Evidence to Practice

Benefits, Limitations, and Value of Abuse-Deterrent Opioids

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Source of Review

The Institute for Clinical and Economic Review (ICER) issued a final evidence report,[1] including a systematic literature review and cost-benefit analyses, to support a July 20, 2017, public meeting of the New England Comparative Effectiveness Public Advisory Council on abuse-deterrent (AD) opioids. We summarize key findings of the report and provide our independent assessment of their implications for health policy. While acknowledging the importance of reducing stigma in clinical discourse, we use the term *abuse* for consistency with the report nomenclature.

Background

Between 2000 and 2015, drug-poisoning deaths—primarily involving opioids—contributed more to lost life expectancy in the United States than the 12 leading causes of death combined.[2] In 2015 alone, more than 33 000 Americans died from an opioid-related overdose.[3] In the face of this worsening opioid crisis, drug companies have advanced tamper-resistant opioid formulations as a tool to mitigate opioid abuse and extend market exclusivity.[4] These AD opioids are generally difficult to snort or inject (or to get a high from when snorted or injected). Although the US Food and Drug Administration has approved 10 AD opioids to date (**Table**), AD OxyContin (Purdue) claims 90% of the market.[1]

In preparing its report,[1] ICER reviewed 2 categories of AD opioid studies. The first category comprised 15 premarket, active- and placebo-controlled, crossover trials in which healthy, recreational drug users were given preprepared, crushed AD opioids and were asked whether they liked the drug ("drug-liking") and whether they would take it again ("drug-taking"). Of these trials, 7 evaluated the potential for oral abuse, and 8 evaluated the potential for intranasal abuse. The second category consisted of 26 postmarket, time-series analyses of the impact of the introduction of AD OxyContin on rates of abuse, overdose, or diversion (use of a drug by persons to whom it was not prescribed) among different groups, including the general population, recreational drug users, and patients with opioid use disorders.

ICER also conducted 2 cost-benefit analyses. The primary cost-benefit analysis was based on modeling 100 000 initiators of AD and non-AD, extended-release opioids for nonmalignant chronic pain over a 5-year period. Abuse probabilities and health care costs were derived from claims data, and drug costs were taken from the Federal Supply Schedule. Separately, ICER examined the impact of universally substituting non-AD opioids with AD opioids in Massachusetts using data from the state's prescription monitoring program.

Summary of Findings

Most premarket studies reported significantly lower drug-liking and drug-taking scores for preprepared, crushed AD opioids compared with non-AD opioids. Likewise, postmarket analyses reported significant reductions in OxyContin abuse after the introduction of the reformulated AD product, ranging from 12% to 75%. Declines were steeper for nonoral abuse than for oral abuse. However, several analyses reported increased abuse of other opioids. For example, one investigation found a 42% increase in heroin abuse and a 20% increase in the abuse of other oxycodone products. A similar theme

Table. US Food and Drug Administration (FDA)–Approved Abuse-Deterrent Opioids

Brand Name (Manufacturer)	Type of Opioid	Approval Year	Wholesale Acquisition Cost[a]	Year of Last-Expiring FDA-Listed Patent	Non-Abuse-Deterrent Generic Available?[b]
OxyContin (Purdue)	Oxycodone	2010	20 Tablets (15 mg): $101.38	2030	No
Targiniq (Purdue)	Oxycodone	2014	Discontinued	2025	No
Embeda (Pfizer)	Morphine	2010	30 Capsules (100 mg of morphine/4 mg of naltrexone): $746.53	2029	Yes
Hysingla (Purdue)	Hydrocodone	2015	60 Tablets (80 mg): $1735.22	2031	No
MorphaBond ER (Daiichi Sankyo)	Morphine	2015	100 Tablets (15 mg): $540.00	2028	Yes
Xtampza ER (Collegium Pharmaceutical, Inc)	Oxycodone	2016	100 Capsules (9 mg): $369.02	2036	No
Troxyca ER (Pfizer)	Oxycodone	2016	Not yet marketed	2027	No
Arymo ER (Egalet US Inc)	Morphine	2017	100 Tablets (30 mg): $865.00	2033	Yes
Vantrela ER (Teva Pharmaceutical Industries Ltd)	Hydrocodone	2017	Not yet marketed	2029	No
RoxyBond (Inspirion Delivery Sciences)[c]	Oxycodone	2017	Not yet marketed	2028	No

Abbreviation: ER, extended release.

