

FENTORA[®] (fentanyl buccal tablet) CII

United States Food and Drug Administration

**Joint Meeting of Anesthetic and Life Support Drugs and
Drug Safety and Risk Management Advisory Committees**

May 6, 2008

FENTORA[®] (fentanyl buccal tablet) CII Regulatory History and Overview

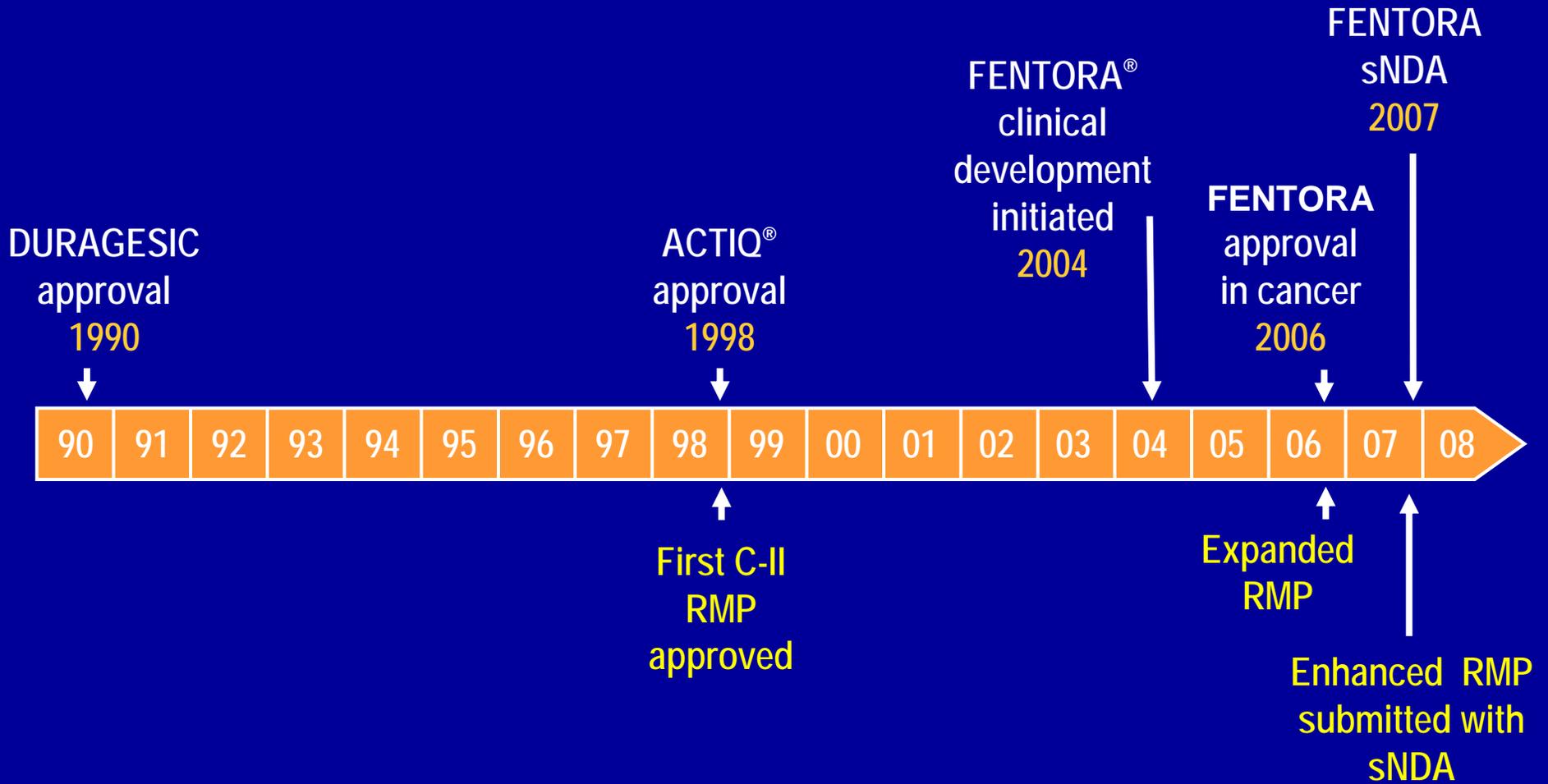
Eric A. Floyd, PhD

**Vice President, Worldwide Head Regulatory Affairs
Cephalon, Inc.**

Proposed Indication

FENTORA[®] is an opioid analgesic indicated for the management of breakthrough pain in patients who are taking around-the-clock opioid medications for their underlying persistent pain

Regulatory History



The Questions We Face Today

- ◆ Need for expanded indication
- ◆ The safe use of FENTORA[®] in the expanded patient population
- ◆ Manage the risks of overdose, abuse, and diversion

Overview of FENTORA[®] RiskMAP Strategy

- ◆ **Registration system**
 - Prevent risk of overdose
- ◆ **Controlled growth via controlled launch**
 - Mitigate the risks of abuse and diversion
- ◆ **Extensive surveillance**

Agenda for Presentation

Medical Need/ Breakthrough Pain

Perry G. Fine, MD
Professor of Anesthesiology
Pain Research Center
University of Utah, Salt Lake City

Efficacy

Mitigating Risk of Abuse and Diversion

John Messina, PharmD
Senior Director, Clinical Research
Cephalon, Inc.

Clinical and Postmarketing Safety

Mitigating Risk of Overdose

Juergen Schmider, MD, PhD
Corporate Safety Officer and Vice President
Global Pharmacovigilance and Epidemiology
Cephalon, Inc.

Closing Remarks

Lesley Russell, MBChB, MRCP
Executive Vice President and Chief Medical Officer
Cephalon, Inc.

Consultants

Sandra D. Comer, PhD
Columbia University

Nabarun Dasgupta, MPH
University of North Carolina, Chapel Hill

Aaron M. Gilson, PhD
U of Wisconsin, School of Medicine and Public Health

Howard Heit, MD, FACP, FASAM
Georgetown University

Robert N. Jamison, PhD
Harvard Medical School

Sidney H. Schnoll, MD, PhD
Pinney Associates

Addressing Treatment Needs of Patients With Breakthrough Pain: Optimizing Benefit and Minimizing Risk

Perry G. Fine, MD

Professor of Anesthesiology

Pain Research Center

University of Utah, Salt Lake City

Breakthrough Pain in Patients With Chronic Pain Is a Highly Relevant Clinical Problem

Opioids and Chronic Pain

- ◆ Opioid therapy is a component of comprehensive pain care for patients with chronic cancer and noncancer pain that is poorly responsive to other therapies
- ◆ Chronic pain has 2 components
 - Persistent pain
 - Breakthrough pain
 - In opioid-tolerant patients

Inclusion of Breakthrough Pain Within Prescribing Information

OXYCONTIN

(oxycodone HCl
controlled-release)

...Patients should be advised to report episodes of **breakthrough pain**...

...Patients who experience **breakthrough pain** may require dosage adjustment or rescue medication...

AVINZA

(morphine sulfate
extended-release)

...Is of most benefit when a constant level of opioid analgesia is used as a platform from which **breakthrough pain** is managed...

...In the event that **breakthrough pain** occurs, AVINZA may be supplemented with a small dose...of a short-acting analgesic...

DURAGESIC

(fentanyl
transdermal system)

...Some patients still may require periodic supplemental doses of other short-acting analgesics for **breakthrough pain**...

Breakthrough Pain—Definition

- ◆ Breakthrough pain (BTP) is typically defined as a transitory exacerbation of pain that occurs on a background of otherwise controlled chronic pain^a
- ◆ Patients entering the FENTORA[®] clinical program
 - Had chronic pain of ≥ 3 months' duration
 - Were opioid tolerant
 - Taking ≥ 60 mg of oral morphine/day, or an equianalgesic dose of another opioid for ≥ 7 days prior to enrollment

^a Portenoy RK, et al. *Pain*. 1990;41:273-281.

Breakthrough Pain Is Similar in Cancer and Noncancer Patients

Characteristic	Patients with cancer BTP n = 63	Patients with noncancer BTP n = 228
Prevalence	64%	74%
Frequency (median)	4 episodes/day	2 episodes/day
Onset to peak intensity	43% in 3 minutes	46% in 5 minutes
Duration (median)	30 minutes	60 minutes

Portenoy RK, et al. *J Pain*. 2006;7:583-591.

Portenoy RK, et al. *Pain*. 1990;41:273-281.

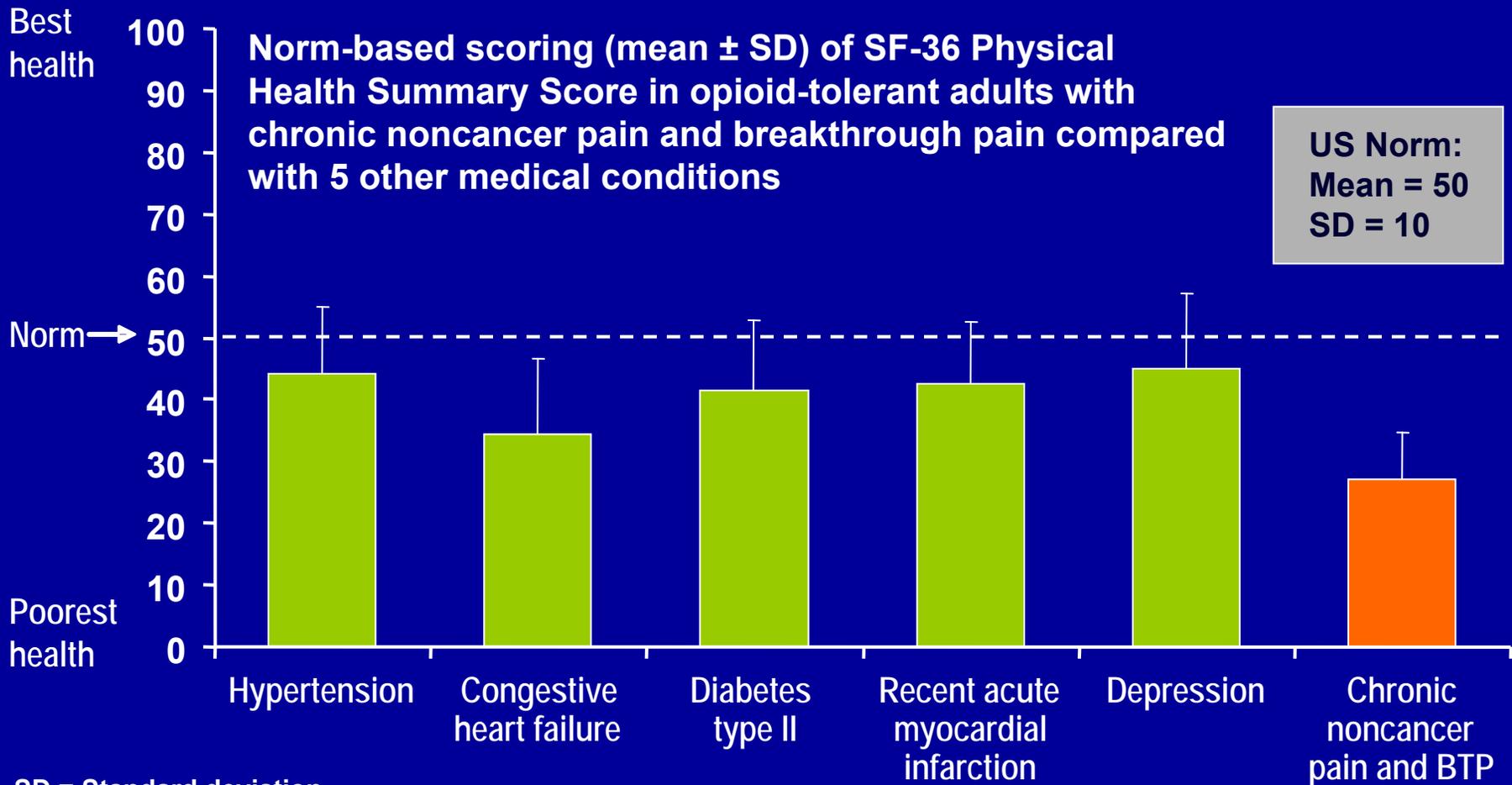
Cancer and Noncancer Chronic Pain Share Common Features

- ◆ The final pathways that lead to the perception of pain are common to chronic cancer and noncancer pain conditions

BTP pathophysiology	Cancer-related BTP n = 63	Noncancer-related BTP n = 228
Nociceptive somatic	33%	38%
Nociceptive visceral	20%	4%
Neuropathic	27%	18%
Mixed	20%	40%

No Medications Approved for the Management of Chronic Noncancer Breakthrough Pain

Quality of Life in Opioid-Tolerant Patients With Chronic Pain and Breakthrough Pain



SD = Standard deviation.

Chronic noncancer pain and breakthrough pain group, n = 941 patients entering FENTORA® clinical studies

Norm-based data for the 5 other medical conditions taken from Ware JE, et al. *SF-36 Physical and Mental Health Summary Scales: A User's Manual*. Boston, MA: Health Assessment Lab, 1994.

