Abuse Deterrent Formulations of Opioids: Effectiveness and Value

Draft Evidence Report

May 5, 2017

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The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. ICER receives funding from government grants, non-profit foundations, health plans, provider groups, and health industry manufacturers. For a complete list of funders, visit http://www.icer-review.org/about/support/. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at http://www.icer-review.org

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For a complete list of stakeholders from whom we requested input, please visit: https://icer-review.org/material/adf-stakeholder-list/

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Table of Contents

List of Acronyms Used in this Report

ADF	Abuse-deterrent Opioid Formulation with an FDA label
AHRQ	Agency for Healthcare Research and Quality
CI	Confidence interval
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare and Medicaid Services
DEA	Drug Enforcement Administration
DSM	Diagnostic and Statistical Manual
ER	Extended release
ER/LA	Extended release/Long acting
FDA	Food and Drug Administration
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IR	Immediate release
LA	Long acting
MAT	Medication Assisted Treatment
NAVIPPRO	National Addictions Vigilance Intervention and Prevention Program
NIH	National Institutes of Health
NPDS	The National Poison Data System
ND	No data
NR	Not reported
NSDUH	National Surveys on Drug Use and Health
OC	OxyContin
ORF	Reformulated OxyContin
PDMP	Prescription Drug Monitoring Program
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RADARS	Researched Abuse, Diversion, and Addiction-Related Surveillance System
REMS	Risk Evaluation and Mitigation Strategy
RCT	Randomized controlled trial
SE	Single entity
SKIP	Survey of Key Informants' Patients Program
VAS	Visual Analog Scale

Executive Summary

An executive summary will be provided as part of the full Evidence Report.

1. Background

1.1 Introduction

Background

Opioids are substances that act on specific receptors in the brain and produce a variety of effects such as pain relief, euphoria, respiratory depression, constipation and others.[1] They are either directly extracted from opium, obtained from the pods of poppy varieties, or produced semi-synthetically and synthetically. Opioids are used to treat cases of acute and chronic pain that arise from a variety of causes, ranging from trauma to advanced illness. Every year, 100 million people in the United States suffer from pain. Among those patients with pain, 9-12% of these individuals will experience pain that becomes chronic, meaning lasting longer than three months.[2] Opioid therapy is an essential component of pain management for many patients, but the addictive and euphoric properties of these drugs make them vulnerable to misuse, abuse, addiction, and possible death by overdose.

Since 1999, the number of deaths from prescription opioids in the U.S. has increased nearly fourfold, rising in parallel with the volume of dispensed prescriptions;[3] since 2009, use of prescription opioids has killed more persons annually than car accidents.[4] The health care utilization consequences are also significant; for every one death from prescription opioids, it is estimated that there are 10 treatment admissions for abuse, 32 emergency room visits for misuse or abuse, 130 people who are dependent, and 825 people who report non-medical use of these drugs.[5]

A variety of measures have been implemented to attempt to mitigate the opioid abuse crisis, one of which is the introduction of abuse-deterrent formulations (ADFs) of these drugs. An increasing number of ADF forms of extended release prescription opioids, approved by the FDA based on guidance published in 2015,[6] have reached the market during the last few years.[7] The following table provides an overview of different approaches for obtaining abuse-deterrence:

Table 1. Overview of Abuse-Deterrent Approaches

Abuse-deterring approach	Properties	Examples
Physical and chemical barriers	Resists cutting, grinding, pulverizing; dissolving produces a viscous substance that cannot be drawn into a syringe	High-molecular-weight polyethylene oxide in Oxycontin®, Arymo®, Hysingla®
Agonist/antagonist combination	Opioid with a corresponding antagonist; antagonist released only through tampering.	Naltrexone in Embeda®
Aversive agent	Opioid is combined with an aversive agent released during tampering	Niacin used in Oxecta® for intranasal abuse-deterrence. Oxecta® is not an FDA approved ADF.
Prodrug	Opioid is released after the parent drug is ingested and metabolized (usually requires stomach enzyme); opioid is not activated through alternative route of administration (e.g., snorting)	Activation of PF614 in the gastrointestinal tract by pancreatic trypsin leading to the production of free oxycodone.[8]

As specified by the FDA, the abuse-deterrent technology does not change the addictive properties of the opioid itself, and while ADFs deter abuse, they are not abuse proof,[6] and abusers are very innovative for circumventing abuse-deterrent technologies.[9]

ADFs are part of multipronged strategies and actions to combat the public health epidemic of prescription opioid deaths. In many states, legislation has been introduced to combat the epidemic of overdose deaths from prescription opioids, often with language encouraging consideration of use of ADFs.[10] In New England, legislation in Maine and Massachusetts mandates insurance coverage of ADFs. Other strategies include educating clinicians to reduce initiation of opioid use, shortening the duration of prescriptions, and monitoring of prescriptions.

This report will focus on the effectiveness, safety, and economic impact of ADFs relative to non-ADF opioid treatment, and consider the evidence and potential cost-effectiveness of different strategies to replace non-ADF formulations with ADFs in specific populations.

Scope of the Assessment

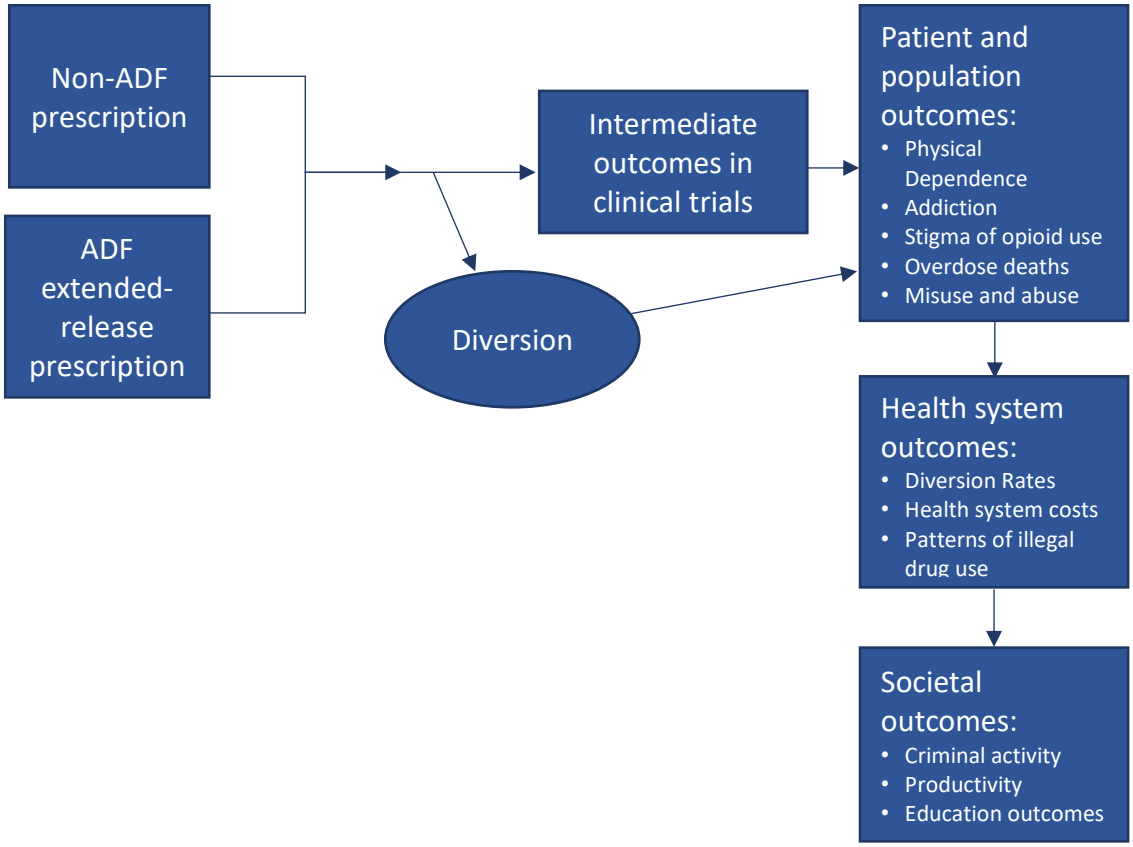
The scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. We conducted a systematic literature review using best practices for search strategy development and article

retrieval. Evidence was culled from randomized controlled trials as well as high-quality systematic reviews; observational studies were considered given the difficulty of conducting randomized controlled trials for non-medical use of opioids. Our evidence review included input from experts, patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Analytic Framework

The analytic framework for this assessment is depicted in Figure 1.

Figure 1. Analytic Framework



Populations

The population of focus for the systematic review of the clinical impact of ADFs included all persons using opioids for therapeutic (i.e., both as prescribed and misused) and non-therapeutic purposes (i.e., abuse, addiction). For modelling purposes, the population has been defined more narrowly, as described in section 6 of the present report.

Interventions

The interventions of interest were abuse-deterrent opioid formulations with an FDA label (ADFs). Opioids with abuse-deterrent properties but without an FDA label recognizing these properties were not included in the assessment. Currently, ten opioid products have U.S. FDA-approved abuse-deterrent labeling.[11] However, only five products are available in the U.S. marketplace as of April 30, 2017. The nine ADFs that were included in this review are for extended-release (ER)

opioids only. RoxyBond®, the only ADF for an immediate release (IR) oxycodone formulation, was approved by the FDA on April 20, 2017[7] and has therefore not been included.

Oxycodone:

- Oxycontin® (oxycodone extended release, available on the market)
- Xtampza® (oxycodone extended release, available on the market)
- Troxyca® ER (oxycodone + naltrexone extended release; approved, but currently not available on the market)
- Targiniq® ER (oxycodone + naloxone extended release; approved, but currently not available on the market)

Hydrocodone:

- Hysingla® ER (hydrocodone extended release; available on the market)
- Vantrela™ ER (hydrocodone extended release; approved in January 2017, but not currently on the market)

Morphine:

- Embeda® (morphine + naltrexone extended release; available on the market)
- Morphabond™ (morphine extended release; approved, but currently not available on the market)
- Arymo™ ER (morphine extended release, approved in January 2017, but not currently on the market)

Comparators

The comparators of primary interest included non-abuse-deterrent formulations of specific opioids as appropriate.

Outcomes

Patient & Population Level: The impact of ADFs on individual patients was assessed by evaluation of the following outcome measures, including addiction rates and other clinical outcomes, but many of which are surrogate outcomes currently being used by the FDA in granting marketing approval. Importantly, outcomes related to pain alleviation and tolerability were not included, as ADFs are considered bioequivalent to their relevant non-ADF counterparts.[12]

- Patient/Population Level Outcomes
    - Abuse Potential Endpoints
        - VAS measures (0-100) of drug liking, take drug again, and overall drug liking

        - Tampering
    - Real World Evidence of Abuse and Misuse
        - Overdose and fatality
        - Abuse/misuse
            - Physical evidence of misuse/abuse
            - Self-reported misuse/abuse
            - Route of administration for misuse/abuse
        - Addiction

- Health System Level Outcomes
    - Health system costs
    - Drug loss and diversion rates
    - Patterns of illegal drug use
    - Doctor shopping
    - Prescription utilization

- Societal Level: Where evidence is available, we also sought to capture the societal impact of ADFs, including outcomes related to the criminal justice system, worker productivity, and education.

The analysis of outcomes was based on a systematic literature review of peer reviewed publications and on evidence from the grey literature meeting ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Timing

Evidence on intervention effectiveness and harms were derived from studies of any duration.

Settings

All relevant settings were considered, including inpatient, clinic, office, and home settings.

2. The Topic in Context

2.1 Overview

Opioids are risky medications. While they are the strongest analgesics available, they also are responsible for abuse, addiction, and death. This is not surprising, as both therapeutic and harmful effects rely on the same receptor in the central nervous system and are therefore present in all opioids. Together with Canada, the U.S. has the highest per capita consumption of prescription opioids worldwide.[13-15] Around 10% of patients receiving opioids for the first time use them for more than three months. Of those patients, about 25% begin non-medical use and 10% become addicted.[16] ADFs may deter important steps towards addiction: chewing, intranasal and intravenous routes of abuse.[17] Swallowing pills whole is the most common form of abuse and is not deterred by ADFs.[18]

In this report, the term ADF is only used for these drugs with abuse-deterrent properties as recognized by the FDA. In order to be defined as 'abuse deterrent' in the drug label, there must be sufficient evidence of abuse deterrence according to FDA standards, which is based on premarket studies and mandatory real world studies after drug approval.[6]

The dramatic and parallel increase in the use of prescription opioids and deaths from overdose of these substances has leveled off recently, but a continuing increase in opioid deaths is now driven by heroin and illegally produced synthetic opioids such as fentanyl.[3]

However, despite the overall increase in opioid prescriptions, many patients with chronic pain receive inadequate analgesia.[19] Some patients report increased difficulties of access to ongoing treatment with prescription opioids, as described below in the section detailing insights gained from discussions with patients and patient groups.

2.2 Use and Abuse of Prescription Opioids

Use of Prescription Opioids

Opioids affect the mu receptor in the spinal cord and in the brain to reduce pain.[20] The mu receptor in the brain is also central to the feelings of reward or pleasure, leading to abuse.[21] The analgesic effects are mediated mainly through the mu receptors' release of substance P in the spinal cord,[20,22] the central neurotransmitter for pain, whereas the rewarding effects involves the dopaminergic system which is implicated in all addictive behavior, including that of alcohol and nicotine.[23]

Most opioids are short-acting and require dosing approximately every 4 hours, with the exception of methadone, which requires dosing only two to three times per day.[24] Methadone is intrinsically long acting (LA), while the other opioids require special formulation that enable extended release (ER). Methadone and the ER opioids are often lumped together under the term ER/LA opioids. In December 1995, OxyContin™ was the first ER opioid approved by the FDA.[7] ER formulations represent about 10% of all opioids prescribed.[25,26] The bioavailability of different opioids varies with the route of administration and can be as low as 10% for an oral administration of oxymorphone.[27]

During the beginning of second half of the 20th century, opioids were infrequently used in the treatment of chronic pain.[28] In 1992, the Agency for Health Care Reseach and Quality (AHRQ) issued a guideline for acute pain management stating that "patients have a right to treatment that includes prevention of or adequate relief from pain and that fears of postsurgical addiction to opioids are generally groundless."[29] Pain management was promoted and recognized as a human right[30,31] and pain included as a "fifth vital sign" in the pain management standards of the Joint Commission on Accreditation of Healthcare Organizations, to be monitored with the same vigilance as blood pressure, pulse, temperature, and respiratory rate.[32,33] In 2012, patient experience in regard to pain management became one component of the newly created Hospital Value-Based Purchasing (HVBP) program, which ties a portion of hospital payment to performance on quality and cost, possibly encouraging physicians to increase the prescription of opioids.[34] These new professional standards, combined with aggressive marketing[35] led to a fourfold increase in the volume of dispensed prescription opioids between 2000 and 2010.[36]

Defining Terms of Abuse

The concepts and terminology of drug related problems are constantly evolving and sometimes contradictory between the different medical specialties. For example, in psychiatry, the Diagnostic and Statistical Manual (DSM-III) chose the term dependence to refer to uncontrolled drug-seeking behavior.[37] In other branches of medicine, the term dependence refers to physical dependence.[38] In the fifth revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the terms abuse and dependence have been replaced with the term substance use disorders.[37]

For our report, we will use the terms abuse, dependence, and addiction with following meanings:

- **Abuse** refers to the "intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect."[6]
- **Dependence** refers to physical dependence: "a state of adaptation that is manifested by a drug class–specific withdrawal syndrome that can be produced by abrupt cessation, rapid

dose reduction, decreasing blood level of the drug, and/or administration of an antagonist."[38]

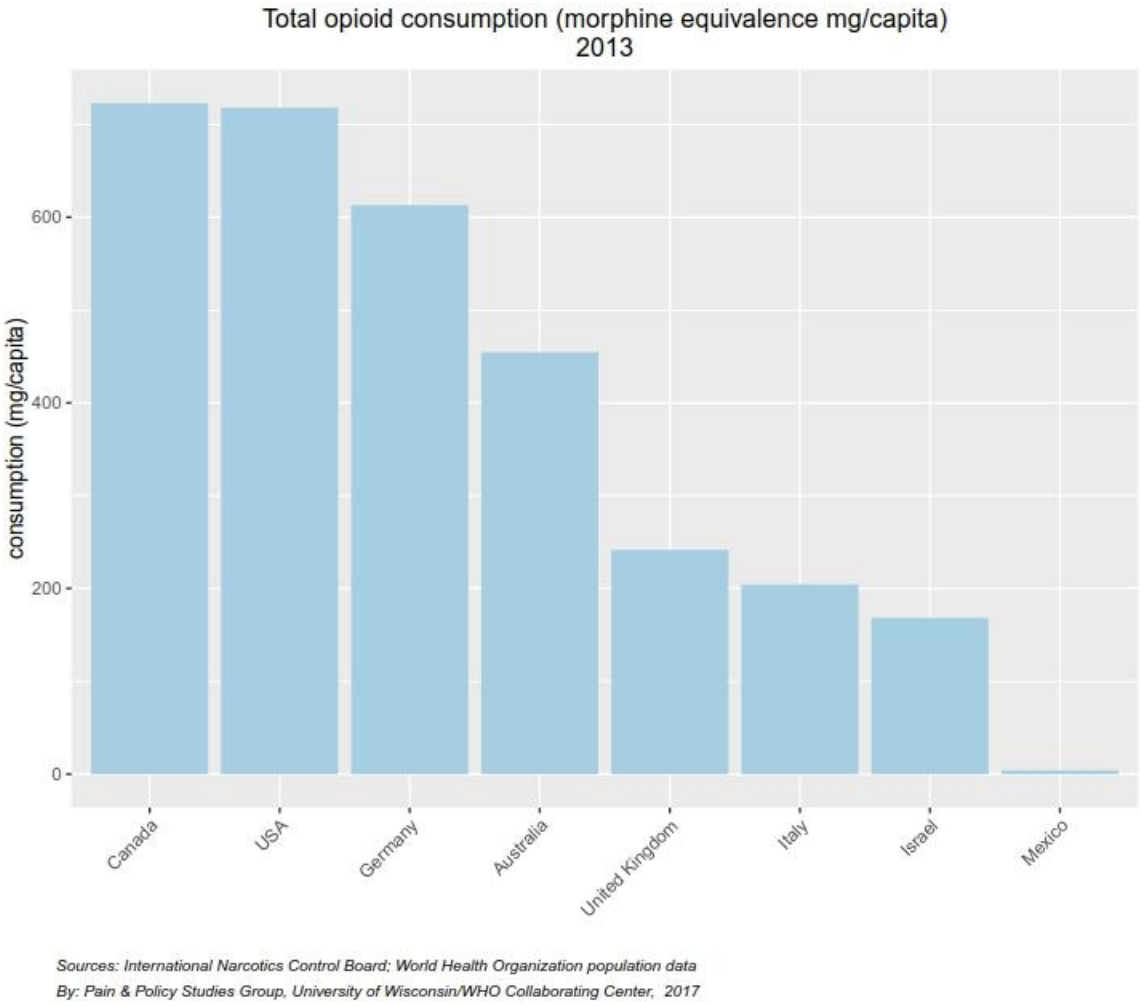
- **Addiction** refers to a "primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving."[38]

Abuse and the Opioid Epidemic

In today's pharmacotherapy, the use of opioids is clinically limited to the treatment of acute or chronic pain as well as the treatment of opioid addiction with methadone. Pain is the most common complaint leading a patient to a physician, and opioids are the most common medications prescribed in the U.S.[39] Diseases of the musculoskeletal system and connective tissue are the predominant indication for both IR and ER opioids with around half of all prescriptions. Cancer accounts for 5 to 10% of prescriptions,[25,40] including treatment in palliative care but also chronic pain in long-term cancer survivors.[41]

The terms opioid overprescribing and overconsumption are often used to describe the current level of opioid use in the US.[42] However, it is extremely difficult to define an appropriate level of overall population-based therapeutic opioid use. Using data from the International Narcotics Control Board, an Adequacy of Opioid Analgesic Consumption measure has been proposed to compare the level of opioid use worldwide for pain treatment. This measure is based on country mortality data for cancer, HIV, and injuries, and is normalized with the average opioid consumption for the top 20 countries with the highest Human Development index.[13] A level of 100% or greater of the Adequacy of Opioid Analgesic Consumption measure is defined as an adequate level of consumption. In 2010, only 7.5% of the world population had adequate consumption with a level of 100% or greater of the Adequacy of Opioid Analgesic Consumption measure.[14] Worldwide, opioid consumption is highest in Canada and the U.S. (Table 2). In the U.S., the volume of dispensed prescription opioids has stabilized recently due to different policy initiatives.[43]

Table 2. Comparison of Total Opioid Consumption[15]



Our clinical knowledge of abuse and addiction is increasingly informed by our understanding of neurobiological mechanisms.[44] Addiction is, however, not simply "a disease of exposure;" a person must also be vulnerable (e.g. genetically), and the exposure must occur at a vulnerable time, such as under conditions of stress or due to age.[45] However, validated tools for predicting an increased risk for abuse are not available.[46]

In susceptible individuals, the exposure to opioids for relieving pain can lead to a spiral of abuse, addiction, and death. Around 10% of patients receiving opioids for the first time will be using them for more than three months. Of those patients, about 25% become non-medical users and 10% become addicted.[16] The progression from medical use to non-medical use, the natural history of abuse and addiction, has not been very well studied. It is generally believed that chewing an ER

opioid is an important step towards addiction, followed by intranasal and intravenous routes of abuse.[17] However even among patients entering drug rehabilitation programs, oral abuse of the IR formulation or the manipulated ER formulation remains the major route, with the exception of morphine (Table 3).

Table 3. Estimated Prevalence of Routes of Abuse[47]*

Prescription Opioid Analgesic	Oral	Snort	Inject
Hydrocodone	88%	25%	<10%
Oxycodone	76%	45%	22%
Morphine	40%	29%	66%
Methadone	71%	10%	<10%

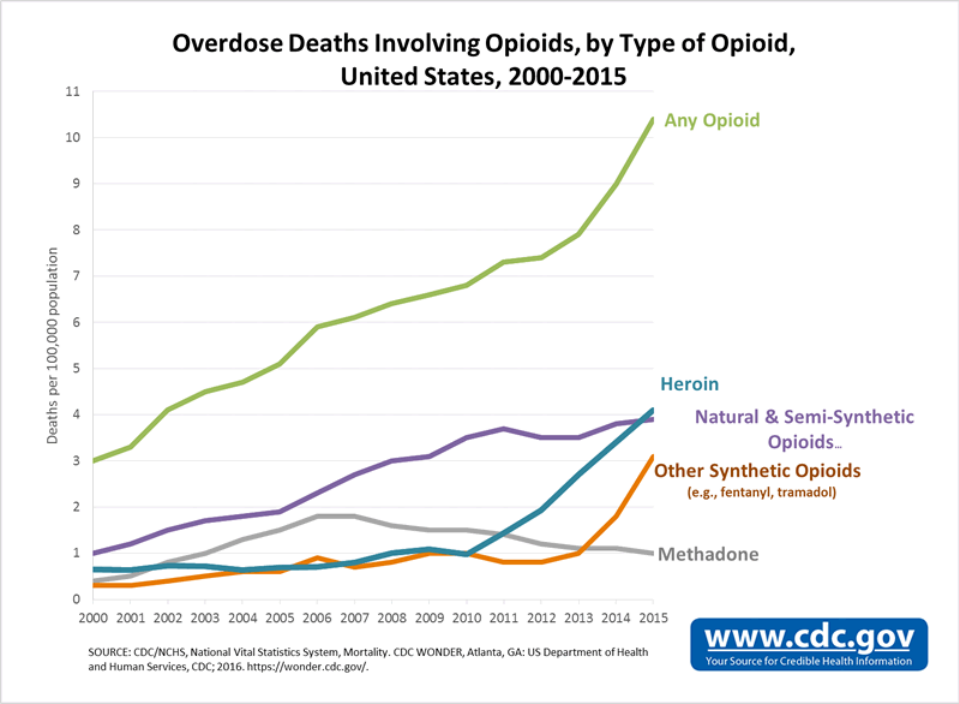
*Abusers often use more than one route

Opioid abusers often manipulate ER opioids and opioids with a low bioavailability for the oral route for a "'dose-dumping' effect (i.e., an increased maximum concentration of the opioid in the brain in the shortest possible time); this is associated with the occurrence of a rapid high and other reinforcing effects, which drive further abuse potential."[48]

Prescription opioids with abuse-deterrent properties are meant to prevent progression of patients to abuse. They are not a treatment for abuse.[18] This means that persons already abusing specific opioids are likely to shift to other opioids or routes of administration if a specific opioid is replaced with an abuse-deterrent formulation. For example, this was the case for Opana® ER, where the replacement in 2012 of the original formulation with an abuse-deterrent formulation for the intranasal route resulted in a shift of abuse instead toward the intravenous route.[49]

Since 2011, the continuing rise in opioid deaths are no longer attributable solely to prescription opioids but also to illicit opioids, mainly heroin and illegally manufactured fentanyl (Figure 2). Death rates and opioid overdoses are concentrated in states with large rural populations, such as Kentucky, West Virginia, Alaska, and Oklahoma.[50] Hot-spots in prescription opioid overdoses show a spread in time from rural to suburban areas.[51] While the death rates have increased overall, the greatest increases have been observed in New England states, with the most significant increase in New Hampshire.[52]

Figure 2. Overdose Deaths Involving Opioids 2000-2015[3]



Diversion

Diversion of opioid analgesics is the transfer of a prescription drug from a lawful to an unlawful channel for distribution or use.[53] Diversion can occur at any of the different points in the drug delivery process: via the original manufacturing site, the wholesale distributor, the physician's office, the retail pharmacy, or the patient.[24] The annual National Survey on Drug Use and Health of the Substance Abuse and Mental Health Services Administration, an annual self-report survey of the civilian, non-institutionalized population in the United States, provides the only population-based data on the sources of prescription opioids for non-medical use.[54] About 50% of people who misused prescription opioids got them from a friend or relative for free, while 22% got them from a doctor and only 4% bought them from a drug dealer.[55,56] The figures vary with the intensity of the abuse: people abusing prescription opioids up to 30 days in a year are receiving the drug for free in 62% of cases. This goes down to 26% for those abusing more than 200 days a year, with drugs increasingly being bought from friends or from drug dealers.[57]

The volume of prescription opioids diverted annually for non-medical use is extremely difficult to estimate. According to one estimation using several public and private databases, about 4% of all prescription opioid doses dispensed in 2002-2003 were used non-medically.[58] Street prices of specific opioids can be a good indicator of drug availability, demand, and abuse potential.[59]

2.3 The FDA Designation for Abuse-Deterrent Formulations of Opioids

The first two abuse-deterrent formulations of an opioid were introduced in the US in 1960 and 1978. Lomotil® and Motofen® contained opioids for the treatment of diarrhea with atropine being added as an aversive agent to prevent abuse. Talwin NX® followed in 1982, using naloxone as an opioid antagonist.[60] Following the general process of drug approval, the FDA did not list abuse-deterrent properties, or "tamper resistant" properties as they were known at that time, in the label without epidemiological evidence on the real-world effectiveness of abuse-deterrent formulations.[61] As a result, some opioids with abuse-deterrent technologies are available on the market without official recognition in the FDA drug label.[62] Among the different approaches to diminish the abuse potential of opioids, as described in the background section, ADFs currently on the market use only physical and chemical barriers and agonist/antagonist combinations.

In 2013, the FDA published the draft guidance *Abuse-Deterrent Opioids — Evaluation and Labeling* that was approved in 2015.[6] The guidance contains four types of data requirements: the first three categories are premarket studies, mandatory for FDA approval, while category 4 is mandatory to be conducted after said approval (Table 4). It should be noted that OxyContin was approved with an ADF label in 2010,[7] prior to the mandatory requirement of category 4 studies.

Table 4. FDA Data Requirements for the Approval of an ADF Label[6,63]

Category	Type of studies	Description[63]
1	Laboratory Manipulation and Extraction Studies	Studies designed to evaluate physiochemical properties, characterize a product's abuse-deterrent properties and the degree of effort required to defeat those properties
2	Pharmacokinetic Studies	Studies designed to compare pharmacokinetic profiles of an intact and manipulated ADF product to a comparator drug through one or more routes of administration
3	Clinical Abuse Potential Studies	Studies conducted in drug-experienced, recreational user populations designed to assess the impact of potentially abuse deterrent properties
4	Postmarket Studies	Studies designed to determine whether an ADF product results in meaningful reductions in abuse, misuse and related adverse clinical outcomes

Results of category 1 to 3 premarket studies are surrogate outcomes for abuse liability, meaning that they can be considered reasonably likely to predict clinical benefit.[64] These premarket studies can be considered validated as to their analytic performance, but they have not been validated regarding their relationship to being able to predict clinical benefit.[65] The methodology of the category 3 clinical abuse potential studies is described in section 4.3 of this report. The scientific

foundation and interpretations of clinical abuse potential studies are constantly evolving,[6] and while they are seemingly reasonable, they are not validated as to their ability to predict the real-world impact on abuse.[6]

Currently, nine ER opioids and one IR opioid have received labeling describing abuse-deterrent properties (see Table 5). The only generic ADFs on the market are authorized generics of OxyContin:[66,67] the pills are identical to the original pre-reformulated OxyContin, and the price is higher than all extended release generics approved by the more common Abbreviated New Drug Application (ANDA) process.[68]

The first postmarket studies for prescription opioids with abuse-deterrent properties approved by the FDA are scheduled for completion in 2018 and 2019 for Hysingla® ER and Embeda®, respectively.[69]

Table 5. Opioids with Abuse-Deterrent Properties in the FDA Label (ADF)

Brand name	Active Substance	Abuse-deterrent approach	Abuse-deterrent route in FDA label	Note
Oxycontin®	oxycodone	physical and chemical barriers	intranasal injection	FDA approval in 2010, market share of over 90% of ADFs
Xtampza®	oxycodone	physical and chemical barriers	intranasal injection	oxycodone microspheres, FDA approval in 2016
Troxyca® ER	oxycodone	agonist/antagonist combination	oral intranasal	FDA approval in 2016, but currently not available on the market
Targiniq® ER	oxycodone	agonist/antagonist combination	intranasal injection	FDA approval in 2014, but currently not available on the market
RoxyBond®	oxycodone	physical and chemical barriers	intranasal injection	Only IR ADF. Approved by the FDA on April, 20, 2017. Not included in the comparative clinical effectiveness assessment of this report.
Hysingla®	hydrocodone	physical and chemical barriers	oral intranasal injection	FDA approval in 2014
Vantrela™ ER	hydrocodone	physical and chemical barriers	oral intranasal injection	FDA approval in 2017
Embeda®	morphine	agonist/antagonist combination	oral intranasal	FDA approval in 2014
Morphabond®	morphine	physical and chemical barriers	intranasal injection	FDA approval in 2015, but currently not available on the market
Arymo® ER	morphine	physical and chemical barriers	injection	FDA approval in 2017. Deterrence through intranasal route refused by the FDA for the label due to Morphabond® exclusivity, but the FDA allows Egalet to include information on intranasal abuse deterrent properties in its marketing[70]

ADFs and their non-ADF counterparts have the same profile of adverse effects when used as prescribed.[12] However when abused, the ADFs may present particular safety issues, such as precipitated severe withdrawal symptoms when an ADF with an agonist/antagonist combination is chewed or crushed.

