



Risk Mitigation in Reality: Best Practices from a Transmucosal Fentanyl REMS

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Disclosures: Dr Brennan will receive an honorarium from Cephalon, Inc.

This initiative is sponsored by and
developed in collaboration with Cephalon, Inc.



About “Ready for REMS”

- > **Ready for REMS** is an educational initiative developed by leading pain management experts in collaboration with Cephalon to raise awareness and prepare healthcare providers for FDA-mandated Risk Evaluation and Mitigation Strategies (REMS) for opioids
 - The Ready for REMS initiative is sponsored by and developed in collaboration with Cephalon, Inc.
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Objectives

After this session, you will have the information and resources to:

1. Understand the evolution of risk management in pain medicine
 2. Apply the principle of balance with opioid treatment
 3. Be familiar with the requirements of a Transmucosal Immediate Release Fentanyl (TIRF) REMS (using the ACTIQ[®] and FENTORA[®] REMS as a model)
 4. Support the implementation of REMS in your pain practice
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Agenda

- > Evolution of risk management and general introduction to REMS
 - > Balancing the risks and benefits of opioids
 - > REMS:
 - Components
 - Clearing up opioid REMS confusion
 - A TIRF REMS (ACTIQ and FENTORA)
 - > Best practices
 - > Resources for REMS
 - > Q&A
-



Evolution of Risk
Management

Risk Management Timeline

Early 1990s

Risk Management Plans (RMPs)

2000s

Risk Minimization Action Plans (RiskMAPs)

2007

Risk Evaluation and Mitigation Strategies (REMS)

Via the FDA Amendments Act of 2007 (FDAAA), congress gave FDA the authority to require a REMS when FDA determines a REMS is necessary to ensure the benefits of a drug outweigh the risks¹

As of August 25, 2011 there were 140 approved REMS

REMS: Introduction

> Background

- REMS are FDA-mandated requirements intended to ensure that the benefits of certain medications continue to outweigh the risks
- Starting in March 2008, FDA has been able to formally require manufacturers to submit a REMS for drugs or biologics that have a known or potential safety risk

> REMS can be mandated for any medication or class of medication

> Certain opioids, but not all, have been included in this mandate



Treating Pain While Balancing
the Risks and Benefits of Opioids

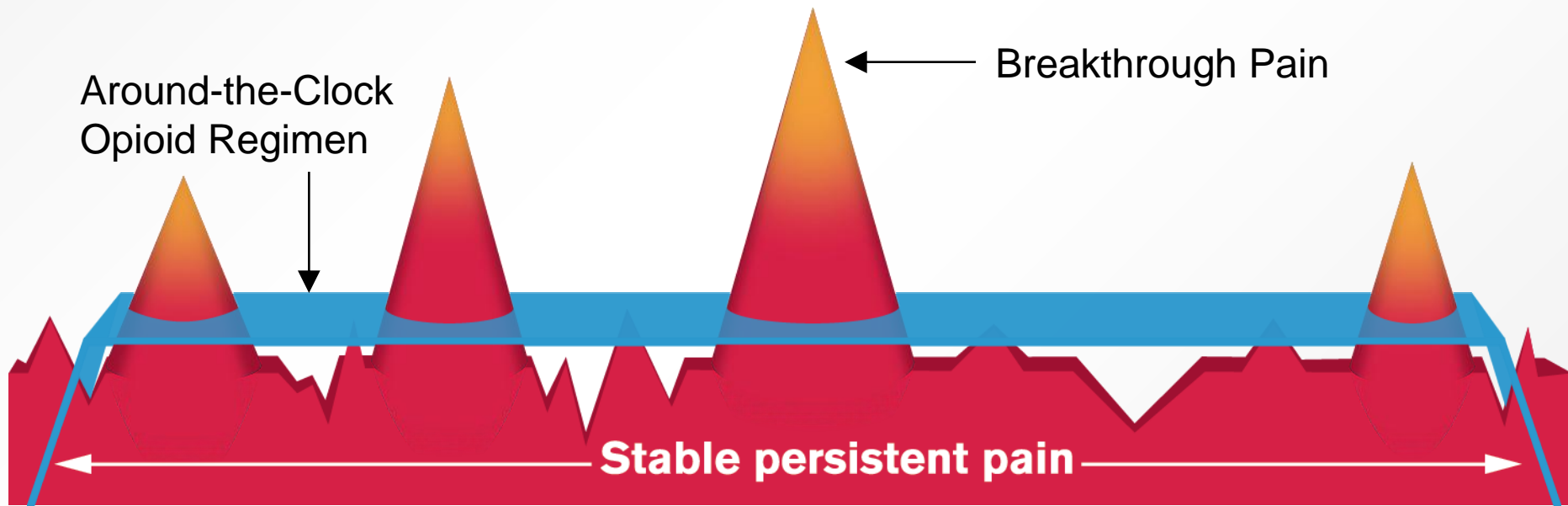
Common Components of Chronic Pain

Baseline or Persistent Pain

Pain that is continuous throughout the day (≥ 12 hours/day) and is managed with around-the-clock (ATC) medication¹