Evidence Supporting the Need for Effective Treatment of BTP in Opioid-Tolerant Patients With Chronic Noncancer Pain

Survey data

- ◆ 74% of patients with BTP
- ◆ 68% using short-acting opioids
- ◆ 65% reported inconsistent efficacy

Prescription data

- ◆ > 80% of FENTORA[®] is prescribed for noncancer BTP

Clinical trial data

At study entry

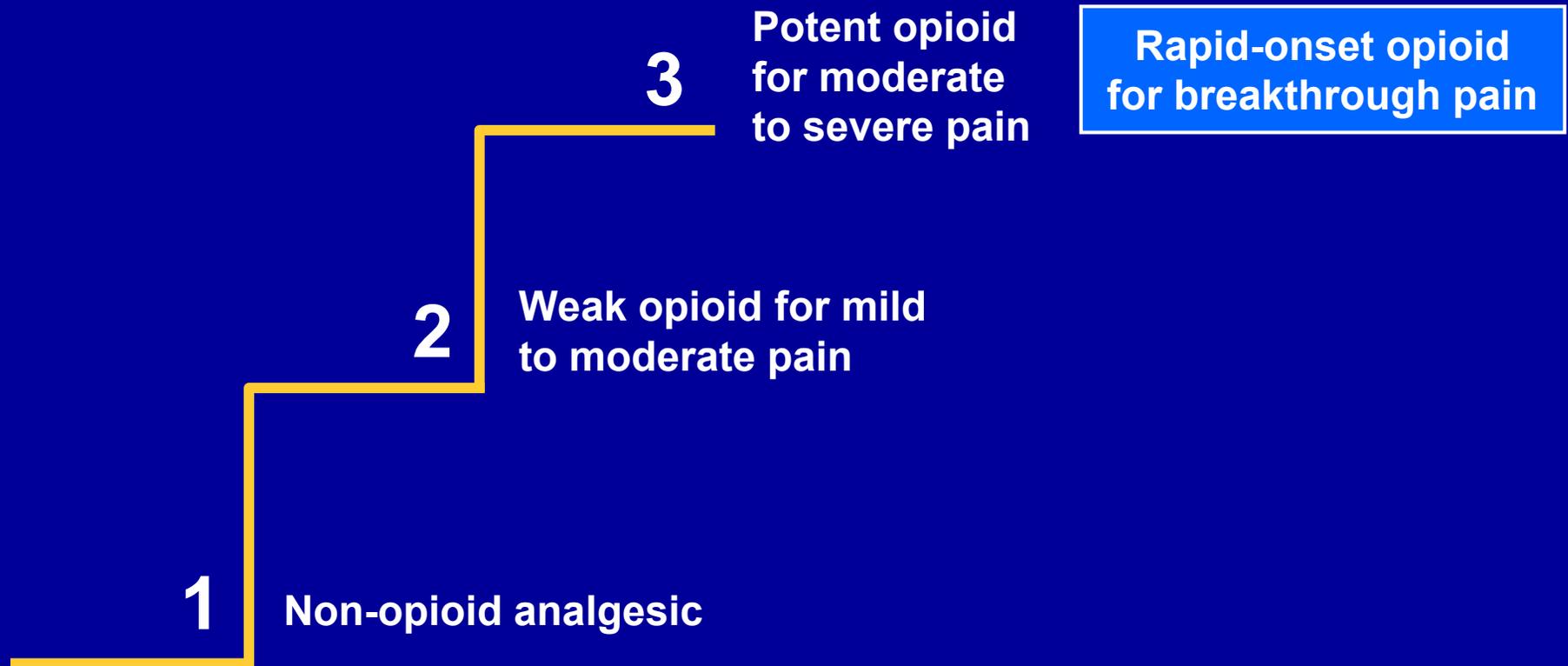
- ◆ All patients on short-acting opioids

At study end

- ◆ Proven efficacy for FENTORA in noncancer BTP in randomized, controlled trials
- ◆ > 70% of patients expressed a preference for FENTORA over previous rescue medication

Breakthrough Pain in Noncancer Chronic Pain Can Be Effectively Treated

Place of Supplemental Opioids in the Management of Chronic Pain



In Practice—Treating Breakthrough Pain With FENTORA[®]

Cancer diagnosis



Noncancer diagnosis



The Central Principle of Balance

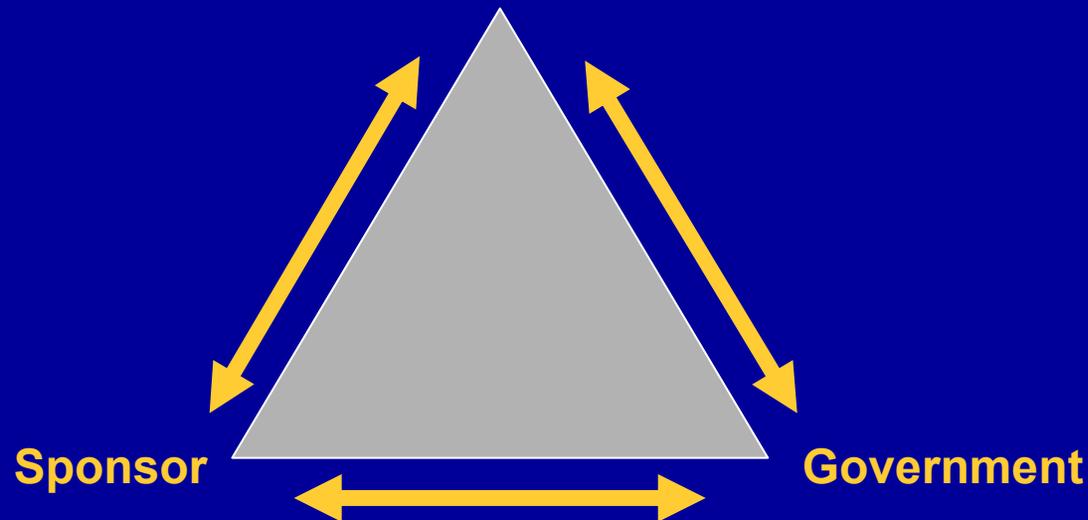
Medical availability

Opioid analgesics are essential and absolutely necessary for the relief of pain

Drug control

Controls are necessary to prevent abuse and diversion, but should not diminish medical usefulness or interfere with legitimate use

Healthcare professionals and patients



FENTORA[®] (fentanyl buccal tablet) CII Efficacy

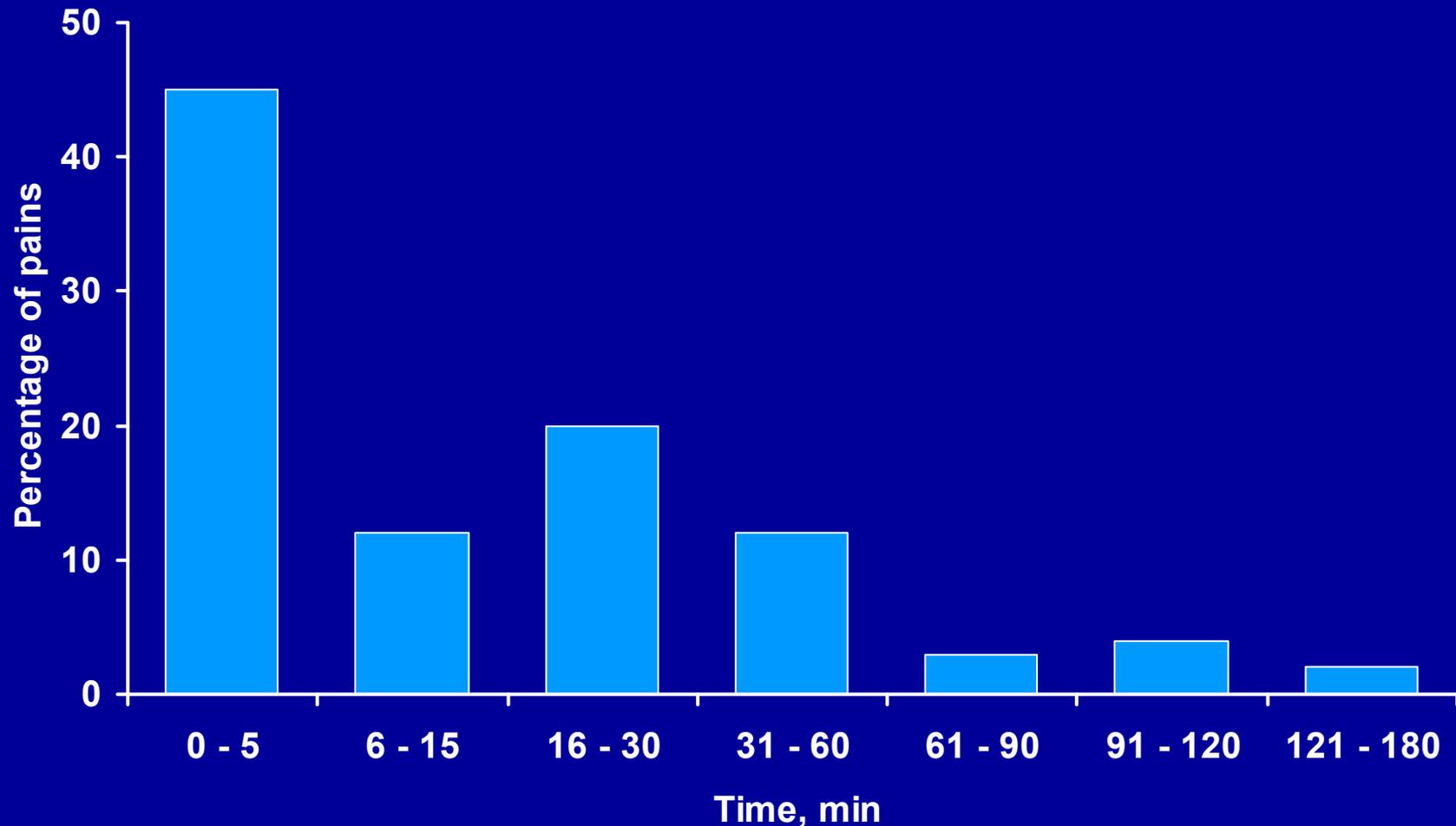
John Messina, PharmD

**Senior Director, Clinical Research
Cephalon, Inc.**

Rationale for FENTORA[®] Development Based on Experience With ACTIQ[®]

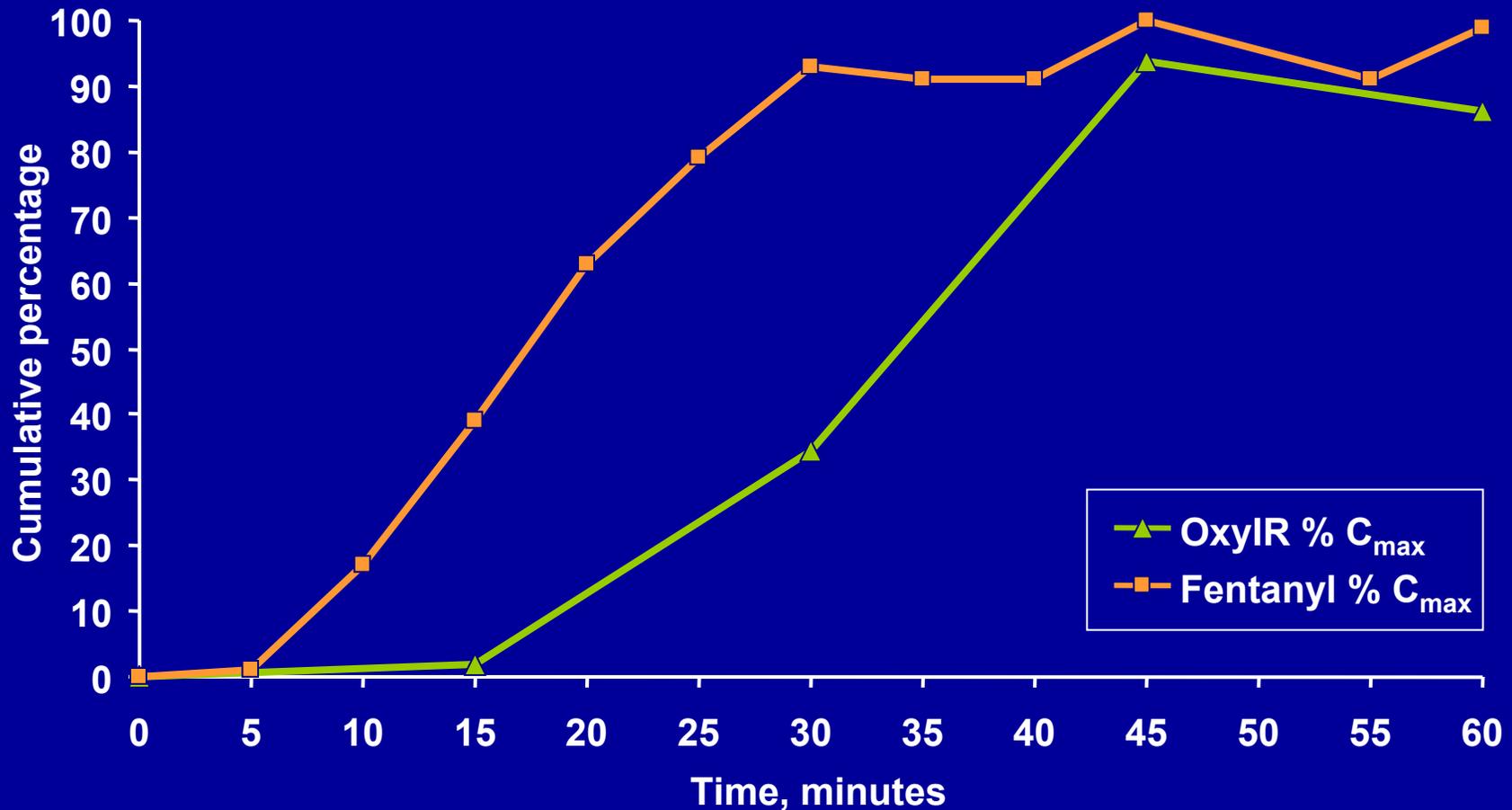
- ◆ ACTIQ used in treatment of noncancer-related BTP
- ◆ Clinical development program for cancer and noncancer BTP indications overlapped
- ◆ FENTORA—tablet designed to deliver fentanyl across oral mucosa more efficiently
- ◆ Pharmacokinetic profile more closely matches onset of BTP

Maximum Intensity of Breakthrough Pain Reached Rapidly



In total, 168 patients provided information about 189 episodes of BTP.
Portenoy RK, et al. *J Pain*. 2006;7:583-591.

Plasma Fentanyl Concentrations From FENTORA[®] More Closely Match Pattern of BTP



FENTORA pharmacokinetic data, N = 199.

Oxycodone data on file (N = 28): Cephalon, Inc. Report No. DP-2007-084.

