Summary

Drugs Under Review

ICER's report reviewed evidence on ten abuse-deterrent formulations (ADF) of opioids. Nine of the drugs were extended release (ER) opioids, and one was immediate release (IR). The report assessed evidence on how effectively the drugs reduce abuse of opioids at both the individual patient and population levels.

New England Comparative Effectiveness Public Advisory Council Votes

The report was subject to public deliberation during a public meeting of the New England Comparative Effectiveness Public Advisory Council. A majority of the Council voted that:

- Evidence is not sufficient to demonstrate a reduced risk of abuse from the only available IR ADF opioid, RoxyBond™.
- Evidence is adequate to suggest a reduced risk of abuse among individual patients prescribed OxyContin® compared to non-ADF opioids.
- Evidence is not sufficient to show a reduced risk of abuse for individual patients being prescribed any of the eight other abuse-deterrent ER opioids, excluding OxyContin.
- At a population level, evidence is not adequate to demonstrate a net health benefit of OxyContin over a non-ADF ER opioid, due to limited evidence and concerns about abuse shifting to other opioids.

Cost-Benefit Analysis and Cost Neutrality

ICER's cost-benefit analysis compared two hypothetical groups of 100,000 non-cancer chronic pain patients over five years. One group received ER non-ADF opioids, while the other received ER ADF opioids.

↓2,300 cases of abuse
prevented among 100,000 people taking ADF opioids versus non-ADF opioids

↑$533 million
additional net costs per 100,000 over five years for ADF opioids versus non-ADF opioids

↓41% average discount
needed to make the drug costs of ADF opioids cost-neutral with non-ADF opioids

Policy Recommendations

Policymakers should be aware that no evidence exists to evaluate the balance of positive and unintended negative effects of mandatory ADF substitution laws. Policymakers and clinical leaders should consider measures to phase in ADFs while ensuring adequate support for other elements of a multi-pronged approach to the opioid crisis.

Manufacturers and payers must recognize a shared commitment to making ADFs affordable to patients and to the health system.

The term "abuse-deterrent formulation" presents a significant risk that the addictive and abuse potential of ADFs will be misunderstood. The FDA should reconsider whether it can use "tamper-resistant formulation" instead.

The full list of policy recommendations is available on page 7 and in the full report.

The opioid problem

Opioid medications are used to treat acute and chronic pain. 100 million people in the US suffer from pain every year, with 9-12% of those people experiencing chronic pain lasting longer than three months.

Opioids are a component of pain management; however, their addictive and euphoric effects create a high risk for misuse, abuse, addiction, and possible death by overdose. Since 1999, the number of deaths attributed to prescription opioids in the US has increased nearly fourfold, rising in parallel with the volume of dispensed prescriptions.

What are abuse-deterrent opioids?

ADF opioids are specially formulated to make the drugs more difficult to manipulate for abuse.

In 2010, the FDA approved Purdue Pharma's reformulated OxyContin® (extended release oxycodone) with a harder-to-crush exterior to reduce the potential for abuse by snorting or dissolving in order to inject. The reformulated opioid was approved as the first abuse-deterrent formulation, and now captures over 90% of the ADF market.

ADFs may be formulated to deter chewing, intranasal, and intravenous routes of abuse; however, swallowing pills whole is the most common form of abuse and is not deterred by ADFs.

In 2015, the FDA issued recommendations encouraging manufacturers to produce ADF opioids. In 2016-2017, the FDA approved five new ADFs.

Drugs under review

ICER's report reviewed ten ADFs. Nine of the ten are extended release (ER) opioids, while one, RoxyBond, is immediate release (IR).

