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Economic Evaluation

Impact of Abuse Deterrent Formulations of Opioids in Patients With Chronic Pain in the United States: A Cost-Effectiveness Model

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A B S T R A C T

Objective: Opioid abuse is a significant public health problem in the United States. We evaluate the clinical effectiveness and economic impact of abuse-deterrent formulations (ADF) of opioids relative to non-ADF opioids in preventing abuse. **Methods:** We developed a cost-effectiveness model simulating 2 cohorts of 100 000 noncancer, chronic-pain patients newly prescribed either ADF or non-ADF extended-release (ER) opioids and followed them over 5 years, tracking new events of opioid abuse and opioid-related overdose deaths in addition to tracking 5-year cumulative costs of therapeutic use and abuse of ADF and non-ADF opioids. Patients in each cohort entered the model for therapeutic opioid use from where they could continue in that pathway, discontinue opioid use, or abuse opioids or die of opioid overdose-related or unrelated causes. In addition, one-way sensitivity and scenario analysis were conducted. **Results:** Over a 5-year time period, using ADF opioids prevented an additional 2300 new cases of opioid abuse at an additional cost of

approximately \$535 million to the healthcare sector. Threshold analyses showed that a 40% decrease in ADF opioid costs was required to attain cost neutrality between the 2 cohorts, whereas a 100% effectiveness in abuse reduction still did not result in cost neutrality. A 43% decrease in diversion with ADFs relative to non-ADF was required to attain cost neutrality. Including a societal perspective produced results directionally similar to the base-case analysis findings. **Conclusion:** ADF opioids have the potential to prevent new cases of opioid abuse, but at substantially higher costs to the health system.

Keywords: abuse-deterrent formulations, abuse-deterrent opioids, ADF, cost-effectiveness analysis, economic evaluation, economic model, opioid abuse, opioid misuse

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Introduction

Every year, some 100 million people in the United States suffer from pain, with about 9% to 12% of these individuals experiencing pain that is considered chronic.¹ In 2016 alone, an estimated 214 million opioid prescriptions were dispensed, and rising in parallel with the volume of dispensed prescriptions has been the number of opioid overdose deaths and addictions, known as the opioid crisis.² The number of opioid-related deaths in the United States has increased nearly 4-fold in the past 2 decades. In 2017 alone, about 49 000 opioid-related overdoses (prescription and illicit) occurred, with more than 40% of these related to the use of prescription opioids.³ In addition to the societal impact of opioid-

related deaths, the level of abuse and misuse of these agents also has significant consequences for healthcare utilization. For example, it is estimated that for every death from prescription opioids, there are 10 treatment admissions for abuse, 32 emergency room visits for misuse or abuse, 130 people who become dependent on opioids, and 825 people who report nonmedical use of these drugs.⁴

To mitigate these issues, state and federal agencies have proposed and implemented various strategies ranging from targeting opioid prescribing practices to enhancing opioid overdose treatment, without any clear evidence on the effectiveness of most of these programs.⁵ One proposed approach has been the mandatory coverage of abuse-deterrent formulations (ADF) of opioid

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1098-3015/\$36.00 - see front matter Copyright © 2019, ISPOR—The Professional Society for Health Economics and Outcomes Research. Published by Elsevier Inc.

<https://doi.org/10.1016/j.jval.2018.12.005>

medications. ADF opioids are prescription opioid analgesics that use technologies that are designed to make them more difficult to abuse. Currently, there are 9 extended-release (ER) and 1 immediate release (IR) ADF opioids approved by the FDA. These ADF opioids have physical and chemical properties that resist manipulation (such as chewing, nasal snorting, smoking, and intravenous injection) or diminish their psychotropic effects. Nevertheless, none of the FDA-approved ADF opioids deter the most common form of abuse—swallowing more than the intended dose of intact capsules or tablets.