First Clinical Program in Opioid-Tolerant Patients With Noncancer-Related BTP

- ◆ Data from four Phase 3 studies submitted with sNDA
 - 3 efficacy/safety (1 pivotal, 2 supportive)
 - Pivotal study assessed efficacy over 12 wk
 - One 18-mo, open-label, safety study
- ◆ Patients were using ATC opioids and treating BTP with opioid
- ◆ Patients began titration at lowest dose (100 mcg), and dose increased until successful dose found
- ◆ Efficacy assessed using within-patient design
 - Patients randomized to sequence of 9 treatments (6 FENTORA[®], 3 placebo) for double-blind periods

Study Population Reflective of Intended Population

Key patient characteristics	Total (N = 941)
Mean age (SD), yr	49 (10)
Women, %	57
Chronic pain condition, % (> 5%)	
Low back pain	55
Neuropathic pain	20
Traumatic injury	10
Complex regional pain syndrome	6
Osteoarthritis	6
Average pain of BTP episode	7/10

Population Characterized by Substantial Comorbidities

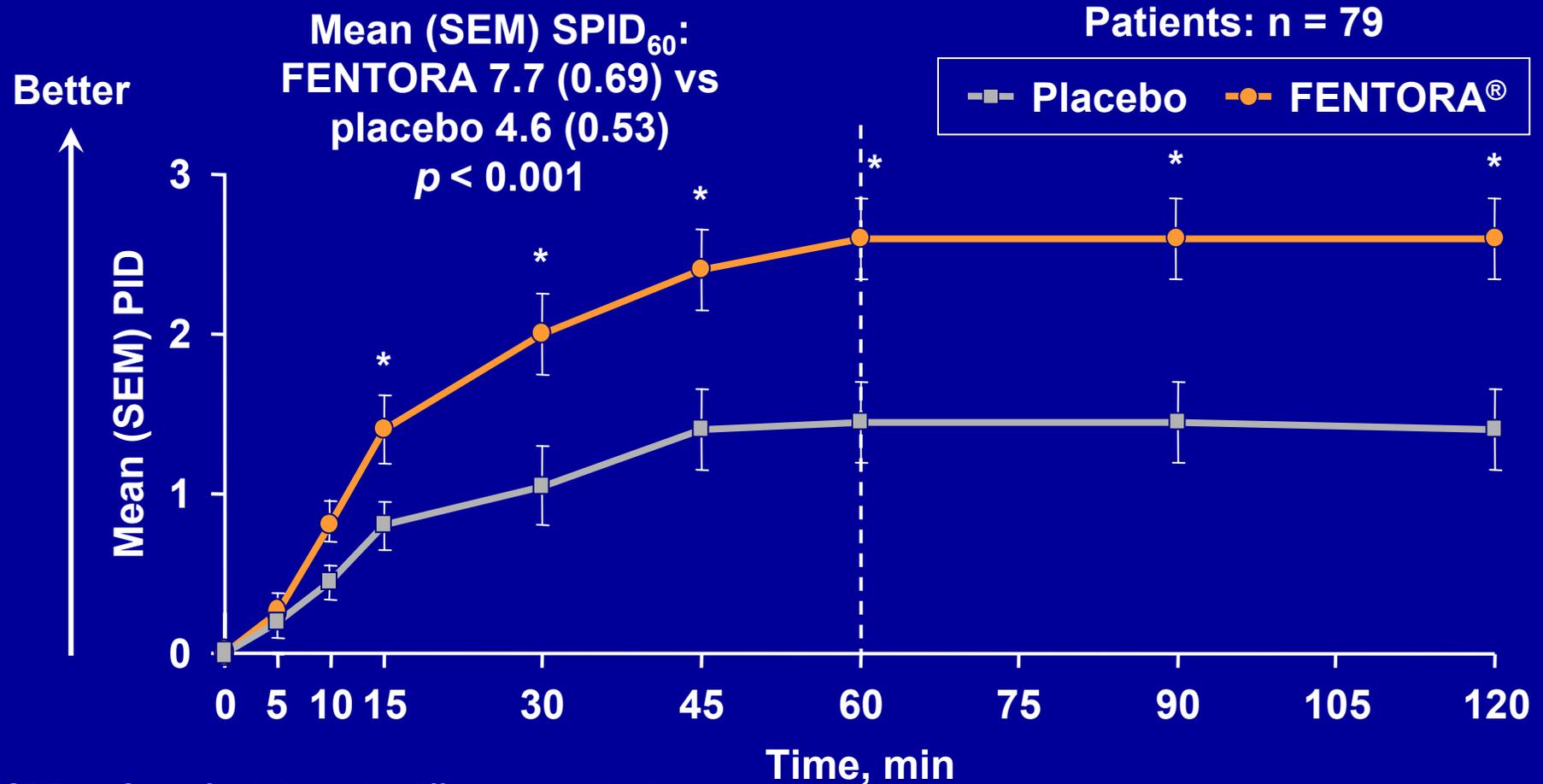
Category	Patients, n (%) N = 941
Musculoskeletal	928 (99)
Neurological	722 (77)
Gastrointestinal	704 (75)
Psychiatric	691 (73)
Genitourinary	554 (59)
Cardiovascular	550 (58)
Respiratory	373 (40)
Endocrine	329 (35)

Significant Doses of Opioid Being Used at Study Entry

Dose, mg	ATC medication		
	Oral opioids	Transdermal fentanyl	Intrathecal medications
ATC	n = 688	n = 223	n = 30
Mean (SD)	211.1 (210)	209.3 (140)	—
Rescue	n = 683	n = 220	n = 29
Mean (SD)	27.0 (27.3)	31.8 (102)	35.2 (47.6)

Reductions in BTP Intensity for 2 Hours

Pain intensity differences (PID) over time after 12 wk of treatment

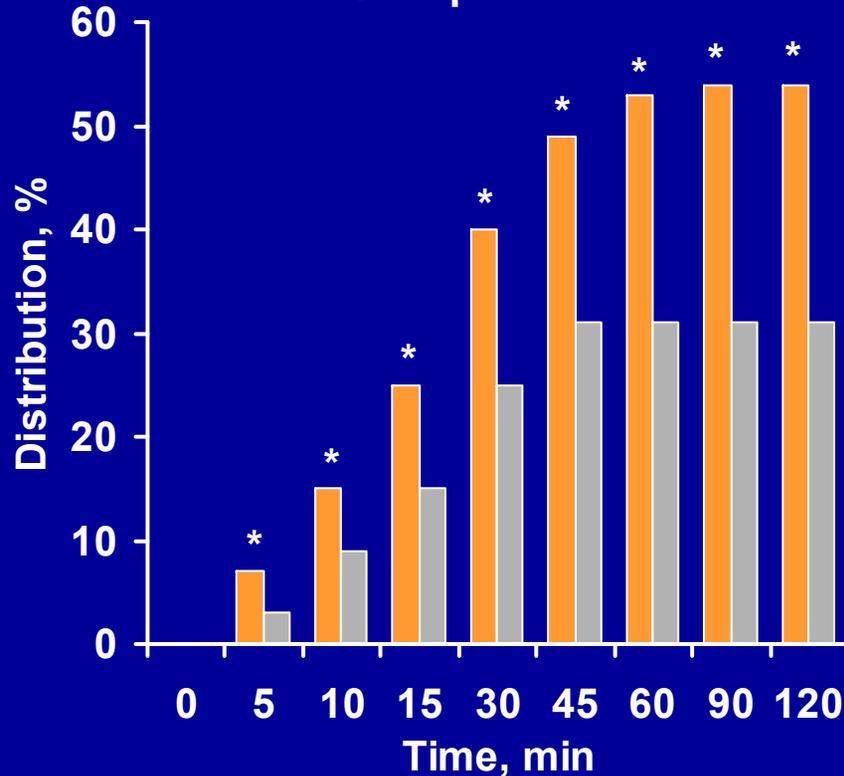


SPID₆₀ = Sum of pain intensity differences at 60 min.

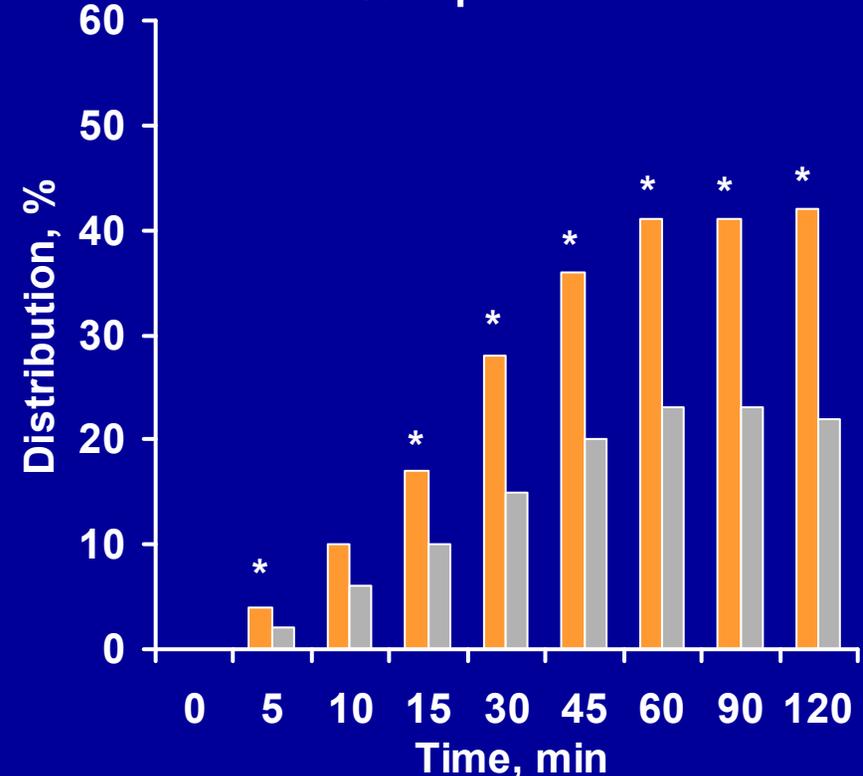
* Nominal $p < 0.05$ vs placebo ANOVA. Study 3052.

Clinically Significant Improvements in Pain Intensity Observed for 2 Hr

Percentage of episodes meeting response criteria after 12 wk of treatment
 $\geq 33\%$ improvement



$\geq 50\%$ improvement

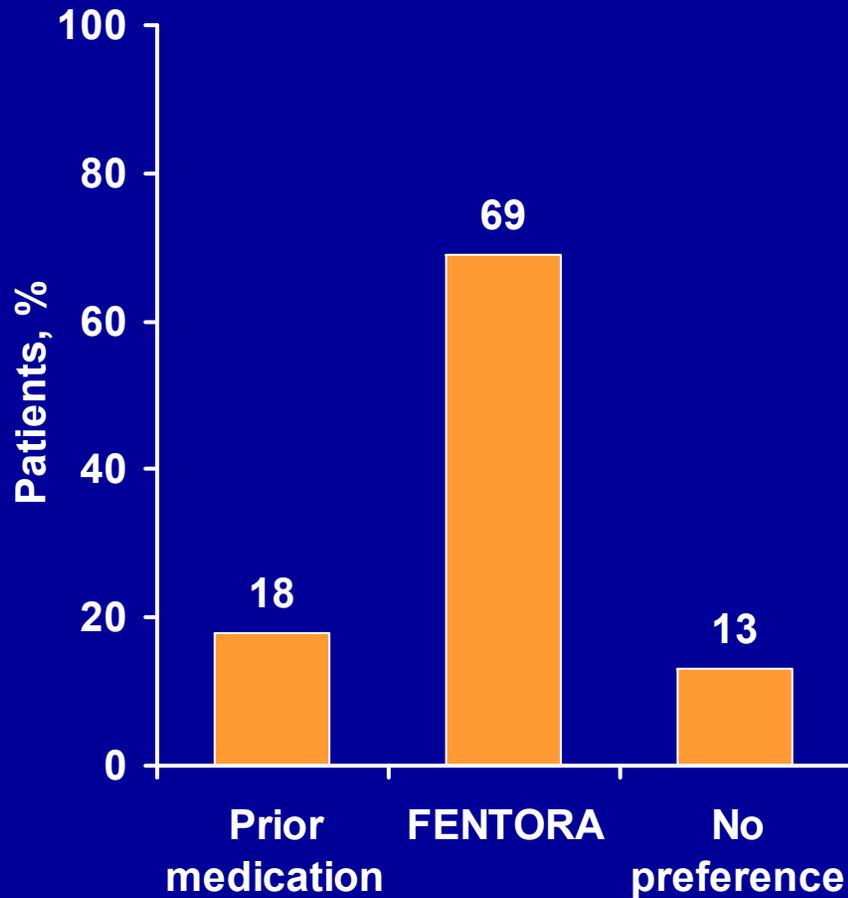


■ FENTORA® (n = 453 episodes)
 ■ Placebo (n = 226 episodes)

*Nominal $p < 0.05$ vs placebo GEE; Study 3052.

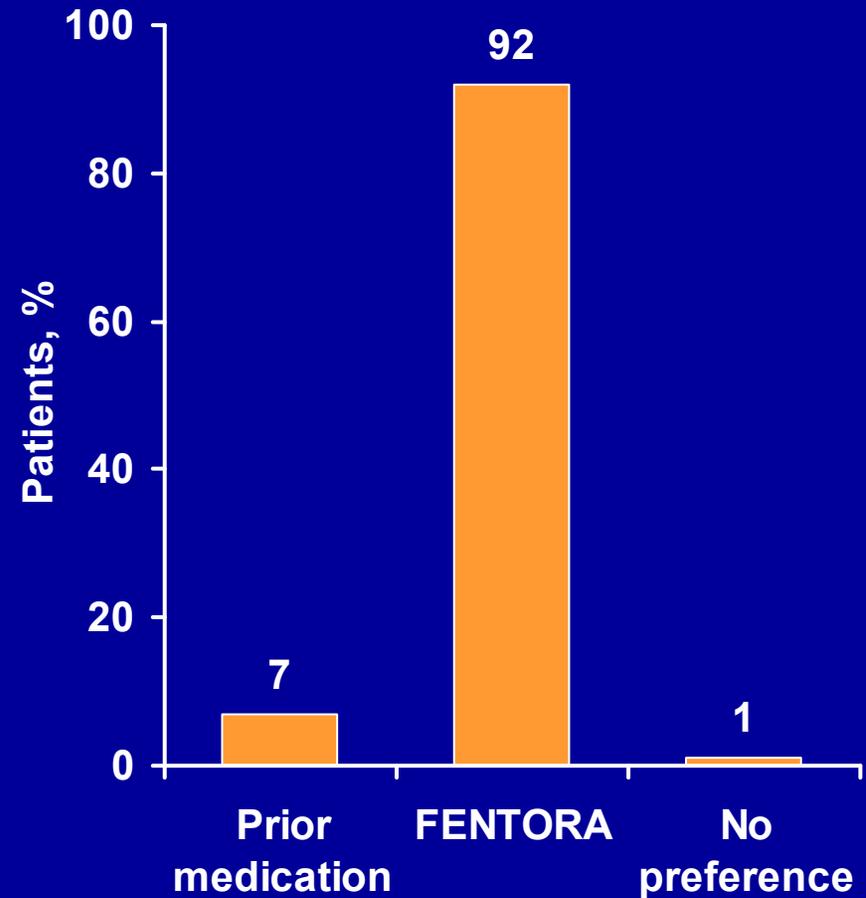
Patients Prefer FENTORA® to Previous Short-Acting Opioids

Which medication would you prefer to use when treating your pain flares?



N = 97

Which medication do you feel worked faster for pain flare control?