Drug name
Hysingla® ER (Hydrocodone, Purdue)
Vantrela® (Hydrocodone , Teva)
Arymo® ER (Morphine, Egalet)
Embeda® (Morphine + naltrexone, Pfizer)
Morphabond® (Morphine extended release, Inspirion Delivery Technologies)
OxyContin® TR (Oxycodone, Purdue)
Xtampza® ER (Oxycodone, Collegium Pharmaceutical Inc.)
Targiniq® (Oxycodone + naloxone extended release, Purdue)
Troxyca® ER (Oxycodone + naltrexone, Pfizer)
RoxyBond™ (Oxycodone immediate release, Inspirion Delivery Technologies)

Abuse-deterrent opioids in public policy

ADFs are relatively new, branded therapies for treating pain, and are more expensive than both their non-ADF branded equivalents and generic versions. Massachusetts, Maine, Maryland, Florida, and West Virginia have passed legislation mandating coverage for ADFs, and similar bills have been introduced in more than 20 other states. Policymakers are challenged on how to structure conversion to ADFs in a responsible and economically feasible manner.

How strong is the evidence that **ADFs** improve outcomes?

Pre-market studies

Abuse potential
Pre-market studies measured either oral or intranasal abuse potential. Studies asked recreational drug users to rate the drug on its likability, as well as how likely they were to take the drug again, in order to measure abuse potential.

Relative to non-ADF comparators, both crushed and intact forms of each ER ADF produced statistically-significantly lower scores for drug liking. Responses to questions about likelihood to take the drug again followed a similar trend.

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.

Post-market studies: Real world evidence

Data on abuse statistics collected after ADF regulatory approval ("post-market" data) is an FDA requirement; however, evidence is currently available only for OxyContin. All evidence consists of time series analyses that examine the period before and after the introduction of reformulated OxyContin in 2010.

Abuse
Evidence on the impact of ADF OxyContin on opioid abuse showed mixed outcomes. Data suggest a decline in abuse of OxyContin after reformulation, with the non-oral route of abuse declining at a significantly greater rate compared with the oral route of abuse. However, several studies also showed an increase in the abuse of other prescription opioids (e.g., ER oxymorphone, ER morphine, IR oxycodone) or heroin, suggesting there may have been a shift in abuse patterns.

Findings from direct interviews with recreational users showed that reformulated OxyContin may have limited impact on changing overall abuse patterns.

Overdoses and fatalities
Limited evidence indicates that rates of overdose and overdose deaths attributed to OxyContin declined after the ADF was introduced, with decreases ranging between 34% and 65%.

During the same period, the rates of overdose deaths attributed to other prescription or illicit opioids increased or remained stable, suggesting that consumers may have switched to abusing other products.

Drug diversion and prescription opioid utilization
Evidence on drug diversion, or the transfer of opioids from lawful to unlawful use, is extremely limited. Available evidence suggests that population-adjusted rates of diversion decreased during the five years following after the introduction of reformulated OxyContin. Evidence on changes in diversion rates of other prescription opioids is inconsistent. Limitations of the data make it difficult to draw firm conclusions on the overall effects of ADFs on diversion.

How strong is the evidence that **ADFs** improve outcomes?

Controversies and uncertainty

Surrogate endpoints: There is considerable uncertainty around whether the surrogate endpoints used in pre-market trials (i.e., measures of "likability") conducted among recreational drug users are predictive of real-world abuse among general pain patients.

Real-world evidence: There are no prospective studies of patients who are newly-prescribed opioids that measured real-world incidence of abuse among ADF and non-ADF users. Current evidence of real-world impact is limited to time series studies, which are subject to potential confounding factors and other biases, including other interventions that may have taken place during the study period (e.g., prescription monitoring programs). There is also no real-world evidence available on ADFs other than OxyContin.

Progression from medical to non-medical use: Evidence is limited on the natural history of abuse and on tools for identifying patients at increased risk for progression.

Overall benefit of ADFs: While limited evidence suggested 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.

ICER evidence rating

- For individual patients prescribed an opioid, evidence provided moderate certainty of a comparable or better net health benefit for OxyContin.
- Evidence for all other ADFs was promising but inconclusive, based on a lack of real-world evidence of the impact of ADFs on rates of abuse, as well as possible safety concerns.
- For the wider population of people using opioids for both therapeutic and non-therapeutic purposes, evidence was insufficient to determine a net health benefit of ADFs.