The reformulation of OPANA® ER (oxymorphone) in 2012 with a high-molecular-weight polyethylene oxide as physical and chemical barrier led to a shift from intranasal to intravenous abuse.[71] "The high street cost of the product coupled with the method of preparation contributed to IV users sharing the drug solution and the equipment used to prepare and inject it," leading to an important outbreak of HIV and HCV infections in Indiana.[71,72] A cluster of thrombotic thrombocytopenic purpura-like illness in Tennessee in 2012[73] seems likely to have been caused by intravenous exposure of substances produced by the tampering of the polyethylene oxide barrier.[74]

These safety issues with the abuse-deterrent technology in OPANA® ER convinced the panel members of the FDA Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee at their meeting on March 13-14, 2017, to conclude that the benefits of reformulated Opana ER no longer continue to outweigh its risks.[74] Polyethylene oxide is also present in nine other ER opioids listed for an oral route of administration, including the ADFs Arymo®, Hysingla®, and Oxycontin®.[49] Safety issues with exicipients after tampering for intravenous abuse have also been raised concering the IR ADF RoyxBond® at the FDA Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee at their meeting on April 5, 2017.[75]

2.4 Policy Interventions: Clinical Guidelines and State Policies

The 2016 Centers for Disease Control and Prevention (CDC) Guideline for Prescribing Opioids for Chronic Pain for patients 18 and older in primary care settings constitutes the most recent professional reference for treatment decisions for chronic pain (outside of active cancer treatment, palliative care, and end-of-life care). The first recommendation of this guideline states that "nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain,"[76] and if opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy as appropriate.[76,77] Considering the abuse potential of opioids, the CDC guideline recommends a universal approach of urine testing to be performed at least annually for all patients receiving an opioid for chronic pain.[76] The evidence on clinical tools for identifying patients that are at higher risk for developing abuse was judged to be insufficient or absent.[46] We have been unable to identify any clinical practice guideline that includes ADFs for treating patients with pain.

The use of opioids in clinical practice is influenced by legislation and regulation at different levels. The production, distribution, and prescribing of prescription opioids is regulated by the Controlled Substances Act (CSA) enacted in 1970.[78] Prescribers need to be registered with the Drug Enforcement Agency.[79] Numerous states are regulating the duration of opioid prescriptions,[79] and all states, excluding Missouri, have instituted prescription drug monitoring programs (PDMPs).[79,80]

Many payers, including the Centers for Medicare and Medicaid Services (CMS), have instituted programs monitoring opioid prescriptions, identifying patients deemed at risk for misuse or abuse.[79]

In August of 2014, Massachusetts became the first state to pass legislation to require pharmacies to automatically substitute ADFs for chemically equivalent non-ADF opioid prescriptions. The law requires insurance carriers to cover ADFs in the same way they cover non-ADF opioids, with no additional cost burden to patients. The Massachusetts law creates a drug formulary commission to determine substitutable abuse deterrent formulations of opioids for their chemically-equivalent generic equivalents. In order to prescribe a non-ADF opioid, a physician must explicitly state 'No Substitution' and provide adequate rationale. While the Massachusetts law was originally set to go into effect in 2016, implementation has been delayed because state officials are still establishing regulatory guidance for insurers and pharmacy providers.

In 2015, Maine also passed ADF legislation requiring all health insurance carriers to provide coverage for ADFs, making them the preferred drugs on any formulary or preferred drug list for both acute and chronic uses. The law prohibits step therapy with non-ADF opioids before use of ADF opioids. In order to pass the legislation, the legislature voted to override the Governor's veto.

In New Hampshire, Vermont, Connecticut, and Rhode Island, legislators have introduced similar legislation that is still undergoing debate. In June 2016, the New Hampshire legislature passed a law that established a commission to study the preventative abuse potential and cost impact of ADFs. With the 2016 election underway—and a new governor entering the executive office—the commission was delayed, and the legislative requirement became void in 2017.

In 2016, legislation was introduced in 20 other states relating to ADF coverage. In 2015 and 2016, Maryland, Florida, and West Virginia passed similar legislation requiring that ADFs are covered with parity to non-ADF equivalents and prohibiting step therapy with a non-ADF opioid. Four states, including Delaware, New Hampshire, Oklahoma, and Virginia, passed resolutions requiring further study of ADFs. Within this legislative context, the assessment of ADFs as an effective and efficient strategy for curbing the epidemic of death from opioid overdose is urgently needed.

During the last decade, numerous policy initiatives have emerged for combatting the epidemic of death from opioid overdose. For example, in 2015, the U.S. Department of Health and Human Services announced three priority areas to combat opioid abuse: (1) opioid prescribing practices to reduce opioid use disorders and overdose, (2) expanded use and distribution of naloxone, and (3) expansion of medication-assisted treatment (MAT) to reduce opioid use disorders and overdose.[81] ADFs are not part of any of the proposed actions in these priority areas.

In 2016, the Obama administration requested $27.6 billion for the fiscal year 2016 to support efforts under the 2015 National Drug Control Strategy to reduce drug use and its effects.[82] This

strategy lead to a memorandum to combat the prescription drug abuse and heroin epidemic that directed federal departments and agencies to provide training to prescribers and to improve treatment for prescription drug abuse and heroin use.[83] Again, ADFs are not part of any of the proposed actions. The FDA Opioids Action Plan seem to be the only policy initiative on the federal level that prioritizes ADFs.[2] In July 2012, the FDA implemented Risk Evaluation and Mitigation Strategies (REMS) class-wide for ER and long-acting opioids that requires manufacturers of these agents to distribute educational information to clinicians and patients and involves clinicians in monitoring of patients and counseling them on safe use.[79]

2.5 Insights Gained from Discussions with Patients and Patient Groups

Chronic pain-focused patient organizations stressed continued, affordable patient access to opioid therapy for daily function while also recognizing the need to curb opioid misuse and addiction. It was felt that the different policy initiatives for reducing the overall use of opioids contributed to increasing difficulties in obtaining prescriptions for long term opioid therapy.

Higher co-payments for ADFs compared to non-ADF ER opioids were seen as a potential barrier to accessing needed opioid therapy. Some patients with chronic pain saw ADFs as a way to access necessary medication without the same level of stigma associated with needing controlled substances. The importance of assessing the value of ADFs was widely recognized by the different stakeholders as an essential step for their rational use.

Overall, patients with chronic pain reported difficulties accessing specialized multidisciplinary pain care. Some patients believe that access to integrated pain management, including medications and complementary approaches such as acupuncture, physical therapy, and mind–body practices would contribute to diminishing the need for prescription opioids.

3. Summary of Coverage Policies

To understand the insurance landscape for abuse deterrent formulations of opioids, we reviewed publicly available 2017 coverage policies and formularies for the six New England state Medicaid programs, Centers for Medicare and Medicaid Services (CMS), and 12 major Silver-level plans on individual marketplaces across New England.

We identified coverage policies for four of the nine drugs in this review, including OxyContin, Xtampza, Hysingla ER, and Embeda. The newest abuse deterrent therapies, including Arymo ER, Vantrela ER, Troxyca ER, and RoxyBond were not covered by any plans in the review. Since Morphabond and Targiniq ER are not launched in the U.S., they also are not covered by any plans in this review.

OxyContin (oxycodone) is most likely to be covered, although more than half of plans still require prior authorization. Xtampza (oxycodone) is the least likely to be covered, and is covered by under one-quarter of plans reviewed. Embeda (morphine) is covered by nearly two-thirds of plans reviewed, and it is least likely to require prior authorization. Despite their different key ingredients, many plans (60%) either cover Embeda (morphine) or Hysingla (hydrocodone), but not both (see Appendix B, Table B1) – and all plans have quantity limits for all opioid therapies in this review.

Table 6. Percentage of New England Commercial Plans that Cover Abuse Deterrent Formulations of Opioids and Coverage Restrictions

	Covered	For those plans with coverage:	
		Prior Authorization	Quantity Limits
OxyContin	92%	58%	100%
Xtampza	23%	100%	100%
Hysingla	62%	67%	100%
Embeda	69%	44%	100%

Coverage policies for ADFs are distinct from coverage policies for generic ER opioids. In general, commercial carriers require prior authorization for ADF ER opioids, requiring patients to try non-abuse deterrent, generic equivalents, or preferred brands first. For example, at Neighborhood Health Plan in Massachusetts, patients can access morphine ER tablets without prior authorization but with quantity limits, while an abuse deterrent opioid like OxyContin requires prior authorization and step edits.

Still, plans vary substantially in their policies for ADF ER opioids, with some plans requiring very simple step edits through preferred therapies and others requiring very detailed risk assessment

and monitoring for abuse. Harvard Pilgrim and Connecticare require step therapy with an immediate release opioid or preferred extended release opioid before authorizing coverage for Hysingla, Embeda, or Xtampza. Anthem Maine has the most extensive prior authorization documentation, closely following recent CDC guidelines. They require prescribers to demonstrate proof of querying the state prescription monitoring program database, as is required by state law, and collecting urine samples every six months for continued coverage. The other Anthem programs in New England do not have such policies. Despite utilization management of these opioid pain therapies, many plans have special allowances for patients with cancer pain.

Examples of these policies are included in Table 7 and can be found in Appendix B.

Medicaid

In New England Medicaid programs, the majority of ADF opioid therapies are non-preferred and require prior authorization with quantity limits. Embeda, however, is a preferred therapy in half of New England state Medicaid programs. In these states, use of Embeda does not require prior authorization.

Many states throughout New England adhere to strict guidelines in their prior authorization documentation. New Hampshire, for instance, requires that prescribers query the Prescription Drug Monitoring database, have a written pain agreement, demonstrate a history of addiction (alcoholism and substance abuse), and see a pain specialist before authorizing use of any long acting opioid. Maine Medicaid requires that patients have a chronic pain management plan and revisit their prescriber in order to reauthorize their prescription. Massachusetts is perhaps the least burdensome, requiring prescribers to demonstrate proof of intolerance and need of therapy.

Table 7. Examples of Prior Authorization Policies

	Connecticare	Anthem Maine	New Hampshire Medicaid
	Example 1: Embeda	**Example 2: Embeda**	**Example 3: All ER Opioids**
Initiating Coverage			
Preferred Agents	Exalgo, fentanyl patch (Duragesic), morphine sulfate ER tabs (MS Contin), Nucynta ER, oxymorphone ER (Opana ER—MD must write for original formulation on prescription)	Fentanyl patch (generic), levorphanol, methadone, methadose, morphine sulfate ER, OxyContin (brand), tramadol ER (generic), oxymorphone ER, hydromorphone ER.	fentanyl patch (generic for Duragesic®) Kadian® morphine sulfate SA (generic MS Contin®) oramorph SA (generic for MS Contin®)
Step therapy	Yes, must fail two preferred agents	Individual has been maintained on a short-acting opioid analgesic, including opioid analgesia as inpatient for post-surgical pain; OR Individual transitioning from one long-acting opioid analgesic to another long-acting opioid analgesic	Failure on two other narcotics for pain treatment for which the requested long acting narcotic is indicated
Cancer and/or Palliative Care Exemption	Not listed	Requests for increased quantity can be approved for the diagnosis of cancer related pain.	Hospice patients and end of life patients are exempt from prior authorization.
Risk Assessment or Agreement	Not listed	Yes, including a pain treatment plan with treatment goals	Confirmation that patient has a written pain agreement
Pain Specialist	Not listed	No	Patient has been referred to a pain management clinic or other clinical specialist
Querying Prescription Monitoring Program (PMP)	Not listed	No	New Hampshire Prescription Drug Monitoring Program (PDMP) has been reviewed within the last 60 days
Authorization Time	60 pills (1-2 months depending on dosage)	3 months	3 months
Continuing Coverage			
Authorization Time	6 months	6 months	6 months
Cancer Exemption	Yes	Yes: Authorized for 1 year for ongoing treatment; Lifetime for palliative treatment	Yes
Risk Assessment or Agreement	Not listed	Yes	Yes
Pain Specialist	Not listed	No	Yes
Querying PMP	Not listed	Yes	Yes
Urine Drug Screen	Not listed	Yes	Not listed

4. Comparative Clinical Effectiveness

4.1 Overview

To inform our analysis of the comparative effectiveness of abuse deterrent formulations of opioids, we abstracted evidence from available clinical and observational studies, whether in published, unpublished, or abstract form. The drugs of interest are included in Table 5 above.

We sought evidence on the effects of ADFs on outcomes relevant to patients, the health system, and society, as listed below.

- Patient/Population Level Outcomes
    - Abuse Potential Endpoints
        - VAS measures (0-100) of drug liking, take drug again, and overall drug liking
        - Tampering
    - Real World Evidence of Abuse and Misuse
        - Overdose and fatality
        - Abuse/misuse
            - Physical evidence of misuse/abuse
            - Self-reported misuse/abuse
            - Route of administration for misuse/abuse
        - Addiction

- Health System Level Outcomes
    - Health system costs
    - Drug loss and diversion rates
    - Patterns of illegal drug use
    - Doctor shopping
    - Prescription utilization

- Societal Level: Outcomes related to the criminal justice system, worker productivity, and education.

4.2 Methods

Study Inclusion Criteria

We included evidence from randomized controlled trials (RCTs) and observational studies (e.g., surveys, database and registry studies). We did not include studies that focused exclusively on the analgesic properties of ADFs without reporting on any abuse-related endpoints. We also excluded studies that "simulated" an ADF (e.g., combining intravenous oxycodone with naltrexone to simulate the ADF form of this combination being abused by intravenous route) rather than administering the actual agent of focus for the review.

In recognition of the evolving evidence base for ADFs, we supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature that met ICER standards for review (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/greyliterature-policy/). We excluded abstracts that also reported data available in peer-reviewed publications.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on abuse-deterrent opioids followed established methods in systematic review research.[84] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[85] The PRISMA guidelines include a checklist of 27 items, further detail of which is available in Appendix A, Table A1.

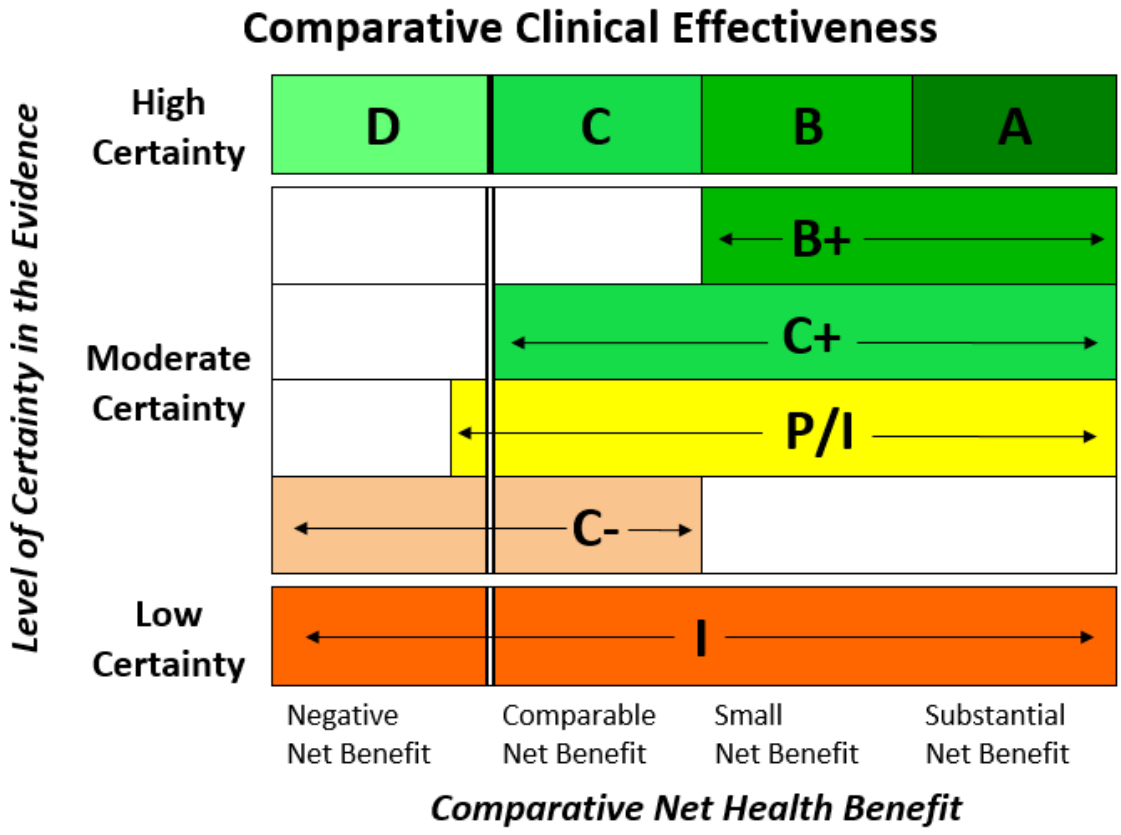
We searched MEDLINE, PsycINFO, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and EMBASE for relevant studies. We limited each search to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. To supplement the above searches and ensure optimal and complete literature retrieval, we performed a manual check of the references of recent peer-reviewed publications and public reports. Further details on the search algorithms, methods for study selection, quality assessment, and data extraction and synthesis are available in Appendix A.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix (see Figure 3) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.[86]

Figure 3. ICER Evidence Rating Matrix



A = "Superior" *- High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" *- High certainty of a small net health benefit*
C = "Comparable"*- High certainty of a comparable net health benefit*
D = "Negative"*- High certainty of an inferior net health benefit*
B+ = "Incremental or Better" *- Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Better" *- Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit*
C- = "Comparable or Inferior" *- Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior*
I = "Insufficient" *- Any situation in which the level of certainty in the evidence is low*

4.3 Results

Study Selection

Our literature search identified 1,424 potentially relevant references. A total of 41 references met our inclusion criteria, of which 15 were premarket studies that evaluated abuse potential endpoints (13 publications; two conference abstracts/posters), and 26 were postmarket studies that primarily evaluated real world impact on levels of abuse and misuse (19 publications; seven conference abstracts/posters). All of the premarket studies were RCTs, while the postmarket studies were entirely observational. Premarket studies that met our inclusion criteria were identified for all ADF interventions of interest, with the exception of Targiniq ER, for which we identified relevant data in its FDA prescribing information. Postmarket studies were only found for OxyContin. The primary reasons for study exclusion included the use of a simulated ADF or use of opioids with abuse deterrent properties that are not labeled by the FDA as an ADF, study outcomes that focused exclusively on pain (we assumed bioequivalence of ADF and non-ADF formulation), and non-comparative study designs.

Quality of Individual Studies

We rated only the studies that were published in peer-reviewed journals. All 13 published premarket studies were rated to be to be of fair quality using criteria from the U.S. Preventive Services Task Force (USPSTF).[87] The studies considered some, but not all important outcomes and used acceptable measurement instruments which were generally applied equally. Of 19 published postmarket studies, we rated 15 as fair quality and four as poor quality using the National Institutes of Health (NIH) Quality Assessment Tool for pre-post studies with no control group as guidance.[88] We did not assign a quality rating to references that were obtained from the grey literature (e.g. conference proceedings). Overall, 83% of our study set received funding from pharmaceutical companies, while another 10% was supported by the RADARS system, an independent nonprofit postmarketing surveillance system that is supported by subscription fees from pharmaceutical manufacturers.

Patient/Population Level Outcomes: Studies that Evaluated Abuse Potential

Premarket studies evaluated the oral and intranasal abuse potential of each of the ADFs by asking recreational drug users to rate how much they liked the drug as well as their likelihood to take the drug again. All studies found significantly less likeability for ADFs versus non-ADF opioids, although the magnitude of difference between ADFs and comparators varied. Similar trends were observed for responses to questions regarding the likelihood of taking the drug again.

Of note, there is no established threshold for what constitutes a clinically-important difference in any "abuse potential" endpoint, so the clinical significance of the findings remains unclear even if statistical differences were noted.

Overview

We identified 16 studies that evaluated the abuse potential of ADFs, of which 15 were premarket studies covering all interventions of interest except Targiniq ER. We did not identify any publication or conference presentation on the premarket findings of Targiniq ER that met our inclusion criteria. However, for completeness, we included premarket findings from two evaluations of Targiniq ER presented in the FDA prescribing information as part of our results. All premarket studies were randomized, double-blind, active- and placebo-controlled crossover trials. The trials were broadly divided into two categories: those that assessed *oral* abuse potential (see Table 8) and those that assessed *intranasal* abuse potential (see Table 9).

Study participants were healthy, non-dependent recreational drug users between the ages of 18 and 55 years. However, one study of the intranasal abuse potential of Targiniq ER, which was identified in the FDA prescribing information, was conducted among dependent opioid users and employed a similar study design. Trial populations were predominantly male (67-90%) and Caucasian (65-90%). Participants who had a positive urine drug screen or were physically dependent on opioids, alcohol, or other drugs were excluded from all but one study measuring the intranasal abuse potential of Targiniq ER. In addition, all trials had a screening phase which consisted of a naloxone challenge test (to determine physical dependence) and a drug discrimination test (to evaluate whether the study subject could distinguish the non-ADF comparator from a placebo). Participants were excluded from the study if they failed any part of the screening phase. There was no universal comparator, but ADFs were generally compared with non-ADFs in the same class. For example, oxycodone ADFs were compared with IR oxycodone; hydrocodone ADFs were compared with IR hydrocodone; and morphine ADFs were compared with ER morphine.

Key measures of abuse potential included maximum levels of "drug liking" ("at this moment, my liking for this drug is…"), which was a primary endpoint in the studies of focus, as well as secondary endpoints of "overall drug liking" (typically measured at 12 and 24 hours post-dose), and "take drug again" ("I would take this drug again" measured at 12 and 24 hours post-dose). Drug liking endpoints were measured using a bipolar 0 to 100mm Visual Analog Scale (VAS), in which 0 represents "strong disliking", 50 represents a neutral response, and 100 represents "strong liking". Response to whether the subject would take the study drug again was measured on a unipolar scale of 0 to 100, where 0 represents "definitely would not take drug again" and 100 represents "definitely would take drug again". Of note, there is no established threshold for what constitutes a

clinically-important difference in any of these endpoints, so the clinical significance of the findings described below remain unclear even if statistical differences were noted.

Results: Premarket RCTs

VAS scores of drug liking, take drug again, and overall drug liking for each of the ADFs under consideration are shown in Tables 8 (oral abuse potential studies) and 9 (intranasal abuse potential studies) below. Relative to non-ADF comparators, both crushed and intact forms of each ADF produced statistically-significantly lower scores for drug liking. Although scores were lower, the magnitude of difference varied considerably across agents. Drug liking in oral abuse potential studies ranged from a 7-point difference between crushed Arymo ER and crushed morphine sulfate ER to a 25-point difference between Hysingla ER and hydrocodone IR solution.[89,90] Similarly, the incremental difference in drug liking varied across intranasal abuse potential studies, ranging from seven points (crushed Vantrela ER vs. hydrocodone powder) to 36 points (crushed Targiniq ER vs. oxycodone IR powder).[91,92] Crushed versions of each ADF generally produced higher drug liking scores than intact oral versions, but both remained lower than the non-ADF comparators. Although the magnitude of difference was typically minimal, there were a few instances of notable differences (e.g., the drug liking scores for intact vs. crushed Troxyca ER were 59.3 and 74.5, respectively).[93] Similar trends were observed for overall drug liking, although statistical significance was not reached in a study of the oral abuse potential of crushed Arymo ER versus crushed morphine ER and a study of crushed Troxyca ER versus crushed oxycodone IR.[90,93]

As with drug liking measures, all studies except one showed less likelihood to take an ADF again versus a non-ADF comparator. The only study that did not follow this pattern was a trial on the oral abuse potential of crushed Troxyca ER, for which scores of take drug again did not statistically differ from crushed oxycodone IR (see Table 8).[93]

Results: Observational Study

A prospective cohort study from Peacock and colleagues may offer additional context to the findings reported in the premarket studies of abuse potential.[94] A total of 522 Australian individuals who regularly tampered with opioids were interviewed; investigators sought to evaluate the level of tampering of reformulated OxyContin, as well as perceived attractiveness of original versus reformulated OxyContin. Compared to original OxyContin, fewer people rated reformulated OxyContin as easy to cut-up (21% vs. 79%; $p<0.05$) and dissolve (14% vs. 74%; $p\leq0.01$).[94] Additionally, whereas only 5% of participants reported pre-reformulated OxyContin to be unpleasant to tamper with and difficult to inject, 50% perceived reformulated OxyContin in this way ($p<0.01$).[94]

Table 8. Premarket Studies Evaluating the Oral Abuse Potential of ADFs

ADF (n)	Dose	Intact & crushed ADFs & active comparators¥	VAS score, E_{max}		
			Drug liking	Take drug again	Overall drug liking
Oxycontin	--	***No oral abuse potential study***			
Xtampza ER[95] (n=38)	**40mg**	Xtampza ER- intact	68.8*	70.2*	69.4*
		Xtampza ER- crushed	73.4*	73.7*	74.2*
		IR oxycodone- crushed	**81.8**	**75.4**	**76.2**
Troxyca ER[93] (n=41)	**60mg**	Troxyca ER- intact	59.3*	48.7*	53.3*
		Troxyca ER- crushed	74.5*	72.5	74.3
		IR oxycodone- crushed	89.8	81.5	81.8
Targiniq ER‡[92] (n=29)	--	Targiniq ER-intact	54.7	38.5	NR
		Targiniq ER-chewed	54.6	32.6	NR
		Oxycodone IR solution	**77.9**	**61.4**	**NR**
Hysingla ER[89] (n=35)	**60mg**	Hysingla ER- intact	63.3†	32.6†	54.9†
		Hysingla ER- crushed	69†	43†	56.8†
		Hydrocodone IR solution	**94**	**86.7**	**84.1**
Vantrela ER[96] (n=41)	**45mg**	Vantrela ER- intact	53.9†	46.4†	49.2†
		Vantrela ER- crushed	66.9†	58.7†	59†
		Hydrocodone IR	**85.2**	**75.2**	**75**
Embeda[97] (n=33)	**120mg**	Embeda- crushed	65.2†	57.7†	58.6†
		Morphine sulfate ER- crushed	**80.8**	**70.7**	**69.8**
Embeda[98] (n=32)	**120mg**	Embeda- intact	67.6†	NR	NR
		Embeda- crushed	68.1†	NR	NR
		Morphine solution	**89.5**	**NR**	**NR**
Morphabond ER	--	***No oral abuse potential study***			
Arymo ER[90] (n=38)	**60mg**	Arymo ER- intact	62†	56†	57†
		Arymo ER- crushed	67*	61.5*	63.5
		Morphine sulfate ER- crushed	**74**	**68**	**67.5**

¥: Placebo arms not included in table, non-ADF comparator arms indicated by bold font; *p≤0.05 vs. active comparator; †p≤0.001 vs. active comparator; ‡ study conducted in opioid-dependent population

Table 9. Premarket Studies Evaluating the Intranasal Abuse Potential of ADFs

ADF (n)	Dose	Intact & crushed ADFs & active comparators¥	VAS score, E_{max}		
			Drug liking	Take drug again	Overall drug liking
Oxycontin[99] (n=30)	**30mg**	Oxycontin- crushed	NR	64*	69.7*
		Original Oxycontin- crushed	**NR**	**89.6**	**87.4**
		Oxycodone IR powder	**NR**	**86.6**	**84.8**
Xtampza ER[100] (n=39)	**40mg**	Xtampza ER- crushed	NR†	47.8†	48.2†
		Oxycodone IR- crushed	**NR**	**71.3**	**71.8**
Troxyca ER[101] (n=28)	**30mg**	Troxyca ER- crushed	60.5†	58.9*	60.2*
		Oxycodone IR- crushed	**92.8**	**88.4**	**85.4**
Targiniq ER‡[92] (n=23)	**40mg**	Targiniq ER-Crushed	59.1	42.6	NR
		Oxycodone IR powder	**94.8**	**93.6**	**NR**
Hysingla ER[102] (n=25)	**60mg**	Hysingla ER- crushed	66.8†	34.6†	NR
		Hydrocodone powder	**90.4**	**83.9**	**83.4**
Vantrela ER[91] (n=45)	**45mg**	Vantrela ER- crushed	72.8*	NR	68.5*
		Hydrocodone powder	**80.2**	**NR**	**77.1**
		Zohydro	**83.2**	**NR**	**79.8**
Embeda[103] (n=33)	**30mg**	Embeda- crushed	69.6†	60.6†	60.8†
		Morphine sulfate ER- crushed	**87.6**	**84.9**	**83.8**
Morphabond ER[104] (n=25)	**60mg**	Morphabond ER- crushed	71.1*	NR*	NR†
		Morphine sulfate ER- crushed	**84.8**	**NR**	**NR**
Arymo ER[105] (n=46)	**60mg**	Arymo ER- crushed	52.5†	50†	50.5†
		Morphine sulfate ER- crushed	**77.5**	**73**	**71**

¥: Placebo arms not included in table, non-ADF comparator arms indicated by bold font;‡: Data from Targiniq FDA label *p≤0.05 vs. active comparator; †p≤0.001 vs. active comparator

Patient/Population-Level Outcomes: Studies that Evaluated Real-World Evidence of Abuse and Misuse

We identified 22 postmarket studies that evaluated real-world evidence on the impact of ADFs on abuse and misuse; all were non-randomized studies focusing primarily on OxyContin and comparators. Comparators were either prescription opioids (e.g. IR oxycodone, ER morphine) or illicit drugs (e.g. heroin). Some studies also compared OxyContin to other prescription opioids as a group, rather than examine individual opioids. This usually included hydrocodone, hydromorphone, morphine, oxymorphone, tramadol, tapentadol, and IR oxycodone. The majority of the studies were time series analyses that compared the time before and after the introduction of reformulated OxyContin. Data for these analyses were obtained from a variety of sources (see

Table 10 for a complete list). Major outcomes examined in these studies include overdose and fatalities, abuse rates, and routes of administration for abuse/misuse. None of the studies included addiction as an outcome.

Table 10. Data Sources Used to Assess the Impact of Reformulation on Oxycontin and Comparators

Data Sources	Description
The National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO)	This is a risk management surveillance program for prescription opioids which uses the Addiction Severity Index-Multimedia Version (ASI-MV) to collect data. ASI-MV is a continuous, real-time, national data stream that assesses pharmaceutical abuse by patients entering substance abuse treatment by collecting product-specific, geographically-detailed information. Abuse was defined as any nonmedical use of prescription product. Positive responses to a series of questions regarding alternative ROAs, source of product and use not as prescribed is also captured as abuse.
National Poison Data System (NPDS)	A poisoning surveillance system that captures 99.8% of poison exposures reported to all poison centers in the USA. The cumulative NPDS database contains information about more than 36.2 million human poison exposure cases. Exposure caused by intentional abuse was defined as an exposure resulting from intentional, improper or incorrect use of a substance to gain a high, euphoric effect or some other psychotropic effect.
National Survey on Drug Use and Health (NSDUH)	A survey of the civilian, non-institutionalized population aged 12 years and older; provides national estimates on the use of illicit drugs, alcohol and tobacco and nonmedical use of certain prescription drugs. It is conducted annually by the Substance Abuse and Mental Health Services Administration; uses state-based sampling design. Abuse (nonmedical use) was defined as use of prescription opioid without a prescription or use for the feeling or experience the drug can produce.
The Researched, Abuse, Diversion, and Addiction Related Surveillance (RADARS) System	Comprised of multiple surveillance programs that independently gather data on prescription drug abuse from different perspectives.
RADARS Poison Center Program	Collects intentional abuse data from participating poison control centers participating across the country. Such data consists of calls to poison centers reporting adverse drug-using experiences and usually requesting assistance. Abuse was defined in the RADARS poison center as exposure resulting from intentional improper or incorrect use of substance where victim was likely attempting to gain a high or euphoric effect or some other psychotropic effect.
RADARS Drug Diversion Program	Collects diversion information from municipal police departments (47%), multi-jurisdictional drug task forces (26%), county sheriff's departments (17%), regulatory agencies such as medical and pharmacy boards (5%), and other (5%) of events related to law enforcement activities or actions related to drugs of abuse.

