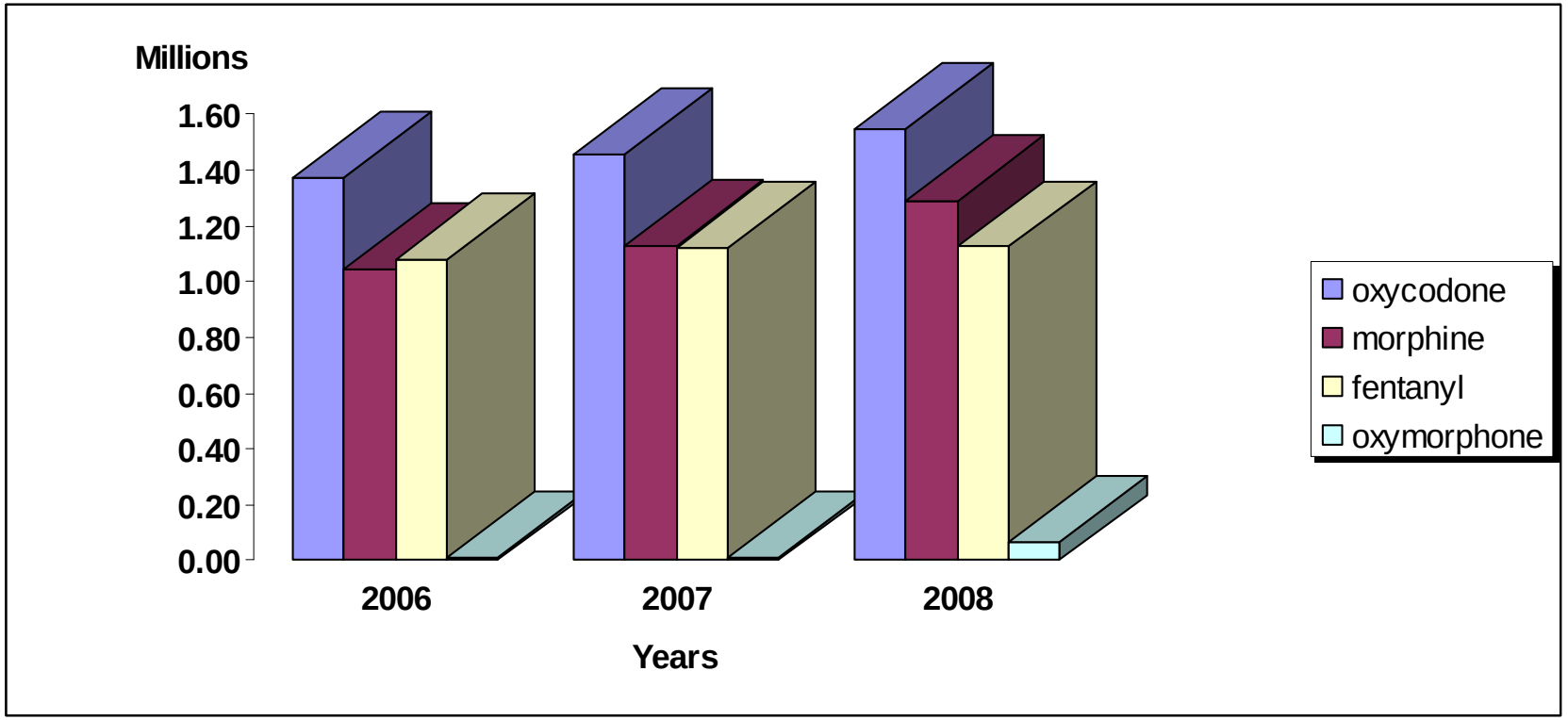
Total projected patients through U.S. outpatient retail pharmacies for immediate-release opioid pain products and hydromorphone, Years 2006 – 2008

SDI Total Patient Tracker, Extracted 8-2009



Total projected patients through U.S. outpatient retail pharmacies for extended-release opioid pain products, Years 2006 – 2008

SDI Total Patient Tracker, Extracted 8-2009



Findings from the Drug Abuse Warning Network (DAWN)

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

Overview

- Background
- Initial findings
- Methods
- Summary of calculations
- Conclusions

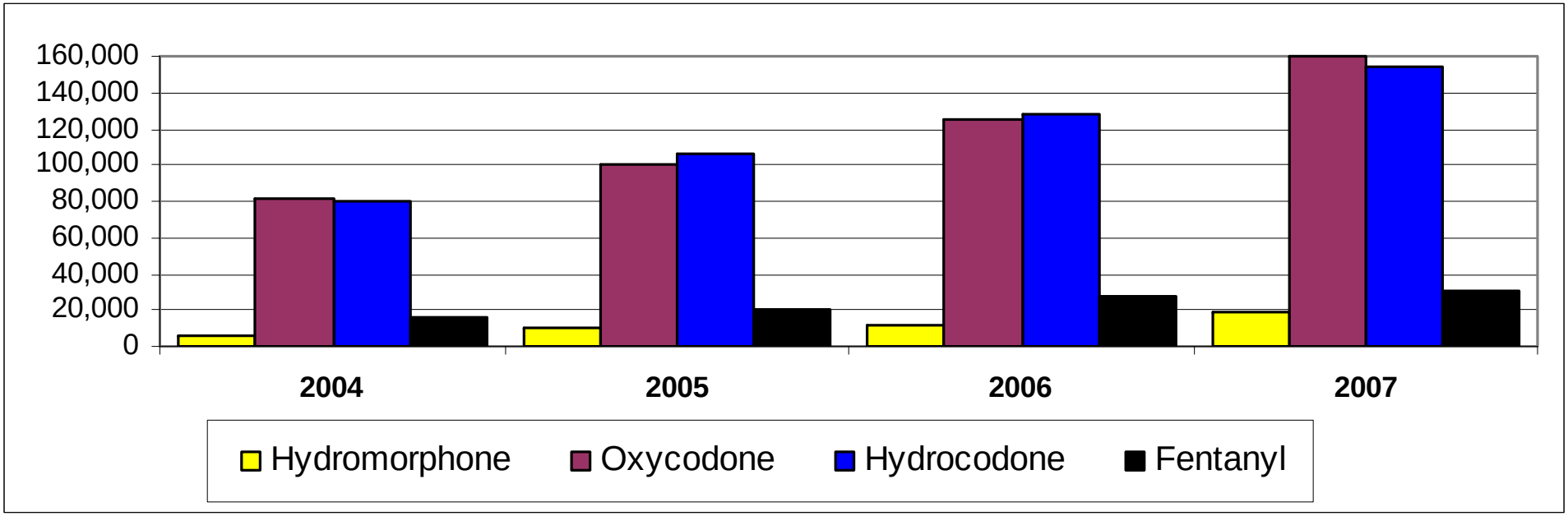
Drug Abuse Warning Network (DAWN)