In 2015, the FDA provided guidance on the 4 categories of studies needed to demonstrate abuse-deterrent properties. The first 3 categories (premarket studies) are mandatory for FDA approval, whereas the fourth category (postmarket) studies are mandatory to be conducted after approval.⁶ A recent review of the premarket studies showed that ADF opioids were less likely to result in “drug liking” and “likelihood to take the drug again” compared with non-ADF counterparts (statistically significantly lower scores on visual analog scale).⁷ Nevertheless, these studies were conducted in recreational drug users, leading to considerable uncertainty around whether they are generalizable to abuse potential in patients with chronic pain. Furthermore, strong real-world evidence is currently lacking to demonstrate the overall public health impact of substituting ADF opioids for non-ADF opioids.⁷ To date, postmarketing evidence is available only for ADF ER oxycodone, and it shows a general decline in abuse and overdose death from ER oxycodone after it was reformulated into an ADF. Nevertheless, some of these studies also found a contemporaneous increase in the rates of abuse or overdose death from other prescription opioids (eg, ER oxycodone, ER morphine, IR oxycodone) or heroin, making it difficult to quantify the net impact of the reformulation of ER oxycodone into an ADF opioid.⁷ In addition, evidence on the impact of ADF opioids on other abuse-related outcomes, such as drug diversion, is extremely limited.⁷

Despite the lack of strong evidence on improved outcomes, ADF opioids are generally more expensive than non-ADF opioids. For example, the Veterans Administration (VA) spent approximately \$100 million on opioids in 2016; if all of these prescribed opioids had been ADF, this would have resulted in the spending of approximately \$1 billion, or 20% of the VA's budget in 2016.⁸ The objective of this analysis was to estimate and compare the costs and benefits of using ER ADF or non-ADF opioids for chronic pain.

Methods

In a cost-effectiveness cohort model, 2 hypothetical cohorts of 100 000 adult noncancer chronic pain patients newly prescribed ADF or non-ADF extended-release (ER) opioids were followed through their respective treatment and opioid use pathways (Fig. 1). All patients, irrespective of cohort, entered the model as therapeutic opioid users, defined as opioid use to treat chronic pain without misuse or abuse. Therapeutic users could discontinue treatment or die of non-abuse-related causes (ie, background mortality). Among therapeutic users, we modeled a rate of opioid abuse for those who remained alive for each year in the model, an annual probability of ceasing to abuse opioids, and an annual probability of death from opioid-related overdose or all other causes among opioid abusers. Patients who remained in the model were followed until the end of the 5-year model time horizon, with annual cycles and no discounting of costs or outcomes owing to the short time horizon of the model. Cumulative costs and outcomes were calculated over 5 years. Baseline patient characteristics (mean age-and-sex ratio) were based on those seen in an observational study that categorized populations by opioid abuse and no opioid abuse (which comprises the general

population without an abuse diagnosis), which we assumed to represent therapeutic use. Patients were assumed to be on opioid treatment for at least 90 days in the model.⁹ Our base-case analysis did not account for effect of diverted abuse or switching to other opioids or heroin for abuse and took a healthcare-sector perspective.

Our analysis relied on several underlying assumptions owing to a lack of robust clinical evidence on certain estimates key to the model. Where possible, we tested these assumptions by varying them across a plausible range in sensitivity analyses. We assumed the following: (1) the rate of abuse remained constant over time for patients who were prescribed opioids, (2) the effectiveness of ADF oxycodone in abuse deterrence applies to all other ADF opioids and is based on the effectiveness of OxyContin post-reformulation, (3) discontinuation of therapeutic opioid use over time was the same in both cohorts, (4) cessation of opioid abuse occurred at 10% annually, with abusers discontinuing midway with only 50% of costs in that year, (5) patients who abuse ADF opioids had the same probability of death from opioid overdose as from non-ADF opioid abuse, (6) nonopioid healthcare unit costs were the same in both cohorts, and finally, (7) there was no difference in the alleviation of chronic pain from ADF and non-ADF opioids because they are considered bioequivalent.^{10,11}

Our model compared all ER ADF opioids currently approved in the United States to treat chronic pain to all non-ADF ER opioids because of lack of data for individual drug comparisons. We did this by weighting drug costs by market share. We set the daily dose for all opioids to 90 mg morphine equivalent dose (MED).¹²