RADARS Opioid Treatment Program (OTP) and the Survey of Key Informants' Patients Program (SKIP)	Interviews new patients entering substance-abuse treatment about medications that they have abused. Abuse was defined in the RADARS SKIP program as use of opioid for nontherapeutic/recreational purpose.
RADARS StreetRx Program	Uses a crowdsourcing website that gathers street price data for drugs using a publicly-accessible website.
IMS LRx database	Covers approximately 65% of all retail prescriptions filled in the U.S. and uses de-identified data with a unique ID that enables multiple prescriptions dispensed to a patient to be linked over time (over 150 million unique patients).
Truven MarketScan commercial database	Provides de-identified pharmacy and medical claims data for commercially insured patients throughout the US Data on abuse is based on ICD-9-CM diagnosis code.

Abuse

Evidence on the impact of reformulated OxyContin on opioid abuse is mixed. The majority of time series studies found that after the abuse-deterrent formulation of OxyContin was introduced, there was a decline in the rate of OxyContin abuse, which ranged from 12% to 75% at different post-reformulation time points in different populations. However, the rate of abuse of other prescription opioids (ER oxymorphone, ER morphine, IR oxycodone) and heroin abuse may have increased during the same period. Furthermore, findings from direct interviews with recreational users showed that reformulated OxyContin may have limited impact on changing overall abuse patterns.

We identified 16 studies that presented evidence on the impact of reformulated OxyContin on abuse in different populations. The results of these studies are summarized below, and grouped into database/surveillance studies or self-reported outcome studies. Table 10 details the specific definition of abuse used in each data source.

Database/surveillance studies

Changes in rates of abuse are reported in Table 11. Using the number of cases received at poison control centers (RADARS poison control data), three studies reported reductions in the population adjusted rates of OxyContin abuse at various post-reformulation time periods.[106-108] For example, at five years post-reformulation, the population adjusted rate of OxyContin abuse was estimated to have declined by 75% (0.056 per 100,00 to 0.014 per 100,000). Concurrently, there was also a 33% decline in the estimated rates of abuse from other prescription opioids during the same period (0.387 per 100,000 to 0.260 per 100,000).[107] Similarly, another study based on the National Poison Data System (NPDS) surveillance system found a significant reduction in the average number of calls

received at poison control centers from OxyContin intentional abuse two years post-reformulation (pre-post change: -36%; p<0.0001).[109] However, in contrast to the RADARS poison center based studies, there was a simultaneous 20% increase in the abuse of other single entity oxycodone (IR and generic ER oxycodone) (p<0.0001). Furthermore, the study found a 42% increase in heroin abuse (p<0.0001).[109]

Based on the RADARS SKIP survey and NAVIPPRO surveillance system, six additional studies observed a 22% to 48% decline in the prevalence of OxyContin abuse among individuals entering substance abuse programs at various post-reformulation periods (see Table 11).[108,110-114] In contrast, these studies observed a significant increase in the prevalence of abuse of other prescription opioids and heroin (see Table 11). For example, based on the RADARS SKIP, which focuses on patients with a primary diagnosis of opioid dependence, one study observed a 38% and 100% increase in the abuse of ER oxymorphone and heroin, respectively, at four years post-reformulation.[111] Furthermore, a NAVIPPRO-based study observed a significant increase of 8% in the abuse of all prescription opioids (including OxyContin) among all patients assessed for substance at 1 year post-reformulation (pre-post relative risk = 1.08, p<0.0001).

Two studies used the NSDUH database, which is designed to estimate the prevalence of non-medical use of drugs in the United States among individuals ages 12 years and older (see Table 11).[115,116] In the first study, Jones et al. reported the prevalence of past-year OxyContin abuse from 2006 to 2013. The prevalence increased progressively from 0.5% in 2006 to 0.7% in 2010; following reformulation in 2010, the prevalence declined to 0.6% in 2011 and was at 0.5% in 2013. The authors, however, noted that the prevalence in 2013 was only significantly different from that of the reformulation year (2010), but not significantly different from that of the other pre-reformulation years (2006-2009).[115] Similarly, a second study used population-adjusted rates to show that compared with 2009, the rate of past year initiation of OxyContin abuse decreased by 19%, 38%, 28%, and 51% in 2011, 2012, 2013, and 2014, respectively; statistical significance was not reported.[116]

We identified three additional studies that used the Truven MarketScan pharmacy and medical claims database to assess the changes in rates of diagnosed opioid abuse.[117-119] In one study by Rossiter et al., which was conducted over a 6 months pre- and 6 months post-reformulation period, the rate of diagnosed abuse among patients primarily on reformulated OxyContin compared with patients that were primarily on the pre-reformulated Oxycontin declined by 23% and 18% among commercially-insured patients and Medicaid patients, respectively (p<0.05). In contrast, there was a non-significant increase in the rate of diagnosed abuse among Medicare patients on post-reformulated OxyContin.[119] Similarly, relative to the pre-reformulation period, Kadakia et al. found a decline in the rate of diagnosed abuse among commercially insured patients on OxyContin and a

simultaneous increase in the rate of diagnosed abuse from ER morphine, ER oxymorphone and IR oxycodone at 3 years post-reformulation (see Table 11).[118] A third study by Michna et al. observed that 28% of commercially insured patients originally on OxyContin (N=15,162) switched to other forms of non-ADF opioids six months post-reformulation; and also noted a significantly higher rate of diagnosed abuse among patients who switched to non-ADF ER opioids (6.7%) or IR opioids (11.3%) than those on reformulated OxyContin (3.5%) during a 15 months study period ($p<0.001$).[117]

Interview/self-reported outcome studies

To give context to the RADARS SKIP data, one study reported additional information from the RAPID program, which is a subset of the SKIP participants willing to give up their anonymity and participate in a follow-up interview. In interviews with 153 RAPID program participants with a history of long-term abuse of OxyContin, 33% of participants indicated that the reformulation had no effect on them and they continued to abuse OxyContin, another 33% indicated that they replaced OxyContin with other drugs as a result of the ADF, and only 3% indicated that the ADF influenced their decision to stop abusing drugs (see Figure 4).[110] Out of those that changed to other drugs (N=51), 70% indicated they switched to heroin; 29% to other prescription opioids while 1 participant (2%) changed to cocaine.[110] This finding was similar to that reported in another study with a similar cohort.[114]

Additionally, we identified three studies conducted in Kentucky (USA), Canada, and Australia among patients with a long history of opioid abuse. All three studies found a decline in self-reported OxyContin abuse post-reformulation.[120-122] However, evidence on changes in abuse patterns (positive urine drug screen or self report) of other opioids was mixed. For example, in the Australian cohort, there was no apparent increase in the self-reported levels of other pharmaceutical opioid use compared to the pre-reformulated period, although these data were limited to only three months post-reformulation, and pre-reformulated OxyContin was still in circulation.[121] In contrast, the Kentucky study covered a one year post-reformulation period and found a significant increase in the past 30-day use of IR oxycodone following reformulation (96% vs. 74%; RR=1.3, 95%CI 1.19-1.42).[120]

Figure 4. Follow Up Interview with RAPID Participants (N=153), Subset of RADARS SKIP

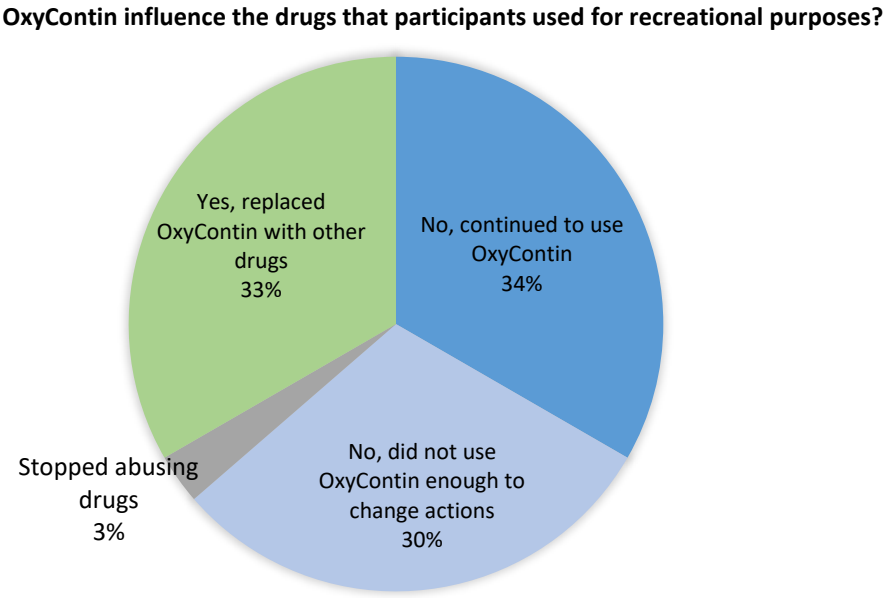


Table 11. Changes in Abuse Pattern of Oxycontin and Comparators

Data source	Timeframe compared		Change in abuse pattern of OxyContin‡		% change of comparators	
	Pre-reformulation	Post-reformulation	Outcome (population)	% change	Heroin	Prescription opioids (excludes OxyContin)
RADARS Poison center[106]	4Q08 - 3Q10	4Q10 - 1Q12	Mean quarterly rate (Cases at poison control centers)	-38*	NM	All other opioids: NS
RADARS Poison center[107]	3Q09 - 2Q10	1Q11 - 2Q15	Mean quarterly rate (Cases at poison control centers)	-75*	NM	All other opioids: -33*
RADARS Poison center[108]	3Q09 - 2Q10	1Q11- 4Q13	Mean quarterly rate (Cases at poison control centers)	-55*	NM	All other opioids: -7*
RADARS SKIP[110,111]	1Q09 - 2Q10	1Q11 – 2Q14	Past month prevalence (Patients with primary diagnosis of opioid abuse)	-42*	+100	ER oxymorphone: +38*
RADARS SKIP[108]	3Q09 - 2Q10	1Q11- 4Q13	Past month prevalence (Patients with primary diagnosis of opioid abuse)	-30*	NM	All other opioids: +16*
RADARS SKIP[114]	4Q09 – 3Q10	4Q10 – 1Q12	Past month prevalence (Patients with primary diagnosis of opioid abuse)	-37	+78¥	All other opioids: +5¥
NAVIPPRO[113]	2Q09 – 3Q10	3Q10 – 2Q12	Past month prevalence (Patients entering substance abuse treatment)	-41*	NM	ER oxymorphone: +246* ER morphine: NS
NAVIPPRO[112]	1Q08 – 3Q10	3Q10 – 4Q11	Past month prevalence (Patients entering substance abuse treatment)	-22*	-11*	ER oxymorphone: +191* ER morphine: NS
NAVIPPRO[108]	3Q09 - 2Q10	1Q11- 4Q13	NC	-48*	NM	All other opioids: -3*
NSDUH[115]	1Q09 – 4Q09	1Q13 – 4Q13	Past year prevalence (US household survey-12 years and older)	-28¥(NS)	NM	--
NSDUH[116]	1Q09 – 4Q09	1Q13 – 4Q13	Past year initiation rate (US household survey-12 years and older)	-28¥†	NM	--
NPDS[109]	3Q09 – 2Q10	3Q10 – 3Q12	Quarterly rates (Calls to poison control centers)	-36*	+42*	Other single entity oxycodone +20*
Claims data[118]	3Q09 – 3Q10	4Q10 – 4Q13	Diagnosed rate (Patients on OxyContin and comparator opioids)	-35*	NM	ER oxymorphone: +236* ER morphine: +44* IR oxycodone: +36*
Kentucky cohort	Pre-3Q10	4Q10 – 1Q11	Past month prevalence (recreational users)	-55†	NM	IR oxycodone: +23
Canada cohort	1 year prior	3Q12-4Q12	Positive urine drug screen (recreational users)	-12*	NM	ER morphine: NS
Australia cohort	1Q14-1Q14	2Q14 – 3Q14	Past month prevalence (recreational users)	-57*	NM	Other opioids: NS

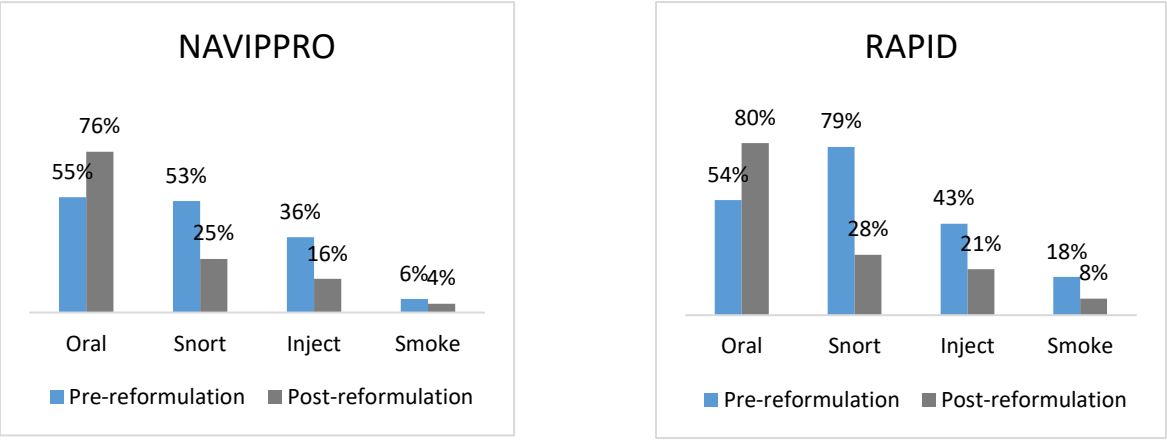
*p<0.01; † value not reported; ¥estimated; NM-not measured; NC-not clear; NS-Not significant; ‡There were some differences in the operational definition of abuse across sources (Table 10).

Routes of Administration of Abuse

Limited evidence suggests there was a reduction in both oral and non-oral abuse of OxyContin following reformulation, however, among those that continued to abuse OxyContin, there was a significant shift from non-oral routes to the oral route of abuse.

We identified three studies that described changes in the route of administration of opioids post-reformulation.[107,111,113] As described above, the three studies reported a decline in the rate of OxyContin abuse post-reformulation. However, the non-oral route of abuse declined at a significantly greater rate compared with the oral route of abuse.[107,113] For example, Severtson et al. reported a 71% decline in OxyContin abuse through the oral route compared with 87% decline in the non-oral route at five years post-reformulation (p=0.006).[107] Furthermore, among patients that abused OxyContin during pre and post-reformulation periods, Butler et al. found a significant increase in the reported use of oral routes of abuse from pre- to post-reformulation period (55% vs. 76%; p<0.0001), while there was a concurrent decrease in the non-oral route of abuse (see Figure 5). Notably, other comparator opioids did not show a similar pattern. Specifically, ER morphine products showed no change in the route of administration profile across study periods, while ER oxymorphone showed a significant increase from pre- to post-reformulation in snorting (62% vs. 69%; p=0.0162) and injection (9% vs. 16%; p=0.0124), and a significant reduction in the oral route (38% vs. 30%; p=0.0056).[113] Similarly, a second study by Cicero et al. based on the RAPID program (N=117) found a significant decrease in the non-oral abuse of OxyContin in the post-reformulation period among patients with a history of OxyContin abuse, while there was an increase in the oral route of administration (see Figure 5).[111]

Figure 5. Changes in the Abuse Routes of Oxycontin Among Participants That Have Taken the Pre- and Post-Reformulated Forms



Overdoses and Fatalities

Limited evidence suggests that rates of overdose and overdose deaths attributed to OxyContin declined after its abuse-deterrent formulation was introduced. Overdose data on other opioids do not show consistent trends across studies, although heroin overdose deaths increased during the post-reformulation period.

Evidence on ADF-related overdose and overdose deaths is extremely limited. Data on the commercially-insured population from Truven MarketScan suggest that rates of OxyContin overdose/poisoning diagnoses decreased 34% from 0.42 per 100 person-years of opioid use in the year before reformulation to 0.28 per 100 person-years of opioid use in the three years following reformulation (p=0.0189); overdoses of ER morphine, ER oxymorphone, IR oxycodone, and IR hydromorphone were not statistically different after reformulation.[108]

Another analysis that used Optum claims data from a large commercial insurer found that overdoses due to prescription opioids decreased by 20% (from 5.48 to 4.38 per 100,000 members per quarter) during the two years following OxyContin reformulation, while the heroin overdose rate increased by 23% (from 1.15 to 1.41 per 100,000 members).[123]

Similarly, OxyContin-related overdose deaths appeared to decline in surveillance datasets following its reformulation. Using manufacturer-reported adverse event data, two Purdue Pharma LP-sponsored studies reported on overdose deaths.[108,124,125] Depending on the period of analysis, reports of OxyContin-related overdose deaths decreased 56-65% (See Table 12 for details).[108,124] By the third year after reformulation, the rate of overdose death had declined 85-87% to reach an average of 3.3 overdose deaths per quarter (vs. 26.0 overdoses/quarter in the year prior to reformulation).[108,124]

Changes in fatality data for comparator opioids are insufficiently reported in the identified literature to enable comparisons, however an analysis from the Wharton School and RAND Corporation estimated that each percentage point reduction of OxyContin misuse after reformulation was associated with an increase of 3.1 heroin deaths per 100,000.[126] Additionally, investigators found no evidence that reformulation affected overall overdose rates across illicit and prescription drugs, suggesting that consumers substituted OxyContin for other opioids.[126]

Table 12. Change in Overdose Fatalities After Reformulation of Oxycontin

Study	Pre-reformulation period	Post-reformulation period	Opioid	Change in overdose fatality reports between pre- and post-reformulation (95% CI)	Change in rate of overdose fatality reports, 3rd year post-reformulation (95% CI)
Coplan 2016[108]	Q3-2009 to Q2-2010	Q1-2011 to Q4-2013	OxyContin	-65% -83% to -27%	-85% 95% CI NR
			Comparator	No data	No data
Sessler 2014[124]	Q3-2009 to Q2-2010	Q3-2010 to Q2-2013	OxyContin	-56% 95% CI NR	-87% -93% to -78%
			ER morphine (MSContin®)*	No data	No data

*Reports of fatalities to the manufacturer of ER morphine (MSContin®) were too few to provide a statistical comparator trend; NR=not reported

Health System Level Outcomes

We identified six references that reported on health system level outcomes, including doctor shopping, drug diversion, and prescription opioid utilization; all were non-randomized studies focusing on OxyContin. The majority of the studies were time series analyses that compared the time before and after the introduction of reformulated OxyContin. Data for these analyses were obtained from RADARS Drug Diversion Program and IMS prescription records (see Table 10). We did not identify any studies that discussed health systeSm costs.

Doctor Shopping

Two studies reported that doctor-shopping decreased 50% after the introduction of reformulated Oxycontin, while it increased 66% for ER oxymorphone and 5% for single-entity IR oxycodone.

One means by which individuals may access opioids for non-therapeutic purposes is through doctor-shopping. Doctor-shopping is "the practice of engaging multiple prescribers and/or pharmacies to obtain excess drugs that can be diverted for non-medical use."[127] There is no accepted threshold to define doctor-shopping, although the two studies we identified that reported on this outcome required individuals to have overlapping prescriptions from two or more unique prescribers and at least three unique pharmacies over a six-month interval.[108,127] Using data from IMS prescription records, both studies reported that doctor-shopping for Oxycontin decreased 50% after reformulation, while it increased 66% for ER oxymorphone.[108,127] Among comparators, changes ranged from an average 25% decrease for IR hydromorphone to a 66% increase for ER oxymorphone; doctor-shopping with IR oxycodone increased 5%.

In an analysis from Chilcoat and colleagues, investigators found that limiting their analysis to a more restrictive definition of doctor-shopping to one associated with specific characteristics associated with abuse and diversion (i.e., younger age, cash payment, and high dosage strength) resulted in a greater estimated decline in doctor-shopping with OxyContin (90%) over the specified period of analysis.[127,128]

Drug Diversion & Prescription Opioid Utilization

After the introduction of reformulated OxyContin, rates of OxyContin diversion fell. Evidence on corresponding changes in diversion rates of other prescription opioids is inconsistent. Sales of OxyContin declined over the same period, while increasing for other long-acting opioids.

We identified three publications that reported on drug diversion (any intentional act that results in transferring a prescription medication from lawful to unlawful distribution or possession)[108] using population-adjusted longitudinal surveillance data from the RADARS Drug Diversion Program (see Table 13).[106-108] In the Drug Diversion Program, law enforcement officers from municipal police departments, drug task forces, county sheriff's departments, and regulatory agencies such as medical and pharmacy boards submit quarterly data on the number of new arrests, street buys and sales involving prescription products. In one study, the average OxyContin diversion rate declined 53% (95% CI 41% to 63%; p<0.001) per population relative to the average rate in the period before the introduction of reformulated OxyContin; the change rates from the pre- to post-reformulation periods were significantly greater than the change observed for other prescription opioids (-6%; p<0.001), which included immediate-release oxycodone, hydrocodone, hydromorphone, morphine, and oxymorphone.[106] A follow-up study by the same investigators showed that population-adjusted rates of diversion continued to decline over five years post-reformulation, reaching an 89% decrease (95% CI 92% to 85%) by June 2015; diversion of other opioids also decreased during this period, albeit at a significantly lower rate (-27%; 95% CI -36% to -16%; p<0.05).[107] Another study from Coplan and co-investigators (2016) also used data from RADARS Drug Diversion Program and reported relatively consistent results (66% decrease in diversion of OxyContin by the end of 2013), although their analysis did not show any change in diversion of comparator opioids.[108]

Changes in OxyContin prescription sales followed a similar pattern to that of diversion rates, with sales falling 24% in the year following reformulation; statistically significant changes in the overall opioid market for extended- and immediate-release products were not detected.[129] Data from a cohort of 31 million commercially-insured individuals suggest that the dispensing rate of OxyContin fell 39% over two years (from an expected 29.1 mg to 17.8 mg of morphine-equivalent dose per member per quarter) while it increased 11% for non-oxycodone long-acting opioid formulations.[123]

Table 13. Population-Adjusted Change in Diversion After Oxycontin Reformulation

Study	Pre-reformulation period	Post-reformulation period	OxyContin Rate of Diversion*	Other Opioids Rate of Diversion*	Population-adjusted change in diversion of OxyContin (95% CI)	Population-adjusted change in diversion of other opioids (95% CI)	Statistical significance
Severtson 2013[106]Ω	Q4-2008 to Q3-2010	Q4-2010 to Q1-2012	Pre: 3.47 Post: 1.63	Pre: 28.0 Post: 26.3	-53% -63% to -41% p<0.001	-6% 95% CI NR p=0.602	p<0.001
Severtson 2016[107]¥	Q3-2009 to Q2-2010	Q1-2011 to Q2-2015	Pre: 1.95 Post: 0.21	Pre: 13.4 Post: 9.8	-89% -92% to -85% p=NR	-27% -36% to -16% p=NR	"statistically different" p=NR
Coplan 2016[108]†	Q3-2009 to Q2-2010	Q1-2011 to Q4-2013	NR	NR	-66% -74% to -55% p<0.001	+6% -8% to +24% p=0.418	p<0.001

Ω "Other opioids" includes immediate-release oxycodone products, hydrocodone, fentanyl, hydromorphone, morphine, oxymorphone, methadone, buprenorphine, tramadol, and tapentadol; ¥ "other opioids" includes hydrocodone, hydromorphone, morphine, oxymorphone, tramadol, tapentadol, and immediate-release oxycodone; † "other opioids" consists of all non-OxyContin Schedule II opioid analgesic tablets and capsules with the active agents of hydrocodone, hydromorphone, morphine, oxymorphone, and immediate–release oxycodone products (methadone and transdermal patches were excluded); *per 1,000,000 population

Societal Level Outcomes

We did not identify any studies that assessed the societal impact of ADFs, including outcomes related to the criminal justice system, worker productivity, and education.

Controversies and Uncertainties

The use of surrogate outcomes (VAS measures of drug liking, take drug again, etc.) in the abuse potential premarket studies for FDA approval of an ADF constitutes an important source of uncertainty concerning the effectiveness of ADFs. Considering that there is no established threshold for what constitutes a clinically-important difference in the "VAS abuse potential" endpoints assessed in these studies, interpretation of observed results remains ambiguous. In addition, there is considerable uncertainty around whether these surrogate endpoints are predictive of real-world abuse and whether the studies that evaluated them reflect how opioids are consumed in the real world. These studies used small, selected populations of non-opioid-dependent recreational drug users who received single, controlled doses of each product under investigation, which may not reflect real-world opioid use or misuse. The uncertainties surrounding the use of premarket studies as an outcome to predict real-world abuse have been stressed by the

FDA, as recently as the advisory committee meeting concerning an ADF label for an IR oxycodone (RoxyBond®) in April 2017: "None of the nine products approved with abuse-deterrent labeling have actually shown, to FDA's satisfaction, postmarketing data that demonstrate reduced abuse in the real world."[130]

Data from real-world evidence poses a different kind of challenge. We found no prospective studies conducted in inception cohorts that measured real-world incidence of abuse among ADF and non-ADF users. Instead, the current evidence of real-world impact is limited to time series, which are subject to potential confounding and other biases. For example, these analyses do not consider other interventions that may have taken place during the study period, such as expansion of prescription drug monitoring plans, implementation of Risk Evaluation and Mitigation Strategies (REMS), and provider education, among many others. In addition, time series may be subject to autocorrelation (i.e., statistical relation between pre- and post-values), which may lead to underestimation of standard errors and overestimation of intervention effects; or conversely, they may be subject to over-dispersion, defined as greater-than-expected variability in observed data based on the assumed distribution.[131] Moreover, the time series we reviewed used different timeframes of analysis and different databases, often only with a short duration of follow-up. While the trends are relatively consistent, the estimates of magnitude vary and the results of the different studies cannot directly be compared.

For prospective inception cohort studies, evidence on the use of clinical risk abuse stratification tools would be important to support clinical decision-making on whether ADFs should be used for any patient who gets an opioid or only those patients at a certain threshold of abuse risk. Results of a recent systematic review on this question came to the conclusion that the evidence on clinical tools for identifying patients that are at higher risk for abuse was insufficient or absent.[46]

Evidence on the progression from medical use to non-medical use and on the natural history of abuse and addiction is also needed. It is believed that chewing an ER opioid is an important step towards dependence and addiction, followed by intranasal and intravenous routes of abuse,[17] which explains the use of certain physical or chemical barriers in the development of ADFs. However, none of the studies in the assessment included addiction as an outcome, so the impact of ADFs on the progression to non-medical use is unknown. Furthermore, the overall net benefit of introduction of ADFs into the system cannot be fully determined from the available evidence in these studies. Although limited evidence from most of the time series studies suggest a decrease in Oxycontin-specific abuse and overdose following reformulation, many of the studies also found a shift towards abuse of other prescription opioids and heroin, the extent of which may not be fully captured in these studies. There may be a tipping point at which more widespread access to ADFs would show system-wide benefits; however, current evidence from a single survey suggest that

only about 3% of a small cohort of long-term abusers of OxyContin stopped abusing drugs as a result of reformulation, while many others continued to abuse OxyContin or switched to other forms of opioids including heroin.[110]

Uncertainty also remains on the association between the introduction of ADFs and increases in the rates of heroin use or deaths. Evidence from time series studies suggest a rise in the use of heroin following OxyContin reformulation.[109,114] As discussed above, one study by RAND and Wharton that explored the relationship between state variation in OxyContin misuse and heroin death found that each percentage point reduction of OxyContin misuse after reformulation was associated with an increase of 3.1 heroin deaths per 100,000.[126] However, other studies have shown that rates of heroin use and overdoses began increasing prior to the introduction of ADFs.[132,133]

Additionally, we currently do not have any real-world evidence for the other ADFs, as their entry into the US market is very recent. While postmarket studies are mandatory with FDA approval, the first postmarket studies for ADFs other than OxyContin are not scheduled for completion until 2018 and 2019, for Hysingla® ER and Embeda®, respectively.[69]

Summary

Using the ICER Evidence Matrix, we assigned evidence ratings for each of the ADFs of focus compared to non-ADF prescription opioids. ADFs and their non-ADF counterparts are bioequivalent, producing the same analgesic benefits, and have the same profile of adverse effects when used as prescribed.[12] For opioid naïve patients, based on the surrogate outcomes of "likability" used in premarket studies, we judge the comparative clinical effectiveness of all ADFs, including OxyContin, to be "C+". Even though we have reasonably high certainty that ADFs do not provide inferior net health benefit compared to non-ADFs, without stronger real-world evidence that ADFs reduce the risk of abuse and addiction among newly prescribed patients, our judgment is that the evidence can only demonstrate a "comparable or better" net health benefit (C+).

We believe there can be even less certainty in a judgment on the comparative clinical effectiveness of ADFs versus non-ADF opioids if the question is the net health impact of introducing or substituting ADFs for non-ADFs to the broad population of users and abusers of opioids. The evidence on the impact of OxyContin reformulation shows a decrease in OxyContin-specific abuse, but also a shift in some cases toward other routes of administration, toward other prescription opioids, and toward heroin. Given the limited evidence base on this mix of positive and negative outcomes, we do not feel there is adequate evidence to discount the possibility that the balance would be net harmful overall across the entire population, especially over the next several years in the current landscape. We therefore judge there to be insufficient evidence ("I") with which to

judge the net health benefit, at the population level, of the introduction or substitution of ADFs for non-ADF opioids.

Table 14. ICER Rating on the Comparative Net Health Benefit of ADF versus non-ADF Prescription Opioids

Intervention	Comparator	Outcome	ICER Rating
Individual, opioid-naïve patient			
ADF	**Non-ADF**	Risk of Abuse and Addiction	C+
Overall population			
ADF	**Non-ADF**	Risk of Abuse and Addiction	I

5. Other Benefits or Disadvantages

In this section of our review, we seek to provide information on other benefits or disadvantages offered by the intervention to the individual patient, the delivery system, public health or the public that would not have been considered as part of the evidence on comparative clinical effectiveness.

Patients report feeling stigmatized when prescribed opioids, given their widespread and publicized potential for abuse. Some patients report that having an ADF prescription would diminish this stigma, meaning they have a prescription that purportedly cannot be abused. For physicians, ADFs could, as part of a multi-pronged strategy, allow physicians to feel comfortable treating severe pain adequately without feeling forced to limit prescriptions as they might be otherwise.