Breakthrough Pain (BTP)

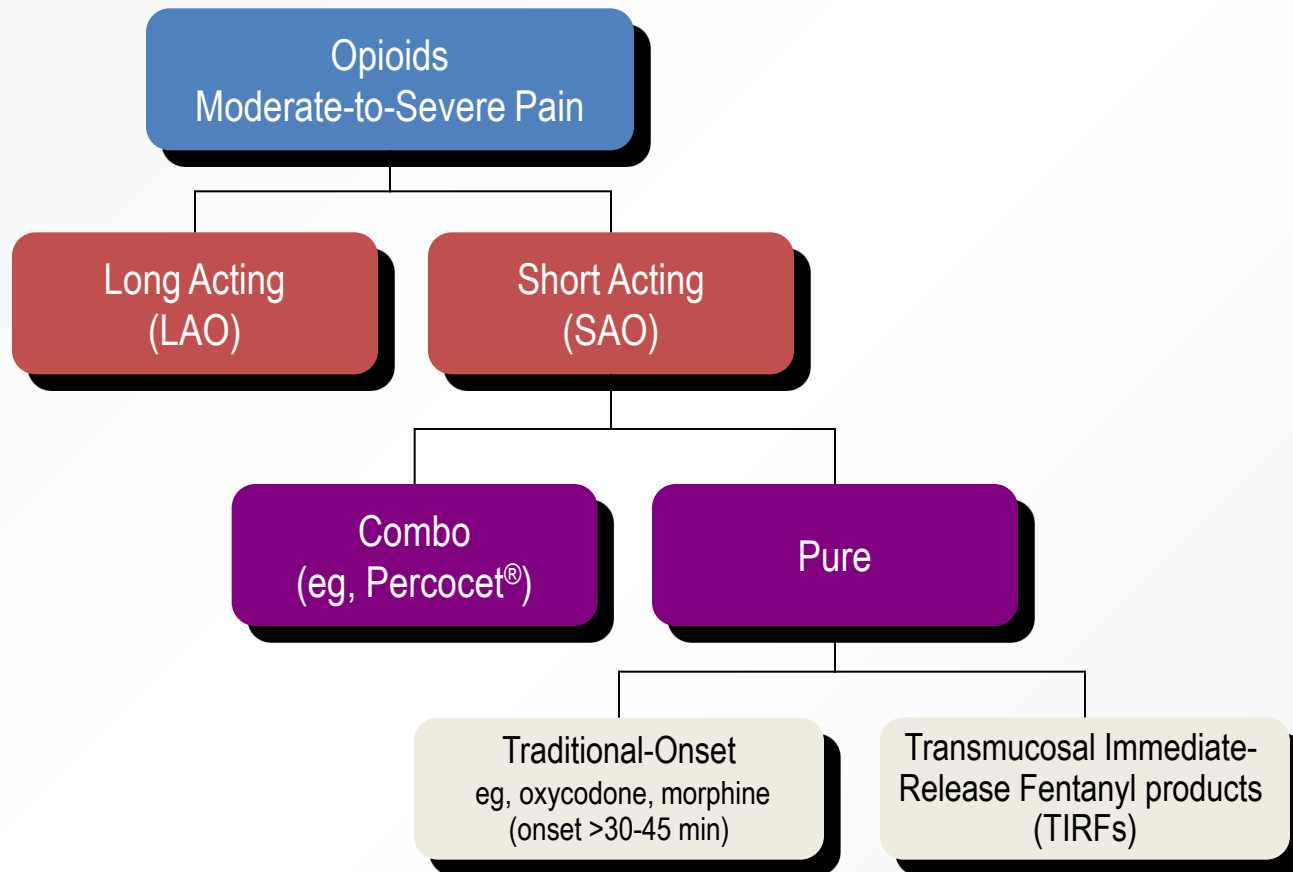
A transitory exacerbation, or flare, of moderate-to-severe pain in patients with otherwise stable persistent pain²



1. Portenoy RK, Hagen NA. *Pain*. 1990;41(3):273-281.
2. Bennett D et al. *Pharmacol Ther*. 2005;30(5):354-361.

Opioids for Pain Treatment

Classification of opioids by type



The Principle of Balance with Opioid Therapy

- > Both the APS/AAPM and the WHO acknowledge that opioids are an essential treatment option in the management of patients with moderate-to-severe pain^{1, 2}
- > However, opioids are associated with significant risks, including misuse, abuse, addiction, and overdose



APS = American Pain Society; AAPM = American Academy of Pain Medicine; WHO = World Health Organization.