N = 98

Effect of FENTORA[®] Well-Matched to BTP Characteristics

- ◆ Efficacy of FENTORA demonstrated in noncancer-related BTP
- ◆ Clinically relevant improvements in BTP observed
- ◆ Efficacy seen throughout 12 wk
- ◆ Patients enrolled in clinical studies reflect intended population

FENTORA[®]

Clinical Trial and Postmarketing Safety

Juergen Schmider, MD, PhD

**Corporate Safety Officer and Vice President,
Global Pharmacovigilance and Epidemiology
Cephalon, Inc.**

Clinical Trial Safety Noncancer BTP

Clinical Safety Noncancer BTP Trials Patient Exposure

- ◆ 1299 patients treated in clinical trials with FENTORA®
- ◆ 941 patients in noncancer BTP trials
 - 227,047 patient treatment days

Clinical Safety Noncancer BTP Trials Adverse Event Profile

Adverse event	n (%)
Nausea	222 (24)
Application site events	116 (12)
Vomiting	114 (12)
Back pain	105 (11)
Dizziness	107 (11)
Headaches	100 (11)
Somnolence	95 (10)
Constipation	67 (7)
Arthralgia	66 (7)

Clinical Safety Noncancer BTP Trials Overdose

◆ 10 patients

- Intentional exposure (2)

- Suicide attempt
- Polysubstance abuse

Addressed in
proposed
Package Insert

- Unintentional exposure (8)

- Multiple dose strengths available during titration

- Exact circumstances unknown

- No overdose deaths

◆ 1 non-study subject with fatal overdose

Cancer vs Noncancer BTP Safety Frequent AEs

Preferred term	Noncancer BTP N = 941	Cancer-related BTP N = 358
Nausea	222 (24)	110 (31)
Application site events	116 (12)	31 (9)
Vomiting	114 (12)	63 (18)
Dizziness	107 (11)	83 (23)
Back pain	105 (11)	20 (6)
Headaches	100 (11)	52 (15)
Somnolence	95 (10)	41 (11)
Constipation	67 (7)	48 (13)

Cancer vs Noncancer BTP Safety Nonserious Adverse Events

FDA-defined pooled terms	Noncancer N = 941, PYR = 673.6			Cancer N = 358, PYR = 128.0			
	Patients, n	Events, n	Rate/ 100 PYR	Patients, n	Events, n	Rate/ 100 PYR	
Higher in noncancer	Withdrawal	16	17	2.5	1	1	0.8
Higher in cancer	Dizzy	55	71	10.5	71	131	102.3
	Lightheaded	59	80	11.9	22	68	53.1
	Syncope	6	6	0.9	3	3	2.3
	Sedation	127	163	24.2	53	84	65.6
	Confusion	30	39	5.8	27	37	28.9
	Likeability of opioid	12	14	2.1	9	9	7.0
	Fall	33	36	5.3	10	12	9.4
	Fracture	26	28	4.2	5	10	7.8
Car accident	2	2	0.3	1	1	0.8	

PYR = Patient-years.

All severities were included. Cluster of events subsequent to the same incident were counted only once for each pooled term (eg, 9 fractures caused by a motor vehicle accident).

Cancer vs Noncancer BTP Safety Conclusion

- ◆ **Cancer and noncancer safety profile largely comparable**
- ◆ **Adverse events of interest more frequent in cancer population (except withdrawal)**

Assessment of Abuse and Diversion Risk Within Clinical Trials

Assessment of Abuse and Diversion Drug Abuse

- ◆ 21 patients with drug abuse events
 - 8 (< 1%) patients had a reported event of drug abuse
 - 13 patients tested positive on random urine drug screen for illicit substance or non-prescribed medication
- ◆ Similar rates observed with trials for other opioids

Assessment of Abuse and Diversion Aberrant Drug-Related Behavior

- ◆ Aberrant drug-related behaviors are signals for potential substance abuse disorders
 - **Neither indicators nor surrogates for a diagnosis of abuse or addiction**
- ◆ Post-hoc analysis of clinical trial database for occurrence of potential aberrant drug-related behaviors
 - Patient characteristics associated with aberrant behaviors were evaluated

Assessment of Abuse and Diversion

Aberrant Behavior Analysis

Events indicative of substance abuse or overdose	Aberrant behaviors				
		Behaviors involving use of study medication		Behaviors not involving use of study medication	
• Abuse/dependence (described by investigator)	8 (<1%)	• Fear of addiction	6 (<1%)	• Motor vehicle accident	4 (<1%)
• Positive UDS	13 (1%)	• Report of medication theft	35 (4%)	• Discharged from pain-management practice	2 (<1%)
• Overdose	10 (1%)	• Report of lost study medication	5 (<1%)	• Using non-prescribed medication	4 (<1%)
		• Overuse of study medication	44 (5%)	• Lost to follow-up	33 (4%)
		• Unapproved use of drug to treat another symptom	2 (<1%)	• Seeking prescriptions from other sources	1 (<1%)
		• Unreliability	2 (<1%)	• Acquiring opioids from other medical sources	1 (<1%)

UDS = Urine drug screen.

Postmarketing Safety

Postmarketing Safety

Postmarketing Patient Exposure

- ◆ Cumulative from launch (October 2006) through December 31, 2007
- ◆ 2,175,287 patient treatment days
- ◆ 20,000 unique patients

Postmarketing Safety Adverse Event Profile

Adverse event	n
Application site events	125
Nausea	34
Drug ineffective	20
Drug ineffective for unapproved indication	19
Vomiting	17
Somnolence	13
Drug prescribing error	11
Dry mouth	10
Hyperhydrosis	10
Withdrawal/drug withdrawal syndrome	10

Postmarketing Safety Diversion and Nonmedical Use

- ◆ 2 cases of diversion (fatal)
 - Partner of patient
- ◆ 2 cases of nonmedical use
 - Drug dependence
 - Drug abuse

Postmarketing Safety Accidental Exposure

- ◆ 1 report in adults
- ◆ No reports in children

Postmarketing Safety Use in Opioid Non-Tolerant Patients

Data source and methodology	< 60 mg/day morphine eq.	≥ 60 mg/day morphine eq.
Spontaneous postmarketing reports ^a	14% (208/1497)	86% (1289/1497)
IMS prescription claims database ^b	23%	77%
Verispan with IMS methodology ^b	25%	75%
	No pain product	Any pain product
Verispan VOCON concurrency analysis ^b	41%	59%

Addressed in RiskMAP

^a Cumulative through Dec 31, 2007 (n = 1989).

^b 2007.

Postmarketing Safety Reports of Medication Error

	Prescribing	Dispensing	Patient use	Total
Dose conversion	5	3		8
Administration route	3 SL		3 SL, 2 PO, 5 Unk	13
Frequency of use	2	0	1	3
Other	1		1	2
Total	11	3	12	26

Addressed in RiskMAP

Postmarketing Safety Fatalities/Life-Threatening Events in Patients

Case ID	Age/sex	Indication	Events (PT)
US020247	34/F	Headache	Accidental OD; drug dispensing error
US021000 (LTE)	34/F	Migraine, trigeminal neuralgia	OD; loss of consciousness; respiratory arrest
US021127	44/F	Migraine	Arrhythmia, multiorgan failure; anoxic encephalopathy
US021157	40/F	Chronic back pain and radiculopathy	Drug toxicity

Specific RiskMAP Interventions

Root Cause Analysis

◆ Root causes

- Prescribing errors
- Lack of awareness about appropriate patient selection
- Lack of understanding of dosage and administration associated with use of FENTORA®

◆ Points of intervention

Prescribing



Dispensing



Patient use



Specific RiskMAP Interventions

Targeted Interventions

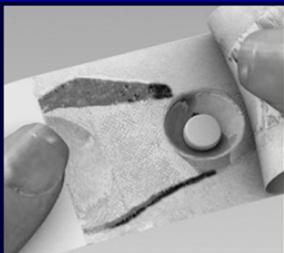
◆ Dear Healthcare Professional letter addressing all subsequent points



- ◆ Point of prescribing
 - Changes to Package Insert and Medication Guide



- ◆ Point of dispensing
 - Changes to Medication Guide and carton
 - More instructions on dosing with FENTORA[®]
 - NotifyRx[™]: Computer-Facilitated Messaging System (screen pop-ups)



- ◆ Patient use
 - Changes to Medication Guide and carton
 - Do not use FENTORA more often than instructed
 - Patient Kit - addition of a safety activation card



Specific RiskMAP Interventions Package Insert Changes

Reports of serious adverse events, including deaths in patients treated with FENTORA have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of FENTORA for any other fentanyl product may result in fatal overdose.

...

FENTORA is not indicated for use in opioid non-tolerant patients including those with only as needed (PRN) prior exposure.

FENTORA is contraindicated in the management of acute or postoperative pain including headache/migraine. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients.

When prescribing, do not convert patients on a mcg per mcg basis from Actiq® to FENTORA. Carefully consult the Initial Dosing Recommendations table.

When dispensing, do not substitute a FENTORA prescription for other fentanyl products. Substantial differences exist in the pharmacokinetic profile of FENTORA compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl. As a result of these differences, the substitution of FENTORA for any other fentanyl product may result in fatal overdose.

Special care must be used when dosing FENTORA. If the breakthrough pain episode is not relieved after 30 minutes, patients may take ONLY one additional dose using the same strength and must wait at least 4 hours before taking another dose.

- ◆ **Boxed Warning**
- ◆ **Indication and Usage**
- ◆ **Contraindications**
- ◆ **Warnings**
- ◆ **Precautions**
- ◆ **Information for Patients and Caregivers**
- ◆ **Dosage and Administration**

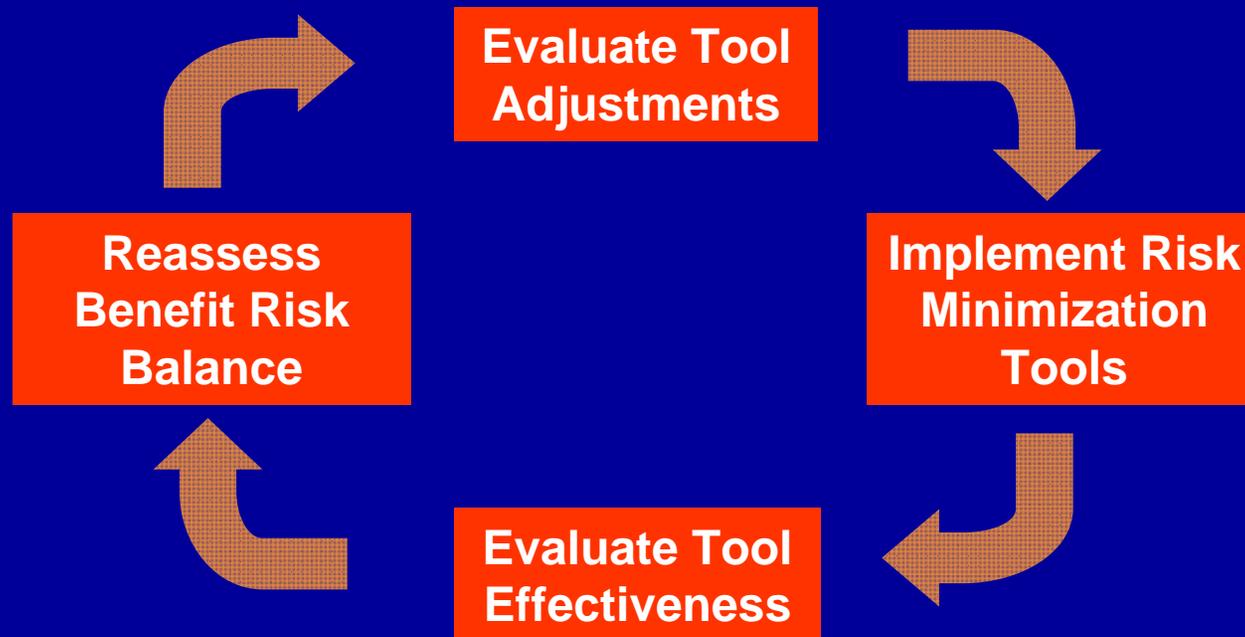
Postmarketing Safety Conclusions

- ◆ Consistent with clinical trial safety and tolerability
- ◆ Consistent with fentanyl
- ◆ Risk of overdose specifically addressed in RiskMAP

FENTORA[®] Risk Management

FENTORA[®] RiskMAP

Overview of Risk Management



FENTORA[®] RiskMAP

Risk Identification

Risks	Goals
Abuse and diversion	Abuse should not occur
	Diversion should not occur
Overdose	Should be used only by opioid-tolerant individuals
	Unintended (accidental) exposure should not occur
	Dosage and administration instructions should be provided to and understood by anyone who may prescribe, dispense, or use FENTORA

FENTORA[®] RiskMAP

Tools and Interventions

1. F1 Blister
2. Carton label
3. Medication Guide (originally patient leaflet)
4. Package insert
5. Educational introductory letters to HCPs
6. Risk management training to field reps
7. Product returns and disposal
8. Physician and pharmacist education
9. Reports of diversion and abuse
10. Web site
11. Blister label
12. Pharm Alert
13. Physician education to Pain Centers of Excellence
14. Pharmaceutical compendia
15. Counseling messages
16. Counseling aids
17. Emerging Solutions in Pain (ESP)
18. Prescriber education targeted to members of professional societies
19. Patient Kit with Safety Activation Card (pilot)
20. NotifyRx messaging (pilot)
21. Healthcare education (PROTECT) for prescribers, pharmacists, patients
22. RFID (pilot)
23. PEDIGREE
24. Tamper-resistant prescription pads
25. Catalina newsletter
26. Auxiliary Rx labels
27. Pharmacy checklist/stamp
28. Book on appropriate opioid prescribing
29. Secure Resource Folder
30. RiskMAP Core Visual Aids
31. Speaker programs
32. Speaker training
33. Safety letters responding to reports of inappropriate patient selection and/or dosing
34. Controlled Voice Enrollment Registration System (COVERS)