Model Inputs

Clinical inputs

Rates of abuse with ADF (3.647%) and non-ADF opioids (2.818%) were assumed to be the same as those from an observational study that measured rates of abuse (identified via ICD-9 codes) pre- and postreformulation of ER oxycodone (see Appendix Table 1 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2018.12.005>).¹³ Data on discontinuation of therapeutic use of opioids, which ranged from 17.2% in year 1 to 40.4% in year 5, were sourced from a claims analysis (see Appendix Table 1 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2018.12.005>).¹⁴ Opioid discontinuation was defined as a period of at least 182 days with no new prescription opioid claim from the last opioid prescription claim while enrolled in the dataset. Mortality included opioid-related overdose deaths in patients with abuse and age- and sex-specific all-cause mortality for all patients, from Social Security Administration actuarial life tables.^{15,16}

Cost inputs

Healthcare costs included costs of prescribed opioids and non-opioid costs such as emergency room visits, inpatient and outpatient visits, and associated professional fees. All nondrug costs were inflated to 2017 values, and the latest available 2018 drug prices were used in the model (Table 1). Prices for individual ADF and non-ADF opioids were sourced from the Federal Supply Schedule (FSS) using a 90 mg MED daily dose. We used the FSS database because it is a publicly available source of discounted prices (paid by Federal agencies) and aligns with the recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine for analyses from the healthcare sector and societal perspectives.^{17,18} ADF and non-ADF opioid prices were weighted by market share, based on the 12-month incident use of prescription ER opioids from February 2016 to January 2017 in Massachusetts.¹⁹ More details on individual opioid prices and market share are available in the Appendix Tables 2 and 3 (see Supplemental Materials found at <https://doi.org/10.1016/j.jval.2018.12.005>).^{20,21}

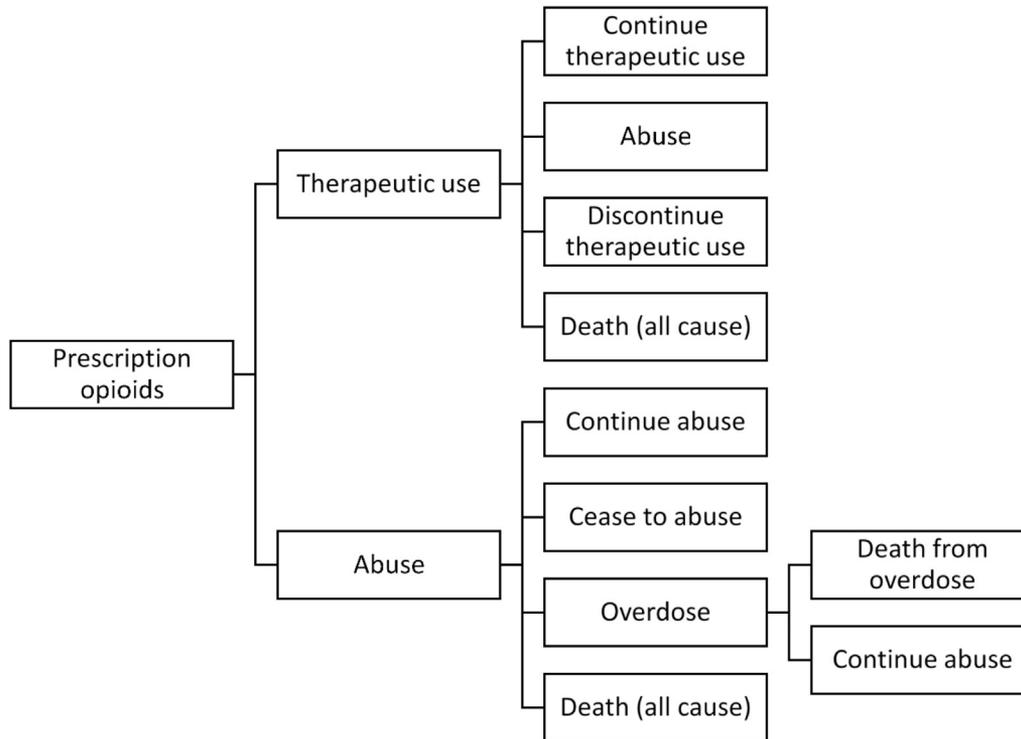


Fig. 1 – Model schematic. Patients in both abuse-deterrent formulations and non—abuse-deterrent formulations cohorts follow the same pathway. Model schematic represents one cycle.