1. WHO's Pain Ladder. <http://www.who.int/cancer/palliative/painladder/en/>. Accessed August 2011.

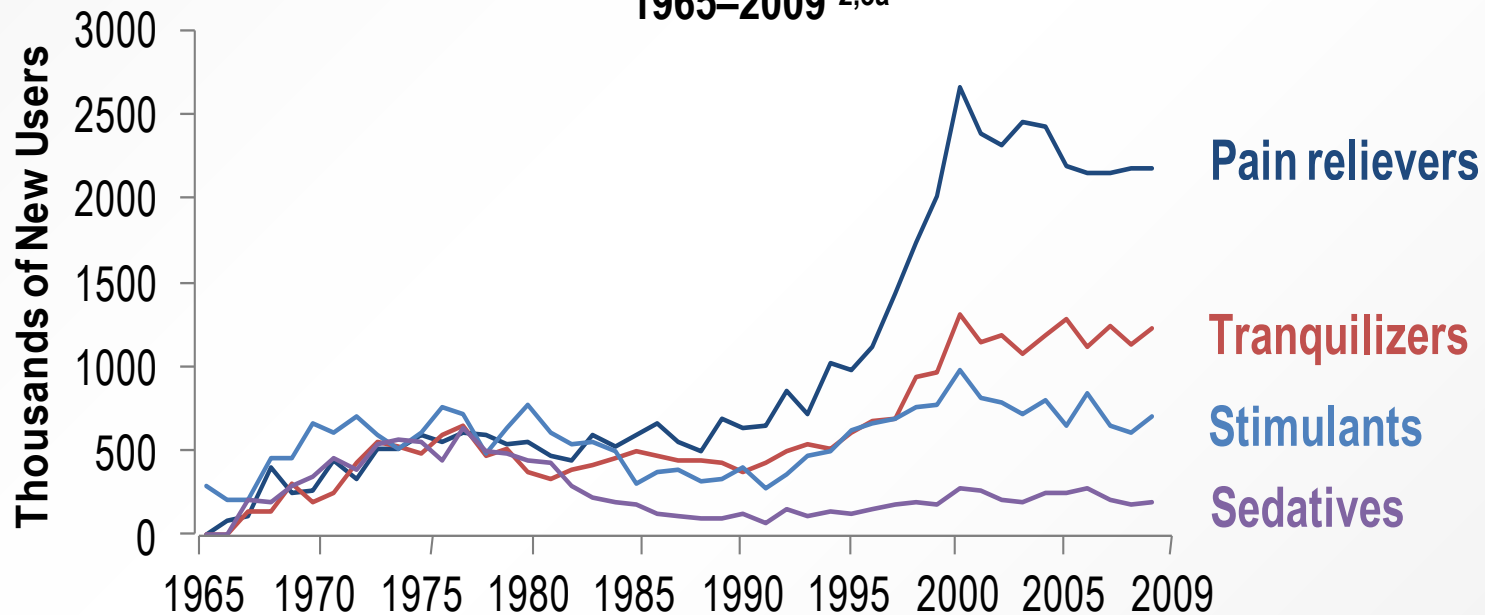
2. American Pain Society. Clinical Practical Guidelines. http://www.ampainsoc.org/pub/cp_guidelines.htm. Accessed August 2011.

REMS Aim to Mitigate the Risk of... Nonmedical Use of Opioids



Greater availability of opioids has benefited patients with pain but has also been associated with increased nonmedical use¹

Initiation of Psychotherapeutics for Nonmedical Use, 1965–2009^{2,3a}



^aData from 1965–2001 include all ages; data from 2002–2009 include ages 12 and older.