Discussions about the necessary controls on opioid prescribing need to also take into account the need for chronic pain patients to have reliable access to pain medication as part of a comprehensive pain management program.[134]

Legislation and policy mandating or encouraging use of ADFs often includes other components targeted at reducing opioid abuse and misuse. However, no evidence seems to have been generated to date on the effects of these multi-component strategies, or on the importance of ADF policy relative to other components.

Safety issues have been raised with ADF technologies after tampering for intravenous use for Opana®ER (oxymorphone)[49,74] and for RoxyBond®.[75] These risks could also arise with the intravenous abuse of other ADFs that use similar technologies.[49]

Finally, ADFs are currently available only for the extended-release opioid formulations that comprise around 10% of all prescription opioid use. Broader understanding of the benefits of ADF formulations are urgently needed, with the first immediate-release ADF approved by the FDA as of April 2017, but not yet available on the market.

6. Cost-Benefit and Potential Budget Impact of Abuse-Deterrent Opioid Formulations

6.1 Overview

We conducted analyses of the potential economic impacts of abuse-deterrent formulations (ADF) of opioids. We developed a model to evaluate the costs and benefits of ADF opioid use, comparing a hypothetical population of chronic pain patients who were newly prescribed either extended-release (ER) ADF opioids or ER non-ADF opioids over a five-year time-horizon from the perspective of a third-party payer covering a commercially-insured population. Due to the varied nature of the underlying conditions leading to chronic pain and the lack of published data on utility parameters in opioid users, this model used a cost-benefit rather than a cost-utility framework.

The benefits were defined in terms of the reduction in abuse-related outcomes, such as the number of incident cases of abuse, the number of opioid overdose-related deaths, and subsequent health care resource use. The aim of this analysis was to estimate and compare the costs and benefits of using ADF opioids or non-ADF opioids for chronic pain (e.g., reduced numbers of deaths associated with opioid abuse). Our model objective was to attempt to answer two key research questions: 1) what are the potential net costs and outcomes of using ADFs compared to non-ADFs, and 2) what levels of effectiveness in abuse reduction and in price difference would be needed for ADF opioids to achieve cost neutrality or net savings relative to non-ADF opioids?

Importantly, this analysis did not explicitly include the costs of externalities such as diversion to heroin and other non-ADF opioids that may occur in reaction to the abuse-deterrent properties of ADFs, due to lack of data directly attributing these patterns to ADF use and the focus of the model on clinical and economic impacts among the chronic pain patients themselves. We tested this as a scenario analysis using various assumed estimates for the level of diversion and the relative risk (RR) of diversion with ADF opioids. This analysis also did not compare the benefits of ADFs to other strategies to address abuse of opioids, such as non-opioid pain management strategies, prescription monitoring, or addiction treatment programs.

In addition to developing a cost-benefit model using a hypothetical cohort of patients, we also conducted a state-specific policy analysis that analyzed the health and economic burden associated with opioid use in the states of Massachusetts and Vermont if all non-ADF ER opioid prescription users in the state were to be converted to ADF ER opioid prescriptions.

6.2 Cost-Benefit Model

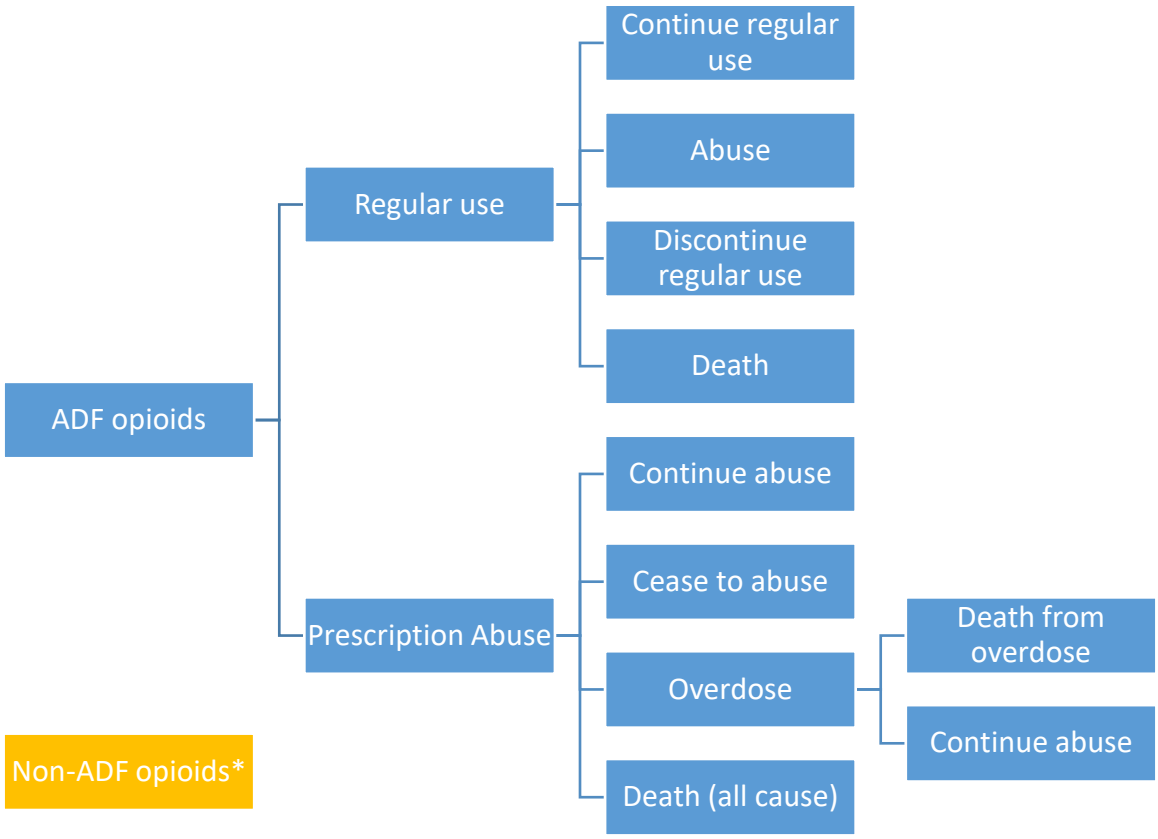
Methods

Model Structure

The cohort model was developed in Microsoft Excel (Microsoft, Redmond, WA) and used a decision tree structure (depicted in Figure 6), with nodes corresponding to outcomes of opioid use in 100,000 non-cancer chronic pain patients with a new extended-release (ER) opioid prescription who followed either an ADF opioid or a non-ADF opioid treatment pathway over a five-year time horizon. We did not include cancer patients in the model, as there may be different considerations when determining appropriate pain management for these patients (e.g., focus on immediate-release rather than ER opioids). Once patients are prescribed an opioid, they have a probability each year of opioid abuse or of continuing regular use. Patients in the regular use pathway continued using opioids for pain management until they discontinued due to death or end of treatment. Those who remained in regular use at the end of each year were subject to a risk of abuse in each subsequent year of the model. Patients with abuse had increased healthcare resource utilization and costs specific to opioid abuse (including overdose). Patients with abuse could continue abusing every cycle, discontinue abuse, or experience death from overdose or other causes (all-cause death).

For this analysis, the cohort was assumed to receive long-term ER opioid prescriptions, defined as those for longer than 90 days.[135,136] Resource utilization for regular use and abuse categories included the mean number of outpatient physician office visits, hospitalizations, emergency room (ER) visits, and rehabilitation services. The model included costs of ADF and non-ADF opioid drugs as well as costs of associated health care resource utilization.

Figure 6. Model Schematic Representing One Cycle for the ADF Opioid Cohort



*Similar decision tree for non-ADF opioids

The model cycle length was one year, with a time horizon of five years. Costs and outcomes were calculated annually as well as cumulatively over the five-year period, and compared for the ADF and non-ADF opioid cohorts. Costs and outcomes were not discounted because of the relatively short time horizon. This evaluation was conducted from a health care system perspective, and thus focused on direct health care costs only.

Table 15. Key Assumptions

Assumption	Rationale	Source
Baseline characteristics of the ADF opioid prescription cohort (reported below) were assumed to be the same as those in the non-ADF cohort.	Patient characteristics in this claims analysis were similar to those seen in a national survey of opioid use.	Rice et al., 2014[137]
While incidence of opioid abuse differs between ADF and non-ADF opioid cohorts, abuse episodes are assumed to have the same health care resource utilization and costs in both cohorts.	Lack of published data on healthcare resource use related to ADF and non-ADF opioid abuse specifically	Rice et al., 2014[137]
Effects on heroin or other opioid use that might result from opioid abusers receiving an ADF opioid were not included, as we are considering only new opioid prescriptions in the cohort model.	Lack of robust published data on effects of ADF opioid use on abuse of heroin and other illicitly obtained drugs	
Base case model did not include diversion from prescription use or abuse.	Lack of data on effects of ADF use on drug-switching behavior among abusers obtaining through diversion	
Model did not include outcomes related to pain alleviation and tolerability.	ADFs are considered bioequivalent to their relevant non-ADF formulation.	Schaeffer, 2012[12]
Base case assumed abuse-deterrent effectiveness of ADF Oxycontin® in a commercially-insured population when calculating the difference in health and economic outcomes between ADF and non-ADF opioids.	Oxycontin® has majority of market share among ADFs, and largest real world evidence base available.	IMS data on file[138];Rossiter et al., 2014[119]
Daily dosage for both ADF and non-ADF opioids is assumed to be 90mg morphine equivalent dose (MED), split over three doses daily.	Reflects dosage beyond which patient monitoring is recommended.	CDC report[139]
Cohort model does not account for switches to other prescription opioids or use of illicit opioids such as heroin.	Model aims to analyse potential benefit of ADF opioids as replacement for non-ADF opioids in patients with new opioid prescriptions, focusing only on effects on abuse and not that of other opioid drugs. In addition, illicit opioid use and associated costs would fall outside a health care system perspective.	
Rate of discontinuation of regular use of opioids was assumed to be the same for ADF and non-ADF cohorts.	Found no published evidence that rate of discontinuation of regular opioid use differed.	

Annual rate of cessation of opioid abuse was assumed to be 10% in both cohorts. In the year of cessation, the patient was assumed to incur 50% of abuse-related health-care resource use and costs prior to dropping out of model after cessation of abuse.	Found no published literature on this rate, or on utilization and costs in year of cessation of abuse.	
In the scenario analyses, diverted abuse in the non-ADF cohort was assumed to be 1.25, 1 and 0.75 cases for every prescription abuse. The relative risk of diversion with ADF opioids was varied as well.	Data suggests that prescription opioid abuse contributes to approximately equal number of cases of diverted abuse. Only one study showcases relative risk of diverted abuse in ADF opioids, specifically Oxycontin®.	SAMSHA, 2016[140] Severtson et al., 2016[141]

Target Population

The population for the base-case hypothetical cohort included adults aged 18 years and older with chronic non-cancer pain and new prescriptions for long-term ER opioid use. Baseline characteristics of the hypothetical cohort were assumed to be similar to those reported in an observational study using administrative claims data from 2006 to 2012 [137] in which two groups of patients, one with evidence of regular opioid use and the other with evidence of abuse, were matched on age, gender, presence of other non-opioid substance-abuse diagnoses, and other comorbidities. Data on age and gender from this analysis determined background mortality for this model (Table 16).

We modeled two distinct cohorts, each including 100,000 patients with: 1) new ADF ER opioid prescriptions, and 2) new non-ADF ER opioid prescriptions. As mentioned previously, we did not model the effects of diversion to heroin and/or switching to abuse of other opioids due to the lack of good quality data on these impacts. While we assume that these would occur more frequently with prevalent use and abuse of ER opioids than with the new users modeled here, the results of this model can provide insight into whether the net economic benefit of ADFs compared to non-ADFs might balance out the cost of switching to abuse of heroin or other opioids.

Table 16. Model Cohort Characteristics

	Opioid abuse	Regular use	Primary source
Mean Age (SD)	36.5 years (14.6)	37 years (16.3)	Rice et al., 2014[137]
Male	56.4%	54.7%	

The comparison represents a matched sample

Treatment Strategies

We compared FDA-approved branded ADF opioids to branded and generic non-ADF opioids. Costs for a typical ADF and non-ADF opioid were calculated as a weighted average of their market share, based on the number of incident users of these opioids in Massachusetts.[138] A list of opioids and their market share within the ADF and non-ADF groups is available in Appendix G, table G1. Opioids with ADF properties but without an FDA-approved ADF label fell into the non-ADF opioid category in our analysis. While there are several ADF opioid formulations, we used efficacy data on Oxycontin® in the new user cohort model because it is the only ADF for which data on effectiveness in deterring abuse were available.

For each ER opioid drug, we assumed a strength of 90mg morphine equivalent dose (MED) as a daily dose, split into three doses of 30mg MED, except in the case of Nucynta®, for which the split was four doses a day to reach the 90mg MED threshold. Details on the drugs included are available in Appendix G, table G3.

Model Inputs

Model inputs were estimated from several sources, including observational studies and published reports. The inputs that informed our model are described below, separated into clinical and cost inputs.

Clinical inputs

Incidence of abuse

For the new user cohort, we included the incidence of abuse for ADF and non-ADF opioids as reported by Rossiter et al. for a commercially insured population.[119] We used data from the period before OxyContin® reformulation to simulate abuse in the non-ADF cohort, and data following reformulation to estimate abuse in the ADF cohort. Abuse was defined based on the ICD-9 diagnosis codes for opioid abuse, dependence and poisoning, as described below. All inputs can be found in Table 17.

Opioid discontinuation

Opioid discontinuation in regular users ranged from 17.2% in year one to 40.4% in year five after initiating ER opioid use, based on a claims analysis by Martin et al. using data from a national commercial health care network from January 2000 to December 2005.[142] Discontinuation was assumed to be the same for regular users in both the ADF and non-ADF cohorts (Table 17). The other reason for discontinuation of regular opioid use was all-cause mortality.

Healthcare resource utilization

Estimates of healthcare resource utlization included annual mean numbers of hospitalization days, emergency visits, outpatient visits, rehabilitation facility days, and other visits such as skilled nursing facility visits, sourced from a commercial claims study by Rice et al. (Table 17) that included opioid users from January 2006 to March 2012.[137] Resource utilization was found to be statistically-significantly lower for patients with regular use compared to those with abuse. Resource use within each of these categories was not assumed to differ across the ADF and non-ADF cohorts other than as a function of the probability of abuse.

Mortality

The model accounts for mortality from opioid overdose (Table 17) as well as all-cause mortality (Appendix G, table G4). The background all-cause mortality matches the cohort's age and sex characteristics and was obtained from the Social Security Administration's actuarial life tables.[143] The risk of mortality from opioid overdose was assumed to be the same for patients with abuse in both the ADF and non-ADF cohorts.

Table 17. Clinical Inputs

Input	Value		Source
Incidence of non-ADF ER opioid abuse	3.647%		Rossiter et al., 2014[119]
Incidence of ADF ER opioid abuse (Oxycontin®)	2.542%*		Rossiter et al., 2014[119]
Annual percentage of discontinuation of prescription opioid use	Year 1 – 17.8% Year 2 – 28.4% Year 3 -- 34.6% Year 4 – 38.2% Year 5 – 40.4%		Martin et al., 2011[142]
Mean Annual Health Care Resource Utlization			
	Regular use	**Abuse**	
Hospitalization days	0.9	4.5	Rice et al., 2014[137]
Outpatient visits	14.4	19.7	
ER days	0.8	2.5	
Rehabilitation facility days	0.2	6.5	
Other visits	1.9	3.1	
Prescription drug fills**	22.4	31.6	
Death from overdose	5.9/100,000		Compton et al., 2016[133]

*Calculated from point estimate of 2.818% reported in the analysis, by removing the assumption of a 25% decrease in efficacy to account for potential switching to other opioids

**Assumed to include only non-opioid prescription fills

Costs

All costs were calculated annually and included both drug and non-drug costs. All costs were inflated to 2016 dollars using the medical care component of the US Consumer Price Index.[144]

Drug costs

We could not calculate net prices for all drugs using our standard source (SSR Health, LLC), as this source relies on publicly-disclosed net sales figures for branded drugs from publicly-traded companies and several of the opioids in this review were either generic or brands of privately-owned drug manufacturers. We therefore used data from the Federal Supply Schedule (FSS) to calculate discounted prices of all opioids.[145] The FSS supports the acquisition of pharmaceutical drugs, medical equipment, and supplies and service contracts for the VA and other federal organizations. We weighted ADF and non-ADF prices by market share, based on IMS data on incident use of prescription ER opioids from February 2016 to January 2017. When there was more than one price for the same drug, as in the availability of multiple generics of the same non-ADF formulation, an average price per dose was calculated.

Health care costs

We derived annual costs of health care resource use from the claims study by Rice et al., described above.[137] Cost inputs are shown in Table 18 below.

Table 18. Cost inputs

Input	Value		Source
ADF Opioids – 90mg MED			
Cost per daily dose*	$11.60		FSS, 2017[145]
Annual cost	$4,234		Calculation
Non-ADF Opioids – 90mg MED			
Cost per daily dose*	$5.82		FSS, 2017[145]
Annual cost	$2,124		Calculation
Mean Annual Health Care Costs			
	Regular use	**Abuse**	
Hospitalization	$2,643	$6,586	Rice et al., 2014[137]
Outpatient visits	$4,505	$6,160	
ER	$982	$3,565	
Rehabilitation	$55	$2,053	
Other visits	$460	$1,383	
Prescription drug fills**	$2,305	$3,186	

*Market-sharebased weighted average cost of drugs within each category. Drugs are listed in Appendix table D1.
**Assumed to include only non-opioid prescription fills.

Sensitivity Analyses

Threshold analyses were conducted to test for cost-neutrality, by varying the inputs related to incidence of abuse in the non-ADF and ADF cohorts, and by varying opioid drug costs in both cohorts.

One-way sensitivity analyses for key inputs used 95% confidence intervals or ranges based on plausible values from the published literature when available; where not available, input parameters were varied by +/- 25%. The one-way sensitivity analyses tested the robustness of the estimated cost difference between the two cohorts when parameters were varied within plausible ranges. We also conducted multiple scenario analyses. First, we introduced diversion into the model, varying it from 1.25 to 0.5 cases of diverted abuse for every case of prescription abuse in the non-ADF cohort. We also varied the relative risk of diversion of ADF opioids compared to non-ADF opioids, with the objective of identifying the percentage decrease in diversion with ADF opioids at which cost-neutrality could be achieved between the two cohorts.

Results

Table 19 shows the clinical outcomes of our base case analysis over a five-year time horizon. The results indicate that the ADF opioid cohort had approximately 3,100 fewer cases of incident abuse and approximately 8,850 fewer abuse-years compared to the non-ADF cohort, as well as 0.5 fewer overdose deaths.

Table 19. Burden of Abuse and Abuse-Related Deaths Due to ADF and Non-ADF Opioids

Outcome (at 5 years)	ADF opioids	Non-ADF opioids	Increment (ADF – Non-ADF)
Incident abuse	7,450	10,532	-3,082
Person-years of abuse	21,091	29,943	-8,852
Overdose deaths	1.25	1.77	-0.52

Table 20 shows results for the total healthcare costs of the two cohorts, the total prescription opioid costs, and the incremental differences between the two cohorts. Using ADF opioids resulted in an additional $511 million in spending over five years compared to using non-ADF opioids. The difference in prescription opioid costs between the ADF and non-ADF cohorts is approximately $645 million over the five years. The use of ADF opioids resulted in lower abuse-related costs, but the higher costs of prescription ADF opioids resulted in overall greater costs in the ADF opioid patient cohort. Details of health care resources utilized and associated costs can be found in Appendix G, tables G7 and G8.

Table 20. Total Estimated Health-Care Costs of ADF and Non-ADF Opioids at Five Years

	ADF opioids	Non-ADF opioids	Difference (ADF – non-ADF)
Regular use*	$3,123,262,001	$3,042,279,103	$80,982,898
Abuse*	$510,590,928	$724,896,371	-$214,305,443
Prescription opioid costs (entire cohort)	$1,301,831,255	$657,301,870	$644,529,385
Total	$4,935,684,184	$4,424,477,344	$511,206,840

*Excludes prescription opioid costs

Table 21 below shows results for the costs per new case of abuse prevented, per abuse-year prevented, and per overdose death prevented when using ADF opioids compared to non-ADF opioids.

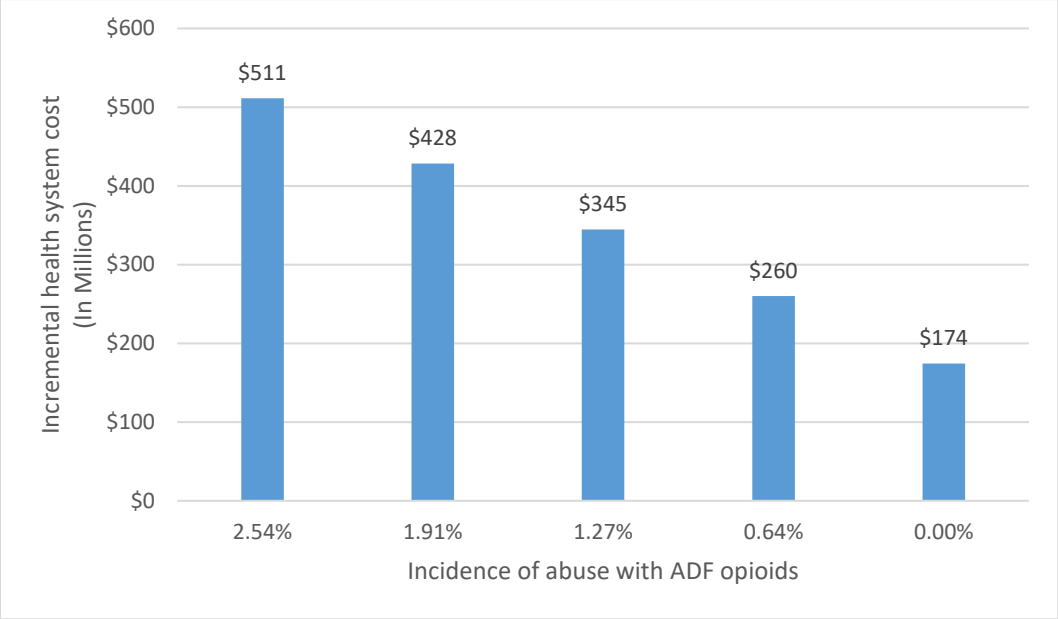
Table 21. Cost Per Incremental Outcome of ADF Opioid Versus Non-ADF Opioid

Incremental outcome	Cost
Preventing one new abuse case	$165,868
Preventing one new abuse year	$57,749
Preventing one overdose death	$977,119,566

Cost-neutrality threshold analysis

Table 22 indicates the required change in effectiveness at reducing incident cases of abuse (holding all else constant) and in price (holding all else constant) for ADF opioids to attain cost-neutrality when compared to non-ADF opioids. First, we increased the effectiveness of ADFs in reducing abuse (i.e., decreased the incidence of abuse in the ADF opioid cohort) to identify the point at which cost-neutrality between the two cohorts would be achieved. However, decreasing this incidence from the base case estimate of 2.54% to 0 (that is, assuming ADF opioids completely eliminate cases of abuse) still resulted in net costs over five years of approximately $174.4 million compared to that of the non-ADF opioid cohort (Figure 7).

Figure 7. Incremental Health System Cost of ADFs at Increasing Levels of Effectiveness (Decreasing Incidence Of Abuse)



When ADF opioids are assumed to have 100% effectiveness in preventing abuse (i.e., zero incidence of abuse with ADF opioids), the cost per (a) new abuse case prevented was approximately $16,600, (b) $5,800 per abuse-year prevented, and (c) $98.6 million per overdose death prevented, compared to non-ADF opioids (Table 22).

Table 22. Cost per Incremental Outcome of ADF Opioid Versus Non-ADF Opioid when ADF Effectiveness in Preventing Abuse Is Assumed To Be 100%

Incremental outcome	Cost
Preventing one new abuse case	$16,560
Preventing one new abuse year	$5,825
Preventing one overdose death	$98,550,421

In a separate threshold analysis, we kept the base case incidence of abuse in each opioid cohort constant, and varied the ADF opioid drug cost to achieve cost-neutrality. Average daily ADF opioid costs would need to be reduced from $11.60 to $7.04 at 90mg MED per day, or a 39% discount from current pricing, to achieve cost neutrality.

Table 23. Cost-Neutrality at Five Years

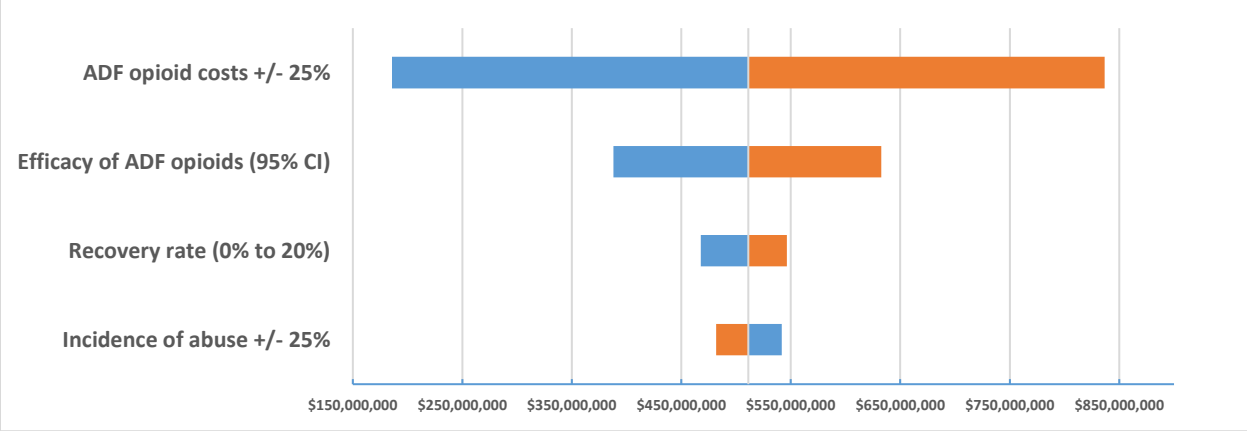
	Base-case cost	Cost to attain cost-neutrality	Percentage difference
ADF opioid average daily drug cost*	$11.60	$7.04	-39.3%

*Indicates drug cost per day at 90mg MED daily dose

One-Way Sensitivity Analyses

Detailed findings of the one-way sensitivity analyses can be found in Figure 8 and Table 24. Results were most sensitive to uncertainty to costs of ADF opioids followed by uncertainty in the efficacy of ADF opioids. Varying the parameters within plausible ranges did achieve cost-neutrality between the two cohorts.

Figure 8. Tornado diagram for overall health care cost-difference between ADF and non-ADF opioids



Base case cost difference is $511,206,840

Table 24. Tornado Diagram Inputs and Results

Parameters	Low Input	High Input	Low Result	High Result
ADF opioid costs (+/- 25%)	$8.70	$14.50	$185,749,026	$836,664,654
Efficacy of ADF opioids (95% CI)	0.01599	0.03489	$388,134,556	$632,677,654
Recovery rate (0% to 20%)	0%	20%	$467,820,712	$546,491,073
Incidence of abuse (+/- 25%)*	0.02735	0.04559	$541,673,004	$481,687,917

*The incidence of abuse was varied such that the percentage difference in incidence between ADF and non-ADF opioids was kept constant, and the same as that seen in the base case.

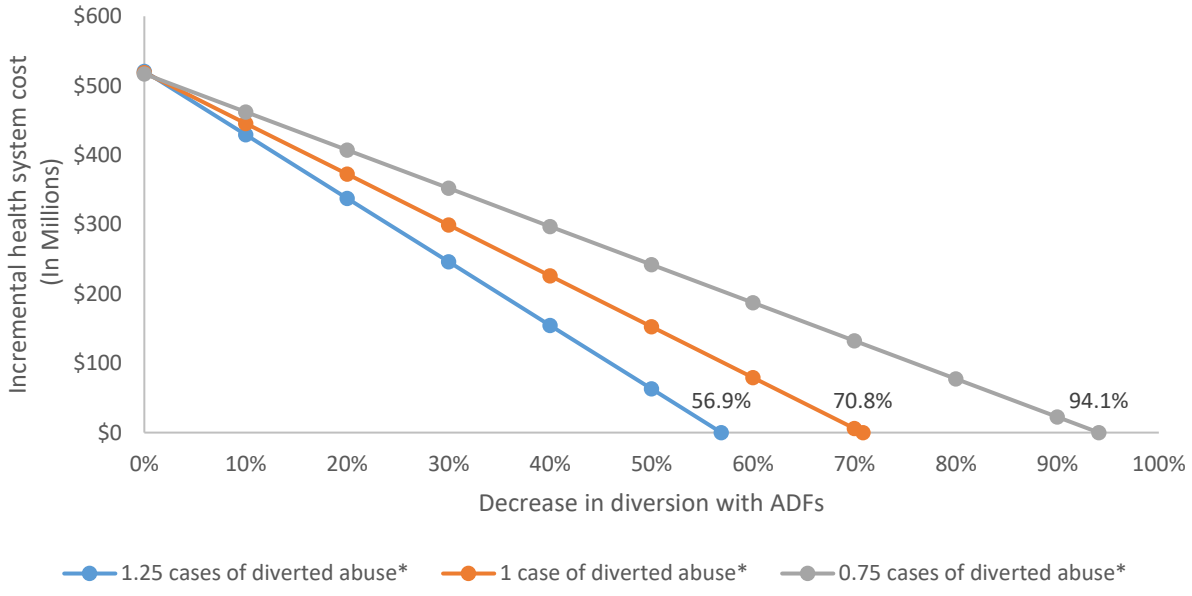
Scenario Analyses

Diversion

Data on rates of opioid diversion and abuse indicates that there are approximately 1.25 cases of diverted abuse for every case of prescription opioid abuse.[140] Based on this diversion rate, using ADF opioids results in additional spending of approximately $521 million over five years. To achieve cost-neutrality, diversion in the ADF cohort would need to decrease by approximately 57% relative to the non-ADF cohort. Reducing the rate of diversion to 1:1 and 0.75:1 ratios required greater reductions in diversion risk to achieve cost neutrality (Figure 9).

The results of this analysis must be viewed with two important considerations in mind. First, we have examined only the impact of reductions in the risk of diversion of the opioid used in the cohort initially. It is recognized that ADF formulations may deter diversion of that formulation but also increase abuse of other opioids and heroin. Second, the costs of diversion are not in fact incurred by the cohorts in our analysis (chronic pain patients); while some of these costs may represent real costs to the health system, this is entirely dependent on the extent to which diversion occurs with first-degree relatives of chronic pain patients or others covered by the same health system.