FENTORA® RiskMAP Points of Intervention

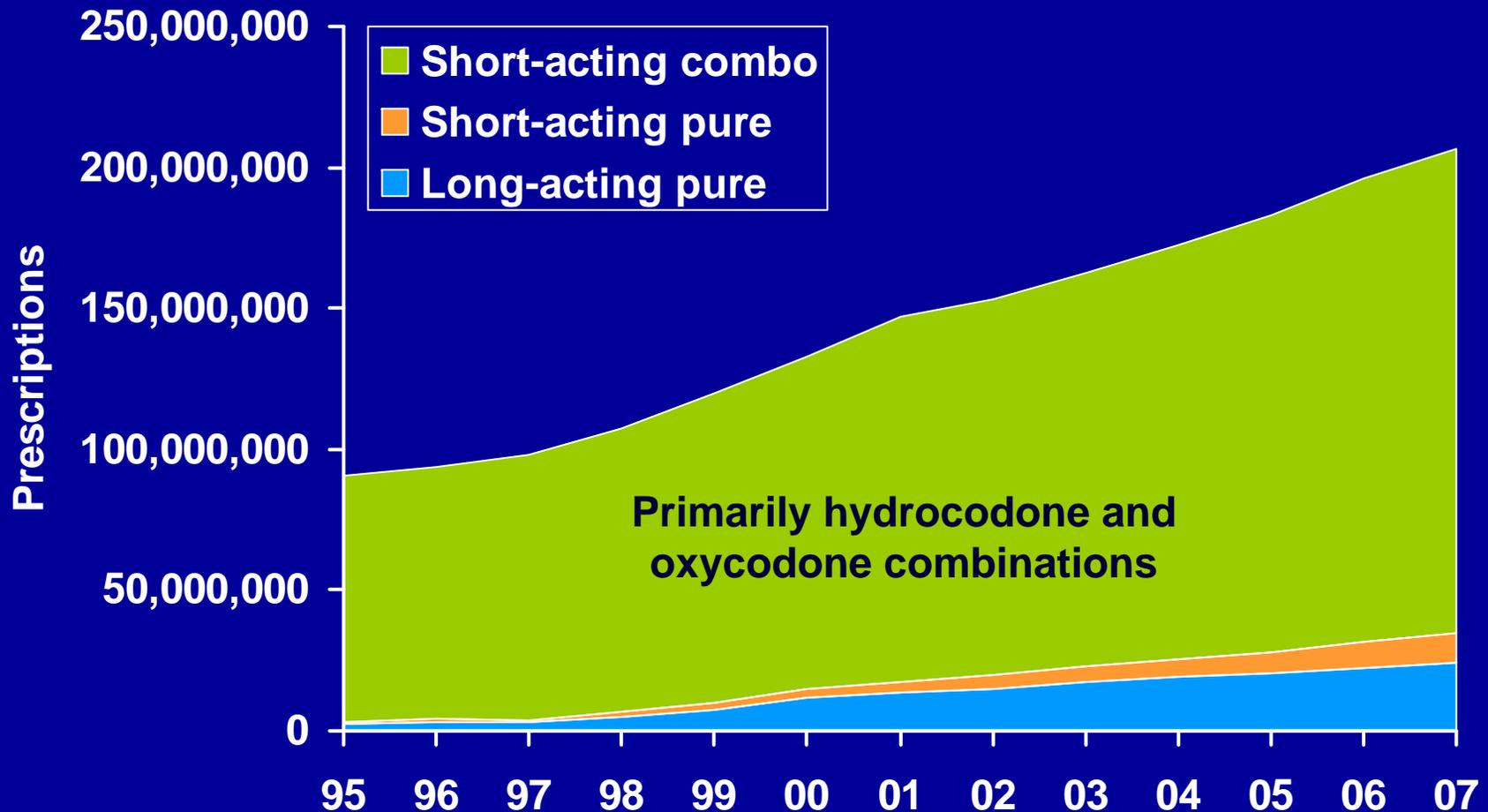


FENTORA[®] RiskMAP Mitigating Risk of Abuse and Diversion

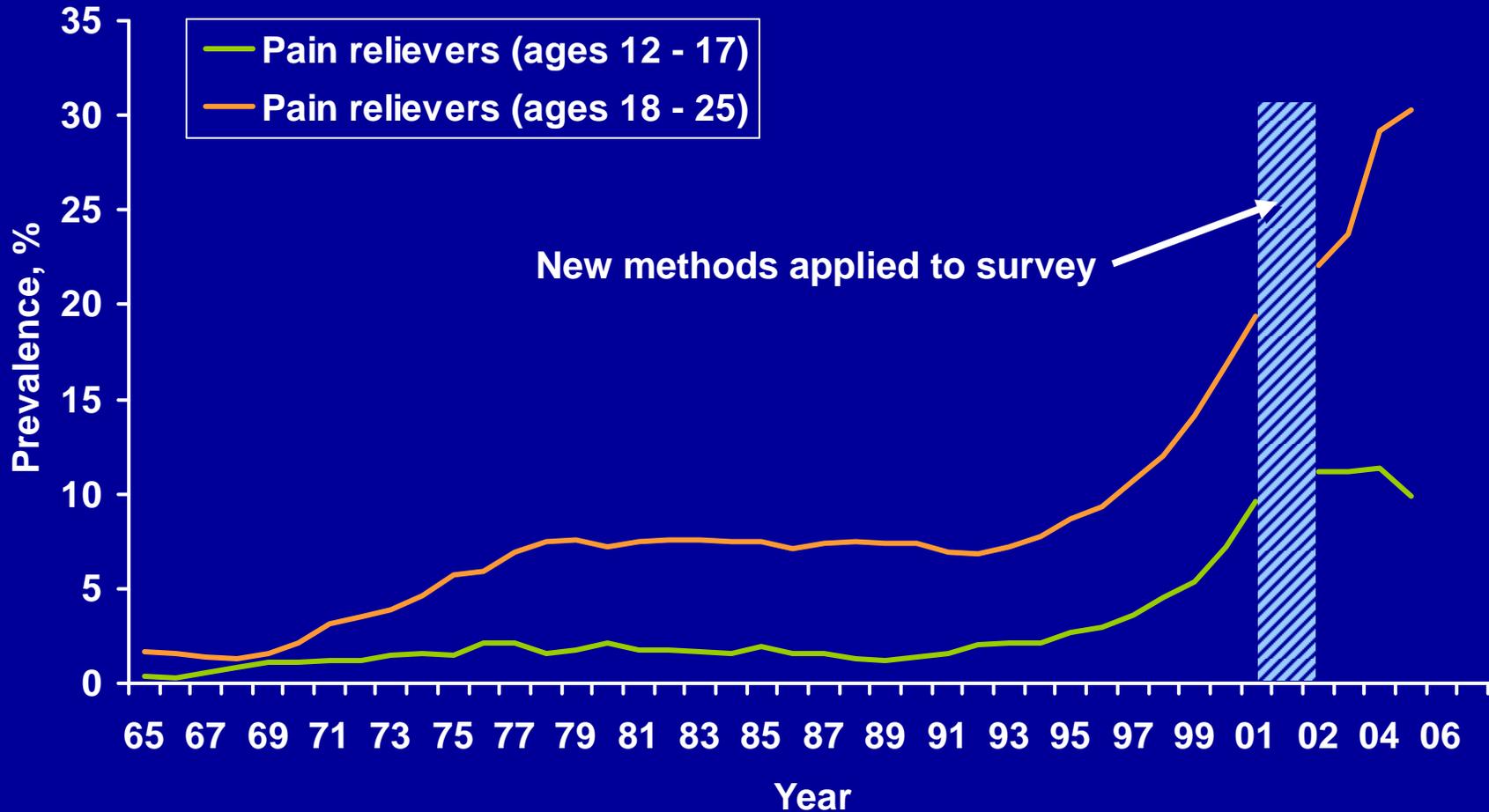
John Messina, PharmD

Prescriptions for Opioids Have Been Steadily Rising

Opioid market 1995 - 2007

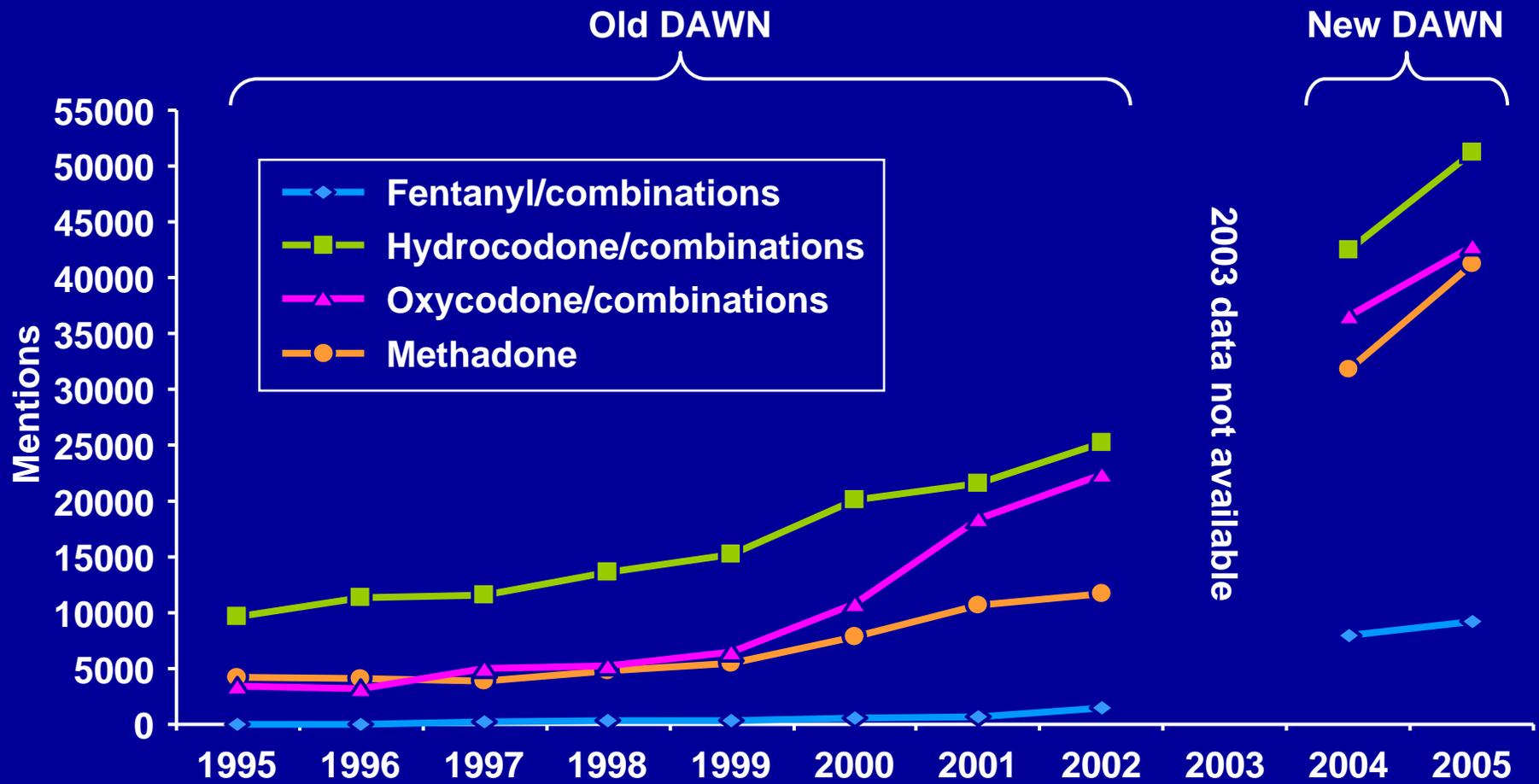


Nonmedical Use of Pain Relievers Has Also Been Increasing



National Household Survey on Drug Abuse (NHSDA)—Lifetime Nonmedical Use, 1965 to 2001
 National Survey on Drug Use and Health- Lifetime Non-Medical Use 2002-2006
 Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse.

Comparative Rates of Emergency Room Mentions in Drug Abuse Warning Network



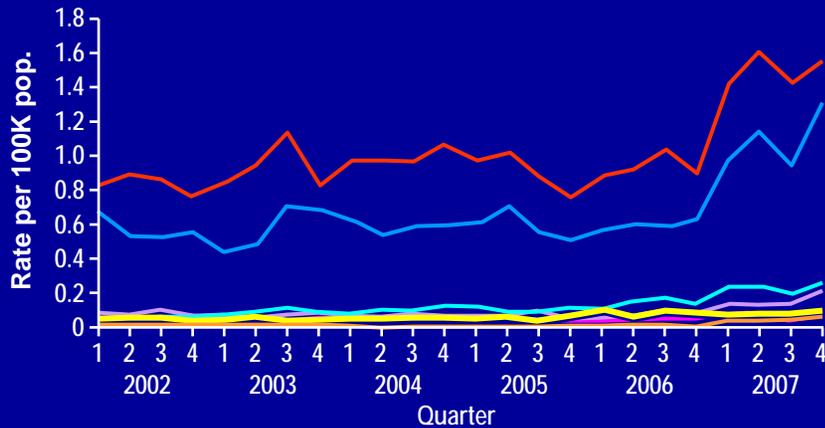
Source: Drug Abuse Warning Network – Emergency Department.

Real-Time Surveillance Systems

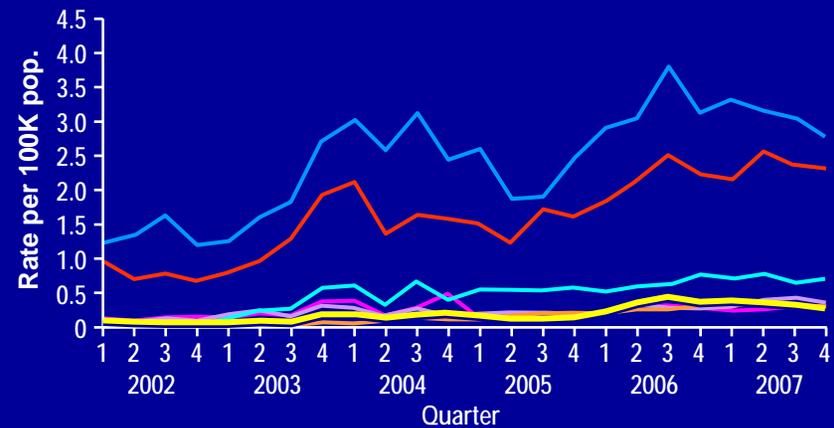
- ◆ Captures events and calculate rates of misuse, abuse, and diversion of prescription opioids and stimulants
- ◆ Covers 90% of US population with information from every state
- ◆ Information gathered from 4 sources
 - Poison centers
 - Law enforcement
 - Key informants
 - Opioid treatment programs

