PATIENT ACCESS CHALLENGES FACING ABUSE-DETERRENT FORMULATIONS OF OPIOID ANALGESICS

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Massachusetts State House
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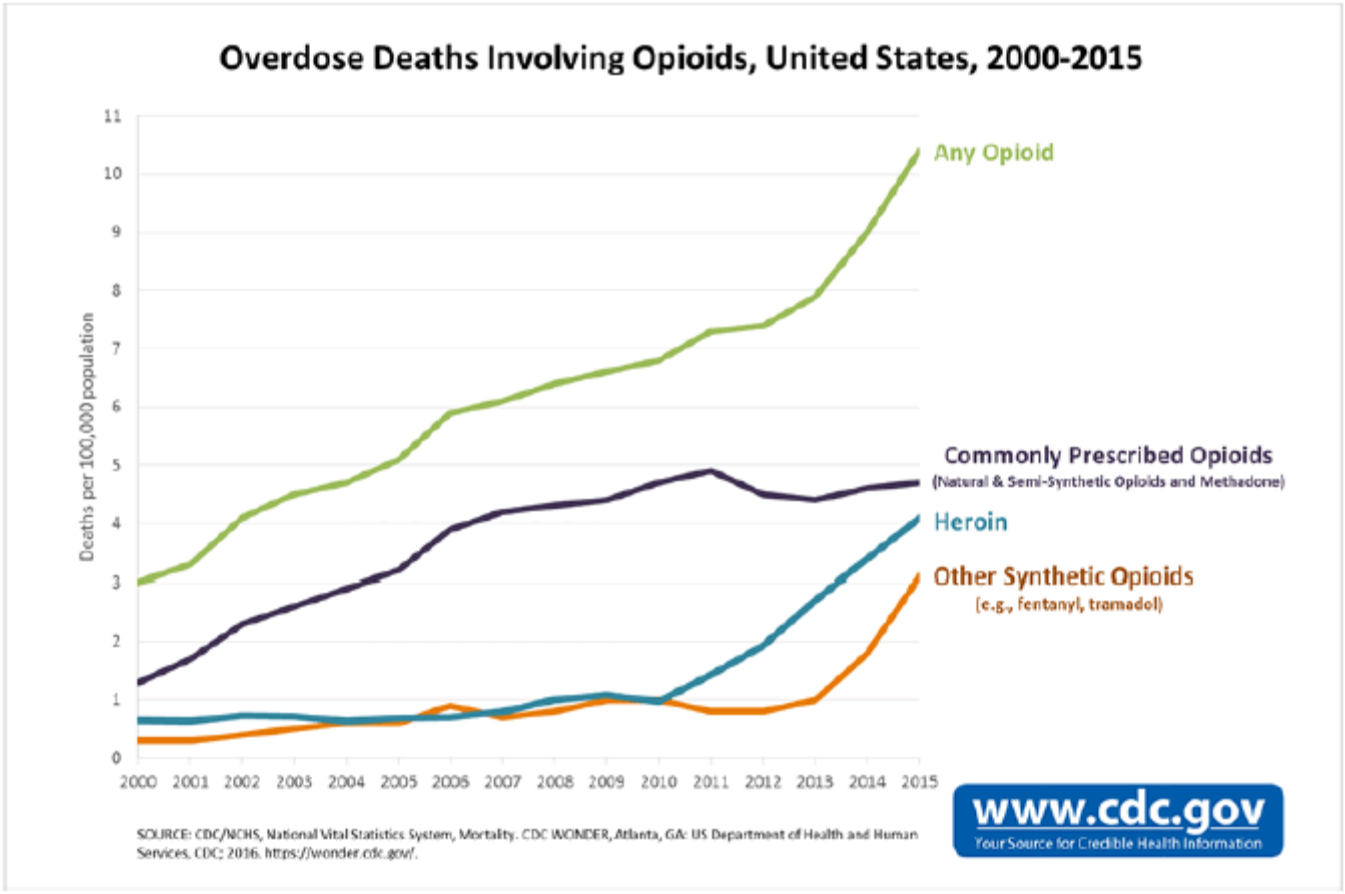
The national context



ICER

Tufts Center for the Study of Drug Development
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U.S. an Outlier

- 20% of non-cancer pain patients are prescribed an opioid, compared to <5% in other industrialized nations

- U.S. has 4% of the world's population, yet 30% of global opioid supply, and ~4 times the number of opioid prescriptions as the average of other industrialized nations – most of these are for generic opioids that are not abuse-deterrent