Figure 9. Incremental Costs of Diversion and Percentage Decrease In ADF Opioid Diversion Required to Achieve Cost-Neutrality



*For every case of prescription abuse with non-ADF opioids

6.3 Prior Published Evidence, Model Validation

To the best of our knowledge, ours is the first model analyzing and reporting the health and economic outcomes of ADF and non-ADF opioids in both regular users and opioid abusers. This approach can provide a more realistic estimate of the overall burden of ADFs and non-ADFs to relevant policy stakeholders. Our model's internal validity was assessed by stress-testing the model through variations in inputs across a wide range of estimates. In addition, we reviewed other published, ADF-related economic models to assess external validity,

Rossiter et al. studied the incidence of abuse and costs associated with the introduction of reformulated Oxycontin® among ER opioid users.[119] Their findings on the incidence of abuse pre- and post-reformulation have been used in our model, and have been described in the methods section. For a commercially-insured population, the authors calculated an excess medical cost associated with a case of diagnosed abuse at $9,456 versus a regular user, and an excess cost of $7,565 for an undiagnosed abuse case compared to a regular user. They applied incidence of abuse (as seen in NSDUH data) and calculated costs to the US population in 2011, assuming a 1:5 ratio of diagnosed to undiagnosed abuse, and reported annual savings of $430 million associated with the use of ADF Oxycontin® rather than pre-reformulation oxycodone. In contrast, our study indicates a cost burden associated with all ADF opioids in the market. There are key methodological differences between the two models that lead to these different results. First, Rossiter et al. did not include opioid prescription drug costs incurred for patients, either those with regular use or those with abuse, so savings calculations were based on other healthcare services alone. Our model has indicated that this is a key driver of costs in the model, and outweighs the savings in other healthcare services to a substantial extent. Rossiter et al. justify excluding prescription drug costs by citing a lack of statistically significant difference in prescription costs between patients with abuse and regular use; however, they did not consider the cost difference between non-ADF opioids and Oxycontin®. Second, the Rossiter et al. study includes an abuse cohort alone and not a cohort of new users of opioids (regular use and incident abuse) as in the ICER model. Third, the Rossiter study attempted to account for diversion and switching to other opioids and heroin for abuse by assuming the reduction in incidence of abuse with Oxycontin® was only 75% of the reduction observed in their claims analysis. The ICER model assumed the fully-observed reduction in abuse after reformulation. Fourth, the cost-savings reported by Rossiter et al. include commercial, Medicare and Medicaid populations, while the ICER model accounts for only the commercially-insured population. Finally, Rossiter et al. report findings at a single year while the ICER study projects results over a five-year period.

White et al. developed a budget impact model that reported annual savings ranging from $0.6 billion to $1.6 billion from use of a theoretical ADF opioid in the US population, with the amount saved dependent on the uptake rate of ADF opioids.[146] The theoretical ADF opioid was assumed to have therapeutic properties and the clinical efficacy of ADF ER oxycodone HCl. The number of cases of opioid abuse was derived from a claims database as well as the 2005 NSDUH survey. The authors reported total annual health care costs of $11 billion associated with prescripton opioid abuse. While both the ICER model and the White et al. model report health care resources and costs avoided with ADF opioid use, the two models examine different populations. The ICER model projects abuse incidence in a new patient cohort, while White et al. model calculate abuse numbers by applying abuse prevalence derived from their database analysis to the US population. Perhaps most importantly, the White et al. model assumes the cost of ADF opioids to be the same as branded ER oxycodone while the ICER model uses a market-basket price for ADF and non-ADF opioids, with a substantial difference observed in daily costs.

Winegarden, in an issue brief, calculated the net benefit of opioids using estimates from studies by Rossiter et al. and Kirson et al. [147,119,148] The cost savings per patient treated with ADF opioids was calculated by multiplying the reduction in rate of diagnosed abuse as reported by Rosster et al. with the additional costs per abuse case from a health system perspective as reported by Rossiter et al. and from a societal (non-health care expenses) perspective as reported by Kirson et al. The two cost-savings results were then summed to arrive at a net cost-saving (benefit) per patient, at $4,645. The final net benefit per opioid patient on ADFs ranged from $1,834 to $4,033, depending on the additional costs of ADF opioids (least to most expensive opioids). From the resources Winegarden used to calculate the cost benefit of ADF opioids, it can be inferred that the author considered a US population cohort, unlike the ICER model, which employed a hypothetical cohort of new patients.

In summary, one of the major differences between the ICER model and other models are the populations that enter the models, with ours being a hypothetical cohort of new opioid users while other models used a US prevalent cohort. In addition, these models examine health care resource use and economic burden associated with opioid abuse cases but do not associate health care resource use and economic burden with regular use ADF and non-ADF opioids when calculating a potential benefit with ADF opioids. These differences lead to markedly different conclusions, with ADF opioids found to be cost-saving in these earlier models while leading to an additional cost burden in the ICER model.

6.4 State-Specific Analysis

We also developed a state-specific analysis as an extension of the new patient cohort model, examining the health outcomes and economic impact of converting an existing population of chronic pain patients on ER opioids from current ADF and non-ADF prescribing patterns to using entirely ADF opioids. We used data on the patterns of prescription opioid use in each of the New England states for which data were available. The analysis is currently informed by data pertaining to opioid use and abuse in Massachussetts and Vermont. Importantly, this model takes a prevalence approach, using data on both existing and new opioid users to inform state-specific findings.

Methods

The state-specific model uses the same general model structure as the cohort model (Figure X). Methodological differences from the cohort model are described below.

Model changes

We replaced the hypothetical cohort population of 100,000 with the actual number of prevalent cases of prescription ER opioid use in each state. The model calculates health outcomes and costs over one year using 2015 claims data for a population of prescription ER opioid users who have been prescribed opioids for non-cancer pain. This model also employs state-specific rates for deaths from overdose (Appendix G, table G5).[149]

Model assumptions

1. We included only non-cancer pain related ER opioid users by applying the ratio of state-specific cancer to non-cancer incident opioid use to the prevalent ER opioid use population.[138,150,151]
2. The proportion of prevalent opioid use that was ER was estimated by assuming the percentage of prescription opioid patients was equivalent to the percentage of ER prescription opioid fills, as reported in a 2012 IMS report.[138]
3. We assumed the market share for opioids to be the same as that seen in the incident population, as we did not have data on this market share for the prevalent population.
4. Since we obtained opioid costs in Massachusetts directly from claims data, we did not have to calculate the average opioid costs using a 90mg MED per day rule in this case.

The number of patients estimated to be on ADF and non-ADF opioids is shown in Appendix G, table G6, along with data on drug market share and rate of death from overdose for Massachusetts and

Vermont (Appendix G, tables G1, G2, and G5). Mean daily cost for ADF and non-ADF opioids in Massachusetts and Vermont are shown in Table 25 and 26. The mean daily cost of opioids in Massachusetts was obtained from a claims analysis undertaken by the Commonwealth of Massachusetts Health Policy Commission (HPC), specifically for this report.[152] The sample of patients in HPC's claims database was limited to 2014 claims data for those with commercial insurance through Blue Cross Blue Shield MA, Harvard Pilgrim, and Tufts Health Plan.

Table 25. Mean Daily Opioid Costs in Massachusetts

	ADF opioids	Non-ADF opioids
Cost per day	$15.90	$3.44

Table 26. Mean Opioid Costs in Vermont

	ADF opioids	Non-ADF opioids
Cost per day (90mg MED)	$10.63	$5.70

Results

Massachusetts

We estimate a total of approximately 173,000 prevalent users of prescription ER opioids in Massachusetts, using 2015 data, of which approximately 60,000 were prescribed ADF opioids and approximately 113,000 prescribed non-ADF opioids. If all prescription opioid users in the state were prescribed ADF opioids, there would be approximately 1,100 fewer cases of abuse in one year while prescription opioid costs would increase an additional $513 million. Total health care costs would be estimated to increase by approximately $490 million per year if all non-ADF prescription users in Massachusetts were converted to ADF prescriptions users (Table 27).

Table 27. Outcomes When Converting All Prescription Opioid Users to ADF Opioids in Massachusetts

	Mixed ADF/non-ADF opioid use	All ADF opioid use	Difference
Abuse cases	5,080	3,957	-1,123
Prescription opioid costs	$489,973,820	$1,002,828,480	$512,854,660
Total healthcare costs	$2,445,826,256	$2,945,163,377	$489,973,820

Vermont

We estimate a total of approximately 20,000 prevalent users of prescription ER opioids in Vermont, using 2015 data, of which approximately 4,000 were prescribed ADF opioids and approximately 16,000 prescribed non-ADF opioids. If all prescription opioid users in the state were prescribed ADF opioids, there would be approximately 160 fewer cases of abuse in one year while prescription opioid costs would increase an additional $29 million. Total health care costs would be estimated to increase by approximately $27 million per year if all non-ADF prescription users in Vermont were converted to ADF prescriptions users (Table 28).

Table 28. Outcomes When Converting All Prescription Opioid Users to ADF Opioids in Vermont

	Mixed ADF/non-ADF opioid use	All ADF opioid use	Difference
Abuse cases	612	454	-158
Prescription opioid costs	$48,386,787	$76,955,788	$28,569,001
Total healthcare costs	$273,252,749	$299,918,362	$26,665,612

6.5 Summary and Comment

The findings from our new-patient hypothetical cohort model indicate that prescribing ADFs to a population of 100,000 patients with chronic non-cancer pain prevents approximately 3,100 new cases of abuse over a 5-year time-period, but will also increase costs to the health system by approximately $511 million. In addition, based on our primary model estimates and assumptions, total cost neutrality could not be achieved even if ADF opioids were 100% effective in preventing abuse. Our other key sensitivity analysis suggested that cost neutrality could be achieved between the two cohorts if ADF costs were discounted by approximately 40%.

Applying this model to the Massachusetts ER opioid prescription use population, converting the entire population to ADF opioid prescriptions from the current mix of ADF and non-ADF opioid prescriptions would cost the health system an additional $490 million annually, but at the same time prevent approximately 1,100 cases of opioid abuse per year. Applying the model to the Vermont ER opioid prescription use population, converting the entire population to ADF opioid prescriptions from the current mix of ADF and non-ADF opioid prescriptions would cost the health system an additional $27 million annually, but at the same time prevent approximately 160 cases of opioid abuse per year.

Limitations

Our model has several limitations. For one, our model assumes a static estimate for incidence of opioid abuse that does not change over time. Owing to a lack of data on this, we did not vary this incidence in a scenario analysis. We also assumed death from overdose to occur only in the abuse population and not in the regular use population, which therefore excludes any risk of accidental overdose. In addition, our model only accounts for overdose death as an event, and does not include the incidence of overdose generally due to a paucity of available data. One can assume, however, that a significant proportion of utilization of emergency department and hospital services was for overdose.

The market-basket of ADF and non-ADF opioids currently used to calculate weighted average opioid drug costs have been derived from Massachusetts data, as we have been unable to find a robust source of national data. The data source we used for background non-opioid prescription costs potentially includes opioid prescription costs as well. While this would impact overall costs, it would not be expected to materially affect the difference in costs between the two cohorts. Our source for annual rates of ER opioid discontinuation was in fact based on data for both IR and ER opioids. Per-person annual costs and health care resources utilized by regular users as well as abusers was assumed to be the same each year, and did not differ over time. In a real-world setting, health care use and costs would likely change each year post-abuse diagnosis.

Perhaps most importantly, our primary model analyses do not include diversion to a population outside the existing cohort. One might argue that such diversion represents a true cost to the health system, but so are the costs of switching to other opioids or heroin among individuals frustrated by ADF properties, which are also not included in this model due to a lack of robust data. We have conducted a scenario analysis examining different assumed levels and relative risks of diversion of ADF and non-ADF opioids, but these again focus only on the reduced costs associated with preventing diversion of the medication used to treat chronic pain in the cohort, and do not account for any increased use of legal or illicit opioids. Finally, in our state-specific analysis, we applied the efficacy of ADF and non-ADF opioids seen in a commercially insured population to the entire state-specific population using ER prescription opioids, owing to a lack of data split by commercial and non-commercial opioid prescription users.

Summary

The results of both our cohort and state-based analyses suggest that ADFs have the potential to substantially reduce the incidence of opioid abuse relative to non-ADF formulations among patients initially prescribed these drugs for therapeutic purposes, but will also increase overall costs to the health system. Further research is required to ascertain how the balance of reduced diversion of

prescribed opioids versus increased use of other legal and illicit opioids affects clinical and economic outcomes in these populations.

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APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Table A2. Search Strategy of Medline 1996 to Present with Daily Update, PsycINFO, EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Cochrane Central Register of Controlled Trials on December 7, 2016

1	Delayed-Action Preparations/ or (extended release or controlled release or slow release or sustained release or delayed release).ti,ab.
2	embeda.ti,ab.
3	(Naltrexone/ and Morphine/) or (naltrexone and morphine).ti,ab
4	1 and 3
5	Morphine/ or morphine.ti,ab.
6	1 and 5
7	2 or 4 or 6
8	(xtampza or oxycontin or oxycodone naltrexone combination).ti,ab
9	Oxycodone/ or oxycodone.ti,ab.
10	1 and 9
11	8 or 10
12	hysingla.ti,ab.
13	Hydrocodone/ or hydrocodone.ti,ab.
14	1 and 13
15	12 or 14
16	targiniq.ti,ab.
17	(Oxycodone/ and Naloxone/) or (oxycodone and naloxone).ti,ab.
18	1 and 17
19	16 or 18
20	7 or 11 or 15 or 19
21	limit 20 to (english language and humans and yr="2000 -Current") [Limit not valid in PsycINFO,PsycTESTS,Books@Ovid,CDSR,ACP Journal Club,DARE,CCTR,Your Journals@Ovid,CLCMR; records were retained]
22	(guidelines or practice guideline or letter or editorial or news or case reports).mp.
23	21 not 22
24	Delayed-Action Preparations/ and Analgesics, Opioid/
25	(abuse deter* adj5 formulation?).ti,ab.
26	(abuse deter* adj5 opi*).ti,ab.
27	(tamper resist* adj5 formulation?).mp.
28	(tamper resist* adj5 opi*).mp.
29	Analgesics, Opioid/ and Drug Compounding/
30	Opioid-Related Disorders/pc [Prevention & Control]
31	Prescription Drug Misuse/
32	30 or 31
33	24 or 25 or 26 or 27 or 28 or 29
34	32 and 33

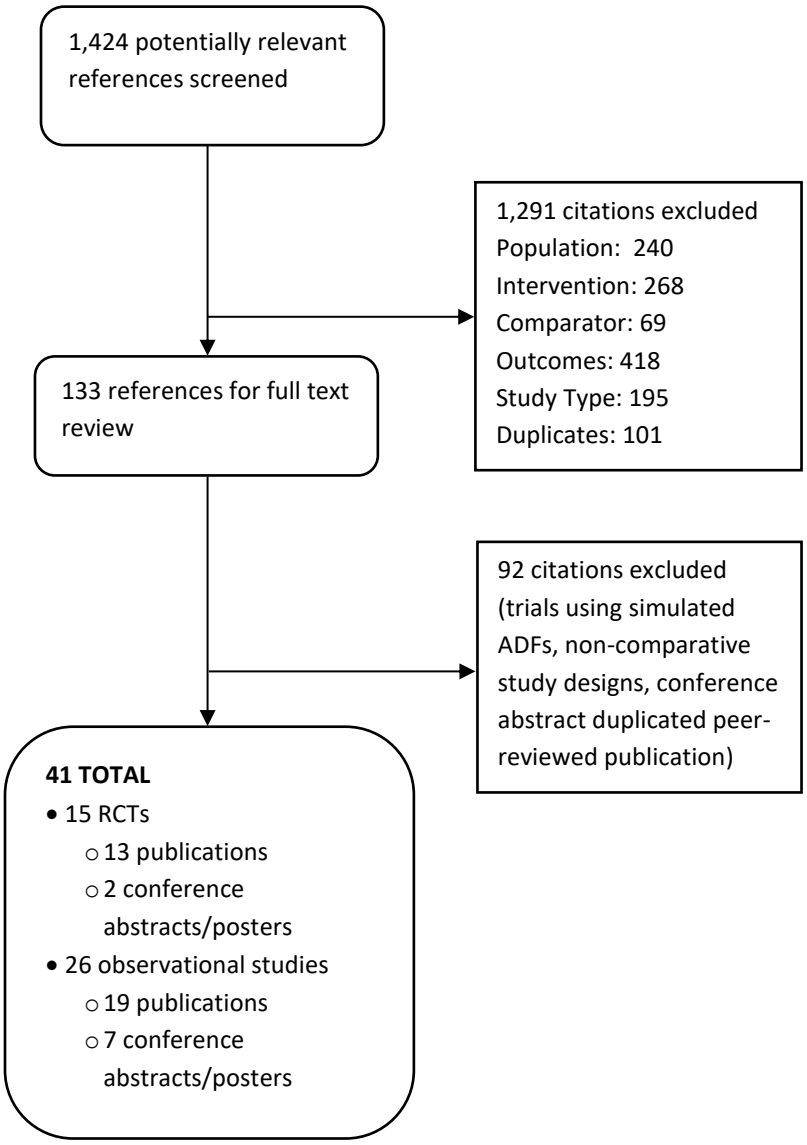
35	limit 34 to (english language and humans and yr="2000 -Current") [Limit not valid in PsycINFO,PsycTESTS,Books@Ovid,CDSR,ACP Journal Club,DARE,CCTR,Your Journals@Ovid,CLCMR; records were retained]
36	(guidelines or practice guideline or letter or editorial or news or case reports).mp.
37	35 not 36
38	23 or 37
39	remove duplicates from 38

Table A3. Search Strategy of EMBASE on October 19, 2016

#1	Oxycontin
#2	Xtampza
#3	Troxyca OR oxycodone NEAR/5 naltrexone
#4	targiniq OR 'naloxone plus oxycodone'
#5	hysingla OR 'hydrocodone bitartrate'
#6	Vantrela
#7	embeda OR 'morphine sulfate plus naltrexone'
#8	Morphabond
#9	arymo
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
#11	naltrexone:ab,ti
#12	morphine:ab,ti
#13	hydrocodone:ab,ti
#14	oxycodone:ab,ti
#15	'controlled release formulation'/exp OR 'extended release':ab,ti OR 'controlled release':ab,ti OR 'delayed release':ab,ti OR 'slow release':ab,ti OR 'sustained release':ab,ti
#16	'narcotic analgesic agent'/exp OR opi*:ab,ti
#17	(abuse NEAR/5 deter*):ab,ti OR (tamper* NEAR/5 resist*):ab,ti
#18	#16 AND #17
#19	('abuse deter*' NEAR/5 formulation?):ab,ti OR ('tamp* resist*' NEAR/5 formulation?):ab,ti
#20	#18 OR #19
#21	#15 AND #20
#22	#11 OR #12 OR #13 OR #14
#23	#21 AND #22
#24	#10 OR #23
#25	#24 AND [english]/lim AND [2000-2016]/py
#26	#25 AND [medline]/lim
#27	#25 NOT #26
#28	#27 AND [humans]/lim AND [animals]/lim
#29	#27 AND [animals]/lim
#30	#27 AND [humans]/lim

#31	#30 NOT #28 NOT #29
#32	#31 AND ([editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim)
#33	#31 NOT #32
#34	#33 NOT 'case study' NOT 'case report'

Figure A1. PRISMA flow Chart Showing Results of Literature Search for Abuse Deterrent Formulations



Appendix B. Public and Representative Private Insurer Coverage Policies

Table B1. New England Coverage Scan

	Connecticut		Maine		Massachusetts			New Hampshire		Rhode Island		Vermont	
	Anthem (Wellpoint Inc Group)	Connecticare	Anthem (Wellpoint Inc Group)	HPHC Maine	BCBS of MA	Neighbor-hood Health Plan	Tufts Health Plan	Anthem (Wellpoint Inc Group)	HPHC New Hampshire	BCBS of RI	Neighbor-hood Health Plan of RI	BCBS of VT	MVP Grp
Oxycodone													
OxyContin (Purdue, 2010)													
Covered	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
PA*	Yes	Yes	No	No	Yes	No	No	No	No	Yes	Yes	Yes	Yes
QL**	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Xtampza (Collegium, April 2016)													
Covered	No	No	No	Yes	No	No	No	No	No	No	No	Yes	Yes
PA	No	No	No	Yes	Yes	No	No	No	No	No	No	Yes	Yes
QL	No	No	No	Yes	Yes	No	No	No	No	No	No	Yes	
Hydrocodone													
Hysingla (Purdue, 2014)													
Covered	No	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes
PA	No	Yes	Yes	No	Yes	No	No	No	No	No	Yes	Yes	Yes
QL	No	NL	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes
Morphine													
Embeda (Pfizer, Approved: 2009; Relaunched: 2015)													
Covered	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes
PA	No	Yes	Yes	No	Yes	No	No	No	No	No	No	No	Yes
QL	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes

* QL. Quantity Limits; **PA. Prior Authorization

Table B2. New England Medicaid Program Coverage Scan

	Connecticut	Maine	Massachusetts	New Hampshire	Rhode Island	Vermont
OxyContin (Purdue, 2010)						
Preferred	No	No	No	No	No	No
PA*	Yes	Yes	Yes	Yes	Yes	Yes
QL**	Yes	Yes	Yes	Yes	NL	Yes
Xtampza (Collegium, April 2016)						
Preferred	No	No	No	No	No	No
PA	Yes	Yes	Yes	Yes	Yes	Yes
QL	Yes	Yes	Yes	NL	NL	Yes
Hysingla (Purdue, 2014)						
Preferred	No	No	No	No	No	No
PA	Yes	Yes	Yes	Yes	Yes	Yes
QL	Yes	Yes	Yes	NL	NL	Yes
Embeda (Pfizer, Approved: 2009; Relaunched: 2015)						
Preferred	No	Yes	No	No	Yes	Yes
PA	Yes	No	Yes	Yes	No	No
QL	Yes	Yes	Yes	NL	NL	Yes

* QL. Quantity Limits

**PA. Prior Authorization

Figure B1. Example of Detailed Coverage Policy from Anthem Maine

Hysingla ER (hydrocodone bitartrate extended-release)

Override(s)	Approval Duration
Prior Authorization Quantity Limit	Initial request: 3 months Maintenance Therapy: Additional prior authorization required for each additional 6 months Individuals receiving for terminal diagnosis and receiving palliative care/end-of-life therapy: Lifetime Individuals receiving for cancer pain related to active cancer therapy: 1 year

Medications	Comments	Quantity Limits
Hysingla ER (hydrocodone bitartrate extended-release)	Non-Preferred	20mg, 30mg, 40mg, 60mg, 120mg: 1 tablet per day 80mg, 100mg: 2 tablets per day

Quantity Limit Override Criteria
For approval of increased quantities of Hysingla ER (hydrocodone bitartrate extended-release), the following criteria must be met: I. Requests for increased quantity can be approved for the diagnosis of cancer related pain. Note: It may be possible in some instances to use a higher strength of the requested medication and take fewer tablets/capsules to achieve the same total daily dosage requested

I. Initial requests for Hysingla ER (hydrocodone bitartrate extended-release) may be approved when the following criteria are met:

A. Individual is 18 years of age or older; **AND**

B. Individual has a diagnosis of pain severe enough to require daily, around-the-clock, long term opioid treatment (please document diagnosis); **AND**

C. Individual has one of the following:

   a. An inadequate response to alternative treatment options, such as but not limited to non-opioid analgesics and immediate-release opioids; **OR**

   b. Alternative treatment options would otherwise be inadequate to provide sufficient management of pain; **OR**

   c. Individual has contraindications to non-opioid analgesics (such as NSAID use in individuals with active ulcer condition/gastrointestinal bleeding, renal failure)[1];

AND

D. Individual is not opioid naïve as noted by the following:

a. Individual has been maintained on a short-acting opioid analgesic, including use of opioid analgesia as an inpatient for post-surgical pain; **OR**
b. Individual is transitioning from one long-acting opioid analgesic to another long-acting opioid analgesic;

AND

E. Prescriber has consulted with individual regarding risks of opioid therapy; **AND**
F. Clear treatment goals have been defined and outlined as part of overall plan; **OR**
G. Individual has one of the following:
a. Diagnosis of cancer related pain and is actively undergoing cancer therapy; **OR**
b. Diagnosis of terminal illness and is receiving palliative/end-of-life care.

II. Requests for continuation of Hysingla ER (hydrocodone bitartrate extended-release) may be approved when the following criteria are met:

A. Individual has a diagnosis of moderate to severe pain and requires around-the-clock long term opioid treatment (please document diagnosis); **AND**
B. Individual has one of the following:
a. An inadequate response to alternative treatment options, such as but not limited to non-opioid analgesics and immediate-release opioids; **OR**
b. Alternative treatment options would otherwise be inadequate to provide sufficient management of pain; **AND**
C. Therapy with long-acting opioid has resulted in meaningful improvement in pain AND function; **AND**
D. Risk assessment has been performed including the following:
a. Urine drug screens have been obtained within the past year to assess for adherence to therapy; **AND**
b. State prescription drug monitoring program (PDMP) data has been reviewed (where available). **OR**
E. Individual has one of the following:
a. Diagnosis of cancer related pain and is actively undergoing cancer therapy; **OR**
b. Diagnosis of terminal illness and is receiving palliative/end-of-life care.

III. Requests for Hysingla ER (hydrocodone bitartrate extended-release) may not be approved for the following:

A. Individual is requesting or using as an as-needed analgesic; **OR**
B. Individual has one of the following conditions:
a. Significant respiratory depression; **OR**
b. Acute or severe bronchial asthma or hypercarbia; **OR**
c. Known or suspected paralytic ileus.

IV. Requests for Hysingla ER (hydrocodone bitartrate extended-release) must also meet the following criteria (in addition to the above criteria in **I.-III.**):

A. Individual has had a trial and inadequate response or intolerance to two preferred long-acting agents;

Preferred agents: Fentanyl patch (generic), levorphanol, methadone, methadose, morphine sulfate ER, OxyContin (brand), tramadol ER (generic), oxymorphone ER, hydromorphone ER. **OR**

B. Individual has completed titration and is already maintained on a stable on dose of the requested drug; **OR**

C. The preferred long-acting opioids are not acceptable due to concomitant clinical situations, such as but not limited to:

a. Known hypersensitivity to any ingredient which is not also in the requested non-preferred agent; **OR**

D. Hysingla ER (hydrocodone bitartrate extended-release) abuse deterrent may be approved if the individual has need for an abuse deterrent formulation based upon a history of substance abuse disorder OR individual's family member or household resident has active substance abuse disorder or a history of substance abuse disorder.

NOTES:

1. Specific drug therapy and contraindication to therapy should be reported

2. Long-acting opioid analgesics have a black box warning regarding risk of addiction, abuse and misuse, respiratory depression, risks of accidental exposure and risks for neonatal opioid withdrawal syndrome. Long-acting opioid analgesic use can lead to addiction, abuse and misuse which can lead to overdose and death. Individuals should be assessed before prescribing and monitored regularly during therapy for development of these behaviors or conditions. Serious, life-threatening or fatal respiratory depression may occur while using long-acting opioid analgesics. Individuals should be monitored, particularly upon initiation or upon dose increases. Accidental exposure, especially in children, can result in fatal overdose. Prolonged exposure to long-acting opioid analgesics during pregnancy can result in neonatal opioid withdrawal syndrome. If opioid use is required for prolonged periods of time in a pregnant woman, the individual should be advised of the risk of neonatal opioid withdrawal syndrome and ensure appropriate treatment will be available. Some long acting analgesics (hydrocodone based) may interact with cytochrome P450 3A4 inhibitors, resulting in increased opioid concentration. In addition, discontinuation of a cytochrome P450 3A4 inducer may also result in an increase in opioid concentration. Monitor individuals receiving these opioid analgesics and any cytochrome P450 3A4 inhibitor or inducer. Co-ingestion with alcohol can increase plasma concentrations of some long-acting opioid analgesics (i.e., Embeda). This can potentially lead to a fatal overdose.

Key References:

Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2016. URL: http://www.clinicalpharmacology.com. Updated periodically.

DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm.

DrugPoints® System (electronic version). Truven Health Analytics, Greenwood Village, CO. Updated periodically.

Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2016; Updated periodically.

Figure B2. Excerpt of Coverage Policy from Harvard Pilgrim

Xtampza ER® (oxycodone extended release capsules)

Clinical Information: Dose and Quantity Requested:	
Date Requested:	**Length of Treatment** (please be specific)**:**

Documentation of Medical Necessity: (please check all that apply):

1. Please indicate the patient's diagnosis: _____
2. Does the patient have pain severe enough to require daily, around-the-clock long-term opioid treatment?

   Yes No
3. Has the patient tried and failed Oxycontin (brand or generic)? Yes No

If no, please provide clinical rationale why OxyContin cannot be used (e.g. ease of administration, difficulty swallowing, etc.)

_____

_____

4. **For renewal requests:** Has the patient experienced improvement while on therapy? Yes No
5. Please provide additional information pertinent to this request:

_____

_____

_____

By signing this form, I attest (i) the information is true and accurate to the best of my knowledge and (ii) that the documentation supporting the information provided on this form is recorded in the patient's medical records.

Prescribing Clinician or Authorized Representative Signature: _____ **Date:**_____

Figure B3. Excerpt of Maine Medicaid Prior Authorization

State of Maine Department of Health & Human Services
MaineCare/MEDEL Prior Authorization Form

OPIATE LIMITS PA. Prior authorization is not required for preferred medication for members in a nursing facility, hospice care and members receiving opioids for symptoms of Cancer or HIV/AIDS. Prior authorization will also not be required for members using 30mg or less MSE per day. Please refer to mainecarepdl.org for additional criteria including MSE conversion limitations.

	Dosage	Days' Supply	
Drug Name	Strength	Instructions	Quantity

Medical Necessity Documentation Required: (Attach copies of supporting office notes.)
Why is this medication necessary for this member? (Please include members medical diagnosis)

Acute Pain:
Have you diagnosed this patient with acute pain?
Yes No
Has this patient already completed 15 days of opioid medication treatment for acute pain in the last 12 months?
Yes No

(Please note that if the patient has already received three refills beyond the first 15 days this PA will be denied.)

If the PA is for a long acting narcotic, please explain why it is medically necessary to treat short-term acute pain?

Chronic Pain: (non-acute only)
Have you diagnosed this patient with long-term non-acute (Chronic Pain)?
Yes No

Have you and this patient established a Pain Management Plan consistent with MaineCare policy Section 80?
Yes No

Is the patient currently participating in one of the covered treatment options
Yes No
If yes which one?

If no when is the first appointment?

Is this PA intended to authorize opioid medications for treatment of headache, back pain, neck pain or fibromyalgia?

Yes No

If yes, please attach second opinion note recommending that opioids be used as part of a Pain Management Plan for this patient.

If this PA request is for more than 300mg of morphine sulfate equivalent (MSE) per day please state the timeframe for tapering down to less than 300mg of morphine sulfate equivalent

Appendix C. Previous Systematic Reviews and Technology Assessments

We identified one systematic review evaluating the impact of abuse deterrent formulation on abuse and other abuse related outcomes.

California Health Benefit Review Program.
Analysis of California Assembly Bill AB 623 Abuse-Deterrent Opioid Analgesics

The California Health Benefit Review Program (CHBRP) assessed the medical and public health impacts of ADFs as part of a broader evaluation of a new bill to be enacted on the use of abuse-deterrent opioid analgesics in the state of California. The review examined the impact of ADFs on opioid abuse, including a possible shift of abuse to other prescription opioids, other routes of administration, or to illicit drugs (e.g., heroin). Although the introduction of ADFs was shown to reduce some forms of abuse of the reformulated drug (particularly those related to inhaling or injecting), some of the studies reviewed by CHBRP suggested that there was a shift to other routes of administration or abuse of other opioid analgesics and/or to illicit drugs (such as heroin) following the introduction of ADFs. The authors concluded that the impact of ADFs on abuse is ambiguous and further epidemiologic surveillance and study is required to ascertain its effectiveness.