Nonopioid healthcare costs (in-patient, out-patient, observation stays, professional visits, and nonopioid prescription drugs) were taken from a claims analysis conducted specifically for this analysis by the Commonwealth of Massachusetts Health Policy Commission. This analysis used a 2014 sample of the Massachusetts All-Payers Claims Database (APCD) that includes commercial medical and pharmacy claims and personal spending that

includes retail prescription drugs; hospital, physical, and clinical care services; and other covered services, across 3 payers in Massachusetts. Of the 3199 commercially insured patients included in the sample set, 176 and 861 patients had a diagnosis of abuse and therapeutic use with ADF opioids, respectively, whereas 374 and 1788 patients had a diagnosis of abuse and therapeutic use with non-ADF opioids, respectively.²² Overdose-related costs were accounted for in the emergency-department cost category in the claims analysis.

Table 1 – Cost inputs

Input	Value	Source
<i>ADF opioids—90 mg MED</i>		
Price per daily dose*	\$11.82	FSS, 2017 ¹⁷
Annual price	\$4314	Calculation
<i>Non-ADF opioids—90 mg MED</i>		
Price per daily dose*	\$6.00	FSS, 2017 ¹⁷
Annual price	\$2190	Calculation

Mean annual healthcare costs

Mean annual costs	Therapeutic use patients	Abuse patients	
Healthcare resource utilization	\$19 770	\$31 784	Commonwealth of Massachusetts Health Policy Commission ¹⁹
Nonopioid prescriptions	\$8787	\$7466	

ADF indicates abuse-deterrent formulation; MED, morphine equivalent dose; FSS, Federal Supply Schedule.
 * Market-share-based weighted average cost of drugs within each category.

Sensitivity analyses

We conducted threshold analyses for cost neutrality between the 2 cohorts at 5 years by varying estimates of the effectiveness of abuse deterrence and the weighted average drug price in the ADF opioid cohort. We also conducted one-way sensitivity analyses for key inputs, varying these estimates across reported 95% confidence intervals or when ranges were unavailable, varying them by ±25% of the point estimate.

Scenario analysis

In a scenario analysis, we included abuse from opioid diversion in the model. We calculated the reduction in relative risk of diversion required when using ADF opioids to achieve cost neutrality relative to non-ADF opioids for varying risks of diversion using non-ADF opioids. As an additional scenario analysis, we conducted the analysis from a modified societal perspective by including costs for productivity loss and criminal justice or incarceration associated with opioid abuse. Details on methodology for this scenario are available in the Appendix (see Supplemental Materials found at <https://doi.org/10.1016/j.jval.2018.12.005>). We also conducted an analysis measuring the cost-effectiveness of ADF oxycodone compared with non-ADF oxycodone formulations.

Model outcomes

Model outcomes include total healthcare costs, number of new cases of abuse, person-years of abuse, and opioid-related overdose deaths in each cohort. Healthcare costs, comprising opioid drug costs and nonopioid costs, were calculated for each cohort, weighted by clinical probabilities governing patient pathways in each cohort and the incremental difference in costs between the 2 cohorts. We used these outcomes for the 2 cohorts to calculate the incremental cost per abuse case prevented, per person-year of abuse prevented, and per overdose death prevented.

Results

Health and cost outcomes presented in Table 2 are cumulative over 5 years (Table 2). These results indicate that ADF opioids are effective in preventing approximately 2300 new cases of abuse and approximately 6600 abuse years relative to non-ADF opioids. Given the age of the target population and no differential effects in mortality owing to the short, 5-year time horizon of the model, we did not calculate life-years lost. Abuse-related costs using ADF opioids are lower than those of non-ADF opioids by approximately \$274 million, but these savings are offset by substantially higher ADF opioid drug costs (approximately \$651 million) and higher nonopioid therapeutic use costs (approximately \$158 million), thus resulting in an additional financial burden of approximately \$535 million to the health system. This translates to the health system paying approximately \$232 000 to prevent one new case of abuse and approximately \$81 000 to prevent one abuse-year by using ADF opioids in place of non-ADF opioids. ADF opioids marginally decrease opioid overdose-related death and are estimated to cost the health system approximately \$1.3 billion to prevent one death from opioid overdose, relative to their non-ADF counterparts.