RADARS Results for Rates of Prescription Opioid Abuse per 100,000 Population

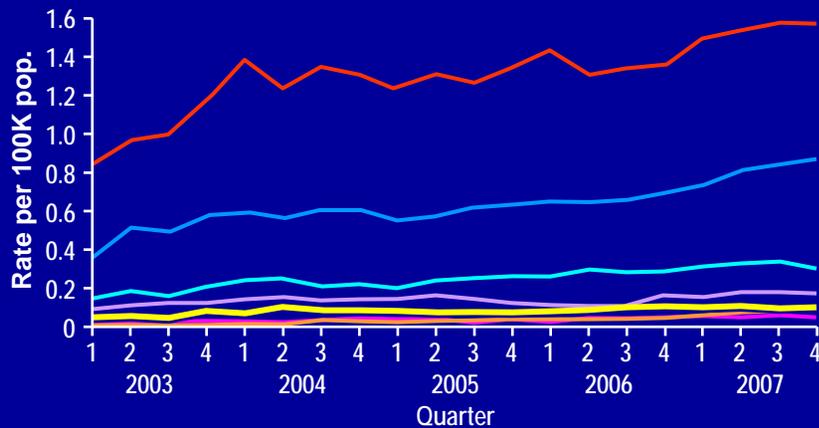
Drug diversion



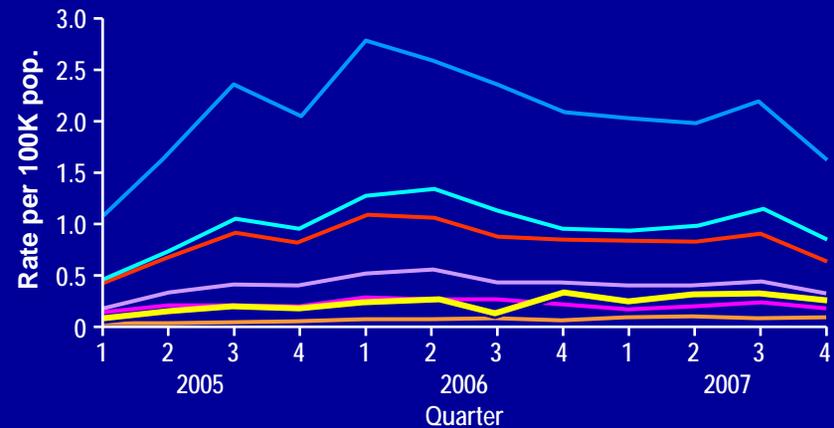
Key informant



Poison centers



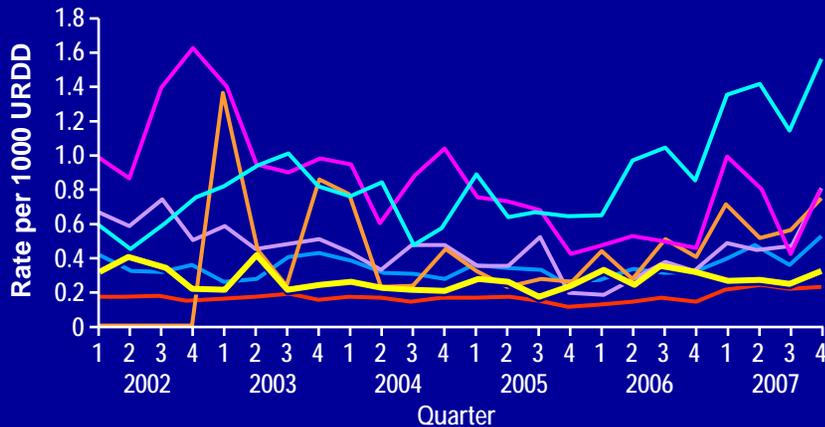
Opioid treatment programs



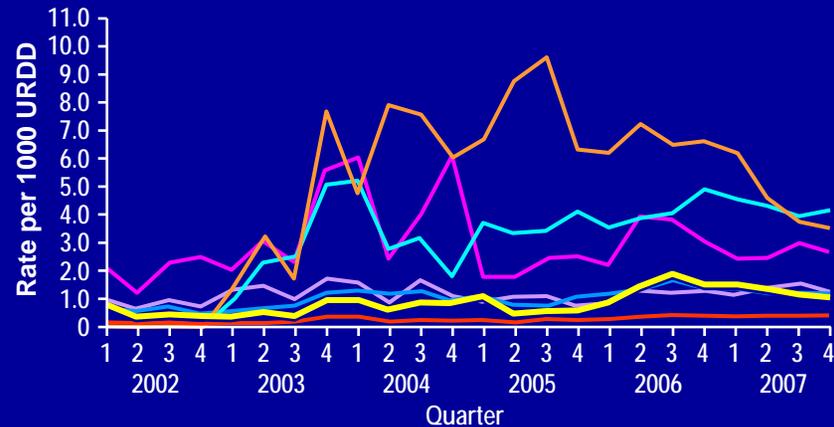
- Buprenorphine
- Hydrocodone
- Methadone
- Oxycodone
- Fentanyl
- Hydromorphone
- Morphine

RADARS Results for Rates of Prescription Opioid Abuse—URDD

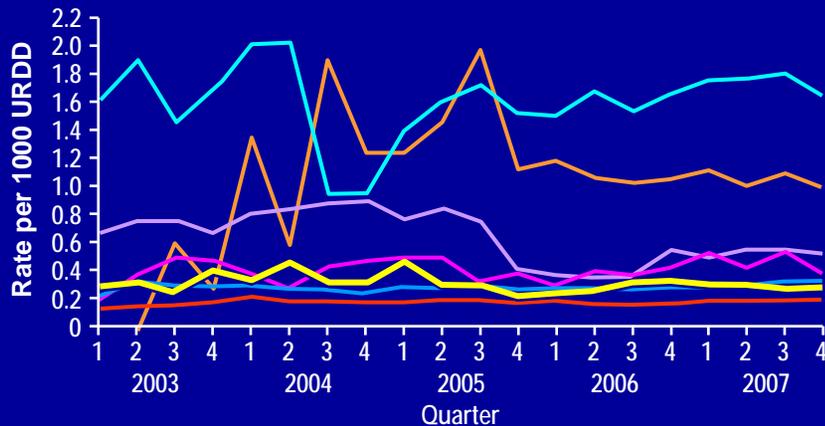
Drug diversion



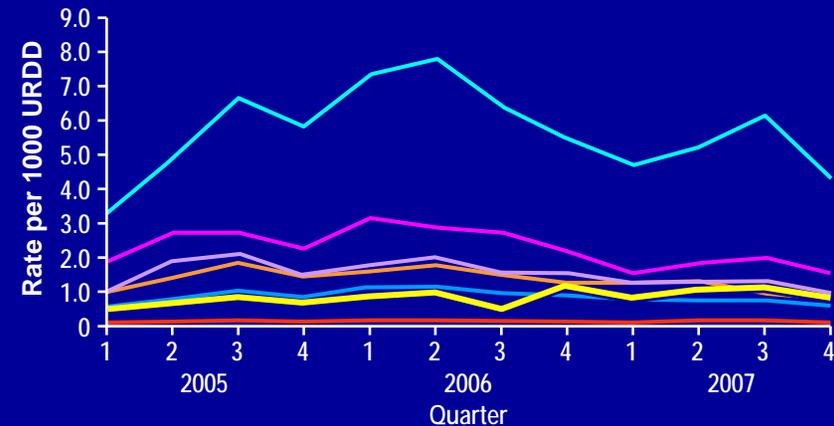
Key informant



Poison centers



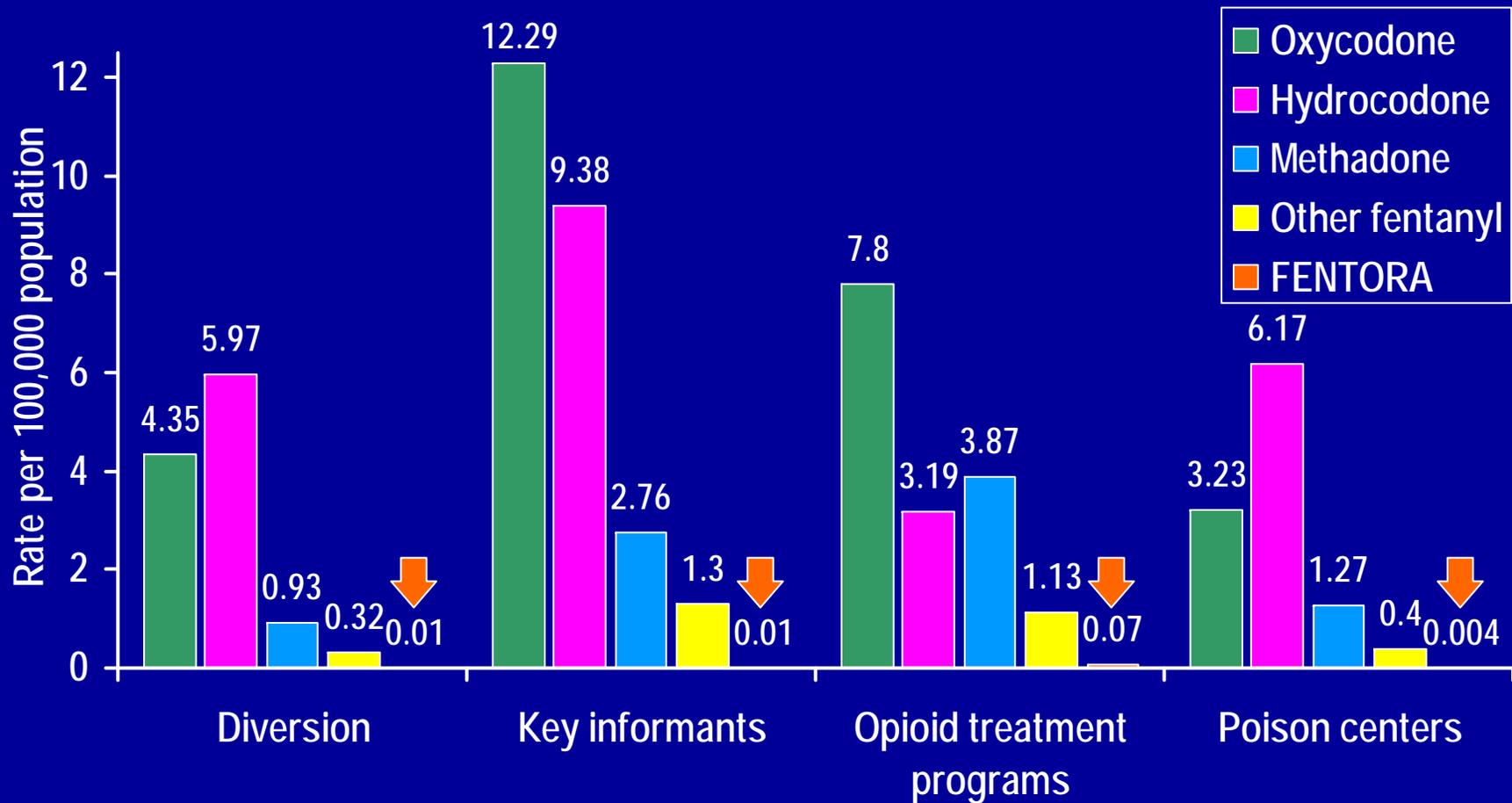
Opioid treatment programs



- Buprenorphine
- Hydrocodone
- Methadone
- Oxycodone
- Fentanyl
- Hydromorphone
- Morphine

URDD = Unique recipients of dispensed drug.

RADARS Results for Rates of Abuse in 2007 by Component



Goal of FENTORA® RiskMAP— Abuse and Diversion Should Not Occur

◆ Mitigation strategies

- Control availability and growth of FENTORA**
- Provide information and education to healthcare professionals and patients**
- Employ multiple surveillance systems**
- Actively intervene**

FENTORA® Indicated for a Subset of Chronic Pain Patients

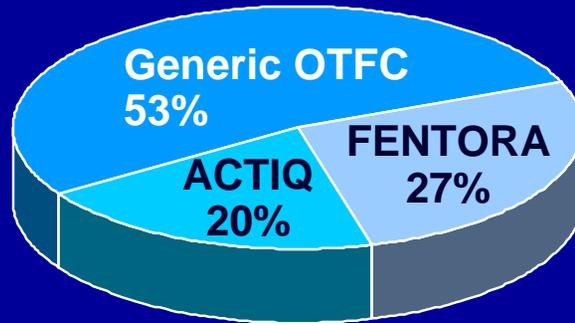
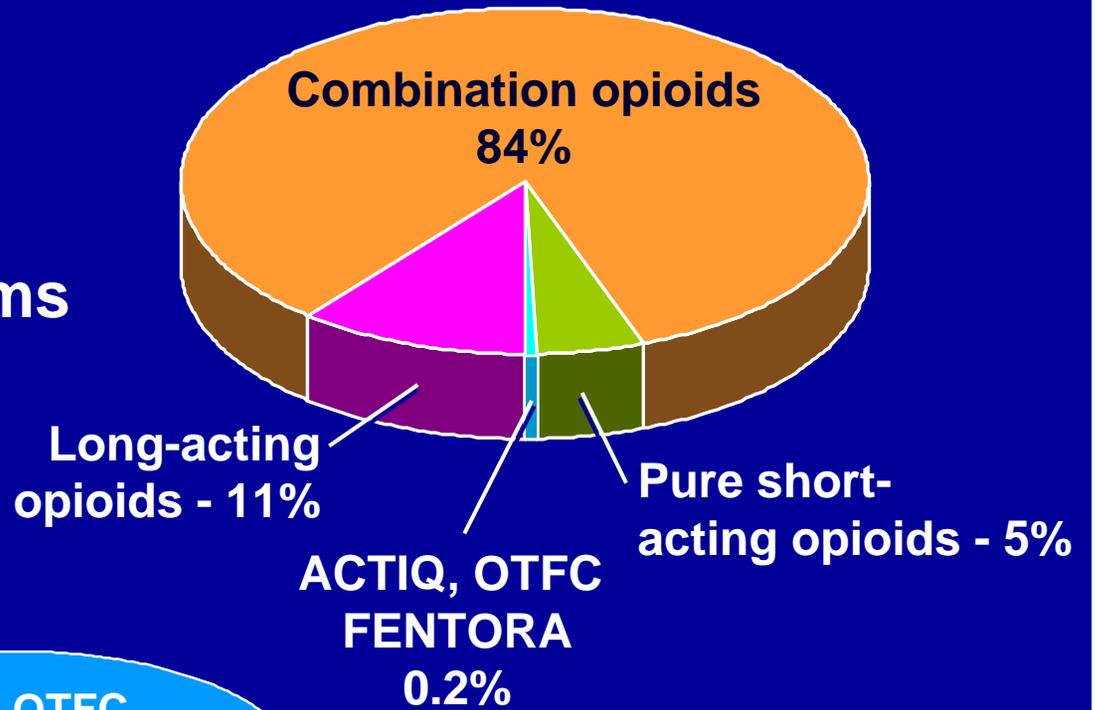
	Prevalence	Diagnosed	Treated for pain	Treated w/ opioids
Cancer	813,750	651,000	488,250	341,775
Back pain	9,026,240	5,867,056	4,693,645	891,793
Arthritic pain	11,486,400	7,007,248	5,758,976	593,724
Neuropathic pain	9,648,679	6,965,190	6,147,833	860,697
Totals	30,975,069	20,490,494	17,088,704	2,687,989

Adjusted for comorbidity.