What is a fair price for **ADFs** based on its value to patients and the health care system?

Cost-benefit analysis

ICER's cost-benefit analysis compared two hypothetical groups of 100,000 non-cancer chronic pain patients over five years. One group received ER non-ADF opioids, while the other group received ER ADFs. ICER calculated a weighted average price for ADF opioids and non-ADF opioids based on real world data for a standardized daily dose. The average cost of an ADF was $11.60 per day and a non-ADF opioid cost $5.82 per day. This cost included average discounts calculated using data from the Federal Supply Schedule.

The model found that, compared to non-ADF opioids, ADFs prevented approximately 2,300 new cases of abuse, but cost the health system an additional $533 million per 100,000 patients over five years.

Cost-neutrality analyses

ICER varied ADF effectiveness, the external impact of reducing diversion, and price in order to better understand their impact on cost-effectiveness outcomes. These analyses tested for cost neutrality, i.e., the point at which health system spending in the two groups was equal over five years. None of the cost-neutrality scenario analyses account for the effects of switching to other opioids or heroin.

1. ADF effectiveness: ICER found that at 100% effectiveness, or preventing all cases of abuse, ADF opioids would still cost the health system an additional $113 million over five years.

2. Diversion reduction: If ADF opioids reduce the relative risk of diversion by at least 35%*, they would attain cost-neutrality relative to non-ADF opioids. This scenario does not include the effect of any potential shift in abuse to other opioids or heroin.

**Assuming 1.25 diverted opioid abuse cases for every case of prescription opioid abuse*

3. Cost Reductions to Reflect Added Value: At current prices, ADFs would need to undergo significant cost reductions to achieve cost neutrality.

$5.82
Average cost of a non-ADF

$11.60
Average cost of an ADF

↓ **41% discount**
from current weighted average ADF prices

$6.86

Average ADF price at which they would be cost neutral with non-ADFs, accounting for decreases in abuse-related costs.

This price still provides an 18% premium for manufacturers over the price of generic ER opioids.

Societal perspective

Using the same hypothetical groups of 100,000 people prescribed an ER ADF and 100,000 prescribed a non-ADF, ICER also included a modified societal perspective that considered costs of criminal justice, incarceration, and productivity loss due to opioid abuse. **The difference in total net spending between the ADF and non-ADF cohorts over five years was reduced by $140 million, but costs remained $393 million higher in the group taking ADF opioids.**

Public Deliberation and Evidence Votes

New England Comparative Effectiveness Public Advisory Council Votes

The New England Comparative Effectiveness Public Advisory Council (New England CEPAC) deliberated on key questions raised by ICER's report at a public meeting on July 20, 2017. The results of the votes are presented below. More detail on the voting results is provided in the full report.

1. For a patient being considered for a prescription of an immediate release opioid, is the evidence adequate to demonstrate a reduced risk of abuse for patients using **RoxyBond versus non-ADF immediate release opioids**?

Yes: 2 votes	No: 10 votes

2. For a patient being considered for a prescription of an extended release opioid, is the evidence adequate to demonstrate a reduced risk of abuse for patients using **OxyContin versus non-ADF extended release opioids**?

Yes: 9 votes	No: 3 votes

3. For a patient being considered for a prescription of an extended release opioid, is the evidence adequate to demonstrate a reduced risk of abuse for patients using **all other ADFs, excluding OxyContin, versus non-ADF extended release opioids**?

Yes: 1 vote	No: 11 vote

4. For a patient being considered for a prescription of an extended release opioid, is the evidence adequate to demonstrate a net health benefit **on a population level with the use of OxyContin versus non-ADF extended release opioids**?