[a] As of September 5, 2017, from online drug pricing software (Red Book; Truven Health Analytics).

[b] The same capsule or tablet and extended-release or immediate-release form.

[c] Immediate release.

emerged from 3 studies that assessed diversion; significant declines were seen for OxyContin diversion, whereas mixed results were noted for other opioids.

In the primary cost-benefit analysis, there were 2300 fewer cases of abuse but no difference in opioid-related death among AD opioid initiators than among non-AD opioid initiators. Initiation of treatment with an AD opioid resulted in a $533 million increase in spending, with lower abuse-related costs outweighed by higher drug prices (mean price, $11.60 vs $5.82 per day). Prevention of one case of abuse cost $231 000, and prevention of one overdose death cost $1.4 billion. Cost-neutrality could be achieved by reducing the price of AD opioids by almost half, to $6.86 per day. In the Massachusetts model, universal substitution of non-AD with AD was predicted to prevent 850 new cases of abuse in one year, translating to $599 000 per case averted and $475 million overall.

Limitations of the Evidence

The available evidence on AD opioids was limited in several respects. The primary outcomes assessed in the premarket trials—drug-liking and drug-taking—were surrogate measures of abuse that have yet to be robustly validated in real-world settings.[5] Participants in these trials were also not diagnosed as having substance use disorders. Therefore, it is unclear to what extent the findings are generalizable to most at-risk patients.

The postmarket, time-series analyses may have been subject to confounding by secular trends. The spread of prescription monitoring programs, risk evaluation and mitigation strategies, and more rigorous continuing medical education programs on appropriate opioid prescribing practices could have contributed to the decrease in OxyContin abuse, as well as to the increase in illicit opioid abuse found in some studies. A recent analysis designed to isolate the effect of the introduction of AD OxyContin from such secular trends found that opioid switching, for example to heroin or fentanyl, extinguished AD benefits.[6]

Policy Implications

The findings of the ICER report,[1] with which we agree, have 3 primary implications for health policy. First, prescribing AD opioids in place of non-AD opioids may be merited in certain cases given evidence of reduced abuse and diversion of AD products. However, this decision should be made on a case-by-case basis, factoring the limitations of the evidence, the higher price of AD opioids, and emerging data suggesting an increased risk of opioid switching among AD opioid users. Health care professionals should also carefully consider alternative approaches to pain control, such as nonopioid analgesics, nonpharmacologic interventions, and—in the postoperative setting—shorter opioid prescriptions.

Second, efforts to require automatic substitution of prescriptions for non-AD opioids with AD opioids, as in Massachusetts,[7] are misguided. Such a policy would be extremely costly and divert resources away from other approaches to mitigating opioid abuse and addiction. Major shifts in opioid supply must be considered in a global context of broad availability of riskier black-market alternatives,[8] as well as the existence of other evidence-based interventions, including naloxone access[9] and opioid use disorder treatment.[10]

Third, current AD opioid prices are unjustified and inappropriately strain health care budgets. The results of the cost-benefit analyses should pressure drug companies to make AD opioids more affordable.

Conclusions

Selective use of AD opioids may be effective in mitigating opioid abuse and reducing drug diversion. However, their widespread use would be cost prohibitive and may have the unintended consequence of promoting switching to more dangerous opioids. Greater investment in alternative interventions may be more useful to combat the growing opioid crisis.

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