1. Pletcher MJ, et al. *Drug Alcohol Depend.* 2006;85:171-176.

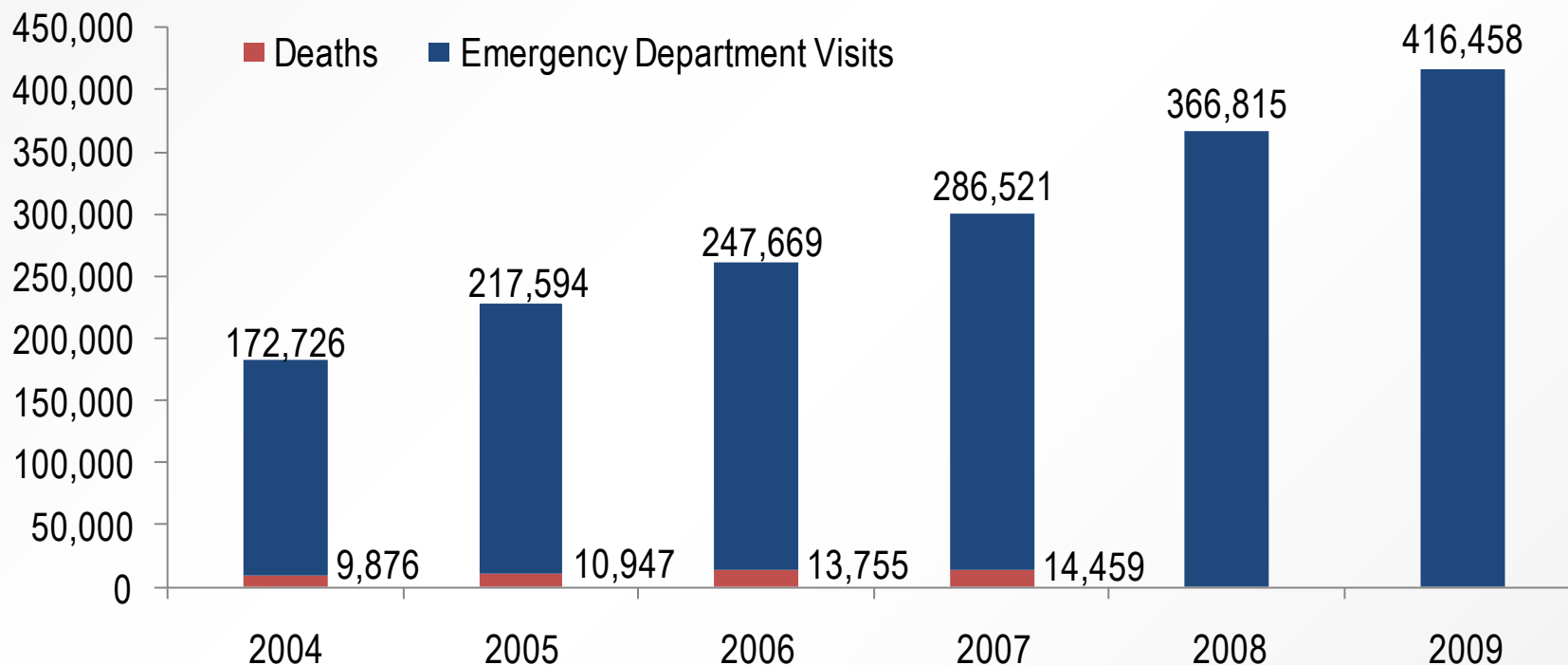
2. Substance Abuse and Mental Health Services Administration (SAMHSA), US Department of Health and Human Services (DHHS). Rockville, MD: 2003. NHSDA Series H-22, DHHS Publication No. SMA 03-3836.

3. SAMHSA, DHHS. Rockville, MD: 2009. NHSDA Series H-38A, DHHS Publication No. SMA 10-4586.

REMS Aim to Mitigate the Risk of... Opioid Overdose Resulting From Misuse



Deaths and Emergency Department Visits Involving Opioids^a



^aData from 2008 and 2009 on deaths not available.

1. Drug Abuse Warning Network. 2009.

2. National Center for Health Statistics. *MMWR*. 2010;59(No. 32):1026.

3. Warner M, Chen LH, Makuc DM. NCHS data brief, no. 22. Hyattsville, MD: US DHHS, CDC, National Center for Health Statistics; 2009. Available at <http://www.cdc.gov/nchs/data/databriefs/db22.htm>. Accessed April 12, 2011.

The Principle of Balance with Opioid Therapy

- > REMS are intended to minimize these risks while maintaining access for patients who need opioid medications





Components of REMS

Components of REMS

While there are different components of REMS, an individual program does not have to include all of these:

**Medication
Guide/PPI***

Educational tools provided to each patient when drug is prescribed / dispensed

**Communication
Plan**

For example, letters to healthcare providers, communications to professional societies, professional education, etc.

**Elements to
Assure Safe Use**

Special requirements or restrictions to optimize safe use of products

**Implementation
System**

System to monitor, evaluate, and improve elements to assure safe use

**Timetable for
Assessment**

Minimum FDA requirement: 18 months, 3 years, and 7 years after REMS approval (only compulsory element for all REMS programs)

*PPI: patient package insert.

Components of a REMS

Of the five components, the two that are most relevant to prescribers are the Medication Guide/Patient Package Insert and Elements to Assure Safe Use