Source: Analysis of secondary data reports by Cephalon Market Research Department.

FENTORA® Represents a Small Fraction of Opioid Prescriptions

- ◆ 204 million prescriptions for opioids in the US
- ◆ ACTIQ®, Generic Forms of ACTIQ, and FENTORA represent 0.2% of those prescriptions



FENTORA has been prescribed by 5900 physicians

OTFC = Oral transmucosal fentanyl citrate.

Controlled Launch Plan Associated With Expanded Indication

- ◆ At launch, commit within RiskMAP to limit face-to-face detailing to current FENTORA[®] prescribers (~ 6,000)
- ◆ After 12 mo, assess safety and surveillance information and review with FDA
 - If safety data allow, expand to additional ~ 6,000 prescribers
- ◆ Additional stepwise expansions up to a maximum of ~ 30,000 provided safety data allows

FENTORA[®] RiskMAP Tools to Minimize Abuse and Diversion

Labeling and policy

- ◆ Schedule II
- ◆ Package Insert
- ◆ Carton label
- ◆ Medication Guide
- ◆ RFID
- ◆ e-Pedigree

Print communications

- ◆ Introductory letters to Drug Diversion Authorities
- ◆ Core Visual Aid (CVA) with pt tear sheet
- ◆ Patient selection CVA
- ◆ Tamper-resistant Rx pads
- ◆ Patient use kit with safety card
- ◆ Pharm Alert
- ◆ SECURE reprint folder

- ◆ ESP tool kit
- ◆ PROTECT initiative
- ◆ Book: "Responsible Opioid Prescribing" by Fishman & FSMB

In-person communications and Distance-learning initiatives

- ◆ Sales force interactions
- ◆ Cephalon speaker programs
- ◆ Emerging Solutions in Pain (ESP)
- ◆ PROTECT initiative
- ◆ Independent CME

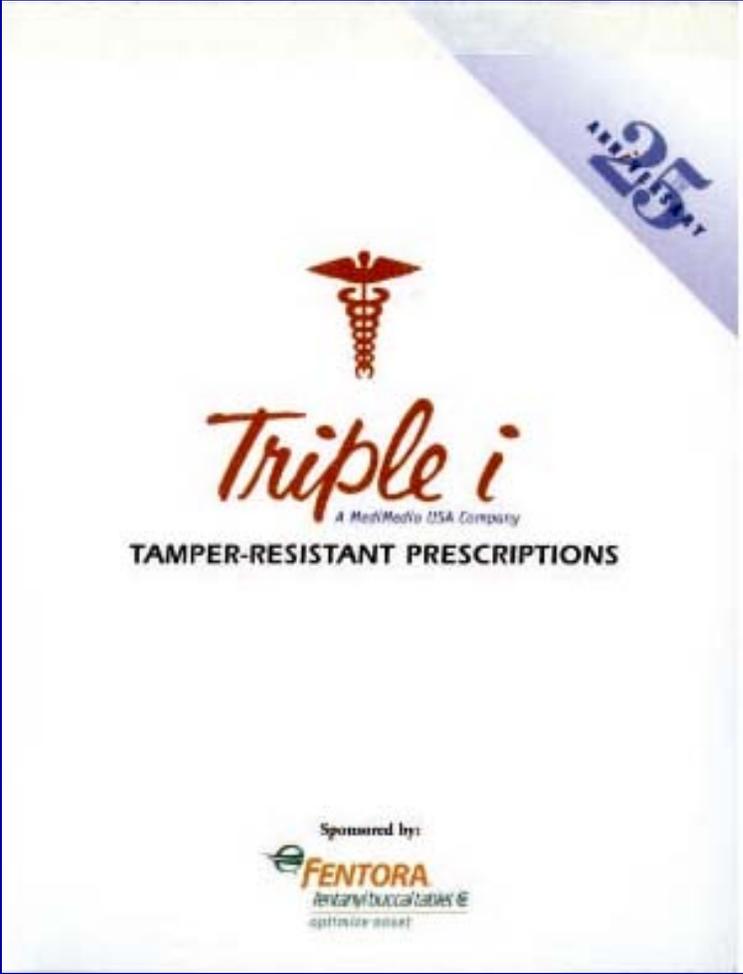
Computer-based initiatives

- ◆ SECURE Web site
- ◆ ESP Web site and tool kit
- ◆ Principles in Rational Opioid Therapy: Education, Collaboration & Translation (PROTECT)

FENTORA® RiskMAP Radio Frequency Identification (RFID)

- ◆ **Designed to track shipments of medication**
 - **Tagging cases and pallets of FENTORA**
- ◆ **Automatic identification method relying on storing and remotely retrieving data using RFID tags**
- ◆ **Increases speed and accuracy with which inventory can be tracked and traced**
- ◆ **Carton level tagging Q1 2009**

FENTORA® RiskMAP Triple-I Tamper-Resistant Prescription Pads



JOHN Q. SAMPLE, M.D.
PRACTICE NAME
123 MAIN STREET
SUITE 100
ANYTOWN, CA 90210
555-555-5555
DEA # AS1234567 CA Lic No. 12345

Rx

NAME _____ DOB _____
ADDRESS _____ DATE _____

RX (Please Print)

THIS IS NOT A PRESCRIPTION - DO NOT DISPENSE

Do Not SUBSTITUTE INITIALS _____

QUANTITY:
 1-24 ____
 25-49 ____
 50-74 ____
 75-100 ____
 101-150 ____
 151 AND OVER ____

UNIT _____
REFILL NR 1 2 3 4 5

_____ DATE _____

PRESCRIPTION IS VOID IF MORE THAN ONE CONTROLLED SUBSTANCE IS WRITTEN PER BLANK. TRI051025_123456789-1_01_12345_0001 0001

FENTORA® RiskMAP

Emerging Solutions in Pain (ESP)

Continuing Medical Education Program

- ◆ **Initiative developed to address critical issues in pain management**
- ◆ **Provides guidance on implementing best practice techniques**
 - **Understanding federal and state regulations**
 - **Evidence-based scientific data**
 - **Validated tools**
 - **Content driven by leading pain and addiction medicine experts**

FENTORA® RiskMAP

Emerging Solutions in Pain Elements

- ◆ **Active Web site continually updated with new information and guidance**
- ◆ **Presence at national meetings to provide in-person educational opportunities**
- ◆ **Tool kit**
 - **Appropriate patient selection**
 - **Identification of aberrant or drug-seeking behaviors**
 - **Screening tests to employ when considering starting a patient on opioids**
 - **Techniques to monitor patients once opioid is prescribed**

FENTORA® RiskMAP

Unbranded Cephalon Speaker Programs

Abuse, addiction, and diversion

- ◆ **Educational slide kit developed by experts in pain and addiction medicine**
- ◆ **Slide kit focuses on**
 - **Minimizing risks through appropriate patient assessment, comprehensive treatment plans, and proper documentation**
 - **Optimizing treatment while complying with laws and regulations**

Educational Initiatives for the Public and the Medical Community

- ◆ Partnership for a Drug-Free America
 - Teen abuse of prescription pain medications
- ◆ National Pain Foundation
 - Safeguarding medications
 - Effect of pain medication abuse
- ◆ American Pain Foundation
 - Safe and appropriate use of opioids
- ◆ Federation of State Medical Boards
 - Co-sponsored “Responsible Opioid Prescribing”

FENTORA[®] RiskMAP Comprehensive Surveillance and Assessment

- ◆ **Surveillance systems**
 - **RADARS, DAWN, DAWN Live!, AAPCC**
- ◆ **Review of prescribing data**
- ◆ **Media monitoring**
- ◆ **Internal reviews**
 - **FENTORA[®] Safety Group**
 - **Corporate Safety Board**
- ◆ **External reviews**
 - **RiskMAP Advisory Committee**
 - **FDA**

FENTORA[®] RiskMAP Interventions

- ◆ **Inform appropriate authorities about any illegal activity**
- ◆ **Abuse**
 - **Community-based education**
 - **Local physician and pharmacist education**

Summary

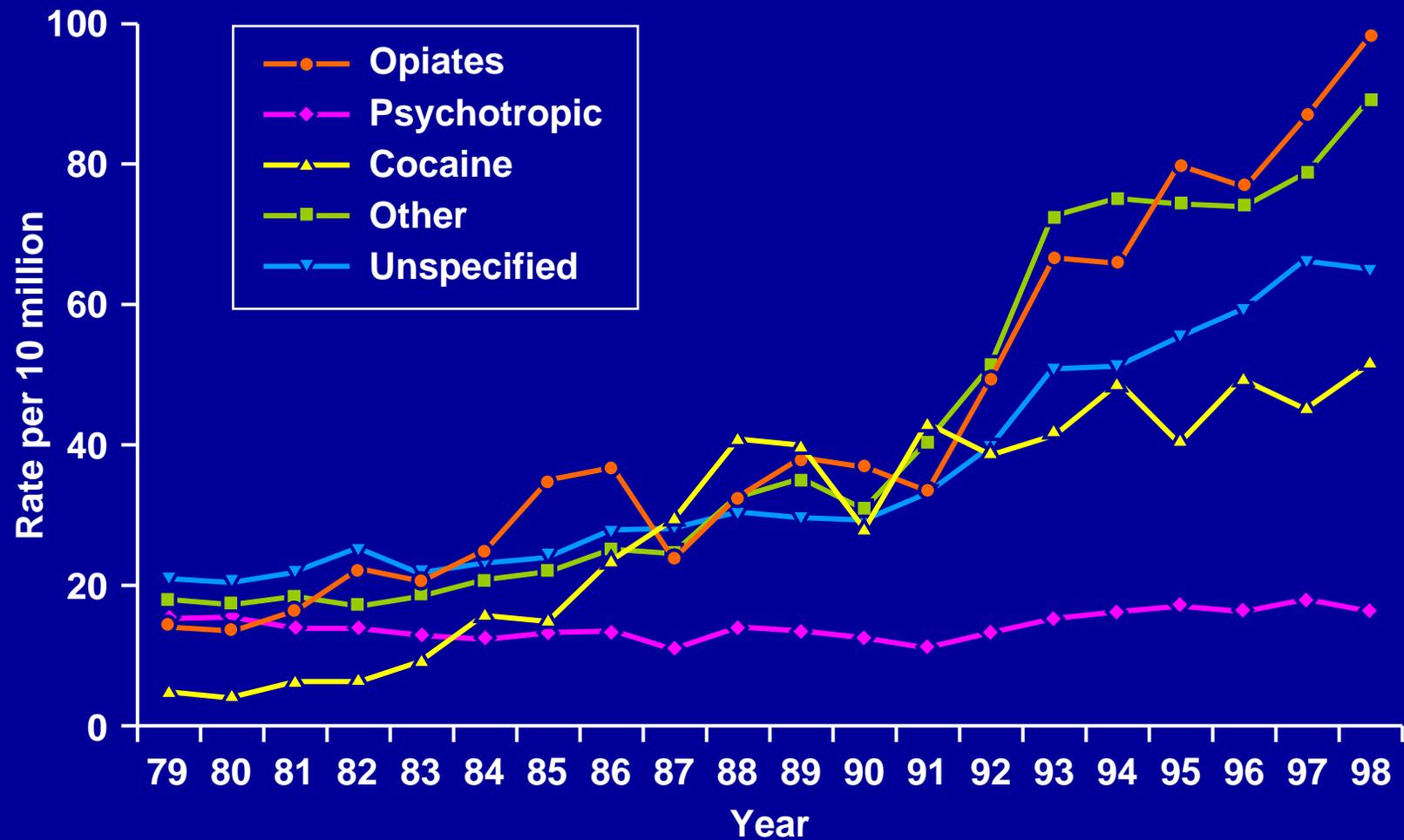
- ◆ **Cephalon recognizes issue of prescription opioid abuse in the United States**
- ◆ **Risk of abuse and diversion can be effectively mitigated with**
 - **Controlled growth**
 - **Prescriber education**
 - **Supply chain control**
 - **Surveillance and intervention**

FENTORA[®] RiskMAP

Mitigating Risk of Overdose

Juergen Schmider, MD, PhD

Unintentional Drug Poisoning Mortality Rates by Drug Category



FENTORA[®] RiskMAP

Mitigating Risk of Overdose

Risks

Overdose

Goals

Should be used only by opioid-tolerant individuals

Unintended (accidental) exposure should not occur

Dosage and administration instructions should be provided to and understood by anyone who may prescribe, dispense, or use FENTORA

FENTORA[®] RiskMAP

Key Messages

◆ Safety messages

- Use only in opioid-tolerant patients
- Do not use for acute pain, postoperative pain, or headache/migraine
- Should only be prescribed by healthcare professionals who are knowledgeable of and skilled in the use of Schedule II opioids
- Do not convert on a mcg per mcg basis from ACTIQ[®] to FENTORA[®]
- Do not substitute a FENTORA prescription for other fentanyl products
- Keep FENTORA in a safe and secure place

◆ Dosing instructions

- Use only 1 more dose of FENTORA after 30 min if necessary
- Wait at least 4 hours before treating another BTP episode
- Do not treat more than 6 BTP episodes per day
- Continue taking your around-the-clock opioid medicine

FENTORA[®] RiskMAP Mitigation Strategy

- ◆ Targeted education and outreach
- ◆ Reminder systems
- ◆ Performance-linked access system

FENTORA[®] RiskMAP

Targeted Education and Outreach

Print Communications

- ◆ Package Insert
- ◆ Medication Guide (originally patient leaflet)
- ◆ Blister label
- ◆ Carton label
- ◆ Patient Kit
- ◆ RiskMAP Core Visual Aids
- ◆ Educational introductory letters to HCPs
- ◆ Catalina newsletter
- ◆ Auxiliary Rx labels
- ◆ Pharmacy checklist/stamp
- ◆ Pharm Alert
- ◆ Independent CME (ESP)
- ◆ Prescriber education targeted to members of professional societies
- ◆ Physician education to Pain Centers of Excellence
- ◆ Pharmaceutical compendia
- ◆ Counseling aids
- ◆ Secure Resource Folder
- ◆ Healthcare education (PROTECT)
- ◆ Book on appropriate opioid prescribing

In-Person Communications

- ◆ Risk management training to field reps (Sales Force interactions)
- ◆ Speaker Programs
- ◆ Speaker training
- ◆ Independent CME (ESP)
- ◆ Healthcare education (PROTECT)

Computer-Based Initiatives

- ◆ SECURE Web site
- ◆ Independent CME (ESP)
- ◆ Healthcare education (PROTECT)
- ◆ Counseling messages

Continuing Education & Distance-Learning Initiatives

- ◆ Independent CME (ESP)
- ◆ Healthcare education (PROTECT)