- Administered by the Substance Abuse and Mental Health Services Administration (SAMHSA)
- Stratified probability sample of hospitals
  - Short-term, general, non Federal hospitals with 24-hour emergency departments (EDs)
- National estimates account for:
  - Sample design
  - Hospital non-response
  - Partial non-response in responding hospital

Selection of Comparator Drugs

- Opioid Analgesic products were selected that included both immediate and extended release formulations
  - Oxycodone (IR & ER)
  - Morphine (IR & ER)
  - Oxymorphone (IR & ER)
  - Fentanyl (transdermal & transmucosal)
  - Hydrocodone (IR only)
- Relative Standard Errors (RSE) were greater than 50 for oxymorphone and fentanyl mucosal products so estimates were suppressed
- Estimates for morphine products were not used, due to “false positives” in toxicology screen

DAWN: Number of Drug Related ED Visits by Drug Type and Year

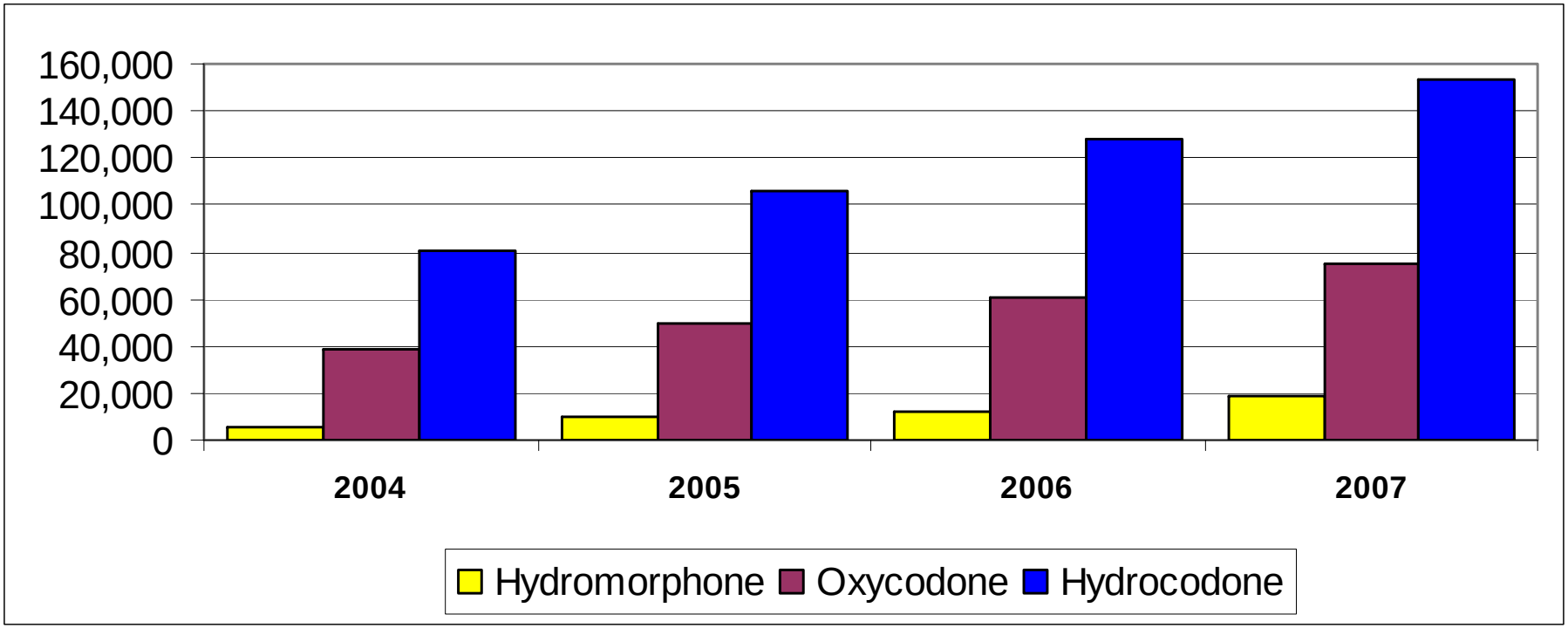


Includes all formulations

Fentanyl products are transdermal

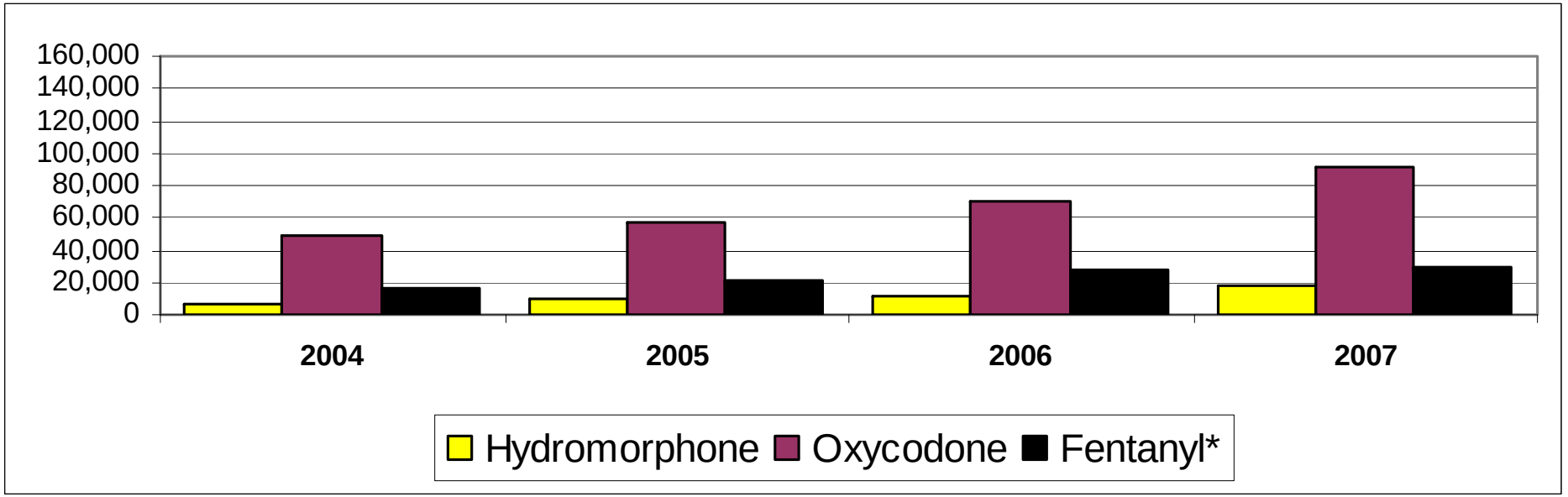
Source: DAWN 2004-2007, SAMHSA

DAWN: Number of Drug Related ED Visits by Year for Immediate Release Opioids



Source: DAWN 2004-2007, SAMHSA

DAWN: Number of Drug Related ED Visits by Year for Extended Release Opioids



Source: DAWN 2004-2007, SAMHSA

* Fentanyl products are transdermal

DAWN: All Drug Related ED Visits

- **Type of case**
  - Suicide Attempt
  - Seeking detox
  - Adverse Reaction
  - Overmedication
  - Malicious poisoning
  - Accidental Ingestion
  - Other
- **Case Disposition**
  - Discharged Home
  - Released to police/jail
  - Referred to detox/treatment
  - Admitted to:
    - ICU/Critical Care
    - Chemical dependency/detox
    - Psychiatric Unit
    - Other inpatient Unit
  - Transferred
  - Left Against Medical Advise (AMA)
  - Died

