Abuse Deterrent Formulations: The Federal Response

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Disclosure

I have no financial disclosures

The thoughts delivered during this presentation are mine only and do not reflect the policy of the FDA

Objectives

To trace the development of abuse deterrent formulations of opioids

To define the expectations for this class of drugs

To demonstrate the effectiveness of ADFs in the continuing attempts to modulate opioid abuse

To consider the unintended consequences of the marketing of ADFs

The History of the Development of ADFs

- 1995 - Development of long acting, extended release opioids marketed to treat pain with fewer side effects – including addiction
- Assertion based on low peak concentrations and release of opioid over 8 -12 hours.
- Individual pills contained large amounts of oxycodone, morphine, and oxymorphone
- Some contained 80 mg oxycodone with daily MSE well over 120 mg.
- Development of these formulations was coincident with change in the philosophy of pain management – " opioids safe and effective"

The History of ADFs – Back Story

- Long standing chronic use/abuse of prescription and illicit opioids in the U.S. – The Soldiers Disease more than 100 years old.
- The problem of opioids is about 4,000 years old
- During the 20th century intermittent opioid spikes followed by attempts at resolution by law enforcement
- After development of LA/ER opioids there was an explosion of illicit use, addiction and a substantial rise in mortality from opioid abuse
- This was followed in the 2000s by a substantial federal response – and the suggestion that ADFs would play a substantial role in reducing the abuse of opioids

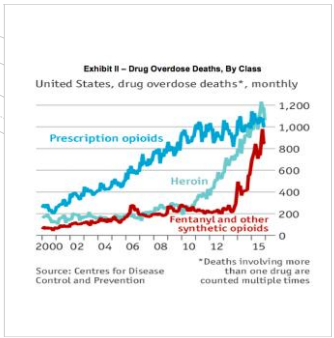
FDA

1. The FDA was fully aware and supportive of this effort by industry
2. Pressure to provide adequate pain control was intense
3. The past history of opioids producing mayhem was considered but other societal issues were considered more important

Beautiful!

Aren't they?

Then This Happened



The Development of ADFs

- Discussions between industry and FDA
- Development of guidance for the development and testing of ADFs
- Substantial outlay of capital by industry
- Multiple methods produced to create abuse deterrence
- General agreement that focus should be on intravenous and intranasal conversion – highest rate of mortality

Various Methods Used to Produce Abuse Deterrence

- ADF opioids are specially formulated to be more difficult to manipulate in order to deter chewing, intranasal, and intravenous routes of abuse.
- However, none of the FDA-approved ADFs deter the most common form of abuse - swallowing more than the intended dose of intact capsules or tablets.

Opioid Products with FDA-Approved Abuse-Deterrent Labeling
OxyContin®TR (Oxycodone, Purdue)
Embeda® (Morphine + naltrexone, Pfizer)
Targiniq® (Oxycodone + naloxone ER, Purdue)
Hysingla® ER (Hydrocodone, Purdue)
Morphabond® (Morphine ER, Inspirion & Daiichi Sankyo)
Xtampza® ER (Oxycodone, Collegium Pharmaceutical Inc.)
Troxyca® ER (Oxycodone + naltrexone, Pfizer)
Arymo® ER (Morphine, Egalet)
Vantrela™ (Hydrocodone, Teva)
RoxyBond® (Oxycodone, Inspirion & Daiichi Sankyo)

Defining Abuse Deterrence

The Questions

- How does one measure deterrence?
- What is the optimal level of deterrence?
- Should all formulations be required to have the same level of deterrence to IV and intranasal use?
- What if a particular formulation deters intranasal use but does not substantially reduce IV use?

Other Questions

- What is the impact of allowing more opioids on the market?
- What message does the regulatory authority send by expanding dramatically the number of high dose opioids being marketed?
- What is the expectation for the immediate and future use of non ADF formulations?
- Can the impact of ADFs on the drug use behavior of non ADF opioids be predicted?