Sensitivity Analyses

Threshold analyses

Increasing the effectiveness (reduction in rate of abuse) of ADF opioids to the hypothetical point where using ADF opioids entirely eliminated abuse would still result in additional health system costs of approximately \$104 million (Fig. 2). Varying the weighted average ADF opioid drug price to achieve cost neutrality would require a 40% price discount in ADF opioids, reducing the price per day from \$11.82 to \$7.06.

One-way sensitivity analyses

Our one-way sensitivity analyses showed that ADF opioid price drove model results the most, with a $\pm 25\%$ price variation

resulting in net health system costs ranging from approximately \$202 million to \$867 million (Fig. 3). The incidence of abuse had the least influence on model results, with the difference in net health system costs between the 2 cohorts ranging from \$509 million to \$560 million (Fig. 3).

Diversion

Based on results from a survey study,²³ we assumed a 1:1 ratio of prescription to diverted abuse; that is, for every case of prescription abuse, there is one case of diverted abuse using non-ADF opioids. We traced the relative risk reduction of diversion that would be required to achieve cost neutrality when using ADF opioids. Figure 4 presents the net incremental health system costs when using ADF opioids relative to non-ADF opioids at varying levels of reduction in risk of diversion with ADF opioids. Our results indicate that ADF opioids would require a 43% risk reduction in diversion to achieve cost neutrality, beyond which they would be cost-saving. A relative risk in diversion ranging from 10% to 40% would result in incremental health system costs when using ADF opioids of approximately \$410 million to approximately \$38 million over 5 years.

Modified societal perspective

We estimated annual societal costs owing to lost productivity (\$17 011) and criminal justice and incarceration (\$3442).^{23–25} Applying these costs to patients who abuse opioids resulted in net spending between the ADF and non-ADF opioid cohorts of approximately \$392 million over 5 years.

Oxycodone-only comparison

In this scenario we estimated cost-effectiveness by comparing only oxycodone formulations in the ADF cohort to those in the non-ADF cohort. We weighted the price of ADF oxycodone based on market share for the 2 oxycodone ADF drugs, namely, OxyContin and Xtampza. The ADF oxycodone cost per day was calculated as \$10.85 and its non-ADF counterpart at \$8.49. This resulted in healthcare sector costs of approximately \$145 million more in the ADF cohort relative to the non-ADF cohort over 5 years and approximately \$63 000 to prevent one new case of abuse using OxyContin.

Discussion

Our cost-benefit analysis of ADF opioids relative to non-ADF opioids in a hypothetical cohort of chronic pain patients newly prescribed ER opioids indicates lower incidence of new cases of abuse, but higher healthcare sector costs over a 5-year period. We estimate that it costs the health system approximately \$232 000 to

Table 2 – Base-case outcomes using ADF and non-ADF opioids over 5 years

Cumulative 5-year outcome	ADF opioid cohort	Non-ADF opioid cohort	Incremental outcome results (ADF minus non-ADF)
New cases of abuse	8229	10 532	–2303
Abuse-years	23 322	29 943	–6621
Opioid-related overdose death	1.38	1.77	–0.39
Therapeutic-use-related costs*	\$8091 million	\$7934 million	\$158 million
Abuse-related costs*	\$966 million	\$1241 million	–\$274 million
Prescription opioid costs	\$1329 million	\$678 million	\$651 million
Total health system costs	\$10 386 million	\$9852 million	\$535 million

All costs are rounded to the nearest million dollars. ADF, abuse-deterrent formulation.

* Only nonopioid costs.