NMUP & ALLMA Case Types

- SAMHSA constructed definitions
- **NMUP** – non-medical use of pharmaceuticals includes overmedication, seeking detox, “other”
- **ALLMA** – all misuse/abuse -- this classification includes all NMUP ED visits plus ED visits where there were illegal drugs or alcohol present

DAWN: Proportion of ED Cases Related to NMUP and ALLMA by Drug Type, 2004 - 2007

	NMUP	ALLMA
Drug Name	**% of all cases**	**% of all cases**
Hydromorphone IR (n= 46,089)	**53%**	**58%**
Oxycodone/combinations		
Immediate release (n= 223,357)	46%	54%
Extended Release (n= 266,910)	54%	67%
Hydrocodone IR (n= 468,247)	45%	52%
Fentanyl/transdermal (n= 95,059)	56%	58%

Source: DAWN 2004-2007, SAMHSA

Case Disposition

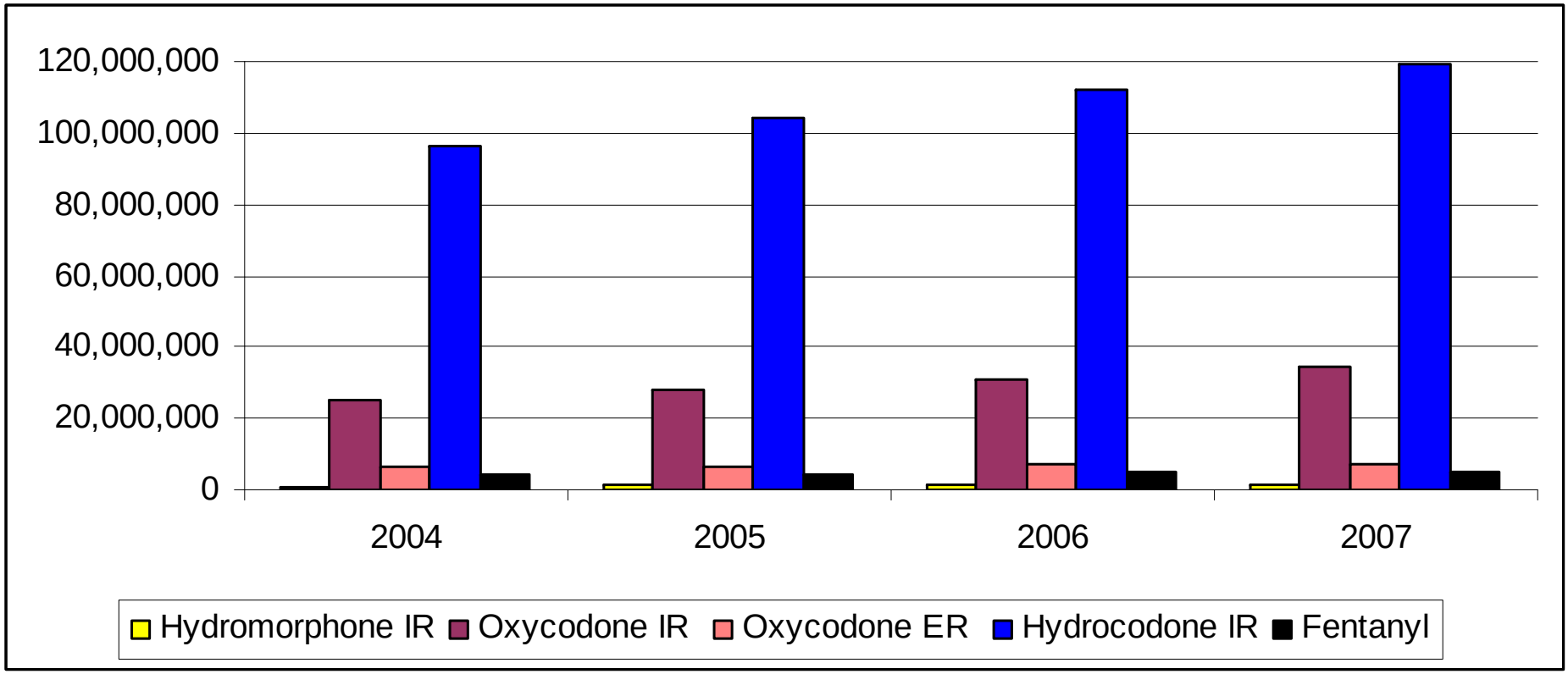
- **Required Follow-up**
  - Admitted to
    - ICU/Critical Care
    - Chemical dependency/detox
    - Psychiatric Unit
    - Other inpatient Unit
  - Transferred
- **Did not require follow-up**
  - Discharged home
  - Left against medical advice (AMA)

DAWN: Proportion of ED Cases that required follow-up by Drug Type, 2004 - 2007

	% of Total Cases
Hydromorphone IR (n=46,066)	**37%**
Oxycodone/combinations	
Immediate release (n=223,357)	33%
Extended Release (n= 266,910)	44%
Hydrocodone (n= 468,247)	33%
Fentanyl/Transdermal (n= 93,645)	39%

Source: DAWN 2004-2007, SAMHSA

Number of Retail Prescriptions by Drug and Release Type, 2004 - 2007



Source: SDI Vector One®: National (VONA). Extracted Aug 2009

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

NMUP Ratio: Number of NMUP ED Visits per 10,000 Retail Prescriptions 2004 – 2007

NMUP Ratios	2004	2005	2006	2007
Hydromorphone IR	**34.6**	**39.7**	**48.8**	**58.7**
Oxycodone IR	7.2	8.7	9.2	9.5
Oxycodone ER	38.4	44.3	46.9	51.6
Hydrocodone IR	4.1	4.5	5.1	5.5
Fentanyl Transdermal	23.5	25.8	33.1	30.4

Sources: National estimates from DAWN, 2004-2007; SDI Vector One®: National (VONA).