The Outcomes of Initial Development

- Some agreement that ADFs would not inhibit oral intake of large quantities of the drug
- The higher cost of ADFs might reduce the use of these opioids
- Overtime it was suggested that ADFS could replace non ADF formulations

Critical Issue

"Abuse Deterrent Formulation" was open to prescriber's imagination

Suggestions that ADF equaled addiction-free arose

Industry may have used this misinterpretation to market a higher profit product

Initial Outcomes

01

Many formulations were produced, tested, and evaluated by scientists and medical officers at the Agency

02

Many more questions arose – Many Advisory Committee meetings 2015 – 2017

Outside advisors asked more questions

Of The ADFs Which Have Received FDA Approval:

How many have actually been approved as abuse deterent?

How Many of the ADFs Have Been Labeled "Abuse Deterrent" by the FDA?

- Answer : Not one
- The key is: "behavior which would be expected to deter abuse" in current drug literature and labeling.

- Why?:
- Post Marketing Drug Evaluations have not demonstrated unequivocal deterrence in large populations

FDA's Attempts to Understand the Behavior of this Class and to Regulate

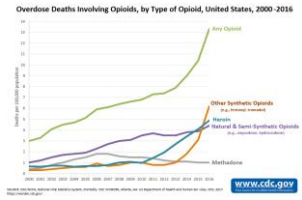
Lessons Learned

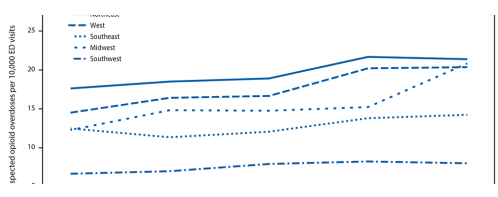
- ADFs will not prevent anyone from swallowing a large number of pills
- Users are increasingly sophisticated in their ability to counter act methods used to deter abuse
- Sometimes, recipes for counteracting the mechanism was on the web before the end of an Advisory Meeting

More Lessons

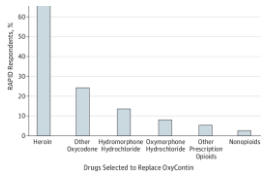
The presence of ADFs did not reduce the number of deaths from opioid poisoning. → Users that were unable to find quantities of available prescription opioid likely switched to heroin, fentanyl , and its congeners. → In one episode, the use of an ADF in a specific population was shown to have dramatically increased the number of cases of Hepatitis C and AIDS

More ADFs Has Not Reduced the Death Rate

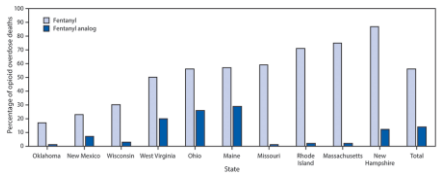




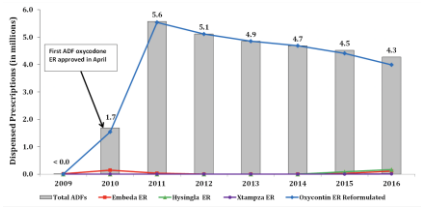
Rates of ED Visits



If the Method is Successful…



The Replacements Become More Dangerous



More Lessons

In one circumstance, exposure to large quantities of drug was related to renal failure

Likely secondary to an additive to the opioid compound

Post Marketing Drug Evaluation – Why Not?

There is really very little incentive for the pharmaceutical firms to provide post marketing data to the FDA

If there is no specific safety signal in the Agency's analysis of the behavior of a drug once marketed, their effectiveness in enforcing this is minimal

ICER Presentation

February 2018

Institute of Clinical and Economic Review

Presentation

February 2018

Abuse-Deterrent Formulations of Opioids: Effectiveness and Value

Presentation to the Massachusetts Drug Formulary Commission

February 5, 2018

ADF Evidence: Pre-market Studies

- Identified 15 randomized crossover trials evaluating oral or intranasal abuse of ADFs vs. non-ADFs in the same class.
- Study participants were *healthy, non-dependent recreational drug users.*
  - Observed outcomes may not be generalizable to chronic pain patients.
- Relative to non-ADF comparators, all ADFs produced statistically-significantly lower scores on VAS "drug liking" and "take drug again" measures.
  - There is no established threshold for what constitutes a clinically-important difference.
  - It is uncertain whether these endpoints are predictive of real-world abuse.