Appendix D. Ongoing Studies

We did not identify any ongoing clinical trials registered on ClinicalTrials.gov that evaluated the abuse and/or abuse potential of either approved or investigational abuse deterrent formulations of opioids. A review of publicly-available correspondence between FDA and drug manufacturers, however, provided some information on the postmarketing reporting required for all agents of focus.

The FDA has required ADF manufacturers to conduct studies assessing whether the properties intended to deter the misuse and abuse of each ADF result "in a meaningful decrease in misuse and abuse, and their consequences, addiction, overdose, and death, in post-approval settings."[153] In addition, the FDA has required several manufacturers to submit nationally representative descriptive studies analyzing ADF utilization (and that of select comparators) as well as the scope and patterns of abuse in diverse populations. The proposed final report submission dates for such studies are summarized in Table D1.

Table D1. Final Report Submission Dates for Required Postmarket Reporting

ADF*	Descriptive study of utilization and abuse	Study to evaluate impact on misuse/abuse, if any, attributable to the abuse-deterrent properties
Xtampza ER	06/2018	06/2021
Troxyca ER	10/2018	10/2018
Targiniq ER	N/A	01/2020
Hysingla ER	N/A	04/2020
Vantrela ER	03/2019	03/2022
Embeda	N/A	04/2020
Morphabond	N/A	02/2021
Arymo ER	03/2019	03/2022

*Detailed reporting requirements for OxyContin were not identified

Appendix E. Comparative Clinical Effectiveness Supplemental Information

Methods: Supplemental Information

Screening for Study Inclusion

Subsequent to literature search and removal of duplicate citations using both online and local software tools, study selection was accomplished through two levels of screening, at the abstract and full-text level. Three reviewers screened the titles and abstracts of all publications identified; all three reviewers worked together to resolve any issues of disagreement through consensus. No study was excluded at abstract-level screening due to insufficient information. Citations accepted during abstract-level screening were retrieved in full text for review. Reasons for exclusion were categorized according to the PICOTS (Population, Interventions, Comparisons, Outcomes, Timing, and Setting) elements during both title/abstract and full-text review.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of pre-market RCTs, using the categories "good," "fair," or "poor".[87] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (inc luding not masking*

outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.

We used the National Institutes of Health (NIH) "Quality Assessment Tool for pre-post Studies with no Control group" presented below as guidance criteria to assess the quality of the postmarket studies.[88]

Table E1. Criteria for Assessing Pre-Post Studies with No Control Group

Criteria for assessing pre-post studies with no control group
1. Was the study question or objective clearly stated?
2. Were eligibility/selection criteria for the study population prespecified and clearly described?
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?
4. Were all eligible participants that met the prespecified entry criteria enrolled?
5. Was the sample size sufficiently large to provide confidence in the findings?
6. Was the test/service/intervention clearly described and delivered consistently across the study population?
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?

Using these criteria, in general terms, a "***good***" study has the least risk of bias, and results are considered to be valid. A "***fair***" study is susceptible to some bias deemed not sufficient to invalidate its results. The fair quality category was broad, so studies with this rating will vary in their strengths and weaknesses and a "***poor***" rating indicates significant risk of bias.

Appendix F. Evidence Summary Tables

Table F1. Pre-Market Studies

Author & Year of Publication (Trial name) Quality rating	Study design (Duration of follow up)	Intervention and dosing schedule	Inclusion and Exclusion Criteria	Patient characteristics	Outcomes
Oxycontin® (oxycodone extended release)					
Harris J of Clin Pharm 2014 [99] **Fair Quality**	RCT double-blind positive- and placebo-controlled five-treatment crossover study	1) Finely crushed OxyContin reformulated (ORF-F) 2) Coarsely crushed OxyContin reformulated (ORF-C) 3) Original formulation OxyContin (OC) 4) Oxycodone powder (Oxy API) 5) OC Placebo N= 30 Subjects self-administered intranasal doses of 30mg doses of placebo, ORF-F, ORF-C, finely crushed OC, and Oxy API in a randomized crossover fashion, with a washout period of at least 48 hours between treatments	Healthy adults 18-55 years old, with a history of nonmedical use of opioids via intranasal route Exclusion: Objective Opiate withdrawal scale (OOWS)≥3 following naloxone challenge test, self-reported drug dependence (past 2 years), or a positive urine drug screen or breath alcohol test	Mean age, yrs (SD): 32.1 (8.99) Male: 86.7% White: 86.7% BMI, range: 19-29.7kg/m^2 Recreational use of other psychoactive drugs 1) Cannabinoids-86.7% 2) Stimulants-53.3% 3) Depressants-30%	Overall drug liking VAS, Emax Mean (SD) 1) 69.7 (29.4) 2) 61.1 (25.8) 3) 87.4 (22.2) 4) 84.8 (18.9) 5) 48.9 (14.8) Take drug again VAS, Emax Mean (SD) 1) 64.0 (38.2) 2) 52.8 (37.4) 3) 89.6 (20.7) 4) 86.6 (23.5) 5) 28.2 (24.3) Subjective drug value, Emax Mean (SD) 1) $17.01 ($16.39) 2) $17.25 ($17.93)

		Prior to the treatment phase subjects go through: 1) A screening phase -This includes a Naloxone challenge test to determine physical dependence 2) A qualification phase: Use of 30mg Oxy API & lactose powder in a randomized crossover, with 24hrs interval; subjects enter double-blind treatment phase if 30mg Oxy API is tolerated		4) Dissociative anesthetics- 30% 5) Hallucinogens- 23.3%	3) $27.95 ($16.03) 4) $27.30 ($17.40) 5) $0.37 ($0.60) *All p values for 1, 3 & 4 ≤0.003 vs. placebo except for 2 which did not differ from placebo on drug liking * All p values for 1 & 2 ≤0.002 vs. 3 & 4 * 1 & 2 did not differ significantly from each other except in drug liking where p value= 0.043
Xtampza® ER (oxycodone extended release)					
Kopecky, 2016 [95] **Fair Quality**	RCT, double-blind, active- and placebo-controlled, triple-dummy, single-dose, 6-way crossover, hypothesis-driven study	1) DETERx Intact (HFHC) 2) DETERx Chewed (HFHC) 3) DETERx Intact (Fasted) 4) DETERx Chewed (Fasted) 5) Crushed IR Oxycodone 6) Placebo N=38 (completer population) HFHC=Taken after a high-fat, high-calorie meal Fasted=Taken after overnight fast of at least 10 hours Prior to the treatment phase subjects go through:	Healthy adult nondependent recreational opioid users aged 18-55 years who have previously taken and tolerated 40-mg of oxycodone hydrochloride Exclusion: lifetime history of drug or alcohol dependence, heavy use of tobacco products	Mean age, yrs (range): 26.2 (18-46) Male: 66% White: 87% All subjects reported a history of recreational opioid use (hydrocodone, oxycodone, morphine, buprenorphine, codeine,	Drug liking VAS, Emax Mean (SD) 1) 68.6 (13.1) 2) 70.8 (11.5) 3) 68.8 (13.0) 4) 73.4 (13.9) 5) 81.8 (11.5) 6) 54.9 (8.4) Overall drug liking VAS, Emax Mean (SD) 1) 68.5 (16.5)[*] 2) 69.8 (17.4)[α] 3) 69.4 (15.3)[α] 4) 74.2 (14.4) 5) 76.2 (16.4) 6) 54.4 (10.1)[*]

		1) A screening phase -This includes a Naloxone challenge test to determine physical dependence 2) A qualification phase: subjects received oral IR oxycodone 20mg or placebo in a double-blind, crossover with 24-hr washout between. Intact study drug (oxycodone DETERx or placebo) was administered first with 50 mL of solution (IR oxycodone or placebo) followed by chewed study drug.		oxymorphone, or heroin)	Take drug again VAS, Emax Mean (SD) 1) 70.6 (18.1) 2) 69.3 (18.9) 3) 70.2 (16.0) 4) 73.7 (14.9) 5) 75.4 (16.8) 6) 52.7 (13.4) *p<0.0001 vs. IR oxycodone α p<0.05 vs. IR oxycodone Mean ARCI Score (SD) 1) 4.1 (4.8)* 2) 4.0 (4.3)* 3) 4.3 (5.0)* 4) 5.3 (5.0)ε 5) 7.1 (5.6) 6) 1.4 (2.7)α *p<0.01 vs IR oxycodone ε p<0.05 vs IR oxycodone α p<0.0001 vs IR oxycodone
Webster L Pain Medicine 2016 [100] **Fair Quality**	RCT, double-blind, double-dummy, positive- and placebo-controlled, single-dose, four-phase, four-treatment, crossover study	1) Crushed DETERx 40 mg IN + Intact PBO-ER PO 2) Crushed PBO-ER IN + Intact DETERx 40 mg PO 3) Crushed OXY-IR 40 mg IN (active control) + Intact PBO-ER PO	Inclusion: Men or nonpregnant, nonlactating women; aged 18 to 55 yrs; recreational opioid users (use of opioids for nonmedical purposes on ≥10	N=39 Mean age, yrs (SEM): 26.77 (1.07) Male, N (%): 28 (71.8)	Overall drug liking (mm) 1) 48.42 2) 62.20 3) 71.78 Take drug again (mm) 1) 47.77 2) 58.98

		4) Crushed PBO-ER IN (PBO control) + Intact PBO-ER PO IN=intranasal; PO=oral; ER=extended release, IR=immediate release OXY=oxycodone powder 1) A screening phase -This includes a Naloxone challenge test to determine physical dependence 2) A drug discrimination test: each subject received either a single IN dose of crushed OXY-IR 20 mg or a single IN dose of crushed PBO-IR and was later crossed-over to the other treatment after 24 hours wash out; subjects were excluded if they could not discriminate between OXY-IR opioid and PBO	occasions during the past year and ≥once in the 12 wks prior to screening); required to have a history of IN opioid use ≥3 times within past year Exclusion: Physical dependence or tolerance to opioids, alcohol, or other drugs (excepting caffeine and nicotine); positive urine drug screen (excluding THC) and alcohol breath test; significant unstable medical condition or chronic disease; positive for infectious disease; contraindication to opioid; heavy smokers unable to abstain from smoking for ≥5 hours during day	White, N (%): 33 (84.6) Mean weight, kg (SEM): 77.35 (2.81) Mean height, cm (SEM): 174.75 (1.32) Mean BMI, kg/m^2 (SEM): 25.27 (0.81)	3) 71.25 ACRI Scores 1) 1.34 2) 3.10 3) 5.93
Troxyca® ER (oxycodone hydrochloride and naltrexone hydrochloride)					

Setnik, 2015[101] **Fair Quality**	Randomized, double-blind, placebo- and active-controlled, 4-way crossover study	1) Placebo sugar sphere (crushed) 2) ALO-02 30 mg/3.6 mg (crushed) 3) Placebo lactose tablet (crushed) 4) Oxycodone IR 30 mg (crushed) N=28 (completer population) 4 treatment periods separated by ≥5 days. Patients underwent naloxone challenge to determine signs of withdrawal (COWS method) followed by 0.6mg. This was followed by drug discrimination phase: participants randomly received in double-blind manner either crushed oxycodone IR 30mg or crushed placebo lactose tablets intranasally for 2 consecutive days. Patients excluded if they can't distinguish placebo from oxycodone.	Healthy adults aged 18–55 years with body weight ≥50 kg and BMI 17.5–30.5 kg/m^2 who were nondependent recreational opioid users; intranasal use of opioids ≥3 times within year before screening visit Exclusion: substance abuse and/or dependence; heavy use of tobacco; positive urine drug screen (excluding tetrahydrocannabinol)	Mean age, yrs (SD): 35.1 (8.4) Male: 86% White: 96% Mean weight (SD): 78.6 (11.3) kg Recreational drug use in last 12 months: 1) oxycodone-46.4% 2) OxyContin-46.4% 3) Percocet-35.7% 4) Cannabinoids-85.7% 5) Alcohol-82.1% 6) Stimulants-60.7%	Drug liking VAS, Emax Mean (95% CI) 1) 51.0 (47.7, 54.3) 2) 60.5 (57.2, 63.8)*,‡ 3) 51.3 (48.0, 54.6) 4) 92.8 (89.5, 96.1)‡ Take drug again VAS, Emax Mean (95% CI) 1) 48.2 (39.4, 57.0) 2) 58.9 (50.1, 67.8)α 3) 46.9 (38.1, 55.8) 4) 88.4 (79.6, 97.2)β Overall drug liking VAS, Emax Mean (95% CI) 1) 50.6 (44.4, 56.8) 2) 60.2 (54.0, 66.4)α,β 3) 51.6 (45.3, 57.8) 4) 85.4 (79.1, 91.6)β *p≤0.0001 versus oxycodone IR 30 mg. ‡p≤0.01 versus corresponding placebo. α p≤0.01 versus oxycodone IR 30 mg. β p≤0.05 versus corresponding placebo.
Setnik Pain Medicine 2016 [93]	Randomized, double-blind, placebo-/active-	1) ALO-02, 40 mg (crushed) 2) ALO-02, 60 mg (intact) 3) ALO-02, 60 mg (crushed)	Inclusion: Healthy, nondependent recreational opioid	N=41 White: 78 percent	Drug liking, Emax VAS scores 1) 70.2 2) 59.3

Fair Quality	controlled, 6-way crossover study, with naloxone challenge, drug discrimination, and treatment phases	4) Oxycodone IR, 40 mg (crushed) 5) Oxycodone IR, 60 mg (crushed) 6) Placebo -Screening: standard medical evaluation -Naloxone challenge: received IV naloxone (0.2 mg followed by an additional 0.6 mg if no signs of withdrawal were observed within the first 30 seconds); withdrawal was assessed using the Clinical Opiate Withdrawal Scale (COWS); a score of <5 on COWS were eligible -Drug discrimination phase: participants had to distinguish between orally administered crushed Oxycodone HCL IR 40 mg and placebo; this was defined as ≥15-point peak increase on the drug liking and take drug again visual analog scale, and ≥30-point peak increase on the high VAS within 2 hours	users (user of opioids for nontherapeutic purposes on ≥10 occasions within the previous year and ≥8 weeks before the screening visit); aged 18 to 55 years; a BMI between 17.5-30.5 kg/m^2 Exclusion: Diagnosis of substance and/or alcohol dependence or treatment for substance and/or alcohol-related disorders; positive urine drug screen or alcohol breath test; any condition where an opioid is contraindicated; evidence or history of clinically significant disease; history of unresolved sleep apnea in last 5 years; other severe acute or chronic	Mean age, yrs (SD): 37.8 (9.3) Mean body weight, kg (SD): 78.1 (9.4) Mean BMI, kg/m^2 (SD): 25.6 (2.3) Common opioids used in previous 12 months: -Oxycodone: 50% -OxyContin: 31.3% -Percocet: 18.8%	3) 74.5 4) 85.5 5) 89.8 6) 51.6 p≤0.05, drug vs placebo group Drug high, Emax (VAS) 1) 46.5 2) 22.5 3) 52.8 4) 78.6 5) 85.7 6) 10.2 p≤0.05, drug vs placebo group Take drug again, Emax (VAS) 1) 58.1 2) 48.7 3) 72.5 4) 83.7 5) 81.5 6) 46.1 p≤0.05, drug vs placebo group Overall drug liking, Emax 1) 64.4 2) 53.3 3) 74.3 4) 80.9 5) 81.8

			medical or psychiatric condition or laboratory abnormality		6) 51.1 p≤0.05, drug vs placebo group
Hysingla® ER (hydrocodone bitartrate)					
Harris, 2016 [102] **Fair Quality**	Single-center, double-blind, positive- and placebo-controlled, randomized, four-treatment crossover study	1) PBO 2) Hysingla (HYD) coarse particles 60 mg 3) HYD fine particles 60 mg 4) Hydrocodone powder 60 mg N=25 (completer population) Treatment administrations were separated by a washout period of five to seven days Treatment periods followed 1) A naloxone challenge: a subset of subjects completed a dose selection phase to identify appropriate intranasal dose of hydrocodone powder. 2) A Qualification phase: eligible subjects self-administered 60mg of hydrocodone powder and placebo powder intranasally in double-blind crossover design, with 24-hr washout between. Subjects had to distinguish	Healthy, moderately experienced opioid users aged 18-55 years with a history of intranasal opioid abuse; ≥10 use opioids in previous year, ≥3 use 12 wks prior to screen, ≥3 intranasal use in past year; BMI 18.0 - 29.9 kg/m^2 and a weight of ≥50 kg; dose of opioid equivalent to ≥40 mg hydrocodone by any route of administration at least once in the past year Exclusion: heavy use of tobacco; history of drug/alcohol dependence; past or planned abdominal	Mean age, yrs (SD): 38.9 (10.21) Male: 90.3% White: 64.5% Mean BMI (SD): 25.3 (2.42) kg/m^2 Recreational drug experience: 1) Cannabinoids-77.4% 2) Stimulants-71% 3) Hallucinogens-38.7% 4) Depressants-16.1% 5) Dissociative anesthetics-12.9%	Drug liking VAS, Emax Mean (SD) 1) 50.6 (0.5) 2) 65.4 (18.4)* 3) 66.8 (18.4)* 4) 90.4 (13.2) Overall drug liking VAS, Emax Mean (SD) at 12/24 hrs 1) 50.2 (0.5) / 50.0 (0.4) 2) 60.8 (16.4) / 52.8 (21.4) 3) 59.4 (24.4) / 55.8 (22.5) 4) 88.2 (13.4) / 83.4 (19.0) Take drug again VAS, Emax Mean (SD) at 12/24 hrs 1) 0.0 (0) / 2.0 (10.0) 2) 33.1 (40.2) / 29.5 (38.3) 3) 36.4 (38.1) / 34.6 (36.4) 4) 84.7 (25.1) / 83.9 (25.6) Subjective drug value, Emax Mean $ (SD) at 12/24 hrs 1) 0.25 (0.0) / 0.25 (0.0) 2) 7.8 (13.2) / 7.4 (13.0) 3) 12.0 (15.7) / 11.0 (15.8)

		between them on "at this moment" drug liking VAS and overall liking/feeling high VAS	surgery; history of asthma or airway disease; history of hypotension		4) 27.7 (14.9) / 27.8 (14.4) *p<0.001 vs. hydrocodone powder
Harris, 2016b [89] **Fair Quality**	single-center, double-blind, positive- and placebo-controlled, randomized, five-treatment crossover study	1) Placebo 2) HYD intact 60 mg 3) HYD chewed 60 mg 4) HYD fine particles 5) Hydrocodone solution 60 mg N=35 (completer population) The following treatments were administered orally: 1) HYD 60 mg tablet intact; 2) HYD 60 mg tablet chewed (2-3 minutes); 3) HYD 60mg fine particles; 4) hydrocodone solution 60 mg; 5) placebo solution. At each treatment visit, subjects received an intact tablet, milled tablet, chewed tablet, and oral solution. All treatments were separated by a washout period of five to seven days. Patients underwent naloxone challenge. Qualification phase: oral solution of hydrocodone 60mg and matching placebo	Healthy, moderately experienced recreational opioid users age 18 – 55 years, weight ≥ 50 kg and BMI 18.0 - 29.9 kg/m^2; chewed an opioid ≥3 times for recreational oral abuse/misuse during previous 12 months; used 60 mg hydrocodone equivalent or higher opioid dose at least once during lifetime; negative urine screen (except cannabinoids and benzodiazepines) Exclusion: heavy use of tobacco; history of drug/alcohol dependence, dental work or clinically relevant dental issues	Mean age, yrs (SD): 36.3 (9.2) Male: 82.5% White: 72.5% Mean BMI (SD): 25.2 (3.02) kg/m^2 Recreational drug experience: 1) Cannabinoids-87.5% 2) Stimulants-77.5% 3) Hallucinogens-32.5% 4) Depressants-32.5% 5) Dissociative anesthetics-20.0%	Drug liking VAS, Emax Mean (SD) 1) 52.3 (7.14) 2) 63.3 (16.0)* 3) 69.0 (17.5)* 4) 89.2 (14.0)‡ 5) 94.0 (10.2) Overall drug liking VAS, Emax Mean (SD) at 12/24 hrs 1) 48.2 (13.1) / 48.1 (13.0) 2) 53.3 (16.8) / 54.9 (22.2) 3) 57.6 (28.3) / 56.8 (28.1) 4) 83.7 (18.0) / 80.1 (22.4) 5) 83.0 (19.2) / 84.1 (19.7) Take drug again VAS, Emax Mean (SD) at 12/24 hrs 1) 3.9 (15.9) / 2.2 (12.8) 2) 19.5 (33.7) / 32.6 (35.5) 3) 41.3 (40.7) / 43.0 (41.2) 4) 82.6 (29.7) / 77.0 (31.5) 5) 84.6 (25.7) / 86.7 (22.8) Subjective drug value, Emax Mean $ (SD) at 12/24 hrs 1) 0.5 (1.4) / 0.5 (1.6)

		solution in double-blind crossover fashion, separated by 24-hr washout period. Subjects required to distinguish treatment and placebo on "at this moment" drug-liking, overall drug liking, high VAS.			2) 6.8 (14.6) / 8.8 (14.5) 3) 11.4 (14.8) / 13.7 (16.5) 4) 24.2 (17.0) / 25.9 (16.5) 5) 22.9 (17.1) / 25.8 (16.8) *p<0.001 vs. hydrocodone solution ‡p-0.015 vs. hydrocodone solution
Vantrela® ER (hydrocodone bitartrate)					
Bond Drg and alc dep 2015 [96] *Conference Abstract*	Randomized, double-blind, triple-dummy, placebo-controlled, crossover study consisted of 3 phases Returned for a follow-up visit ~48 to 72 hours after discharge form the study center	1) Placebo (n=42) 2) Hydrocodone IR (n=39) 3) Hydrocodone ER intact (n=41) 4) Hydrocodone ER crushed (n=42) Split into three phases: Phase A – screening Phase B – qualification phase: randomly assigned in double-blind crossover fashion 60mL of noncarbonated flavored beverage (placebo) and 45mg of hydrocodone IR bitartrate powder reconstituted in 60mL of a noncarbonated flavored beverage with 48-hr washout between. Subjects had to distinguish between placebo and hydrocodone on a drug-liking and overall drug-liking bipolar VAS.	Inclusion: Age 18 to 50 years; BMI between 18 and 32 kg/m^2; history of recreational opioid use ≥10 times in last year and ≥1 within 12 wks; not physically dependent on opioids; negative urine drug screening and alcohol breath test (except THC); women must be surgically sterile, 2 years postmenopausal, or using a medically acceptable contraceptive Exclusion:		Overall drug liking VAS, Emax Mean (SD) 1) 51.1 (7.6) 2) 75.0 (16.8) 3) 49.2 (11.0) 4) 59.0 (19.9) p≤0.0022 in comparison with hydrocodone IR Take drug again VAS, Emax Mean (SD) 1) 47.2 (15.5) 2) 75.2 (17.3) 3) 46.4 (18.3) 4) 58.7 (21.5) p≤0.0022 in comparison with hydrocodone IR Drug liking VAS, Emax Mean 1) 53.2 2) 85.2 3) 53.9

		Phase C – treatment phase, subjects received, in random sequence, separated by a ≥14 day washout	Any clinically significant uncontrolled medical condition or abnormalities; history of drug or alcohol abuse; history of hypersensitivity or idiosyncratic reaction to hydrocodone or hydromorphone		4) 66.9 p≤0.0022 in comparison with hydrocodone IR
Bond 2015b [91] *Conference Abstract*	Randomized, placebo-controlled, double-blind, 5-period crossover	1) IN oral hydrocodone ER, 45 mg 2) IN hydrocodone API, 45 mg 3) intact oral hydrocodone ER, 45 mg 4) IN manipulated Zohydro API, 45 mg 5) Placebo N=45 IN=intranasal; API=active pharmaceutical ingredient 34 participants were evaluable for pharmacodynamic assessments performed through 48 hours after administration of study drug	Inclusion: Participants able to tolerate a 45 mg intranasal dose of hydrocodone API powder; be able to discriminate effects of hydrocodone from placebo		Drug Liking VAS, Emax 1) 57.3 2) 80.2 3) 72.8 (p=0.004 vs 2 and 3); (p<0.001 vs 1 and 5) 4) 83.2 5) 58.6 Overall Drug Liking VAS, Emax 1) 57.8 2) 77.1 3) 68.5 (p=0.004 vs 2 and 3); (p≤0.001 vs 1 and 5) 4) 79.8 5) 57.7
Embeda® (morphine sulfate and naltrexone hydrochloride)					

Johnson F Pain Physician 2011 [154] **Fair Quality**	RCT, 4-way crossover, double-blind, triple-dummy, placebo-controlled 12 weeks	1) Crushed pellets from 2 ER morphine sulfate with a sequestered naltrexone core (MS-sNT) 60 mg capsules 2) Two intact MS-sNT 60 mg capsules 3) Morphine sulfate solution (MSS), 120 mg 4) Placebo N=32 Participants received 4 treatments, one per session, with each session separated by washout period of 14 to 21 days	Inclusion: Aged 18 to 55 years; nondependent healthy opioid users; had experience in non-therapeutic use of opioids on at least 10 occasions within last year and at least once in the 12 wks prior to screening Exclusion: History or presence of clinically significant disease; history of allergic or adverse response to the study drugs or related drugs; used an over the counter medication within seven days prior to first dose of study medication		Drug liking VAS, Emax Mean (SD) 1) 68.1 (17.5) 2) 67.6 (13.1) 3) 89.5 (12.6) 4) 52.2 (4.5) Cole/ARCI Stimulation-Euphoria, Emax (SD) 1) 10.8 (11.2) 2) 11.9 (11.3) 3) 18.4 (11.6) 4) 6.90 (8.2)
Setnik Pain Res & Man 2013 [103] **Fair Quality**	Randomized, double-blinded, placebo-controlled, single-dose,	1) Placebo, 100 mg tablets 2) Crushed EMBEDA – morphine sulfate/naltrexone hydrochloride, 30 mg/1.2 mg ER	Inclusion: Aged 18 to 55 years; healthy nondependent recreational opioid	Mean age, yrs (SD): 35.2 (10.01) Male: 85 percent	Drug liking VAS, Emax Mean 1) 50.9 2) 69.6 3) 87.6

	three-way crossover study 16 weeks	3) Crushed morphine sulfate crushed (CR), 30 mg tablet N=33 Eligible participants underwent a naloxone challenge test, an intravenous 0.2 mg naloxone HCL bolus followed by an assessment for signs of opioid withdrawal. If no signs within 30 seconds, an additional naloxone 0.6 mg bolus dose was administered and observed for 5 mins. This was followed by dose selection phase: crushed morphine sulfate (MS) (30mg) and placebo administered intranasally and double-blinded crossover fashion to the first cohort of four eligible participants; dose escalated to 60mg and 90mg in up to two cohorts. Dose determination based on drug liking bipolar VAS. Drug discrimination phase followed with MS and placebo intranasally, ability to discriminate on drug liking VAS and unipolar high VAS.	user; must have experience with intranasal drug administration (≥3 occasions within last year) Exclusion: Diagnosis of substance and/or alcohol dependence; participated or seeking treatment for substance abuse; has a condition in which an opioid is contraindicated; allergy or history of hypersensitivity to opioids	White: 85 percent Mean weight, kg (SD): 79.18 (8.86) Mean BMI, kg/m^2 (SD): 25.62 (2.75)	p<0.001 for crushed EMBEDA and crushed morphine sulfate CR vs. placebo Overall drug liking VAS, Emax Mean 1) 50.9 2) 60.8 3) 83.8 p<0.001 for crushed EMBEDA and crushed morphine sulfate CR vs. placebo Take drug again VAS, Emax Mean 1) 42.2 2) 60.6 3) 84.9 p<0.001 for crushed EMBEDA and crushed morphine sulfate CR vs. placebo

Setnik Pain Medicine 2013 [97] **Fair Quality**	Randomized, single center, double-blind, placebo-controlled, three-way crossover study	1) Placebo (single-dose, 2 x microcrystalline cellulose) 2) MS Contin (single-dose, 2 x 60 mg morphine sulfate whole tablets manually crushed) 3) EMBEDA (single-dose, solution 2 x 60 mg morphine sulfate with sequestered 2.4 naltrexone hydrochloride whole capsules manually crushed) N=33 A naloxone challenge test consisted of an IV bolus dose of naloxone hydrochloride, 0.2 mg and if there was no evidence of withdrawal within 30 seconds and additional 0.6 mg bolus dose was injected. In the drug discrimination phase, participants received either 120 mg of morphine sulfate or placebo in solution (150ml). Patient eligibility was based on the ability of the subject to distinguish morphine from placebo	Inclusion: Healthy nondependent recreational opioid user Exclusion: Has a history or current diagnosis of substance dependence (excluding caffeine and nicotine); seeking treatment for substance and/or alcohol related disorders; history or presence of clinically significant illness; females who are pregnant, lactating, or planning to become pregnant during the study; allergy or history of hypersensitivity to opioids	Mean age, yrs (SD): 24.2 (3.7) Males: 91 percent White: 97 percent Mean body weight, lb. (SD): 170.2 (29.9) Mean BMI, kg/m^2 (SD): 23.9 (3.5)	Drug liking VAS, Emax Mean (SD) 1) 51.7 2) 80.8 3) 65.2 Overall drug liking VAS, LS Mean 1) 50.5 2) 69.8 3) 58.6 Take drug again VAS, LS Mean 1) 49.5 2) 70.7 3) 57.7

		Treatment phase occurred from days 3-21 and comprised three visits, each with a 2-night confined stay; each treatment period was separated by a minimum of 4 days not to exceed 14 days between dosing			
Stauffer Clin Drug Inves 2009 [98] **Fair Quality**	Randomized, double-blind, placebo-controlled, triple-dummy, four-way crossover study	1) Placebo, 120 mg 2) ALO-01 whole, 2 x 60 mg capsules 3) ALO-01 crushed, 2 x 60 mg capsules 4) Morphine sulfate solution (MSS), 120 mg N=32 Subjects were screened for eligibility through whether they could tolerate a single dose of morphine 120 mg and distinguish between morphine and placebo	Inclusion: Aged 18 to 55 yrs; healthy with a BMI of 21-31 kg/m^2 and weight <55 kg; nondependent opioid users; previously used opioids non-therapeutically for psychoactive effects on ≥10 occasions within previous yr and ≥1 in last 12 wks; a positive drug tests at screening was allowed if it was negative at qualifying session and all treatment sessions; women must have negative pregnancy test and not lactating	Mean age, yrs (SD): 35.0 (7.6) Male: 81 percent White: 69 percent Bodyweight, kg (SD): 82.4 (11.0) BMI, kg/m^2 (SD): 26.4 (2.8)	Drug liking VAS, Emax Mean (SD) 1) 52.2 (4.5) 2) 67.6 (13.1) 3) 68.1 (17.5) 4) 89.5 (12.6) Subjective drug value, Emax Mean ($Can) 1) 2.73 (7.08) 2) 14.22 (15.46) 3) 13.72 (16.98) 4) 28.85 (14.55) ARCI, 0-51 scale (SD) 1) 9.4 (9.8) 2) 13.4 (12.5) 3) 15.7 (13.5) 4) 23.0 (12.8) p<0.001, all comparisons except ALO-01 whole vs ALO-01 crushed (p=NS), ALO-01 crushed vs placebo (p=0.002) and ALO-01 whole vs placebo (p=NS)