ALLMA Ratio: Number of ALLMA ED Visits per 10,000 Retail Prescriptions 2004 –2007

ALLMA Ratios	2004	2005	2006	2007
Hydromorphone IR	**40.9**	**41.9**	**53.5**	**62.7**
Oxycodone IR	8.7	10.0	10.6	11.3
Oxycodone ER	43.6	50.5	59.7	67.5
Hydrocodone IR	4.8	5.3	5.9	6.5
Fentanyl Transdermal	24.4	27.1	34.4	31.9

Sources: National estimates from DAWN, 2004-2007; **SDI Vector One®: National (VONA).**

Limitations

- Calculating abuse ratios using different data sources for numerator and denominator estimates has limitations
  - Data are not linked
    - DAWN
    - SDI Vector One®: National (VONA)
  - Sampling Methodologies
    - DAWN
    - SDI Vector One®: National (VONA) -
  - Populations
    - DAWN -
    - SDI Vector One®: National (VONA)
  - Large numbers produce more precise estimates,
    - i.e. small estimates have larger confidence intervals

Summary

- Prescription data can serve as a proxy for drug availability and provides context for non-medical use.
- The non-medical use of pain relievers derived from DAWN provides information on the public health burden of non-medical use of opioids.
- Non-medical use of pain relievers derived from DAWN continue to increase from 2004 through 2007.
- Prescription drug use of opioids also continues to rise (years 2004 -2007)

Conclusion

- Overall, abuse ratios of non-medical use (NMUP) and abuse (ALLMA) of opioids are higher for extended release opioid products versus immediate release opioid products
- However the abuse ratios (NMUP & ALLMA) for hydromorphone products are higher than for other immediate release opioid products and lower than for extended release opioid products

Abuse Liability of Exalgo
OROS Hydromorphone Extended Release Tablets

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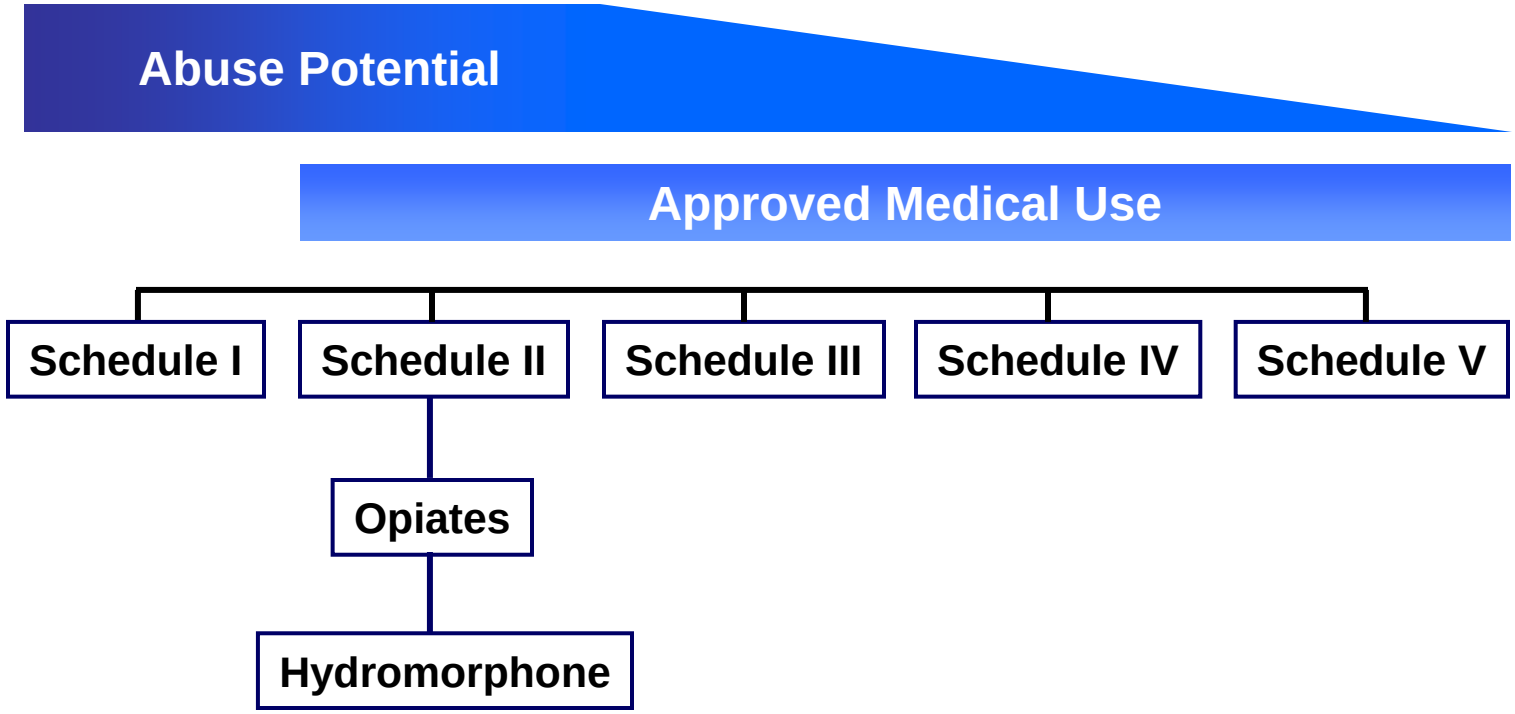
Controlled Substance Staff
Center for Drug Evaluation and Research
Food and Drug Administration

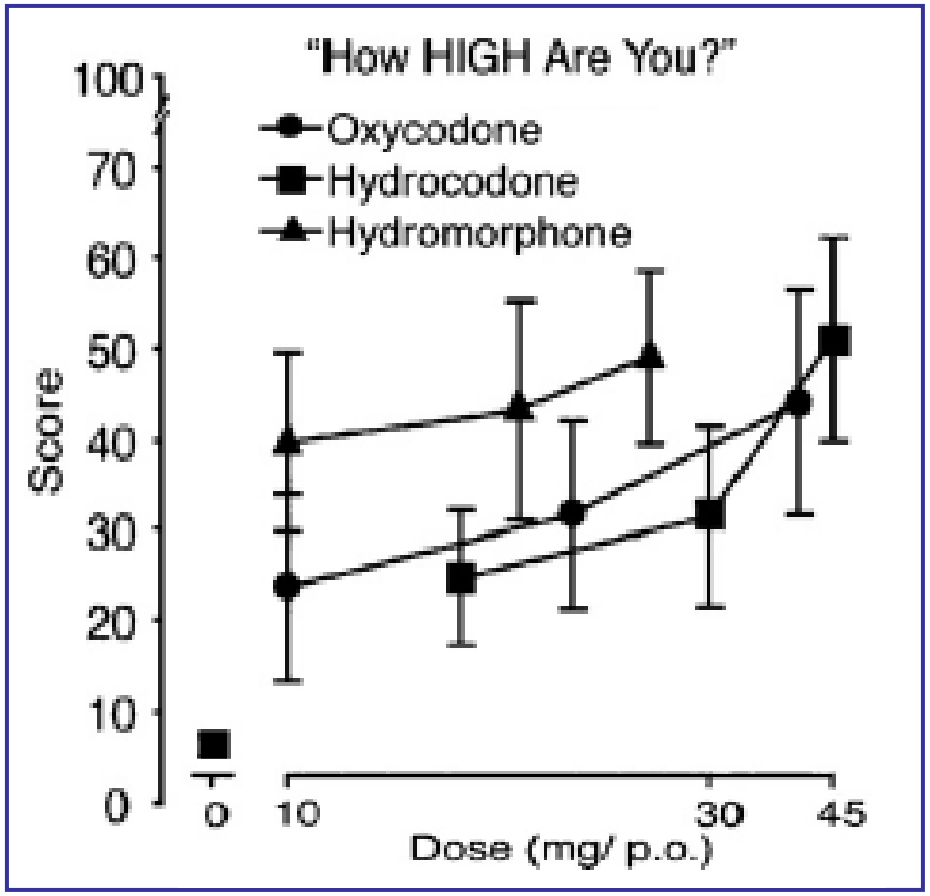
ALSDAC
September 23, 2009

Hydromorphone: Schedule II (CII) under the Controlled Substances Act (CSA)