Post-market Studies (Real World Evidence)

- Post-market data is an FDA requirement for all ADFs; however, evidence is currently available only for OxyContin.[a]
- All 26 identified studies were non-randomized, examining the aggregate periods before (1-2 years before) and after (1-4 years after) reformulation of OxyContin as an ADF.
  - Variety of data sources (e.g. patients entering substance abuse programs; medical claims databases; police reports; spontaneous adverse events).
  - No prospective studies in chronic pain patients.
- **Abuse and Misuse:** Data suggest a 12% – 75% decline in the rate of OxyContin abuse after reformulation, in different study populations and at different time points.
- **Overdose and overdose death:** Limited evidence indicates a 34% to 65% decline in the rates of overdose and overdose deaths attributed to OxyContin after the ADF was introduced.
- **Diversion:** Limited evidence

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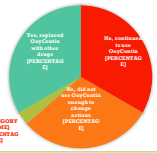
However, several studies also found an increase in the abuse and overdose death from other prescription opioids or heroin during the same time periods, suggesting there may have been a shift in abuse patterns. Examples:

Study among **patients entering substance use disorder programs.**

Changes in the past month prevalence of abuse following reformulation:

- OxyContin: 42% ↓
- Heroin: 100% ↑
- ER oxymorphone: 38% ↑

Direct interview with 153 participants entering substance abuse program: *Did ADF OxyContin influence the drugs that participants used for abuse?*



Cicero TJ, Ellis MS. Abuse-deterrent formulations and the prescription opioid abuse epidemic in the United States: Lessons learned from OxyContin. *JAMA Psychiatry*. 2016;73(5):424-425.

Key Policy Take-Aways

- Policymakers should be aware that no evidence exists to evaluate the balance of positive and unintended negative effects of mandatory ADF substitution laws.
- Policymakers and clinical leaders should consider measures to phase in ADFs while ensuring adequate support for other elements of a multi-pronged approach to the opioid crisis.
- Manufacturers and payers must recognize a shared commitment to making ADFs affordable to patients and to the health system.
- The term "abuse-deterrent formulation" presents a significant risk that the addictive and abuse potential of ADFs will be misunderstood. The FDA should reconsider whether it can use "tamper-resistant formulation" instead.

Observations

01 ADF's have not reduced death rates from opioid toxicity

02 ADF's have increased the cost of opioids for many patients

03 ADF technology can be overcome in most cases

04 ADF's do not prevent the most common form of abuse – swallowing multiple pills

Observations about the FDA

1. Decision making is so opaque that there is often little chance to point out the fallacies in thinking until long after marketing.
2. In the case of ADFs, millions were spent and there is no proof that there was any positive effect.
3. The Agency does not have the authority to enforce many of the requirements for post market testing.

Summary 1

- The approval and marketing of LA/ER Opioids was carried out without due consideration of secondary consequences
- The repercussions of the damage done to the public health was the initiation of production of ADFs
- Neither of these historical observations were tied to profound changes in the education of prescribers about the implications of their behavior

Summary 2

- The regulation of opioids is terribly complex
- Industry was asked to assist in a solution
- This was a good faith effort by the Agency
- It is likely that this effort has done more harm than good.

Questions for the Future

- Should the approval process for opioids be altered?
- Should ADFs be taken off of the market?
- Should ADF labeling be substantially changed?
- Should intense education concerning opioid use and abuse be mandated?

Direct interview with 153 participants entering substance abuse program: *Did ADF OxyContin influence the drugs that participants used for abuse?*

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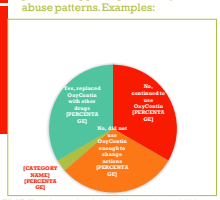

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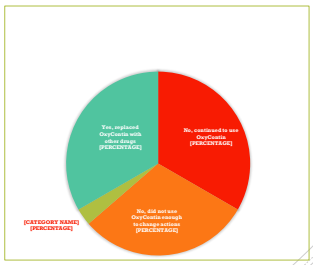
Outcome



Results of ICER Analysis

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