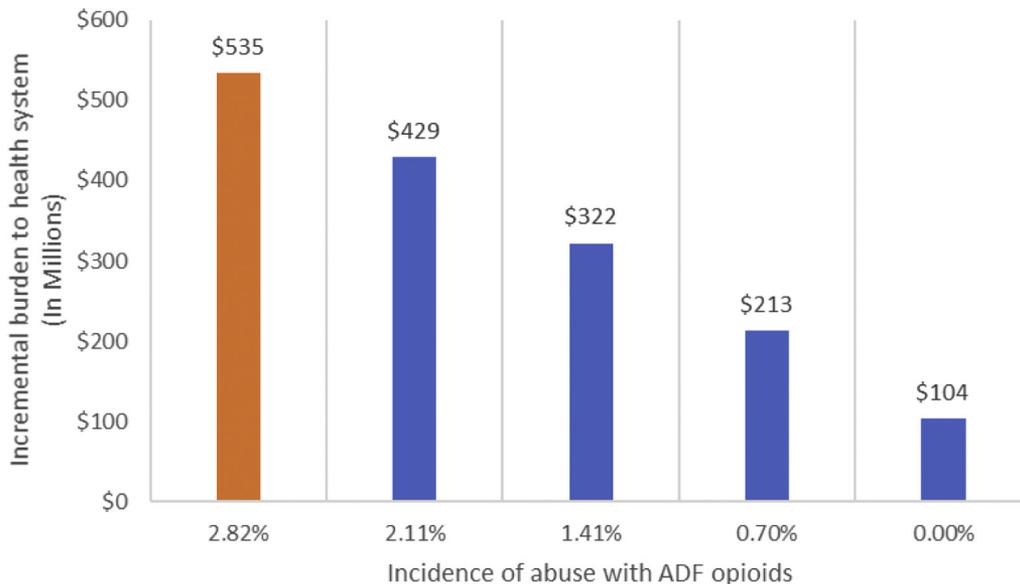


Fig. 2 – Incremental health system costs when using ADFs at varying levels of effectiveness (decreasing incidence of abuse with ADFs). Orange bar represents base-case incremental health system costs. ADF indicates abuse-deterrent formulations.

prevent a new case of abuse and approximately \$1.4 billion to prevent one opioid-related overdose death when using ADF opioids in place of non-ADF opioids. Assuming 100% effectiveness with ADF opioids still resulted in additional costs to the health system, whereas cost neutrality could be achieved if ADF opioids were priced at a 40% discount compared with current prices. Although using ADF opioids lowered indirect costs relative to using non-ADF opioids, these costs did not outweigh the additional financial costs of ADF opioids. ADF opioids would need to reduce diversion by 43% compared with non-ADF opioids to achieve cost neutrality. Our model analyzing the cost-benefit of ADF opioids is the first to include the health and cost outcomes of therapeutic use within a cohort, unlike previous models that only included the health and cost outcomes associated with opioid abuse.^{13,26,27} Because most chronic pain patients who are prescribed opioids use them only for therapeutic purposes, the healthcare resources and costs associated with therapeutic use

form a non-negligible component of the overall healthcare sector financial burden, which is necessary to account for in such models. This approach provides policy makers a more realistic outlook at the financial implications of using ADF opioids, specifically when developing policy recommendations.

Our model has several limitations. First, in the absence of any data on the length of opioid use, we assumed a constant rate of opioid abuse over the time horizon of the model. Second, we limited opioid-related overdose death to only those who abuse prescription opioids, despite the possibility of an increase in overdose death in the ADF cohort as a result of switching to other nonprescribed or illicit opioids. Nevertheless, the data around this are inconclusive.²⁸ Third, although our estimates of net price are based on the FSS, these discounted prices may represent steeper discounts obtained by major government agencies than those received by payers in a commercial setting. Fourth, drug costs are weighted based on ADF and non-ADF market share, whereas