Hydromorphone: Drug Abuse Potential

***Walsh et al.* Drug and Alcohol Dependence 98 (2008) 191–202**



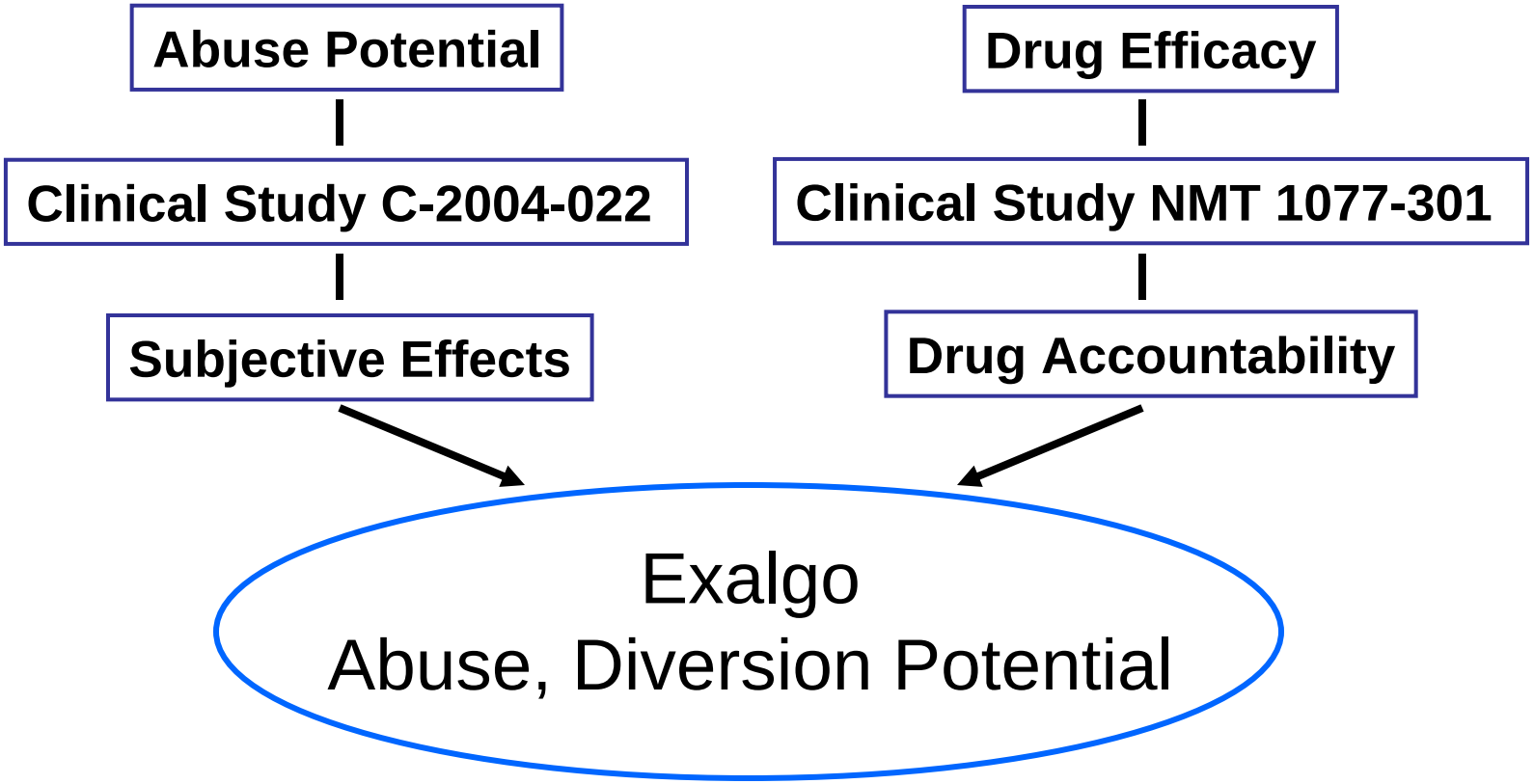
Methods:

- **Opioid-abusing volunteers (*n* = 9)**
- **Oral Administration**
- **Oxycodone (10, 20 and 40 mg)**
- **Hydrocodone (15, 30 and 45 mg)**
- **Hydromorphone (10, 17.5 and 25 mg)**
- **Subjective & objective measures**

Conclusion:

Hydromorphone was modestly more potent (less than two-fold) than either hydrocodone or oxycodone.

Exalgo
A Formulation of Hydromorphone



Abuse Potential Clinical Trial (Study C-2004-022)

Purpose: Evaluate the Abuse Potential of Exalgo Compared to Hydromorphone Immediate Release (IR) in Opiate-Experienced Non-dependent Volunteers.

Screening	Phase A	Phase B
n=64	n=38	n=29
■ **Hydromorphone IR 8 mg (intact)** ■ **Placebo**	■ **Hydromorphone IR 8 mg (intact)** ■ **Placebo** ■ **Exalgo 8 mg (Altered)*** ■ **Exalgo 16 mg (intact)** ■ **Exalgo 32 mg (intact)**	■ **Hydromorphone IR 8 mg (intact)** ■ **Exalgo 64 mg (intact)**

* Dosage form manipulated by the sponsor to overcome the extended-release properties of Exalgo