**Medication
Guide/PPI***

Educational tools provided to each patient when drug is prescribed / dispensed

**Elements to
Assure Safe Use**

Special requirements or restrictions to optimize safe use of products

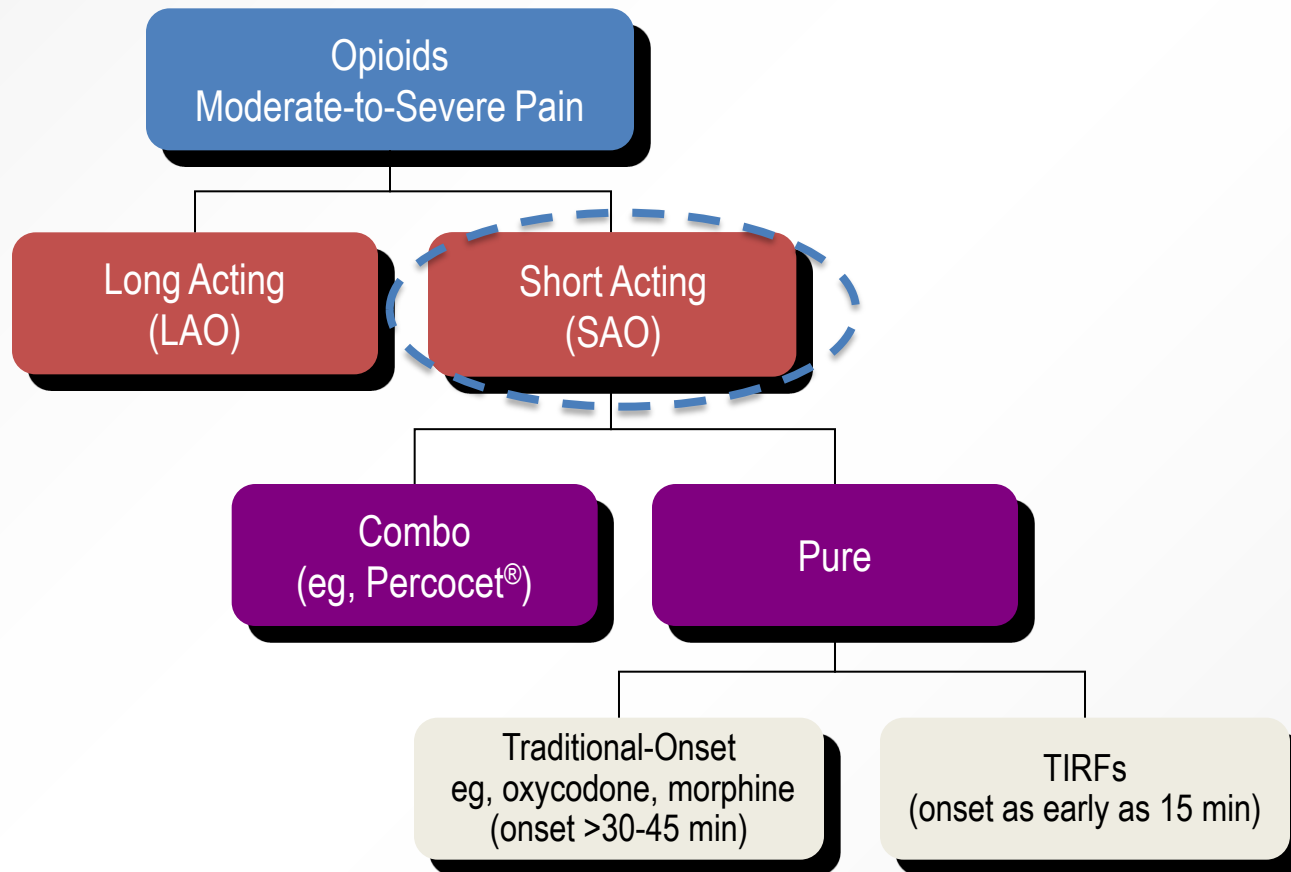
*PPI: patient package insert.

Elements to Assure Safe Use

- > May be required if the drug is associated with a serious adverse event and the medication guide, patient package insert, or communication plan plus assessment are not sufficient to mitigate this risk
- > May require any of the following:
 1. Training / certification of prescribers
 2. Training / certification of pharmacists / pharmacies
 3. Restrictions on where the drug is dispensed
 4. Evidence of patient safe-use conditions
 5. Patient monitoring
 6. Patient enrollment

Clearing Up Confusion About REMS for Opioids

Classification of opioids by type



TIRFs = Transmucosal Immediate-Release Fentanyl products.