FENTORA[®] RiskMAP Reminder Systems

- ◆ Pharmacy checklist/stamp
- ◆ Safety letters responding to reports of inappropriate patient selection and/or dosing
- ◆ NotifyRx[™] messaging (pilot)
- ◆ Safety activation card (pilot)



Reminder Systems

NotifyRx™

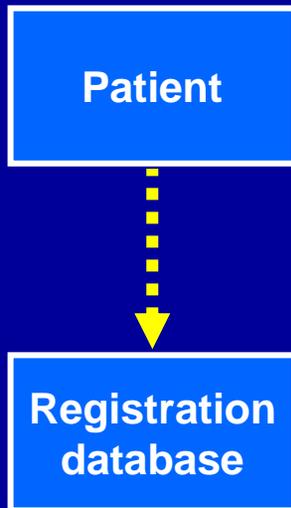


Before dispensing FENTORA:

- ensure that patient is opioid-tolerant
- print the reminder auxiliary label and provide to the patient
- counsel the patient about the proper use and storage of FENTORA
- instruct the patient to read the FENTORA Medication Guide

- ◆ **Hard stop to the transaction to deliver and reinforce the message**
- ◆ **Random override code to acknowledge reading of message**
- ◆ **Transaction can be completed**

Reminder Systems Safety Activation Card

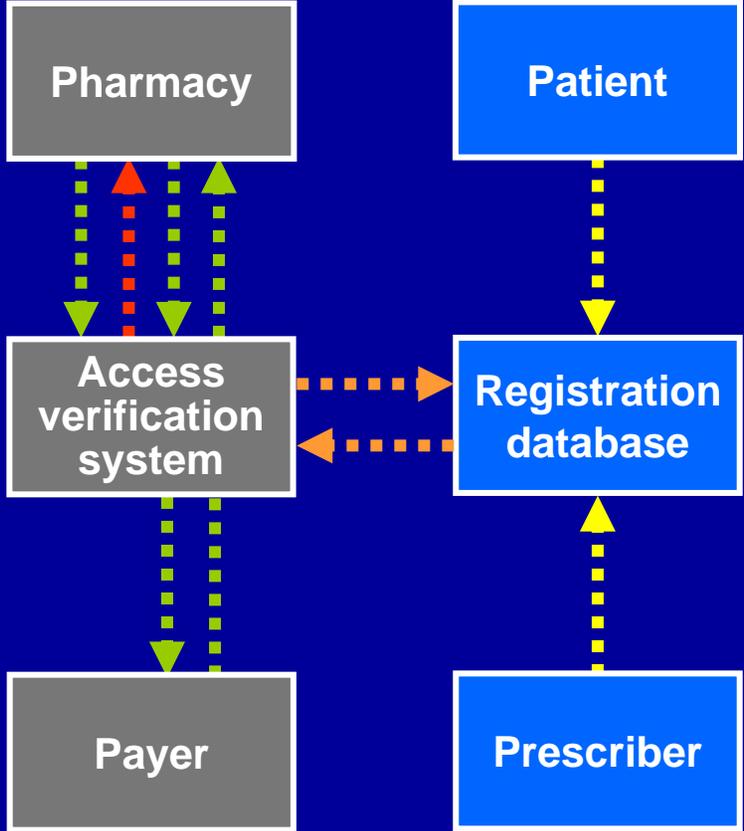


- ◆ Pilot program
- ◆ Vehicle to deliver key safety messages to the patient
- ◆ Patient to call a 1-800 number and listen to key safety information for FENTORA[®]

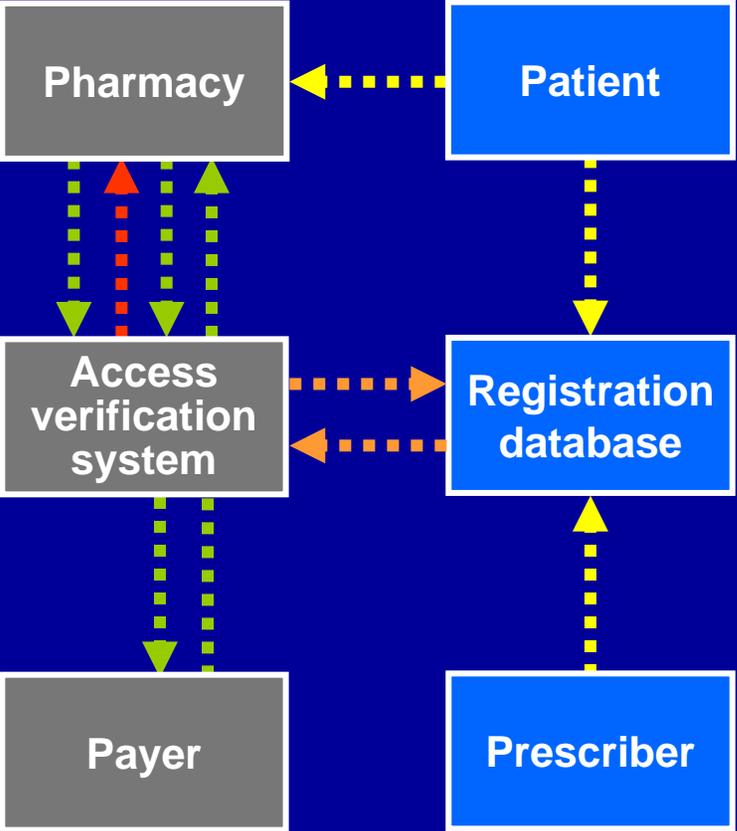
FENTORA[®] RiskMAP Performance-Linked Access System

- ◆ Controlled Voice Enrollment Registration System (COVERS[™])
 - Minimizing risk
 - Maintaining patient access

Performance-linked Access System COVERS™

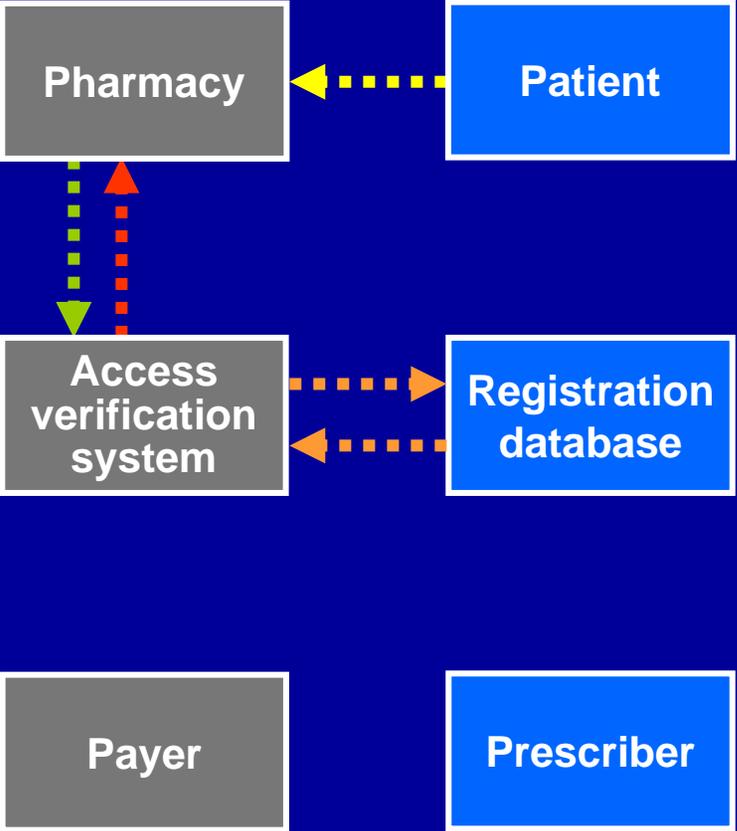


Performance-linked Access System COVERS™



- Before dispensing FENTORA:
- ensure that patient is opioid-tolerant
 - print the reminder auxiliary label and provide to the patient
 - counsel the patient about the proper use and storage of FENTORA
 - instruct the patient to read the FENTORA Medication Guide

Performance-linked Access System COVERS™



FENTORA cannot be dispensed:

- notify patient to register using Safety Activation Card
- notify prescriber to register

FENTORA[®] RiskMAP

Evaluate Effectiveness

- ◆ Pharmacovigilance (adverse event reporting)
- ◆ Surveys
 - Patient, physician, pharmacist
- ◆ Review of prescribing data (IMS)

FENTORA[®] RiskMAP Interventions

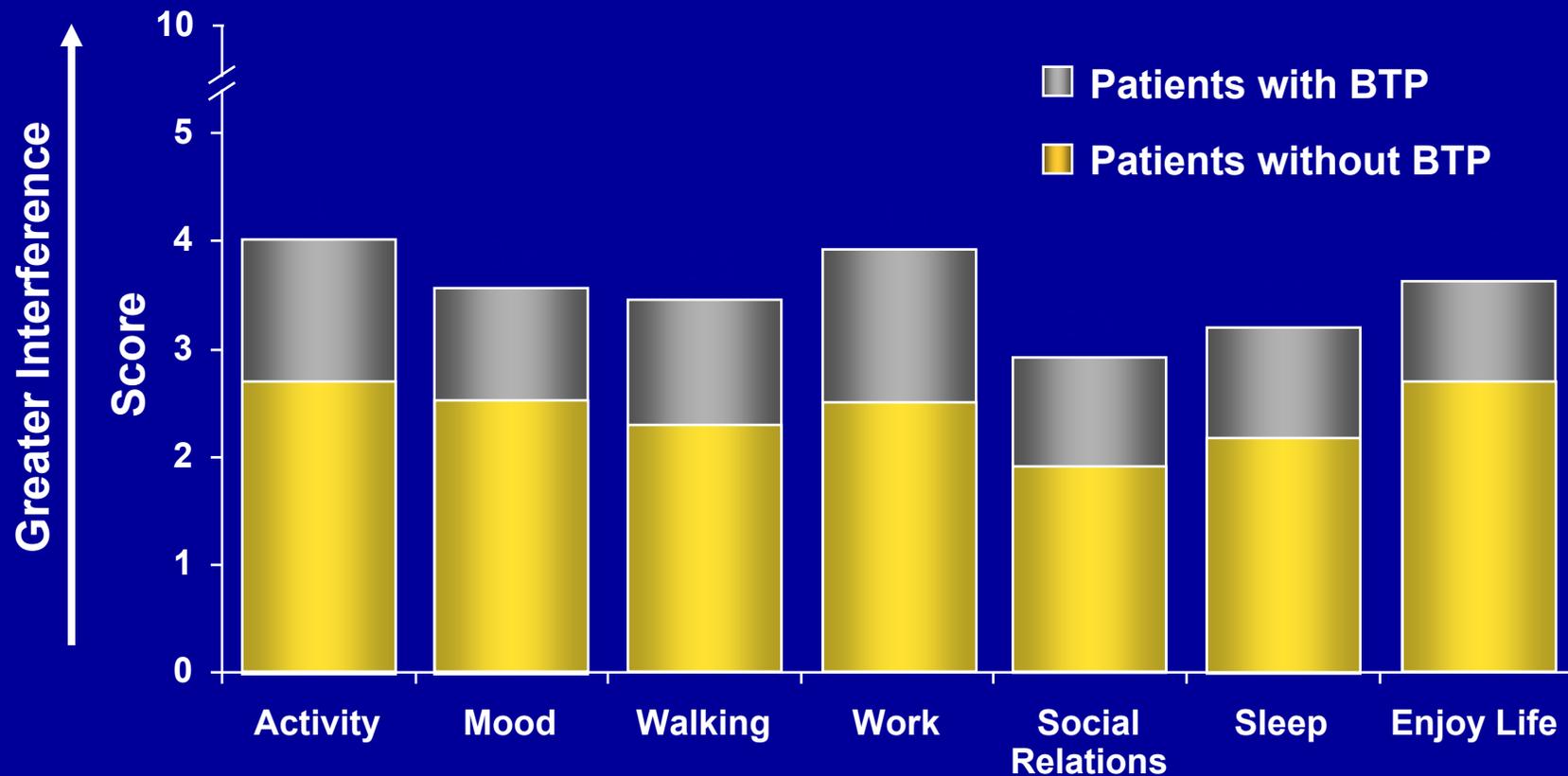
- ◆ **Dear Healthcare Professional letter**
- ◆ **Label change**
- ◆ **Core safety message adjustment**
- ◆ **Message dissemination tool adjustment**
- ◆ **Targeted education of individual prescribers with apparent inappropriate prescribing patterns**
- ◆ **Removing prescriber from registry**

FENTORA[®] RiskMAP Summary

- ◆ **Comprehensive tools to preempt abuse and diversion as well as to monitor for emerging signals and intervene**
- ◆ **An innovative registration system that provides the advantages of a registry while maintaining appropriate access to patients**
- ◆ **Favorable benefit-risk balance: keeping risks at a minimum while preserving patient benefits**

BTP Adversely Affects Function and Quality of Life

Brief Pain Inventory Functional Component Scores



BPI = Brief Pain Inventory.
Portenoy RK, et al. *Pain*. 1999;81:129-134.

Application Site Adverse Events

Safety Analysis Set

Preferred term	Patients, % N = 941
Patients with application site AEs	116 (12)
Irritation	37 (4)
Pain	31 (3)
Ulcer	22 (2)
Erythema	16 (2)
Reaction	7 (< 1)
Vesicles	7 (< 1)
Anesthesia	4 (< 1)
Discoloration	3 (< 1)
Bleeding	2 (< 1)
Discomfort	2 (< 1)
Swelling	2 (< 1)
Nodule	1 (< 1)
Paresthesia	1 (< 1)

Medical History and Age by Aberrant Drug-related Behavior Safety Analysis Set

Medical history	Patients with aberrant drug-related behavior, n (%)		Odds ratio (all/none)	95% CI (all/none)	<i>p</i> value
	Yes n = 156	No n = 785			
Anxiety					
Yes	58 (37)	272 (35)	1.1162	0.8, 1.6	0.5454
No	98 (63)	513 (65)	1.0000	1.0, 1.0	—
Depression					
Yes	78 (50)	438 (56)	0.7922	0.6, 1.1	0.1845
No	78 (50)	347 (44)	1.0000	1.0, 1.0	—
Psychotic sx's / mania					
Yes	9 (6)	21 (3)	2.2274	1.0, 4.8	0.0499
No	147 (94)	764 (97)	1.0000	1.0, 1.0	—
Age group					
≤ 42 years	55 (35)	189 (24)	2.5178	1.5, 4.3	0.0006
> 42 to ≤ 49 years	50 (32)	209 (27)	2.0699	1.2, 3.6	0.0072