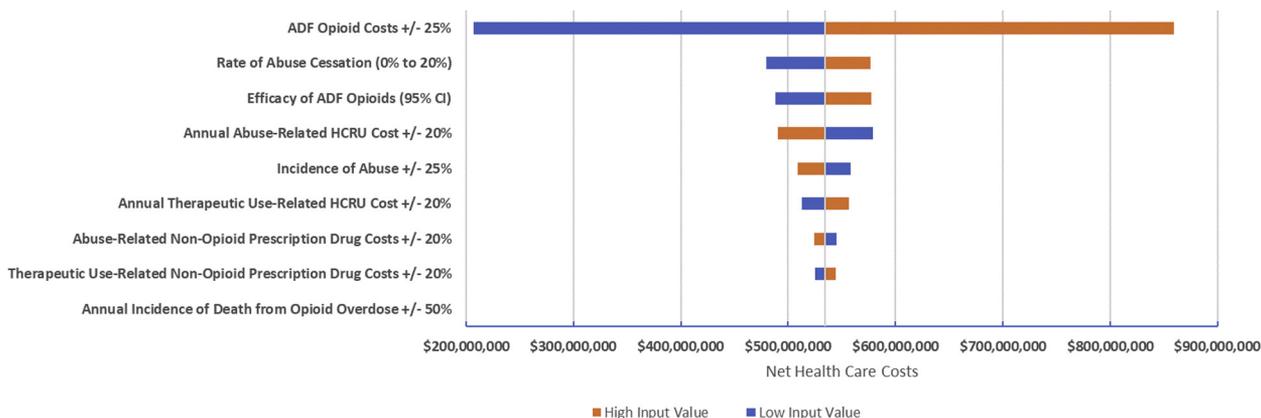


Fig. 3 – One-way sensitivity analysis. Incremental health system costs when using ADFs, over five years. ADF indicates abuse-deterrent formulations.

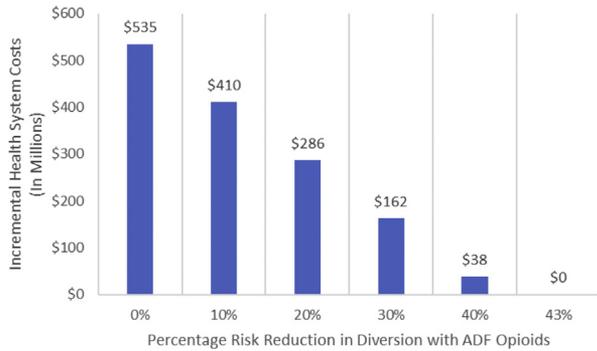


Fig. 4 – Incremental health system costs at different levels of risk reduction in diversion with ADFs. ADF indicates abuse-deterrent formulations.

abuse-related efficacy is sourced from oxycodone formulations alone, based on availability of robust published data. Furthermore, given our market share approach, OxyContin is a key driver of pricing for the ADF cohort because it is most widely used, despite it being relatively cheaper than alternative ADFs that are less prevalent on the market. To address the limitations in our market-share approach and the availability of postmarket data only for the reformulated an ADF oxycodone, we included an ADF oxycodone to non-ADF oxycodone comparison that produced results directionally similar to the base-case analysis.

Fifth, we did not vary nonopioid healthcare costs over time in patients who abuse opioids because we did not find estimates on this beyond 18 months since abuse diagnosis.²⁹ The baseline characteristics of the “therapeutic use” subcohort were assumed the same as the general population seen in Rice et al.⁹ Nevertheless, we use healthcare cost associated with therapeutic use based on claims data that comprised patients with opioid prescriptions with no abuse-related diagnoses.²² The annual rate of opioid discontinuation was sourced from a study that included both ER and IR opioids. Finally, our model’s most significant limitation was the noninclusion of diversion-associated estimates in our base-case analysis. Estimates on diversion are scarce and if available, such as in the study by Severtson et al.,³⁰ they do not account for switching to other opioids, which is also a key component to consider when including diversion in such a model. In addition, including diversion would require introducing a cohort external to the original cohort being included in the model.

Conclusions

Findings from our analysis show that ADFs have the potential to prevent new cases of abuse, but at substantially higher costs to the health system than non-ADFs. Incremental health system costs are most sensitive to ADF opioid prices, with a 40% price discount leading to cost neutrality. There is currently a lack of postmarket real-world data comparing the abuse-related effectiveness of ADF opioids relative to their non-ADF counterparts, which is vital when addressing the health, economic, and societal impacts of these new formulations in addressing the opioid epidemic. Manufacturers and payers are encouraged to generate relevant real-world evidence that can feed into future economic modeling efforts in this space.

Supplemental Materials

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.jval.2018.12.005>.

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