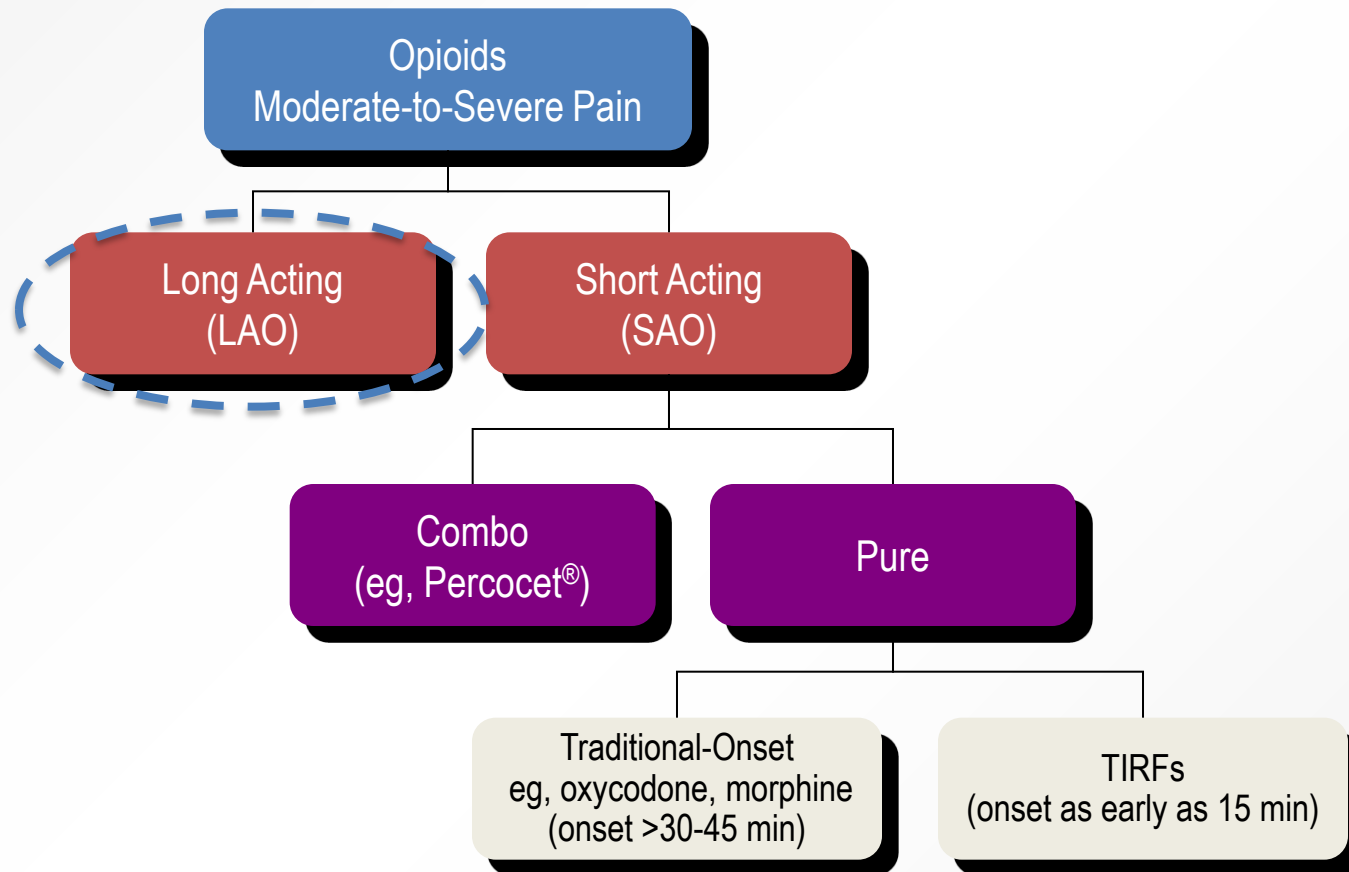
Clearing Up Confusion About REMS for Opioids



- > Short-Acting Opioids – currently no REMS required
 - At an industry meeting in February 2009, FDA was asked, “What is FDA’s position on the possibility that, with a REMS program in place for the long-acting opioids, the abuse community may shift to short-acting or Schedule III opioids?”
 - Agency Response: FDA is examining the possibility that this shift could occur and will take appropriate steps to address it
 - Always refer to FDA web site for a current list of products requiring a REMS
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Clearing Up Confusion About REMS for Opioids

Classification of opioids by type



TIRFs = Transmucosal Immediate-Release Fentanyl products.