			Exclusions: History of substance abuse (alcohol included); opioid addiction or dependence; current psychiatric illness or significant medial or neurological conditions; positive for HIV/hepatitis B&C		
Morphabond® ER (morphine sulfate)					
Webster Pain med 2016 [104] **Fair Quality**	Randomized, double-blind, double-dummy, placebo-controlled, four-way crossover	1) Placebo 2) crushed intranasal ER morphine (60 mg) + intact oral placebo 3) crushed intranasal Morphine ARER (60 mg) + intact oral placebo 4) crushed intranasal placebo + intact oral Morphine ARER (60 mg) Each treatment is separated by a minimum seven-day washout period N=25	Inclusion: Aged 18 to 55 yrs; nondependent opioid users who used for nontherapeutic purposed ≥10 occasions within the last year and at least once in 12 wks prior to screening; must have ≥3 experiences with insufflating drugs within last year Exclusion: Participated in, were participating in, or seeking treatment for	Mean age, yrs (SD): 25.4 (6.57) Male: 85.2 percent White: 96.3 percent Mean BMI, kg/m^2 (SD): 24.9 (3.89)	Drug liking VAS, Emax LS Mean (SE) 2) 84.79 3) 71.13 (p<0.0001 vs. 2 & 4) 4) 67.03 Overall drug liking VAS, p value (vs. crushed intranasal ER morphine) 3) 0.007 4) 0.0025 Take drug again VAS, p value (vs. crushed intranasal ER morphine) 3) 0.0341 4) 0.0103 ARCI (Intact oral morphine ARER vs crushed intranasal ER morphine): 0.0003

		Qualification phase consisted of a three-night inpatient, double-blind session; the naloxone challenge test was an initial dose of 0.2 mg of naloxone hydrochloride through intravenous bolus. If no evidence of withdrawal occurred within 30 seconds, 0.6 mg of naloxone hydrochloride was given and the subject was observed for 5 mins; for the drug discrimination test, subjects received a single, intranasal dose each of morphine sulfate IR and placebo and subjects had to distinguish the morphine from the placebo.	substance abuse disorders; presence of drug or alcohol dependence; except THC, patients were excluded if positive urine drug screen; history or presence of clinically significant disease; any condition in which an opioid was contraindicated		
Arymo® ER (morphine sulfate)					
Smith M Pain Medicine 2016 [90] **Fair Quality**	Randomized, double-blind, triple-dummy, active- and placebo-controlled, four-way crossover, single-center	1) Placebo 2) Morphine-ADER-IMT (60 mg, intact) [abuse-deterrent extended release, injection molded tablet] 3) Morphine-ADER-IMT (60 mg, manipulated) 4) Morphine ER (60 mg, manipulated)	Inclusion: Aged 18 to 55 yrs; experienced, nondependent, recreational opioid users; recreational user has a history of nonmedical use of opioids with ≥10 occasions within the past year and ≥1 in	Male, n (%): 28 (73.7) White, n (%): 35 (92.1) Mean age, yr (SD): 24.3 (4.2) Mean weight, lb (SD): 159.9 (27.2)	Drug liking VAS, Emax Median (SD) 1) 50 2) 62 3) 67 (p=0.007) 4) 74 Overall drug liking VAS, Emax Mean (SD) 2) 57.0 (p<0.001) 3) 63.5 (p=0.13) 4) 67.5

		Everyone received 1 dose of each oral agent in crossover fashion separated by ≥5 days The qualification phase consisted of a naloxone challenge to exclude participants who were opioid dependent, and a drug discrimination test to exclude participants who could not tolerate 30 mg morphine or distinguish its positive subjective effects from placebo	12 wks before screening Exclusion: History of substance and/or alcohol dependence; any condition in which opioids are contraindicated; presence of hepatitis B/C or HIV; history of sleep apnea in the past 5 yrs that hasn't been corrected or resolved	Mean BMI, kg/m^2 (SD): 24.3 (3.9)	Take drug again VAS, Emax Mean (SD) 2) 56.0 (p<0.001) 3) 61.5 (p=0.05) 4) 68.0
Webster L Pain Medicine 2016 [105] **Fair Quality**	Single-center, randomized, double-blind, double-dummy, active- and placebo-controlled five-way crossover	1) Intranasal low volume (IN LV) manipulated morphine ER, 60 mg (n=46) 2) IN manipulated high volume (HV) morphine abuse-deterrent, injection molded tablets (ADER-IMT), 60 mg (n=46) 3) IN manipulated LV morphine-ADER-IMT, 60 mg (n=46) 4) Oral morphine-ADER-IMT, 60 mg (n=46) 5) Placebo	Inclusion: Aged 18 to 55 yrs; experienced nondependent recreational opioid user with experience of IN opioid administration (≥3 occasions within the yr before screening); a recreational user is a nonmedical opioid user with ≥10 occasions within past	Male, N (%): 36 (78.3) White, N (%): 44 (95.7) Mean age, yrs (SD): 28.1 (8.1) Mean weight, lb (SD): 161.8 (26.0)	Drug liking VAS, Emax Median (SD) 1) 77.5 2) 62.0 (p<0.0001) 3) 52.5 (p<0.0001) 4) 68.0 (p=0.0001) 5) 51.0 (p<0.0001) P values related to manipulated ER Overall drug liking VAS, Emax Median (SD) 1) 71.0 2) 51.0 3) 50.5 4) 59.0

		After screening, participants entered a naloxone challenge to exclude opioid-dependent participants Then a drug discrimination test (received IN placebo or morphine, 30 mg IR in a RCT, double-blind, double-dummy manner) to exclude participants who couldn't tolerate 30 mg IR morphine. After IN administration of manipulated high-volume morphine-ADER-IMT, participants were randomized 1:1:1:1 to receive IN manipulated LV morphine ER, IN manipulated LV morphine-ADER-IMT, intact oral morphine-ADER-IMT, and placebo in crossover fashion	year and ≥1 in the 12 wks before screening Exclusion: History of substance and/or alcohol dependence (excluding caffeine and nicotine); any condition in which an opioid is contraindicated; history of sleep apnea in past 5 yrs that has not been resolved or been corrected	Mean BMI, kg/m^2 (SD): 24.0 (2.9)	5) 50.0 p<0.0001 relative to manipulated ER Take drug again VAS, Emax Median (SD) 1) 73.0 2) 50.0 3) 50.0 4) 56.0 (p=0.0003) 5) 50.0 p<0.0001 for other arms relative to manipulated ER

Table F2. Post-Market Studies

Author & Year of Publication (Trial name) Quality Rating	Study Design (Study sites/ Duration of study)	Intervention N	(Inclusion & Exclusion Criteria) Patient characteristics	Outcomes
Oxycontin (oxycontin extended release)				
Black R JPain 2012 [155] ***POSTER ABSTRACT***	Observational design comparing the prevalence, by routes, of past 30-day abuse of ORF in the period after its introduction to that of OC before ORF introduction Uses the ASI-MV, a computer-administered interview based on the Addiction Severity Index for treatment planning for adults Pre-introduction: Jun 2009 – Aug 2010 Post introduction:	1) OxyContin 2) ER Oxymorphone 3) ER morphine N= 104,630 (all respondents)	NAVIPPRO System *Patient characteristics:* Mean age, yrs. (SD): 33.9 (11.6) White (%): 54,737 (54.1) Male (%): 68,496 (65.5) Reported chronic medical problem (%): Yes: 31,747 (30.3) No: 72,612 (69.4) Unknown/NR: 271 (<1) Self-reported pain problem (%): Yes: 32,791 (31.3) No: 71,648 (68.5) Unknown/NR: 191 (<1)	*Changes in past 30 day abuse patterns of OxyContin and comparator opioids before and after introduction of ORF* Percent of product-specific abuse among Rx opioid abusers: pre- / post- / %change (p-value) 1) 23.84% / 11.91% / -50 (<0.0001) 2) 1.95% / 4.55% / +134 (<0.0001) 3) 5.25% / 4.54% / -14 (0.0302) Percent of product-specific abuse among all individuals 1) 4.30% / 2.35% / -45 (<0.0001) 2) 0.36% / 0.89% / +145 (<0.001) 3) 0.96% / 0.89% / -8 (0.2330) *Changes in average number of days per month reported abusing OxyContin and comparator opioids before and after introduction of ORF* pre- / post- / %change (p-value) 1) 11.0 days / 7.3 days / -33.3% (<0.001) 2) 5.2 days / 7.3 days / +40.83% / (0.0023) 3) 9.3 days / 9.3 days / 0.01% / 0.0 days (0.9983)

	Aug 2010 – Jun 2011			*Percent of abuse via specific ROA for OxyContin, ER Oxymorphone and ER morphine before and after introduction of ORF among those who reported abuse* Inject (pre- / post-): 1) 34.3% / 15.6% 2) 8.4% / 11.6% 3) 32.6% / 35.8% Snort (pre- / post-): 1) 58.4% / 27.4% 2) 70.2% / 76.5% 3) 31.1% / 28.5% Oral (pre- / post-): 1) 54.9% / 77.0% 2) 37.3% / 27.1% 3) 48.7% / 44.2%
Butler S Journal of Pain 2016 [156] ***POSTER ABSTRACT***	Cross-sectional, observational study using sentinel surveillance system of substance abuse evaluations Uses the ASI-MV, a standard computerized clinical interview for evaluation and triage in substance abuse treatment settings	1) Crush resistant tablets (CRT) ER opioid category (OxyContin reformulated, Opana ER reformulated, and Nucynta ER) 2) Non-CRT versions of tablets category 3) Original or generic oxycodone ER 4) All morphine ER (excluding EMBEDA) 5) Original or generic Oxymorphone ER	*Patients characteristics* N= 364,329 Male: 56.3% Age 21-34: 64.0% 35-44: 20% >45: 15.9% Region South: 50.4% West: 24.0% Midwest: 19.2% Northeast: 6.4%	*Abuse prevalence of CRTs and comparators by any oral mode of administration involving product manipulation among oral abusers* (prevalence of abuse per 100 abusers) 1) 41.5* 2) 34 3) 34.3 4) 35.3 5) 32 6) 36 *p<0.003 *Non-tampering abuse/abuse by chewing/abuse by dissolving and drinking of CRTs and comparators by*

	Jan 2009 – Mar 2015	6) Oxycodone IR SE	Reported abuse -any Rx opioid: 76,108 (20.9%) -target drugs: 28,107 (7.7%) -by oral route: 18,135 (5.0%)	*swallowing whole among oral abusers (prevalence of abuse per 100 abusers of product by any oral route)* 1) 79/35.5/4.1 2) 90/30/5.2 3) 90/30.4/5.3 4) 82/31/4.9 5) 88.5/26/4.1 6) 87.5/31/5 *note these are estimates taken from a graph
Butler, 2013 [113] **Fair**	Time-series observational study Samples obtained from 357 center in United States and part of the NAVIPPRO surveillance system 14-months pre-release of reformulated ER oxycodone (ORF) & 20-months post release of ORF	1) ER oxycodone (Oxycontin pre-ORF & ORF post-ORF) 2) ER Oxymorphone 3) ER morphine ORF=Reformulated ER oxycodone N=140,496	Included sites that collected data for Oxycontin and ORF in both the pre- and post ORF periods *Patient characteristics:* Age Over 55yrs-3.7% 35 to 54 yrs-32.6% 21 to 34 yrs-53.9% under 21yrs-9.9% Male: 55.6% White: 66.2% Abuse of any prescription opioids: 18.8%	*Changes in rates of abuse: pre-ORF/post-ORF/% change (p value pre- vs. post-)* A) Prevalence of past 30-days abuse among all individuals assessed by ASI-MV 1) 4.06/2.41/-41 (p<0.0001) 2) 0.32/1.11/+246 (p<0.0001) 3) 0.92/0.95/ +2 (0.6634) B Prevalence of past 30-days abuse among prescription opioid abusers assessed by ASI-MV 1) 23.69/ 12.12/ -49 (p<0.0001) 2) 1.87/ 5.54/ +196 (p<0.0001) 3) 5.37/ 4.7/-12 (0.0209) *Changes in routes of administration (ROA): Pre/post (p value pre- vs. post-)* 1) Oral: 54.5% / 76.1% (p<0.0001) Snorting: 52.7% / 25.4% (p<0.0001) Smoking: 6.4% / 4.2% (p=0.0373) Injection: 35.7% / 15.9% (p=0.0002) 2) Oral: 38.2% / 30.1% (p=0.0056)

			Past 30-day ER oxycodone abuse 1) Pre-ORF: 2,894 (24%) 2) Post-ORF: 1,705 (12.1%)	Snorting: 61.8% / 68.8% (p=0.0162) Smoking: 0.2%/1.9% (no statistically significant change) Injection: 8.6% /15.6% (p=0.0124) 3) Oral: 46.7%/45.9% Snorting: 25.3%/25.6% Smoking: 0.9%/1.7% Injection: 45.7%/46.0% (No statistically significant change) *Frequency of abuse in Past 30 Days Reported, mean days: pre-ORF/post-ORF/% change (p value pre- vs. post-)* 1) 10.75 days / 7.48 days / -30.44% (p<0.0001) 2) 5.11 days / 7.78 days /+52.23% (p<0.0001) 3) 9.11 days / 10.07 days / +10.55% (p=0.0909)
Cassidy Pain Medicine 2014 [112] **Fair**	Observational, cross-sectional; time-series analysis study 30 days; the individuals assessed were from the Addiction Severity Index – Multimedia Version (ASI-MV) from January 1, 2008, to December 31, 2011 437 facilities	1) All Rx opioids 2) ER opioids 3) IR opioids 4) Oxycodone ER 5) Oxymorphone ER 6) Morphine ER N=232,874 Prescription opioids as a class, all immediate-release (IR) opioids and all extended release (ER) opioids as	*Patient characteristics* Majority of individuals were between age 18-35: 57.3 percent Median age: 32 years Males: 64.5 percent White: 54.2 Percent Patient population: -Traditional substance abuse treatment (55%) -involvement in the criminal justice system (24.7%)	From 2008-2011 Trends in prevalence of 30-day abuse of opioid analgesics and other drug categories *Total average quarterly percent change (QPC)* Abuse Prevalence: 1) +0.70% 2) +0.97% 3) +0.18% p<0.05 compared to IR opioids Adjusted Abuse Prevalence (per million prescriptions): 1) -0.38% 2) -2.33% (p<0.0001) 3) -0.87% (p<0.05)

		separate categories as well as specific prescription opioid compounds and other drugs of abuse (heroin, cocaine, amphetamine)	-DUIs (7.3%) -Other settings (13.0%) West: 41.4% South: 39.2% Midwest: 15.2% Northeast: 4.1%	Change in prevalence of past 30-day abuse of opioid analgesics after opioid ADF introduction: pre- /and post-ADF period/ pre-post relative percent change (p value): *Rates per 100 assessments* 1) 16.94/18.36/+8.3% (p<0.0001) 2) 12.57/12.88/+10.5% (p<0.0001) 3) 9.70/10.72/+2.5% (p=0.192) 4) 6.49/5.08/-21.7% (p<0.0001) 5) 0.32/0.94/+190.9% (p<0.0001) 6) 1.13/1.10/NR (p=0.677) Change in prevalence of past 30-day abuse of opioid abuse compounds among abuser route of administration: pre-/post-ADF/pre-post RR: *Oral:* 4) 12.88/17.49/0.74 5) 0.17/0.41/2.47 6) 1.27/1.29/1.02 *Snort:* 4) 55.35/33.71/0.61 5) 3.42/13.16/3.85 6) 3.58/2.55/0.71 *Inject:* 4) 50.86/41.49/0.82 5)0.68/5.30/7.82 6) 14.78/25.21/1.71
Chilcoat H Drg and Alc Dep 2016 [127]	Open cohort study covering >150 million patients and 65% of retail U.S.	(# of pre/post patients) 1) ER oxycodone (849,860/2,130,955)	IMS LRx database with 150 million unique patients	Changes in doctor-shopping rates for brand ER oxycodone relative to changes for comparator opioid analgesics and benzodiazepines pre- and post-reformulation of brand ER oxycodone: (pre-/post-period rate/ pre-to post % change):

Fair	prescriptions from IMS LRx longitudinal data 6-month calendar intervals before and after the introduction of reformulated brand ER oxycodone	2) IR hydromorphone (620,444/1,949,226) 3) IR oxycodone APAP (9,335,562/25,167,863) 4) IR hydrocodone APAP (26,479,737/74,140,839) 5) benzodiazepines (15,519,660/43,160,231) 6) ER morphine (663,514/2,164,569) 7) IR oxycodone SE (1,527,554/6,420,004) 8) ER Oxymorphone (103,559/400,809) APAP=acetaminophen SE=single entity		1) 0.25%/0.12%/-50 2) 0.09%/0.06%/-25 3) 0.13%/0.10%/-23 4) 0.15%/0.13%/-13 5) 0.18%/0.16%/-9 6) 0.09%/0.09%/4 7) 0.34%/0.36%/5 8) 0.09%/0.15%/66
Cicero NEJM 2012[114] **Poor**	Self-administered surveys completed anonymously by independent cohorts Additional subset voluntarily agreed to online/telephone interviews for	N=2,566 1) OxyContin 2) Hydrocodone 3) Other opioids 4) Other oxycodone 5) Heroin	Patients entering treatment programs in U.S. for whom a prescription opioid was primary drug of abuse	*Primary drug (%)* (4Q2009-3Q2010)/3Q2010/1Q2011/4Q2011/1Q2012: 1) 35.6*/28/26/15/12.8 2) 24/32/29/29/29 3) 20.1**/17/21/33/32.3 4) 20/21/22/22/26 *Drug used to get high in the last 30 days (%)* 1) 47.4*/48/42/38/30.0 2) 65/73/66/68/65

	qualitative information gathering			3) 61/62/65/68.5/66 4) 60/60.5/61/52/51 5) 9/5/5/15/17 *p<0.001 compared to 1Q2012 **p=0.005 compared to 1Q2012
Cicero Pain 2016 [111] **Fair**	Survey study from Survey of RADARS Key Informants' Patients (SKIP) program and an 85% response rate was attained Subset of respondents (25.5%) said that they were willing to give up their anonymity and participate in a follow-up study, dubbed Researchers and Participants Interacting Directly (RAPID)	1) Original Oxycontin (n=966) 2) Opana ER (n=128)	Aged above 18; entering their substance abuse treatment program; primary diagnosis of opioid abuse (as defined by DSM criteria) *Patient characteristics:* Mean age, yrs 1) 32.8 2) 29.9 Male, % 1) 56.2 2) 58.4 White, % 1) 75.4 2) 84.9 Regions Midwest: 27.9% Northeast: 15.5% South: 33.6% West: 23.0%	Rates of abuse over time (pre- and post-rates) 1) 44.2%/ 25% 2) 5.5%/ 7.6% *total SKIP respondents (n=12,124) Routes of administration for pre- and post- Oxycontin and Opana ER: (pre-/post-/% change (p value)) [%] *RAPID participants; Oxycontin (n=117) and Opana ER (n=35) *Any non-oral* 1) 91.5/47.9/ 47.7 (p<0.001) 2) 94.3/77.1/18.2 (p=0.06) *Inject* 1) 42.7/21.4/50.0 (p=0.001) 2) 60.0/51.4/14.3 (p=0.471) *Snort* 1) 78.6/28.2/64.1 (p<0.001) 2) 80.0/37.1/53.6 (p<0.001) *Smoke* 1) 17.9/7.7/57.1 (p=0.022) 2) 20.0/2.9/85.7 (p=0.052) *Any oral* 1) 63/94/-49.2% (p<0.0001) 2) 20/21/-5.0% (p=0.808)

Cicero T JAMA Psychiatry 2015 [110] **Fair**	Survey study using data from the ongoing Survey of Key Informants' Patients (SKIP) program (n=10,784), part of the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) system that collects and analyzes post-marketing data on misuse and diversion of prescription opioid analgesics and heroin RAPID data come from respondents from the SKIP survey that were willing to give up their anonymity and participate in the interview-based RAPID program (n=244)*82.0%	1) Original (pre-2010) OxyContin formulation 2) Reformulated OxyContin	SKIP program consisted of key informants from more than 150 public and privately funded treatment centers in 48 states Mean age, yrs (SEM) SKIP/RAPID respondents: 34.1 (0.1)/35.9 (0.6) Male, % 50.6/46.4 White, % 78.4/90.4 % of participants from each region: Midwest: 28.5% Northeast: 16.9% South: 31.7% West: 22.9%	Past month abuse of Oxycontin, % -Pre-reformulation (Jan-June 2009): 45.1 -Post-reformulation (Jul-Dec 2012): 26 (p<0.001) -Post reformulation rate reached a plateau at 25 to 30%, with no further decline from 2012 to 2014 Past month abuse of heroin, % -Pre-reformulation (Jan-June 2009): 25 -Post-reformulation (Jul-Dec 2012): 40 (p<0.001) <u>Interview of RAPID participants</u> Residual Abuse (N=153, RAPID) 51 (33.3%) ADF had no effect on drug selection, continue OxyContin abuse 51 (33.3%) replaced OxyContin because of ADFs 5 (3.3%) stopped abusing drugs because of ADFs 46 (30.1%) didn't abuse enough to be influenced Route of Administration (N=244, RAPID) 38 (43%) switch from injecting/inhaling to swallowing 30 (34%) defeated ADF and continued injecting/inhaling 20 (23%) had been swallowing before ADF formulation and ADF had no effect on their continued oral use Transition to Other Drugs among those that replaced Oxycontin (n=55) 70% changed to heroin 25% changed to other oxycodone

	response rate from the SKIP survey January 2009 – June 2014			
Coplan Clin Pharm and Ther 2016 [108] **Fair**	10 studies which examine from 1 year before to 3 years after OxyContin reformulation conducted as part of required FDA postmarketing program. A 6 month transition period (3Q2010-4Q2010) was excluded from calculation to allow for original OC to be depleted. Studies included: National Poison Data System (NPDS); RADARS System Poison Center, System Outpatient Treatment Program (OTP), Study of Key Informants' Patients	1) Original Oxycodone 2) Reformulated Oxycodone 3) Other Schedule II opioids 4) IR Oxycodone (single-entity) 5) IR Oxycodone-Acetaminophen 6) ER Morphine 7) ER Oxymorphone 8) IR Hydrocodone-Acetaminophen 9) Methadone 10) IR Hydromorphone	NAVIPPRO: patients in 1,000 different substance abuse treatment centers in 36 states RADARS OTP: patients in 70 different public methadone maintenance clinics RADARS SKIP: patients at private substance abuse treatment centers University of Kentucky: abusers of OxyContin in rural Kentucky MarketScan: patients commercially insured RADARS Drug Diversion: patients involved in law enforcement cases regarding drug diversion	Rates of OxyContin overdose diagnoses, per 100 person-years 1) 0.42, 2) 0.28 **<u>Changes 1 year before to 3 years after reformulation</u>** *Misuse (Radars Poison Center) (%)* 1-2) -43 3) -6 *Abuse, Radars PC /NPDS/NAVIPPRO/SKIP/OTP/Kentucky study (%)* 1-2) -55/-55/-48/-30/-43/-85 3) -7/-4/-3/16/9/53 *Doctor shopping, IMS prescription data (%)* 1-2) -50 7) 66 *Change in Overdose using population rates, Rate of Diagnosed Events/Adverse Event Database (%)* 1-2) -34/-65 6) 17/NR *Change in death, Adverse Event Database (%)* 1-2) -60

	(SKIP), Drug Diversion Program; a study of individuals in rural Kentucky conducted by U of Kentucky; MarketScan; Fatal adverse events reported to manufacturer; IMS Health Prescription database; National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO)			Opioid prescription rates, pre-reformulation/post-reformulation 1-2) 3.6/2.9 4) 5.1/7.7 5) 19.2/18.5 6) 3.1/3.4 7) 0.4/0.5 8) 66.4/65.0 9) 2.2/2.0
Coplan Pharm and drug safe 2015 [157] ***POSTER ABSTRACT***	Retrospective cohort study from MarketScan commercial database Study period (divided in three times around introduction of reformulated OxyContin): 1 year before (August 2009 – July 2010);	1) OxyContin 2) ER Morphine 3) ER Oxymorphone 4) IR oxycodone single-entity 5) IR hydromorphone	Aged 18 to 64 years; incident or prevalent users of OxyContin or 4 comparator opioids; separate cohorts were included for each drug. Opioid use defined as duration of continuous use: ≤15 days between prescriptions plus 15 days end of last prescription	*Changes in Rates of Diagnosed Addiction/Dependence per 100 Person-Years of Opioid Use in Individuals Dispensed One Opioid (from 1 yr before to 3 yrs after introduction of reformulated OxyContin)* 1) -25% 2) +21% 3) +13% 4) +7% 5) +31% *Rates of Diagnosed Addiction/Dependence per 100 Person-Years of Opioid Use in Individuals Dispensed One Opioid, 2011-2013* 1) 3.00

	3 months' transition period (August 2010 – October 2010); 3 years' after (November 2010 – October 2013) August 2009-October 2013 Diagnosed event of interest: ICD-9 CM diagnostic codes of 304.0x and 304.7x codes			2) 3.18 3) 5.95 4) 5.58 5) 4.89 Changes in rates of diagnosed addiction/dependence per 100 person-years of opioid use in individuals dispensed 1 opioid, % 1) -25 2) 21 3) 13 4) 7 5) 31
Coplan Pharm and drug safety 2013 [109] **Fair**	National Poison Data System (NPDS) covering all US poison centers was used to measure changes in exposures in the year before versus the 2 years after introduction of reformulated extended release oxycodone (ERO) OxyContin	1) ERO Oxycontin 2) Other single-entity (SE) oxycodone 3) Heroin	Data from the NPDS, which captures 99.5% of poison exposures reported to all poison centers in the USA Exposures reported to poison centers are classifieds into reasons: intentional abuse, unintentional therapeutic errors, unintentional general exposures, and adverse reactions	*Changes in number of ERO exposures per quarter from 1 year before to 2 years after reformulations:* Average per quarter intentional abuse, pre-/post-/%change (p value): 1) 130.3 / 83.3 / -36 % ($p<0.0001$) 2) 228.5 / 273.4 / +20% ($p<0.0001$) 3) 355.8 / 505.1 / +42% ($p<0.0001$) Average per quarter intentional misuse, pre-/post-/%change (p value): 1) 51.3 / 40.4 / -21% (p=0.0076) 2) 104.0 / 119.6 / +15% (p=0.0172) 3) 46.5 / 60.4 / +30% (p=0.0025)

	1 year preceding (3Q2009-2Q2010) to the 2 years following (4Q2010-3Q2012)			
Davis Annals of Emer Med 2012 [158] ***POSTER ABSTRACT***	Data from RADARS Drug Diversion Program Approximately 300 drug diversion agents in 50 states and Puerto Rico submit data quarterly on the number of documented drug diversion cases within their jurisdiction for specific prescription drugs Pre-reformulation of OxyContin (October 2008 – September 2010) compared to post-reformulation (October 2010 – March 2012)	1) ER Oxycodone 2) Other prescription opioids		Number of diversion events pre-reformulation/Percentage of 2000 US population covered by RADARS database 2008-Q4 1) 466/37.3 2) 4310/37.3 2010-Q3 1) 488/38.4 2) 3586/38.4Number of diversion events post-re-formulation/Percentage of 2000 US population covered by RADARS 2010-Q4 1) 306/36.3 2) 3282/36.3 2012-Q1 1) 177/45.7 2) 3488/45.7 Average ER oxycodone diversion population rate after reformulation is 53% lower than average population rate before reformulation (p<0.001)

<table>
<tr>
<td>DeVeaugh-Geiss Post Med 2016 [116]

POSTER ABSTRACT</td>
<td>Survey data from The National Survey on Drug Use and Health (NSDUH) were used; NSDUH is designed to provide estimates of the prevalence of nonmedical drugs in the US household population age 12+ years and assesses drug use from a sample of 60,000 individuals per year

Looks at data from 2008-2014 (two years before reformulation and four years after)</td>
<td>1) Oxycontin – One year before reformulation (2009)
2) Oxycontin – Each year post reformulation from 2011 - 2014</td>
<td></td>
<td>Past year initiation of nonmedical use of Oxycontin per 10,000 population
<table>
<tr><th>2009</th><th>2011</th><th>2012</th><th>2013</th><th>2014</th></tr>
<tr><td>19</td><td>15</td><td>12</td><td>14</td><td>9</td></tr>
<tr><td>% Change compared with 2009</td><td>-19%</td><td>-38%</td><td>-28%</td><td>-51%</td></tr>
</table>
Past year initiation of nonmedical use of Oxycontin per 10,000 prescription Oxycontin dispensed
<table>
<tr><th>2009</th><th>2011</th><th>2012</th><th>2013</th><th>2014</th></tr>
<tr><td>868</td><td>746</td><td>635</td><td>773</td><td>551</td></tr>
<tr><td>% Change compared with 2009</td><td>-14%</td><td>-27%</td><td>-11%</td><td>-36%</td></tr>
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Past month nonmedical use of Oxycontin per 10,000 population
<table>
<tr><th>2009</th><th>2011</th><th>2012</th><th>2013</th><th>2014</th></tr>
<tr><td>17</td><td>14</td><td>11</td><td>16</td><td>11</td></tr>
<tr><td>% Change compared with 2009</td><td>-16%</td><td>-31%</td><td>-6%</td><td>-33%</td></tr>
</table>
Past month nonmedical use of Oxycontin per 10,000 Oxycontin prescription dispensed
<table>
<tr><th>2009</th><th>2011</th><th>2012</th><th>2013</th><th>2014</th></tr>
<tr><td>753</td><td>671</td><td>611</td><td>873</td><td>654</td></tr>
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				% Change compared with 2009	-11%	-19%	16%	-13%	
Degenhardt L Drug and Alcohol Dependence 2015 [121] **NOMAD** **Poor**	Methods include: data on pharmaceutical opioid sales; drug use by people who inject drugs regularly (PWID); client visits to the Sydney Medically Supervised Injecting Centre (MSIC); and last drug injected by clients of inner-Sydney needle-syringe programs (NSPs) Conducted in Australia 2009-2014	1) Original Oxycontin, 80 mg 2) Reformulated OxyContin, 80 mg 3) Morphine 4) Heroin N=606 (Jan-March 2014) N=547 (May-August 2014)		Opioid use in the NOMAD cohort, pre-and post-OxyContin formulation *Pre-introduction* % used in past month 1) 56, 2) N/A, 3) 65, 4) 64 % injected past month 1) 55, 2) N/A, 3) 63, 4) 64 % chewed, snorted, dissolved or smoked past month 1) 3, 2) N/A, 3) 4, 4) NR *Post-introduction* % used in past month 1) 16, 2) 8, 3) 44, 4) 49 %injected past month 1) 15, 2) 3, 3) 42, 4) 48 %chewed, snorted, dissolved, or smoked past month 1) 0.2, 2) 1, 3) 4, 4) NR *Past month accidental overdoses reported by the NOMAD cohort* Pre-introduction of reformulated OxyContin 4% (25) of total sample overdosed in past month 3% (17) involved heroin 0.3 % (2) involved morphine 0.3% (2) involved oxycodone Post-introduction of reformulated OxyContin 3% (17) of total sample overdosed in past month					