Pharmacokinetics
Plasma Concentration Profiles

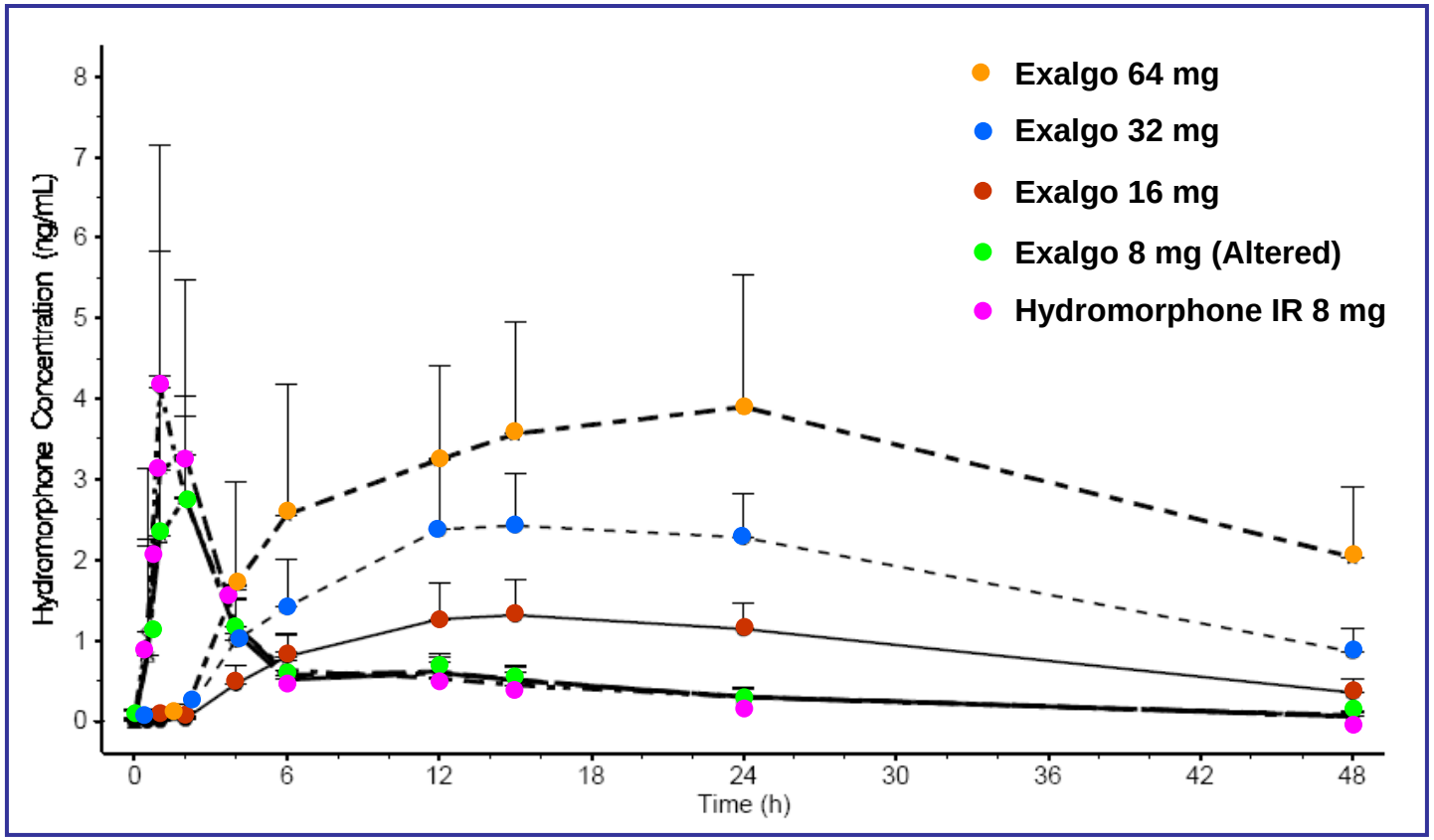
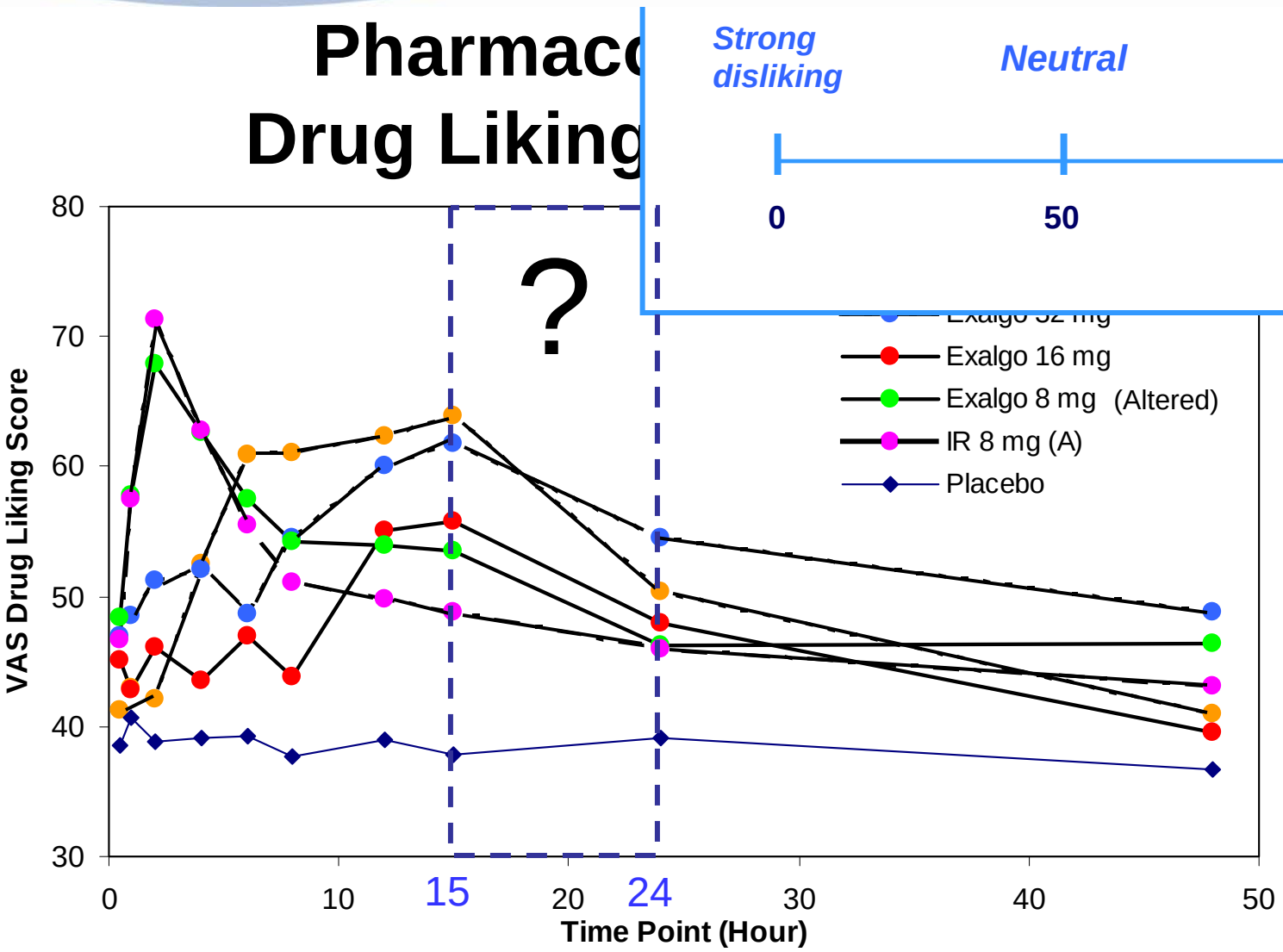
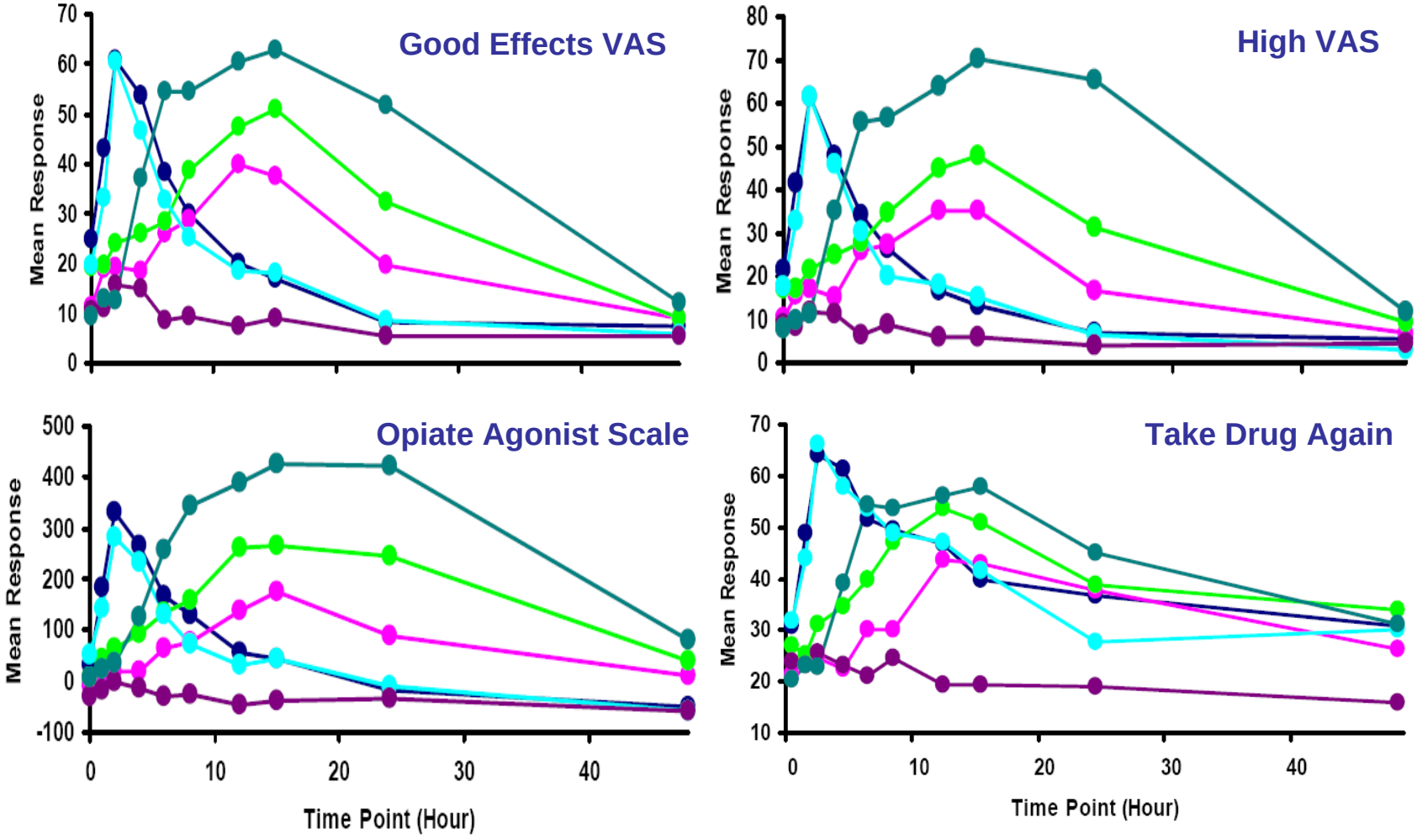