Clearing Up Confusion About REMS for Opioids

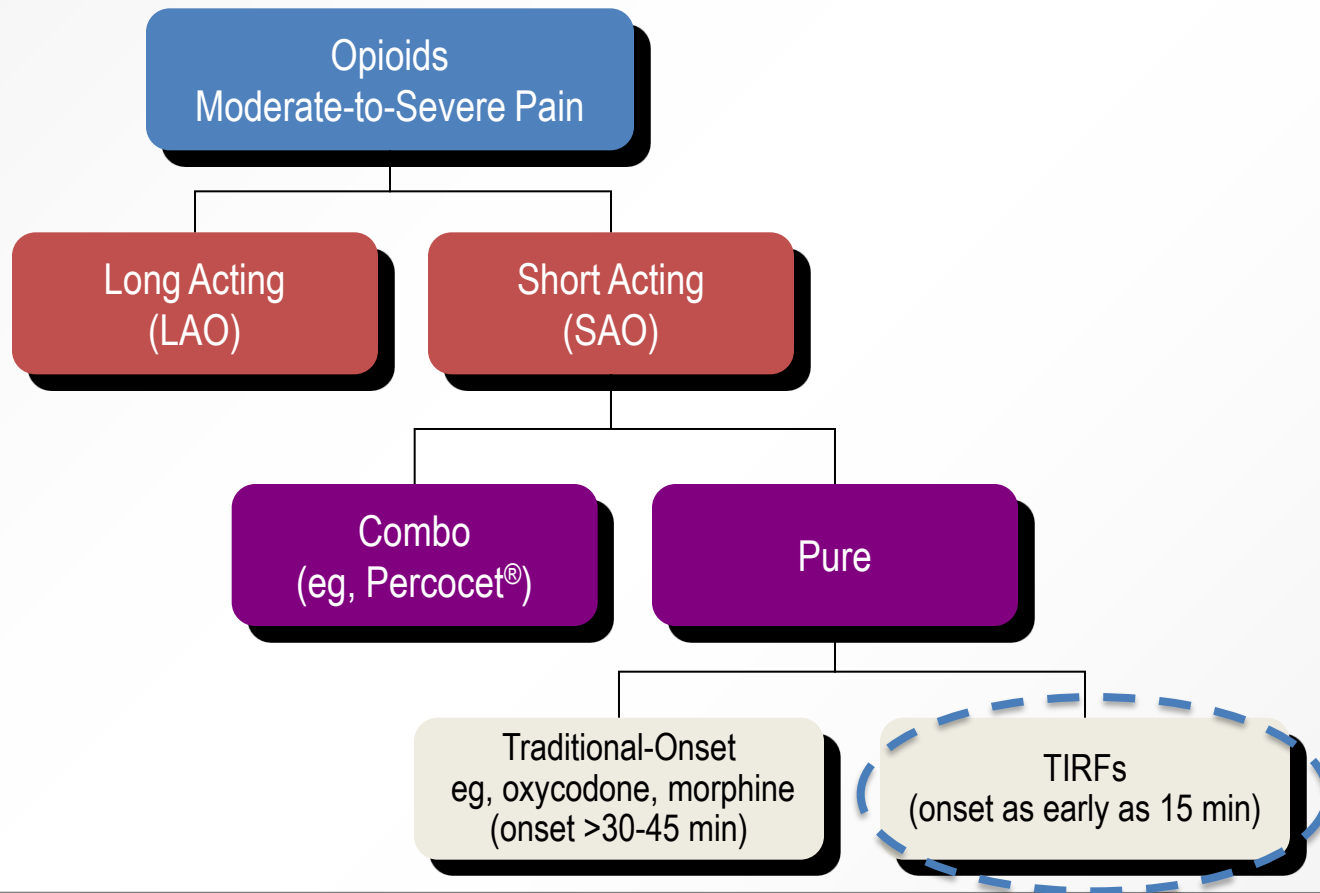


> Long-Acting/Extended-Release Opioids

- In a letter dated April 19, 2011, FDA required manufacturers of long-acting and extended-release opioids to
 - provide educational programs to prescribers
 - provide patient materials that prescribers can use to counsel them on the risks and benefits of opioid use
 - Note: prescriber education is currently not mandatory; although prescribers may continue to prescribe without it, it should be considered a best practice in helping maintain patient safety
 - FDA wants drug makers to work together to develop a single system for implementing the REMS
 - Currently, individual product REMS exist for certain LA/ER opioids
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Clearing Up Confusion About REMS for Opioids

Classification of opioids by type



TIRFs = Transmucosal Immediate-Release Fentanyl products.

Clearing Up Confusion About REMS for Opioids



Rapid-Onset Opioid (ROO) = Transmucosal Immediate-Release Fentanyl (TIRF)

- Currently, individual product REMS exist for TIRFs
- FDA wants TIRF manufacturers to develop a single system (class-wide REMS)
- Several of the currently approved TIRF REMS are similar and it is likely that their REMS will become the class-wide TIRF REMS
- TIRF REMS have different requirements than LA/ER opioid REMS

Approved TIRF REMS As of August 31, 2011
ACTIQ/OTFC
FENTORA
Onsolis
Abstral
Lazanda

Continuity of Care

TIRFs	US Approval	REMS
ACTIQ/OTFC	1999	2011
FENTORA	2006	2011
Onsolis	2009	2009
Abstral	2011	2011
Lazanda	2011	2011

> Specific Issues

- Maintaining continuity of care for current patients
- FDA has allowed a transition period to ensure continued patient access



TIRF REMS Review

Based on ACTIQ and FENTORA REMS

ACTIQ and FENTORA are opioid analgesics indicated only for the management of breakthrough cancer pain in adult patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

ACTIQ is indicated for patients aged 16 years and older.

TIRF REMS Program

A Model of a Transmucosal Immediate-release Fentanyl REMS System*



ACTIQ and FENTORA REMS Program

> Overview

- ACTIQ and FENTORA can only be dispensed by an enrolled pharmacy and only to patients who have been prescribed ACTIQ or FENTORA by an enrolled prescriber
- The ACTIQ and FENTORA REMS program includes distributor, prescriber, pharmacy, and patient responsibilities



Prescriber Enrollment



1. Review the REMS educational module
2. Complete the knowledge assessment
3. Complete the prescriber enrollment form
 - Agree to follow the steps in the REMS program

Inpatient/Outpatient Pharmacy Enrollment



1. Review the REMS educational module
2. Complete the knowledge assessment
3. Complete the pharmacy enrollment form
 - Agree to follow the steps in the REMS program



TIRF REMS Educational Module Based on ACTIQ and FENTORA REMS

ACTIQ and FENTORA are opioid analgesics indicated only for the management of breakthrough cancer pain in adult patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

ACTIQ is indicated for patients aged 16 years and older.