ADF Approvals

ADF Drug	Date of Approval/ Launch	ADF Technology
OxyContin ER - oxycodone - crush/extraction resistant	4/2010/10/2013	Physical and chemical barriers - May prevent chewing, crushing, or extraction by solvents; does not deter abuse of intact tablets
Targiniq ER - oxycodone hydrochloride and naloxone	7/2014	Agonist/antagonist combination - Antagonist (eg, naloxone or naltrexone) may be formulated to be clinically active only when manipulated (crushing, chewing, or dissolving); does not deter abuse of intact tablets
Embeda ER - morphine sulfate and naltrexone	10/2014/1/2015	Agonist/antagonist combination
Hysingla ER - hydrocodone - crush/extraction resistant	11/2014/1/2015	Physical and chemical barriers
MorphaBond ER - morphine sulfate - crush/extraction resistant	10/2015	Physical and chemical barriers
Xtampza ER - oxycodone - crush/extraction resistant	4/2016/6/2016	Physical and chemical barriers
Troxyca ER - oxycodone hydrochloride and naltrexone hydrochloride	8/2016	Agonist/antagonist combination
Arymo ER – morphine sulfate	1/2017	Physical and chemical barriers
Vantrela ER – hydrocodone bitartrate	1/2017	Physical and chemical barriers
RoxyBond IR – oxycodone hydrochloride	4/2017	Physical and chemical barriers