Figure 11.5.3.2.1 from NDA 21-217

Pharmacc
Drug Liking



Similar to Figure 11.5.3.1.6 from NDA 21-217


Good Effects VAS
High VAS
Opiate Agonist Scale
Take Drug Again
Mean Response
Time Point (Hour)
IR 8 mg (A)
Exalgo 8 mg (Altered)
Exalgo 16 mg
Placebo
Exalgo 32 mg
Exalgo 64 mg

Clinical Efficacy Study NMT 1077-301

A Phase III, variable-dose titration followed by a randomized double-blind study of controlled-release Exalgo compared to placebo in patients with chronic low back pain.

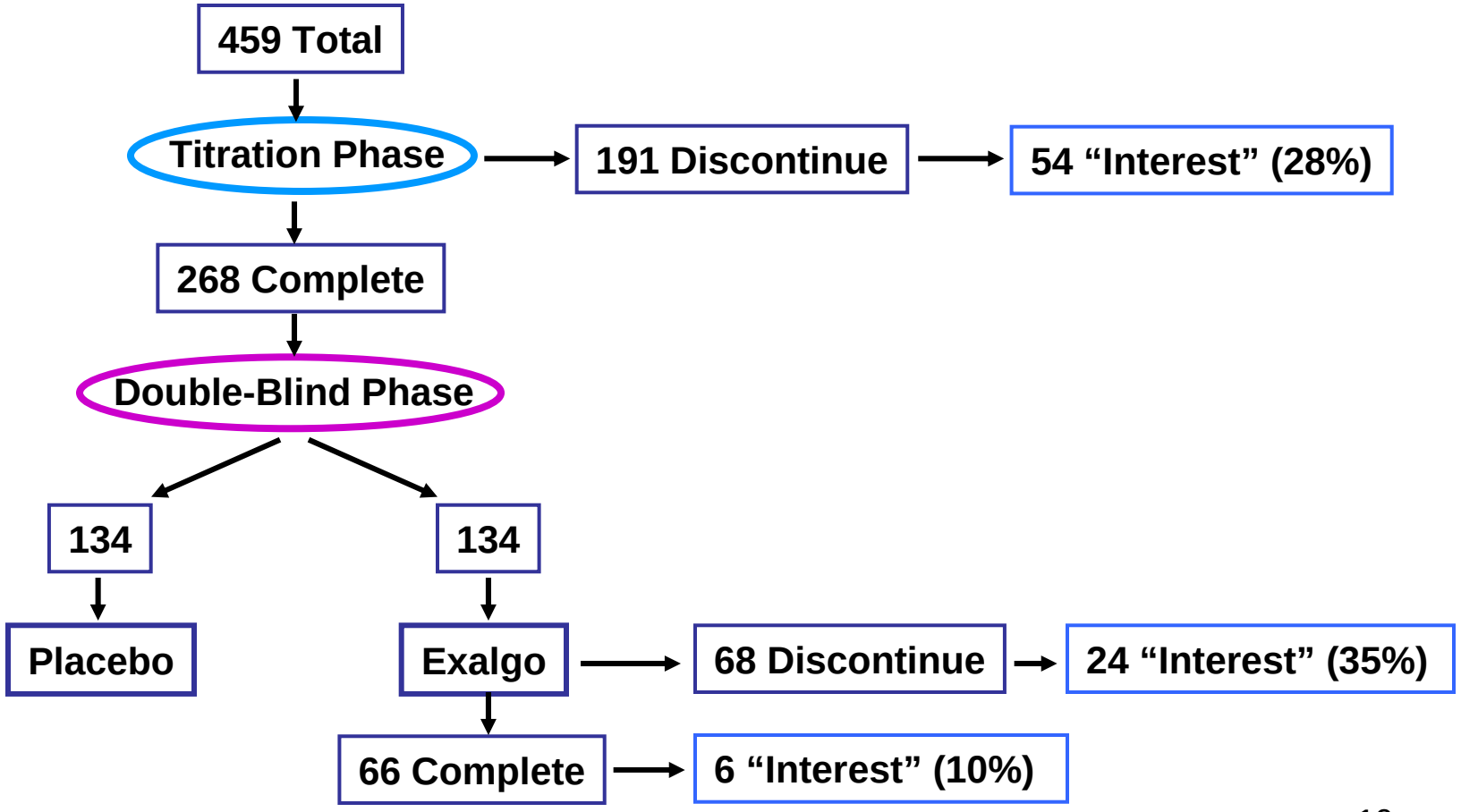
Data the Sponsor Provided:

Narratives for 84 patients who had study medication accountability discrepancies and are considered Patients of Interest.

Issues to Address:

1. **What % of patients had drug unaccountability issue ?**
2. **What % of tablets were not accounted for ?**

CSS Analysis
% of Patient with Drug Unaccountability Issue



CSS Analysis
% Drug Missing

	# Dispensed	# Taken	# Should be Returned	# Returned	# Missing	% Missing
Total	9184	4751	4433	2817	1616	36%
Completed Patients	1852	1232	620	481	139	22%
Discontinued Patients	7332	3519	3813	2336	1477	39%
Conversion and Titration	3108	1229	1879	943	936	50%
Double Blind	4224	2290	1934	1393	541	28%

Conclusions

- Hydromorphone has a high abuse potential at least comparable or slightly higher than oxycodone.
- The PK/PD profile of altered Exalgo 8 mg is similar to that of hydromorphone IR 8 mg.
- Exalgo has a high abuse potential as indicated by the intensity and duration of the positive subjective effects.
- The sponsor's data indicate a high level of drug unaccountability.

In summary, these data are predictive of high levels of abuse and diversion of Exalgo.

Risk Management of Opioids

Anesthetic Life Support Drugs and Drug Safety and Risk Management Advisory Committees

September 23, 2009

Jeanne Perla, Ph.D.
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Division of Risk Management

Outline

- Review of Risk Evaluation and Mitigation Strategies (REMS)
  - History of Food and Drug Administration Amendments Act (FDAAA)
  - Elements of REMS
- FDA's Opioid REMS initiative
- Approved Opioid REMS
  - Onsolis
  - Embeda
- Summary

Food and Drug Administration Amendments Act (FDAAA) Title IX – Drug Safety

- New authorities:
  - Require post-marketing studies and clinical trials
  - Require sponsors to make safety related labeling changes
  - Require sponsors to develop and comply with risk evaluation and mitigation strategies
- Subtitle A took effect March 25, 2008

REMS

- A required risk management plan, as specified in FDAAA, beyond routine professional labeling to ensure the benefits of a drug outweigh the risks

- Is enforceable and included with the approval letter

REMS Elements

May include one or more of the following:

- **Medication Guide or Patient Package Insert**
  - FDA approved patient labeling
- **Communication Plan**
  - FDA approved materials to aid sponsor's implementation of REMS and inform healthcare providers about serious risk(s)

REMS Elements

- **Elements to Assure Safe Use**
  - Prescriber training or certification
  - Certification of dispensers
  - Drug dispensing restricted to certain health care settings
  - Documentation of safe use prior to dispensing
  - Monitoring of patients
  - Enrollment of patients in a registry

REMS
Elements to Assure Safe Use

Must:

- Be commensurate with specific serious risks listed in the labeling
- Not be unduly burdensome on patient access to the drug
- As much as possible, conform with elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs

Management of Opioid Risks

Agency concerns include:

- Increased abuse, misuse, addiction and accidental overdose associated with long-acting and extended-release opioids
- Previous voluntary risk management programs have been ineffective in addressing these risks.
  - Most involved voluntary education to healthcare providers (HCPs) and patients

Opioid REMS Meetings

- Early 2009 the Agency notified sponsors that a REMS would be required for certain opioids.
- Provided an opportunity for sponsors, stakeholders and interested persons to present comments and information on:
  - the elements of a REMS program
  - how to minimize the burden of multiple REMS programs on the health care community and patients while ensuring the benefits outweigh the risks
  - how FDA should assess the effectiveness of the REMS

Considerations of Opioid REMS

- Multiple opioid REMS programs have the potential to:
  - cause a burden on the healthcare system
  - make it difficult for prescribers and other HCPs who dispense medication to be fully aware of each program
  - limit patient access to appropriate opioid pain management

Single Shared Opioid REMS

- Because of multiple opioid products with similar risks, manufacturers of long-acting and extended-release opioid formulations were urged to develop a single shared REMS.
- The manufacturers have formed an Industry Working Group

Where Are We Now?

- Completed several public and stakeholder meetings
- Received numerous submitted comments
- FDA is reviewing these comments
- Considering next steps
- Currently no approved single shared opioid system

Currently Approved REMS

Onsolis*

- A transmucosal fentanyl product
- Indicated for the treatment of breakthrough pain in cancer patients who are also receiving and are tolerant to opioid therapy
- Not included in the single shared opioid REMS
  - Additional risks compared to the immediate and extended release opioids

*Approved July 16, 2009

Approved Onsolis REMS

Restricted program - Focus™

- Medication Guide
- Communication Plan
- Elements to Assure Safe Use
  - Required education and enrollment:
    - prescribers
    - specialty pharmacies
    - patients

Approved Onsolis REMS

- Implementation System
  - Special certification and enrollment of distributors
  - Maintain database of enrolled entities
  - Monitor distribution
  - Monitor dispensing by specialty pharmacies
  - Monitor, audit, and evaluate all active pharmacies, distributors
  - Monitor and evaluate Program, work to improve implementation of these elements
- REMS Assessment
  - Every 6 months for 1 year then annually

Embeda*

- An extended-release (ER) morphine/naltrexone capsule
- Indicated for the management of moderate to severe pain when continuous around-the-clock opioid analgesic is needed for extended periods of time
- Risks similar to other ER opioids
- Will be included in the single shared opioid REMS

*Approved August 13, 2009

Approved Embeda Interim REMS

- Medication Guide
- Communication plan
- Elements to Assure Safe Use
  - None at this time
- REMS Assessment
  - Every 6 months for 1 year then annually

Summary

- FDA has new authorities to help address serious risks
  - Final REMS for opioids is still being developed
- Risk management should reduce identified risks while minimizing healthcare system burden and barriers to patient access
- Two different opioid REMS have been approved
  - Exalgo REMS should conform with elements for other drugs with similar serious risks