Definition of Opioid Tolerance

Opioid-tolerant = at least 60 mg/day oral morphine (or equivalent) around-the-clock for 1 week or longer

Generic name	Dose for opioid tolerance
Morphine	60 (oral) mg/day
Transdermal fentanyl	25 mcg/hour
Oxycodone	30 (oral) mg/day
Hydromorphone	8 (oral) mg/day
Oxymorphone	25 (oral) mg/day

Ensuring patients are opioid-tolerant prior to prescribing a TIRF product is essential to mitigating risk of overdose

Contraindications

- > ACTIQ and FENTORA are contraindicated for patients who are not already tolerant to opioids
 - Serious adverse events, including deaths, have occurred
 - > ACTIQ and FENTORA are contraindicated in acute or postoperative pain, including headache/migraine and dental pain
 - > ACTIQ and FENTORA are contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl
-

Appropriate Use

- > Assess patients for risk factors before prescribing, monitor patients, and keep detailed records of prescribing
 - > ACTIQ and FENTORA are NOT equivalent to each other or to any other fentanyl formulations on a microgram-per-microgram basis
 - Do not convert patients from another immediate-release fentanyl product to ACTIQ or FENTORA without re-titrating according to the prescribing information
 - > Follow dosing instructions carefully
 - > Remind patients/caregivers about safe storage of used and unused medication to protect against accidental exposure and diversion
-

Patient Counseling

- > Explain opioid tolerance
 - Instruct patients that, if they stop taking their around-the-clock opioid medication, they must stop taking ACTIQ or FENTORA
 - > Instruct patients to take ACTIQ and FENTORA exactly as prescribed
 - > Instruct patients not to switch from ACTIQ or FENTORA to another fentanyl product without discussing it with their physician
 - > Instruct patients never to share ACTIQ or FENTORA with anyone else, even if that person has the same symptoms
-

Prescriber Responsibilities



1. Agree to counsel patients, emphasizing the importance of opioid tolerance
 2. Review and complete a Patient–Prescriber Agreement (PPA) form
 3. Review and provide a Medication Guide to patients
-

Inpatient/Outpatient Pharmacy Responsibilities



Inpatient Pharmacy:

1. Pharmacist in Charge or delegate will establish a system for training relevant staff within the institution

Outpatient

1. Pharmacist in Charge or delegate will establish a system for training relevant staff within the pharmacy
 2. An update to their software allows automated verification that prescriber and pharmacy are enrolled and that the Patient–Prescriber Agreement (PPA) has been completed
 3. When conditions are met the pharmacy prints a prescription label and dispenses prescription with a copy of the Medication Guide
-

Patient Responsibilities



1. Patient accepts counseling, reads and retains signed Patient–Prescriber Agreement (PPA), and retains Medication Guide
2. Take prescription to enrolled pharmacy



How does the ACTIQ and FENTORA REMS education fulfill the TIRF REMS requirements?

ACTIQ and FENTORA are opioid analgesics indicated only for the management of breakthrough cancer pain in adult patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

ACTIQ is indicated for patients aged 16 years and older.

Components of a TIRF REMS

Of the five components, the two that are most relevant to prescribers are the Medication Guide/Patient Package Insert and Elements to Assure Safe Use

How do these responsibilities fulfill the TIRF REMS requirements?

Medication Guide/PPI*

Educational tools provided to each patient when drug is prescribed / dispensed

- ✓ **Medication Guide provided to and reviewed with patient**

Elements to Assure Safe Use

Special requirements or restrictions to optimize safe use of products

- ✓ **REMS Education Program and Knowledge Assessment for Prescribers and Pharmacies**
- ✓ **REMS-certified pharmacies only**
- ✓ **REMS system verifications at pharmacy**

*PPI: patient package insert.

READY FOR REMS

Linking REMS with Best Practices

A Model of a Transmucosal Immediate-release Fentanyl REMS System*



Best Practices: Prescribing

- > Awareness of risks and safety information
- > Appropriate patient selection
 - Opioid tolerance
- > Appropriate dosing
 - Conversion
- > Documentation



Best Practices: Patient Communication

- > Documented risk assessment
- > Document patient education
 - Safe use
 - Storage and disposal
- > Open dialogue with patients
- > Opioid agreement
- > Mutual responsibilities



Best Practices: Patient Support

- > Medication Guide provides:
 - Information on medication risks
 - Reference on safe use and storage for patient / family / caregiver
- > Patient encouraged to keep prescriber informed of any changes in drug regimen / schedule
- > 2-Way opioid agreement documents understanding of and commitment to safe use and storage
- > Enrolled pharmacy provides consistent and knowledgeable contact in the community



Administrative Implications for Prescribers

> Additional time

- Prescriber enrollment
(eg, every 2 years)
- Potential longer patient
visit to review REMS
- Office staff training



Tip: Pre-identify a REMS expert in your office to track REMS requirements, talk with representatives, and prepare patients

What Next?

- > You may have already enrolled in another TIRF REMS (Onsolis, Abstral...)
 - > Coming September 20th: Actiq and FENTORA REMS
 - Prescribers will be notified once available
 - Go to web site www.actiqandfentorarems.com and follow instructions to enroll
 - Important to enroll right away to maintain access for your Actiq and FENTORA patients
-

Resources to Help You Prepare

- > In the meantime, stop by the Ready For REMS Resource Lounge in Nolita 1 (across the hall) open from 9:30 AM–7:30 PM today
 - > Pick up these and other resources to help you, your staff, and your patients prepare:
 - HCP REMS Implementation Guide
 - FDA/DEA handouts
 - Patient Brochure on safe use
 - TIRF patient counseling reminders
 - > Meet the Expert Sessions
-