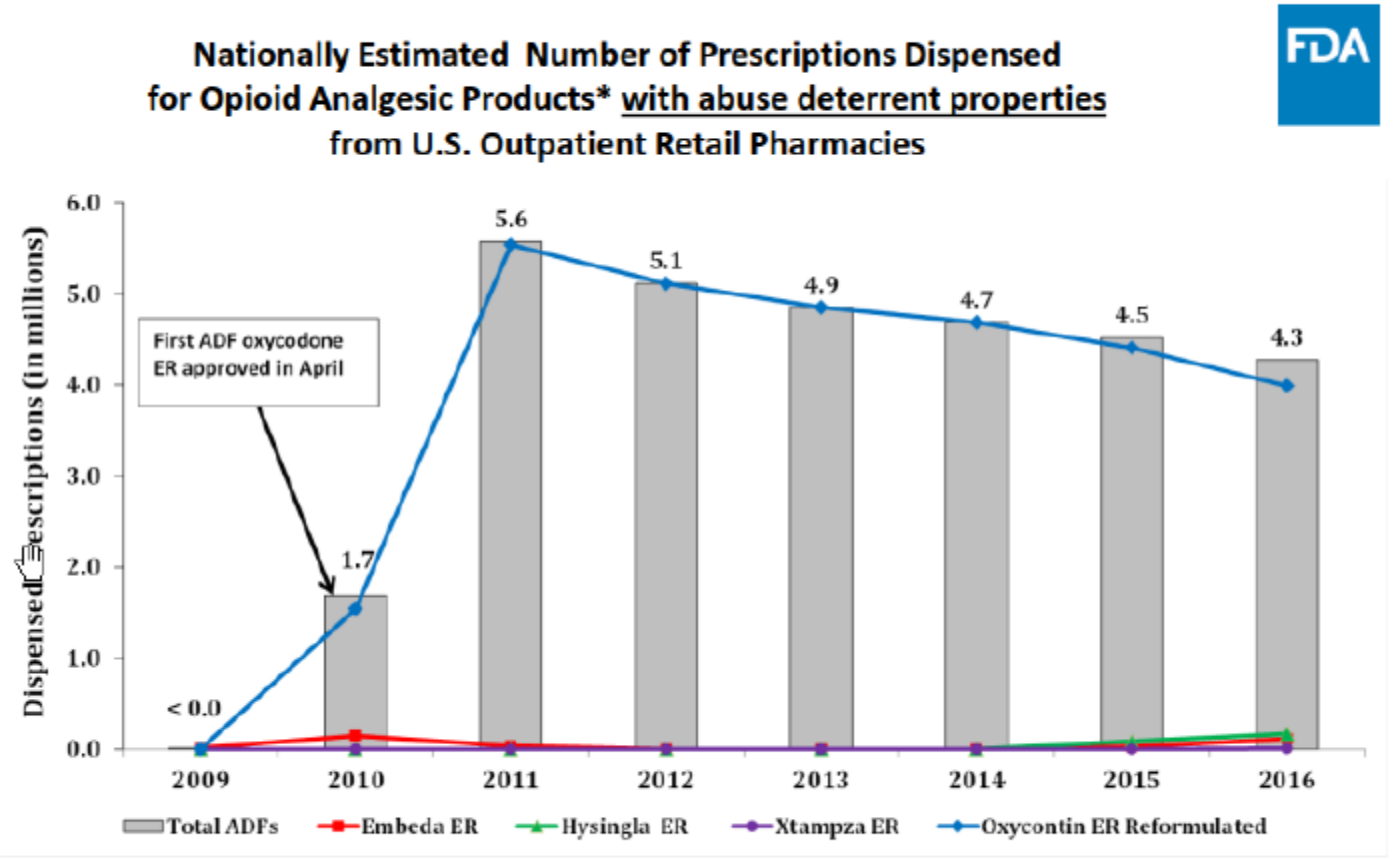
ADFs Pre-Market Assessment

- Pre-market assessments of ADFs suggest they deter abuse in most forms (except oral)

- Pre-market assessments do not guarantee similar results in the real world

- ADFs are not a panacea – still opioids, therefore potentially addictive

Market Shares of different ADFs



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https://www.fda.gov/downloads/Drugs/NewsEvents/UCM565981.pdf#page=10

Patient Access Challenges

- Besides clinical development and regulatory challenges, ADFs face patient access hurdles

- On coverage, insurers continue to favor non-ADF opioids over ADFs and also (mostly) older non-opioid treatments. Standard pain treatment protocol and payer reimbursement remain entrenched in outdated guidelines and introduce unnecessarily powerful and potentially addictive pain agents to patients (eg, Percocet/Vicodin Rx post wisdom teeth extraction).

- To build case for improved ADF uptake and access more real-world evidence is needed for more ADFs, as well as a more robust foundation for budgetary impact analysis based on risk/treatment stratification of patients with chronic pain

Lagging Patient Access

Patient access for ADFs lags in light of:

- Limited evidence regarding comparative effectiveness

- Budgetary impact analysis suggests ADFs would `break the bank' if ***all*** patients would switch from non-ADFs to ADFs

- Exclusion or non-preferred formulary placement of ADFs; continued preferred placement of non-ADFs

Uptake of Generic and Branded ADFs

Opioid Prescriptions in 2015	Generic Opioids	Branded Opioids
Number of pills prescribed	240,120,330	8,853,402
Number of pills with ADF properties*	5,329,632	5,068,398

*These include products with ADF properties that are not necessarily on the label

Sources: Abuse Deterrent Coalition; National Inpatient Sample (NIS) data for 2015

Avalere Study on Medicare Coverage

- ADF OxyContin most likely to be covered (more evidence exists for this drug); ADF Xtampza least likely

- Coverage of ADF OxyContin, a brand-name drug that has received "abuse-deterrent labeling" from the Food and Drug Administration, fell among Medicare Part D plans from 61% to 33% between 2013 and 2015 - steeper decline than non-ADFs

- Non-ADF OxyContin covered by nearly 100% of plans

Medicare Beneficiary Access to Non-ADF Generic Opioids

	Fentanyl ER	Morphine Sulfate ER	Methadone ER
Covered	85%	99%	98%
Covered with Prior Authorization or Step Edits	15%	1%	1%
Not Covered	0%	0%	1%
Total	100%	100%	100%

Source: Managed Markets Insights & Technology (MMIT), 2017

Medicare Beneficiary Access to Branded ADFs

	Xtampza ER - oxycodone	Embeda ER – morphine + naltrexone	Hysingla ER - hydrocodone	OxyContin ER - oxycodone
Covered	8%	54%	23%	37%
Covered with Prior Authorization or Step Edits	1%	1%	9%	2%
Not Covered	91%	45%	68%	61%
Total	100%	100%	100%	100%

Source: Managed Markets Insights & Technology (MMIT), 2017

ICER Analysis

- Limited evidence on clinical effectiveness, particularly for ADFs not named reformulated OxyContin; also questions whether certain surrogate endpoints (eg, drug liking) are predictive of real-world abuse