Yes: 2 votes	No: 12 vote

Policy Consideration Votes

ADF-substitution policies are being considered to shift opioid prescriptions toward abuse-deterrent formulations. Council members were asked to consider these policies in light of the policies' impact on patients, diversion, and illicit opioid use and choose from three possible options:

A. Determine a way for physicians, academics, payers, and policymakers to target ADFs to individuals and families in high risk environments.

B. Allow physicians to determine whether to shift current patients to ADF opioids; require all new opioid prescriptions to be written for an ADF opioid.

C. Require all current non-ADF prescriptions to be substituted with ADF and all new prescriptions to be written for an ADF opioid.

Considering overall health benefit alone, 10 of 12 Council members chose option A**.**

When also considering costs, all 12 Council members voted for option A.

Key Policy Recommendations

For Policymakers

- ADFs should have a growing role in clinical practice since evidence suggests that they are safer for the individual patient. Still, policymakers should be aware that there is some evidence that demonstrates shifts in abuse towards other illicit drugs following introduction of ADFs. As a result, mandatory ADF substitution laws may cause more harm to the overall population, and policymakers and clinical leaders should consider measures to phase in ADFs while ensuring adequate support for other arms of a multi-pronged approach to the opioid crisis.
- At current prices, any rapid requirement for substitution with ADFs would prove unaffordable. Policymakers should avoid approaches to encouraging the use of ADFs that would be so costly that resources would be drained from other efforts needed to address the opioid crisis.

For Manufacturers and Payers

- Manufacturers and payers must recognize a shared commitment to making ADFs affordable to patients and to the health system. Manufacturers should moderate the exercise of monopoly pricing power, and payers should accept paying a premium for ADFs and reduce barriers such as increased out of pocket payments.

For Researchers and Manufacturers

- Robust clinical studies are needed to demonstrate the natural history of opioid abuse and the impact of ADFs on abuse among prescribed patients as well as the broader effects on diversion and drug switching.
- Given that over 90% of opioid prescriptions are for immediate-release (IR) formulations, and that currently, no IR ADFs are on the market, further investment and development by manufacturers for IR ADFs is critical.

For Government Agencies

- The term “abuse-deterrent formulation” is confusing for prescribers, patients, and the public, contributing to a significant risk that the addictive and abuse potential of ADFs will be misunderstood. The FDA should reconsider whether it can use the term “tamper-resistant formulation.”
- The federal government should convene clinical experts, clinical pharmacists, patients, and payers to develop consistent methods to identify patients whose environments represent a high risk for the abuse of opioids.
- Public health policymakers at the federal level should educate the public about the risks of all opioids through a major public health campaign, perhaps modeled on the techniques employed nationally to reduce smoking.

For Payers

- Exploring and removing barriers to access to non-pharmacologic treatments for pain patients will have the dual effect of ensuring access to treatment for patients while also addressing the public health concerns related to prescribing opioids.

Key Policy Recommendations (continued)

For Physicians

- Medical school curricula and physician licensing exams should require physicians to demonstrate a robust understanding of the role of ADFs in clinical practice, specifically addressing misconceptions about the addictive nature of ADFs.
- Prescribing physicians should help patients understand that ADFs are not less addictive than non-ADFs. Physician groups, individual physicians, and clinical pharmacists should develop or share federally-developed materials on the proper storage and use of all opioids.

Conclusion

Comparative clinical effectiveness

With the exception of OxyContin, for which post-market studies provide evidence sufficient to determine a comparable or better net health benefit, evidence was promising but inconclusive for all ADFs prescribed to patients. Evidence was insufficient to show reduction in abuse for a broader population of people who use opioids for both therapeutic and non-therapeutic purposes.

Comparative value

ADF opioids have the potential to reduce the incidence of abuse in opioid-prescribed chronic pain patients relative to non-ADF opioids, but at higher costs to the health care system. Even when important societal costs are included, ADF opioids are still expected to increase overall costs.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care. For more information about ICER, please visit ICER's website (www.icer-review.org).

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