				2.4% (13) involved heroin 0.2% (1) involved morphine 0.2% (1) involved morphine % strongly agreed that they would tamper with drug in future, pre-reformulation/post-reformulation 1) 74/73, 2) NA/20*, 3) 71/73 *p<0.05 compared to pre-reformulation % of those who injected strongly agreed that it is easy to dissolve/cut up/inject, pre-reformulation 1) 27/34/7 2) NR/NR/NR 3) 23/28/10 % of those who injected strongly agreed that it is easy to dissolve/cut/inject, post-reformulation 1) 43*/52*/3 2) 10*/21/50 3) 40/51/6 *p<0.05 compared to pre-reformulation
Havens J Drug Alcohol Depend 2014 [120] **Poor**	Structured interviews assessing opioid abuse were completed by 190 individuals recruited from rural Perry County, Kentucky between December	1) ER Oxycodone 2) IR Oxycodone 3) Reformulated ER Oxycodone 4) Any ER Oxycodone	*Patient characteristics:* N=189 Male: 54.5 percent Median age: 32 White: 97.9 percent Past abuse of opioids:	*Differences in prevalence and frequency of abuse (through any route)* Pre-reformulation prevalence – Overall 1) 0.99, 2) Ref., 3) N/A, 4) N/A Post-reformulation prevalence – Overall 1) 0.62, 2) Ref., 3) 0.34, 4) 0.76 Pre-reformulation frequency – Overall 1) 1.05, 2) Ref., 3) N/A, 4) N/A Post-reformulation frequency – Overall

	2010 and September 2011 Past 30-day abuse and retrospectively reported abuse prior to the reformulation in August 2010		*Original ER Oxycodone:* 100% *Reformulated:* 51.3% *Hydrocodone:* 97.9% *Heroin:* 31.2%	1) 0.35, 2) Ref., 3) 0.01, 4) 0.43 *values are relative rate Prevalence for IR/ER Oxycodone (pre-/post-reformulation) 1) 74% / 33% 2) 74% / 96% Frequency for IR/ER Oxycodone (pre-/post-reformulation) 1) 13.4/1.9 2) 12.8/19.5
Hwang C Pharmacoepidemiology Drug Saf 2015 [129] **Fair**	Segmented time-series analysis using the IMS Health national prescription Audit, a nationally representative source of prescription activity in the USA 12 months prior to and following August 2010	1) IR Oxycodone 2) IR Hydrocodone 3) ER Opioids 4) IR Opioids 5) OxyContin 6) ER oxycodone (OxyContin + generic formulations)	38,000 retail stores, 119 mail service pharmacy outlets, and about 820 long term care facilities, which captured over 70% of all prescription activity in the USA	*Annual prescription growth rate (%)* August 2009-July 2010 1) 14.7, 2) 5.8, 3) -1.1, 4) 19.2, 5) -10.3, 6) 6.0 August 2010-July 2011 1) 6.7, 2) 4.9, 3) 3.9, 4) 12.8, 5) -7.0, 6) -24.9 *Monthly change in the number of prescriptions dispensed (in thousands)* August 2009-July 2010 1) 45.3, 2) 51.6, 3) -0.2, 4) 39.2, 5) -5.2, 6) 3.4 August 2010-July 2011 1) 25.9, 2) 45.7, 3) 0.7, 4) 34.2, 5) -3.7, 6) -15.9* *p<0.01
Jones C Clin J Pain 2016 [115] **Fair**	Data was from the National Survey on Drug Use and Health; state-based sampling	OxyContin	Civilian, non-institutionalized population aged 12 years and older	*Past-year nonmedical use of OxyContin among US overall population age 12 or older (%)* *2006/2007/2008/2009/2010/2011/2012/2013* 0.5/0.6/0.6/0.7/0.7*/0.6/0.6/0.5

	design with independent, multistage area probability samples within each state and District of Columbia Multivariable logistic regression was used to identify individual characteristics associated with past-year OxyContin nonmedical use prior to and after reformulation 2006 through 2013			*Past-year nonmedical use of OxyContin among past-year nonmedical users of pain relievers, (%)* 10.5*/11.4/12.3/13.5/15.4/14.6/11.8/13.0 *Past-year nonmedical use of OxyContin among people with pain reliever abuse or dependence, past-year heroin users, and people with a history of drug injection, (%)* Pain reliever abuse: 20.1*/31.4/32.5/32.6/37.7/37.1/31.1/31.8 Heroin abuse: NR/NR/34.2/38.3/42.0/44.4/43.3/37.6 Ever inject: 7.3/6.3/8.6/10.2/9.1/9.0/9.9/8.6 *p<0.05 compared to 2013
Kadakia A Pharm and drug Saf 2015 [118] ***ABSTRACT POSTER***	Retrospective cohort study using data from Truven MarketScan commercial database August 2009 – October 2013	1) ER morphine 2) ER Oxymorphone 3) IR hydromorphone 4) IR oxycodone single-entity (SE) 5) OxyContin *separate cohorts were included for each opioid	Aged 18 to 64 years; incident or prevalent users of OxyContin or 4 comparator opioids	*Opioid overdose/poisoning diagnosis rate in patients dispensed one opioid, by type of opioid, Percent change (pre-/post reformulation)* 1) +17% 2) 0% 3) +10% 4) -1% 5) -34% *Opioid addiction/dependence diagnosis rate among patients dispensed one opioid, Percent change (pre-/post-reformulation)* 1) +21%

				2) +13% 3) +31% 4) +7% 5) -25% *Opioid abuse diagnosis rate among patients dispensed one opioid, Percent change (pre-/post-reformulation)* 1) +44% 2) +236% 3) -6% 4) +36% 5) -35% *Difference in abuse change per 100 person years from baseline for OxyContin vs. comparator opioids (pre-/post-/%change (p-value))* 1) 0.29 / 0.42 / +44% (0.004) 2) 0.16 / 0.55 / +236% (0.027) 3) 0.64 / 0.60 / -6% (0.158) 4) 0.58 / 0.79 / +36% (0.000) 5) 0.49 / 0.31 / -35%
Michna E Curr Med Res Opin 2014 [117] **Fair**	Truven MarketScan pharmacy and medical claims data in a 6-month period prior to the introduction of the respective reformulation	1) Reformulated ER oxycodone (n=15,162) 2) Reformulated ER Oxymorphone (n=2285) 3) Other ER/LA opioid with abuse-deterrent technology 4) No ER/LA opioid	*Inclusion:* Commercially insured patients, age 18-64; continuous use of ER/LA opioids, at least 120 days' supply; primary ER/LA opioid in the 6-month period from Feb to Aug 2010 (prior to reformulation of OxyContin)	*Following the introduction of reformulated ER oxycodone* Primary drug post-reformulation of ER oxycodone (%) 1) 10,520 (69.4) 3) 3230 (21.3) 4) 1412 (9.3) Primary drug post-reformulation of ER Oxymorphone (%) 1) 157 (6.9) 2) 1149 (50.3)

	Patient extended release (ER)/long acting (LA) opioid utilization in 6-month period from Nov 2010 to May 2011 observed. Assessed whether ER oxycodone patients switched to reformulated ER oxycodone with ADF, switched to non-ADF ER/LA opioids, or discontinued ER/LA opioids; also, evaluated rates of abuse (ICD-9-CM claims) between ADF/non-ADF switch populations	LA=long acting	was ER oxycodone – primary opioid defined as ER/LA opioid that accounted for at least 70% of days' supply of all ER/LA opioids in 6-month period.	3) 581 (25.4) 4) 398 (17.4) *Patients diagnosed with abuse during 15-month study period* ER oxycodone patients Rate of Abuse 1) 3.5% 3) 6.7% 4) 10.9% ER Oxymorphone patients Rate of Abuse 1) 2.5% 2) 2.1% 3) 2.6% 4) 5.0%
Peacock Intl J Drug Policy 2015[94] **Fair**	Prospective cohort study Participants recruited through Needle-Syringe Programs, snowballing and word-of-mouth,	1) Original OxyContin 2) Original OxyContin, after the release of reformulation 2) Reformulated OxyContin N=606	Inclusion: ≥18 years old; English language proficient; extra-medical pharmaceutical opioid use on ≥monthly basis in the last 6 months; reported injecting, snorting, chewing, smoking, and/or dissolving and drinking a pharmaceutical	Attractiveness by NOMAD participants who injected original and reformulated oxycodone, % agree with statement *I would definitely tamper with the oxycodone product:* 1) 84, 2) 79, 3) 53 *The oxycodone product is unpleasant to use (tamper):* 1) 16, 2) 5, 3) 50 *The oxycodone product is difficult to inject:* 1) 0, 2) 0, 3) 47

	opioid substitution therapy clinics/prescribers, community pharmacies, and advertisements in media across Australia. Participants completed structured computer-assisted interviews (Phase 1: Jan-March 2014 prior to release of reformulated oxycodone. Phase 2: May-August 2014 following reformulation).		opioid in the last month and on a monthly or more frequent basis in the past 6 months. Exclusion: Not a resident of the city/state for the 6 months prior to interview; had been in prison for the past month; had only tampered with an opioid substitution therapy medication; reported only using opioid medication as per a doctor's instructions. Mean age: *Only tampered with original formulation:* 41 *Tampered with original and reformulated:* 39 % male: 69	*The oxycodone product is painful to inject:* 1) 0, 2) 11, 3) 40 *The oxycodone product contains fillers that cause safety issues:* 1) 74, 2) 63, 3) 93 *The oxycodone product is easy to cut up:* 1) 79, 2) 79, 3) 21 *The oxycodone product is easy to dissolve:* 1) 67, 2) 74, 3) 14
Rossiter JME 2014[119] **Poor**	Time-series observational study Measure reductions in rates of diagnosed opioid abuse following ER	Pre-reformulation ER oxycodone Post-reformulation ER oxycodone	Commercially insured patients *Abusers (n=2532)/Non-abusers (n=61,421)* Age: 47.9/51.2 Male, %: 47.2/43.9 Medicare eligible patients	Abuse among continuous ERO users following introduction of reformulated ER oxycodone, commercial/Medicare-eligible/Medicaid: *Continuous users of EROs, pre-reformulation (%)* 3.6/1.2/6.2 *Continuous users of reformulated ER oxycodone, post-reformulation (%)*

	oxycodone reformulation; used medical and pharmacy claims for continuous ERO (extended-release opioids). Used 2009-2011 Truven Health Analytics (Truven) de-identified medical and pharmacy claims data for patients with ≥1 Rx drug claim for an opioid during this period. Opioid includes both extended- and immediate-release opioids.		*Abusers (n=272)/Non-abusers (n=19,564)* Age: 74.1/76.9 Male, %: 30.5/33.3 Medicaid patients *Abusers (n=548)/Non-abusers (n=7,770)* Age: 46.9/48.9 Male, %: 37.8/40.2 Patients classified as diagnosed abusers if they had medical claims with ICD-9-CM diagnosis codes for opioid abuse or dependence.	2.8/1.3/5.1 *Relative change in abuse rates, (%)* -22.7*/6.1/-18.0** *p<0.001 **p=0.034 Reduction in number of abusers, commercially-insured/Medicare-eligible/Medicaid/Uninsured *Diagnosed abusers:* 3,673/0/1,371/3,079 *Undiagnosed abusers:* 18,364/0/6,856/15,394
Sankey JOM 2016 [122] **Poor**	Noninterventional, multicenter, prospective historical chart review 2014-November 2015 Prospective historical chart review	1) OxyContin 2) Oxycodone 3) Heroin 4) Morphine 5) Hydrocodone Completer population, n=250	Patients included if methadone maintenance therapy (MMT) and maintained with diagnosis of opioid dependency; if entrance into methadone treatment program no later than March 1, 2011; continued treatment up to	*Mean (SD) per-patient incidence rate of oxycodone-positive UDS during baseline/transition/post-OxyContin periods, %:* *22.4 (27.1)/13.8 (21.5)/10.5 (19.6)* *Mean (SD) decrease in incidence rates from baseline in oxycodone-positive UDS from baseline to transition/baseline to post-OxyContin period, %:* *-8.7 (20.4)/-11.9 (24.1)* *P<0.001 for both*

	conducted in opioid-dependent patients on methadone maintenance therapy in 3 Canadian centers. Two-part study included chart review and self-reported questionnaire. Baseline period: March 1, 2011 to February 29, 2012 Transition period: March 1, 2012 to August 31, 2012 [represents Canadian OxyNeo release] Post-OxyContin period: September 1, 2012 to December 31, 2012	Questionnaire completed, n=177	and including until December 31, 2012; had at least one oxycodone-≥1 positive UDS (urine drug screen) for oxycodone during baseline. Completer patients had ≥36 UDS completed and ≥10 physician visits during baseline and ≥30 UDS and ≥8 physician visits during transition/post-OxyContin periods. UDS visits conducted ≥1/wk and physician visits ≥1/month. *Patient characteristics:* Male, 55.0% Mean age: 33.9 years Route of administration/self-reported nonmedical drug use history, % Heroin: 16.4 OxyContin oral: 26.0 OxyContin intranasal: 36.0 OxyContin IV: 13.2 OxyContin other: 6.0 OxyContin not specified: 12.4	*Self-reported opioid use in Baseline/Transition/Post-OxyContin periods, %* 1) 25.7/14.5/7.4 2) 88.6/79.3/71.3 3) 4.0/4.1/3.7 *Self-reported OxyContin/OxyNEO sourcing, as indicated by questionnaire, %:* Bought from dealer: 74.2/59.3 Prescription from 1 doctor: 38.3/14.8 Prescription from >1 doctor: 5.5/1.9 Bought from friends/family: 34.4/35.2 Free from friends/family: 20.3/16.7 Free from stranger/dealer: 9.4/5.6 Stolen: 4.7/1.9 *Overall incidence rate of oxycodone-positive UDs: 19.5%* *Overall incidence rate of morphine-related-positive UDSs: 10 %* *Ratio of the incidence rates of overall oxycodone-positive to morphine-related positive UDSs:* *1.96* *Ratio of oxycodone-positive UDS incidence rate to morphine-related positive UDS incidence rate by study period* *Mean ratio (SD)* Baseline: 5.49 (9.124)

			Oxycodone not brand specific: 65.6 Preferred route of administration for opioids self-reported in questionnaire, % Oral route: 80.8 Intranasal: 67.8 Chewing: 64.4 Injection: 44.6 7.6% had comorbid chronic pain, 1.2% comorbid acute pain, ≥90% pain not reported	Transition: 1.88 (3.766) Post-OxyContin: 1.02 (1.028) *Change from baseline in ratio (SD))* Transition: -1.99 (5.878) Post-OxyContin: -3.17 (6.181) *Self-reported opioid use in methadone-maintained patients by study period (Baseline / Transition / Post-OxyContin) n (%)* 1) 52(25.7) / 21 (14.5) / 8 (7.4) 2) 179 (88.6) / 115 (79.3) / 77 (71.3) 4) 23 (11.4) / 12 (8.3) / 11 (10.2) 5) 1 (0.5) / 0 (0.0) / 0 (0.0)
Sessler Pharm & Drug Saf 2014 [124] **Fair**	Time series observational study; data pulled from 3Q2009-3Q2013 manufacturer's adverse event reporting database submitted to national drug-regulatory authorities Individual case report narratives were categorized as mentioning an opioid overdose-related	OxyContin pre- and post-reformulation 1. All fatal cases (n=326) 2. Subset of fatal cases of overdose (n=240) Pre-reformulation: (PRE-R) 3Q2009-2Q2010 Post-reformulation: (POST-R) 3Q2010-2Q2013	Frequently involved a person aged 18-64 years *Patient characteristics:* PRE-R/POST-R, male % 1. 63/66 2. 65/68 PRE-R/POST-R, age distribution 13 to <18 yrs, % 1. 5/6 2. 6/9 PRE-R/POST-R, age distribution 18 to <65 years, % 1. 69/68	*Changes in the number of ER oxycodone fatality reports per quarter received by the manufacturer from pre-to-post introduction of reformulated ER oxycodone:* **n=236* *Mean number of fatality per quarter (%change)* All fatal reports (1 year pre/1 year post/2 year post/3 year post) All fatal reports: 32.8 /30.5 (-7) /12.5 (-62) /5.8 (-82) *Fatality reports for ER oxycodone versus all oxycodone:* (1 year pre/1 year post/2 year post/3 year post) % (n/N): 21 (131/637) /22 (122/551) /8 (50/616) /10 (12/120) P<0.0001

<table>
<tr>
<td></td>
<td>event and/or drug abuse-related behavior</td>
<td>3rd year post-reformulation: (3POST-R) 3Q2012-2Q2013</td>
<td>2. 77/71

PRE-R/POST-R, case reporter region, %
Northeast: 1) 17/20, 2) 15/18
Midwest: 1) 16/19, 2) 17/20
South: 1) 39/30, 2) 40/29
West: 1) 18/17, 2) 18/18
Missing: 1) 10/13, 2) 9/14</td>
<td>PRE-R/POST-R, Oxycodone and other opioid mentions, %
<table>
<tr><th></th><th>Group 1</th><th>Group 2</th></tr>
<tr><td>OxyContin</td><td>52/52</td><td>44/41</td></tr>
<tr><td>Oxycodone*</td><td>48/48</td><td>54/57</td></tr>
<tr><td>Other opioid</td><td>30/18</td><td>37/24</td></tr>
<tr><td>Illicit**</td><td>18/16</td><td>22/21</td></tr>
</table>
*not specified formulation, although implied to be OxyContin ER because submitted to manufacturer
**Marijuana, cocaine, amphetamines, and heroin

% change in number of oxycodone ER fatality reports per quarter from PRE-R to 3POST-R
1. -82
2. -87

Ratio (%) of the number of fatalities involving ER oxycodone reported to manufacturer relative to fatalities with any oxycodone as suspect drug reported to FDA PRE-R/first 6 months of 3POST-R:
21/10, p<0.0001</td>
</tr>
<tr>
<td>Severtson Annals of Emer Med 2012 [159]

POSTER ABSTRACT</td>
<td>Time series observational study from October 2008 to March 2012

4 year follow up</td>
<td>OxyContin original formulation and reformulation</td>
<td>Patient characteristics:
Percent of the 2000 US population covered by Poison Center Program:

2008Q4 – 2010Q1: 85.0%</td>
<td>Average ER oxycodone abuse exposure mention population rate after reformulation: 38% (95% CI: 31-45%, p<0.001) lower than the average population mention rate pre-reformulation

Mean ER oxycodone pre-reformulation events/Other prescription opioids events:</td>
</tr>
</table>

	Data from the RADARS System Poison Center Program; Quarterly rates of poison center calls citing abuse of ER oxycodone before reformulation of OxyContin were compared to rates after introduction of reformulation		2010Q2 – 2010Q4: 85.5% 2011Q1 – 2011Q2: 86.0% 2011Q3 – 2011Q4: 89.9% 2012Q1: 90.0%	152/1,440 Mean ER oxycodone post-reformulation events/Other prescription opioids events: 98/1,535
Severtson S Drug Alcohol Depend 2016 [107] **Fair**	Time series observational study; 5-year span following OxyContin reformation Analyzed post-market surveillance of abuse and diversion, poison center data, legal cases, drug abuse treatment programs, and drug street price data	1) OxyContin 2) Other opioids (IR OxyContin, IR and ER: hydrocodone, morphine, hydromorphone, tramadol, oxymorphone, and tapentadol)	RADARS Database: multiple programs with post-market surveillance of prescription medication abuse Poison Center Program: recorded the substances involved in poison center cases classified as intentional abuse Drug Diversion Program: recording drugs involved in cases opened by law enforcement drug diversion investigators Opioid Treatment Program and the Survey of Key Informants' Patients Program:	Population adjusted baseline (2010-Q2) rate of abuse and diversion /projected rate of abuse and diversion in 2015-Q2, per 100,000 population Poison Center program: 1) 0.056/0.014, 2) 0.387/0.260 Drug Diversion Program 1) 0.195/0.021, 2) 1.344/0.983 Opioid Treatment Program 1) 0.574/0.100, 2) 0.986/0.670 Survey of Key Informants' Patients 1) 0.265/0.122, 2) 0.475/0.441 Change in rate of abuse and diversion after reformulation of Oxycontin (projected for 2015-Q2), population adjusted, % Poison Center Program: 1) -75.0* , 2) -32.8 Drug Diversion Program:

			query new patients entering substance-abuse treatment about medications abused StreetRx Program: utilizes crowdsourcing website that gathers street price data for drugs (publicly accessible)	1) -89.4* , 2) -26.8 Opioid Treatment Program: 1) -82.6* , 2) -32.0 Survey of Key Informants' Patients 1) -53.9* , 2) -7.2 *p<0.0001 compared with Other Opioids group Route of administration, oral route/non-oral route change in rate of abuse from pre to post reformulation (%) -71.0/-86.7 (p=0.006)
Severtson S J Pain 2013 [106] **Fair**	Surveillance data collected from the RADARS System Poison Center and Drug Diversion programs were used to estimate rates of abuse exposures, unintentional therapeutic error exposures, and diversion for ERO	1) ERO (extended release oxycodone) 2) all prescription opioids	RADARS System Poison Center and Drug Diversion	*Number of Events for ERO and Other Prescription Opioids* Pre-reformulated ERO Abuse, 2008Q4/2010Q3 1) 158/183 2) 1497/1588 Post-reformulated ERO abuse 2010Q4/2012Q1 1) 101/79 2) 1353/1610 Drug Diversion Program of RADARS – Number of Events, Pre-Reformulated ERO, 2008Q4/2010Q3 1) 466/488 2) 4,310/3,586

	manufactured by Purdue Pharma LP and other opioids in aggregate in the periods before and after the introduction of reformulated ERO 2008-2012			Drug Diversion Program of RADARS – Number of Events, Post-Reformulated ERO, 2010Q4/2012Q1 1) 306/177 2) 3,282/3,488
Coplan P Pharm Drug Saf 2013 [160] ***POSTER ABSTRACT***	Patient safety outcomes were assessed in 4 post-marketing studies: RADARS System Poison Control study, National Poison Data System (NPDS), adverse events or fatalities and/or abuse reported to the manufacturer, and Kaiser Permanente Northwest and Northern California study of opioid overdoses among patients prescribed opioids	1) OxyContin 2) Oxycodone single-entity 2) All Rx opioids		*Change in patient outcomes, 1-year before to 2/2.5 years after ERO Reformulation* Overdose fatalities (Adverse Event Reports) [%] 1) -64 p<0.0001 All fatalities (Adverse Event Reports) [%] 1) -50* 2) 15 P<0.0001 Adverse reactions (NPDS) [%] 1) -34* 2) 15 P=0.0005 Prescribing (IMS NPA) [%] 1) -8.9

	1 year preceding reformulated ERO vs. 2 or 2.5 yrs after reformulation			
LaRochelle M JAMA 2015 [123] **Fair**	Interrupted time series study design using an open cohort from a large national US health insurer claims Segmented regression to analyze changes in outcomes from 30 quarters before to 8 quarters after the 2 interventions January 2003 to December 2012	1) all opioids 2) ER oxycodone 3) other long acting opioids 4) propoxyphene 5) other IR opioids N=31,316,598	Aged 18 to 64 years; enrolled in a commercial health plan; used Optum data which contains all impatient, outpatient, and pharmacy claims from a large US health insurer with member in all 50 states Patients could enter and exit the cohort over the 10-year period on a rolling basis *Patient characteristics:* No. of members/male sex/pop. of white people, millions (by quarter): 2003: 7.2/3.6/5.1 2005: 7.6/3.8/5.3 2007: 8.1/3.9/5.5 2009: 8.1/4.0/5.4 2011: 7.8/3.8/5.2 Q42012: 7.7/3.8/5.1 Age, n in millions	Opioid dispensing rate, mg morphine equivalent dose per member per quarter; estimated instantaneous change in overdose rate in the first post-reformulation change quarter (2011Q1) compared with expected rate based on baseline trend 1) -14.8 2) -4.56 3) 1.09 4) -12.2 5) NA *Ratio of prescription opioid overdose to total prescription opioid dispensing, episodes per million g MED per quarter:* 0.31 / -0.005 / 0.0002 / NA / -0.0067 Intercept/linear trend/quadratic trend/level change) Result of sensitivity analysis: *Scenario 1: 30 Quarter Baseline, Quadratic Model* Opioid dispensing rate, mg MED per member per quarter (Relative change, %) 1) -19 2) -39 3) 11 4) -100

			18-24: 0.9/1.0/10/1.0/1.0/ 1.0 25-34: 1.7/1.7/1.8/1.8/1.7/ 1.7 35-44: 2.0/2.0/2.0/2.0/1.8/ 1.8 45-54: 1.7/1.8/1.9/2.0/1.9/ 1.8 55-64: 0.9/1.1/1.2/1.3/1.4/ 1.4 *organized by year ('03/'05/'07/'09/'11/'12)	5) -16 *Scenario 2: 8 Quarter Baseline, Linear Model* 1) -17 2) -41 3) 4 4) -100 5) -11

Appendix G. Cost-Benefit and Budget Impact Supplemental Information

Table G1: Massachusetts ER Opioid Market share – February 2016 to January 2017

ADF Opioids	
Oxycontin	93.57%
Embeda	1.80%
Hysingla ER	4.24%
Xtampza ER	0.39%
Non-ADF Opioids	
Avinza Brand	0%
Avinza Generic	0.35%
Duragesic Brand	0.12%
Duragesic Generic	17.54%
Exalgo Brand	0.09%
Exalgo Generic	0.85%
Kadian Brand	0.04%
Kadian Generic	2.22%
Methadone HCl Generic	11.96%
Morphine ER Generic	40.44%
MS Contin	0.07%
Nucynta	3.87%
Opana ER Brand	1.61%
Opana ER Generic	1.23%
Oxycodone ER Generic	19.10%
Zohydro ER Brand	0.50%

Table G2: Vermont ER Opioid Market share – February 2016 to January 2017

ADF Opioids	
Oxycontin	100%
Embeda	0%
Hysingla ER	0%
Xtampza ER	0%
Non-ADF Opioids	
Avinza Brand	0%
Avinza Generic	0.95%
Duragesic Brand	0.16%
Duragesic Generic	20.01%
Exalgo Brand	0.11%
Exalgo Generic	0.95%
Kadian Brand	0%
Kadian Generic	2.01%
Methadone HCl Generic	12.64%
Morphine ER Generic	43.77%
MS Contin	0%
Nucynta	2.13%
Opana ER Brand	2.22%
Opana ER Generic	1.59%
Oxycodone ER Generic	13.47%
Zohydro ER Brand	0%

Table G3: Opioid Strength and Number Of Daily Doses to Reach 90mg MED

Opioid	Number of doses per day to reach 90mg MED
ADF Opioids	
Oxycontin 20mg	3
Embeda ER 30mg	3
Hysingla ER 30mg	3
Xtampza 18mg	3
Non-ADF Opioids	
Avinza ER 30mg	3
Avinza 30mg Generic	3
Duragesic 12mcg/hr	3
Fentanyl Patch 12mcg/hr Generic	3
Exalgo ER 8mg	3
Hydromorphone 8mg Generic	3
Kadian 30mg	3
Kadian 30mg Generic	3
Methadone 5mg	4
Morphine ER 30mg Generic	3
MS Contin 30mg	3
Nucynta 50mg	4
Opana ER 10mg	3
Oxymorphone ER 15mg	6
Oxycodone ER 20mg	3
Zohydro ER 30mg	3

Table G4: All-Cause Mortality

	Death Prob. Male	Death Prob. Female	Death Prob. Pop.
Population Age (in years)	55%	45%	
37	0.001774	0.001038	0.001440592
38	0.001861	0.001113	0.001522156
39	0.001967	0.001196	0.001617737
40	0.002092	0.001287	0.001727335
41	0.00224	0.001393	0.001856309
42	0.002418	0.001517	0.002009847

Table G5: New England State-Specific Opioid Overdose Death Rate

State	Death rate per 100,000 population
Connecticut	11.3
Maine	16.3
Massachusetts	17.0
New Hampshire	28.0
Rhode Island	19.8
Vermont	9.6

Table G6: New England State-Specific ER Prescription Opioid Prevalent Users for Non-Cancer Pain in 2015

State	ADF opioids	Non-ADF opioids	Total
Massachusetts	60,222	113,045	173,267
Vermont	3,974	15,915	19,889

Table G7: Health Care Resource Utilization and Costs in Patients Who Abuse Opioids, Over Five Years

	ADF opioids		Non-ADF opioids		Difference (ADF – non-ADF)	
	Resources used	Costs	Resources used	Costs	Resources used	Costs
ER days	55,661	$79,380,639	79,023	$112,698,315	-23,362	-$33,317,676
OP visits	438,607	$137,153,080	622,699	$194,719,030	-184,092	-$57,565,950
Rehabilitation facility days	144,718	$45,700,962	205,459	$64,882,590	-60,741	-$19,181,628
Hospitalization days	100,189	$146,639,606	142,241	$208,187,245	-42,052	-$61,547,638
Non-opioid prescription drug fills	703,552	$70,923,075	998,847	$100,690,939	-295,295	-$29,767,863
Opioid prescriptions		$94,267,071		$67,147,189		$27,119,881

Table G8: Health Care Resource Utilization and Costs in Opioid Regular Use Patients, Over Five Years

	ADF opioids		Non-ADF opioids		Difference (ADF – non-ADF)	
	Resources used	Costs	Resources used	Costs	Resources used	Costs
ER days	228,165	$280,016,593	222,249	$272,756,057	5,916	$7,260,536
OP visits	4,106,973	$1,284,990,038	4,000,484	$1,251,671,598	106,489	$33,318,440
Rehabilitation facility days	57,041	$15,752,943	55,562	$15,344,485	1,479	$408,457
Hospitalization days	256,686	$753,890,828	250,030	$734,343,232	6,656	$19,547,596
Non-opioid prescription drug fills	6,388,625	$657,444,240	6,222,975	$640,397,402	165,650	$17,046,838
Opioid prescriptions		$1,207,564,184		$590,154,681		$617,409,504

Appendix H. Conflict of Interest Disclosures for Expert Reviewers

Name	Title	Disclosures
Alan White	Managing Principal Analysis Group, Inc	I have worked on a number of projects on behalf of pharmaceutical companies, for which Analysis Group, Inc. has received compensation.
Paul Gileno	President U.S. Pain Foundation	Receipt or potential receipt of anything of monetary value, including but not limited to, salary or other payments for services such as consulting fees or honoraria in excess of $5,000 Status or position as an officer, board member, trustee, owner or employee of a health care company, or an organization which receives more than 25% of its funding from health care companies • The U.S. Pain Foundation receives grants from health care companies to fund educational programming
Lewis Nelson	Professor and Chair, Emergency Medicine Rutgers New Jersey Medical School	No conflicts to disclose.
Richard Dart	Director, Rocky Mountain Poison and Drug Center Denver Health and Hospital Authority Professor, University of Colorado School of Medicine; Denver, Colorado	I receive no personal payment for any activity for any entity except Denver Health and Hospital Authority (DHHA). On behalf of DHHA, I direct the RADARS System, which is supported by subscriptions from several pharmaceutical manufacturers as well as the US FDA. No outside party participates in the design, collection, processing or reporting of the data.