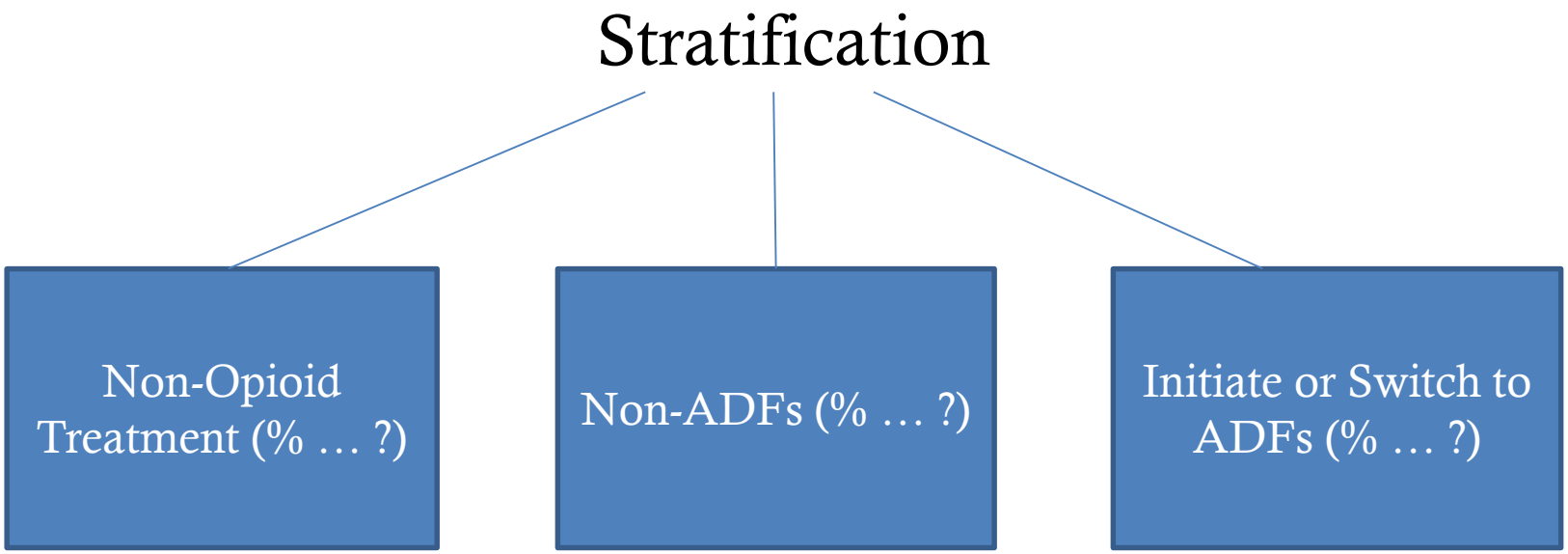
- At current prices, ADFs are not cost-effective: >$100,000 per QALY

- In fiscal 2016 [the VA's] opioid costs were nearly $100 million - 1.9% were for an abuse-deterrent product. Switching all patients to ADF opioids would result in budgetary impact of ~$1 billion annually for ADFs, which is ~20% of the VA pharmacy budget

- Cost-effectiveness and budget neutrality could be achieved if ADF opioids were discounted by 41% from current prices

- Stratification of patients by risk potential would be useful for payers, healthcare providers, and patients. But, ICER says current risk stratification tools are "insufficiently accurate"

Patient (Risk) Stratification



Status of Risk Stratification?

- CDC guidelines state that risk-stratification tools are currently "inadequate" to predict whether a patient will become addicted. Based on?

- Yet, one thing we know is that the U.S. is an outlier in terms of numbers of opioid prescriptions, and that most of these are for generic non-ADFs. Surely, the levels of prescriptions for generic non-ADF opioids are still too high and not supported by clinical evidence.

- The American Pain Society's Annual Meeting in 2015 concluded that we do have tools for stratifying patients with respect to "risk for aberrant behavior related to opioid use," but these tools are not used often enough

Key Policy Challenges

Key Challenges	Policy Measures
Clinical development – carrying out population studies to test abuse-deterrence claims, in addition to developing ADFs that employ new approaches	Support efforts to foster increased R&D investments focused on prodrugs and products deterring oral abuse
Regulatory – establishing a consistent approach to the Risk Evaluation and Mitigation Strategy Program for branded and generic ADFs	Improved clarity and consistency through regulatory guidance on branded ADFs as well as generics
Patient access – payers constitute a bottleneck impeding uptake of ADF products (tend to favor older, generic non-ADFs)	Consider federal and state policies to establish a level playing field for ADF products (eliminate preferred formulary position for non-ADF products)
Education - prescriber training and awareness of various options for treating and not treating pain, including ADF products, is an important step, as is educating payers on potential public health benefits of ADFs	Prescriber training and awareness of various options for treating pain, including ADF products, should begin in medical school; payers should be engaged regarding the public health benefits of ADFs.
Evidence base – post-marketing generation of evidence to demonstrate approved ADFs' clinical effectiveness and abuse deterrence	Continue to develop an expanded evidence base on ADFs' clinical effectiveness using real-world data; ADFs should be part of a multipronged strategy, which includes non-opioid treatment, and better education of prescribers and patients.