

Original Investigation

Abuse-Deterrent Formulations and the Prescription Opioid Abuse Epidemic in the United States

Lessons Learned From OxyContin

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IMPORTANCE In an effort to reduce wide-scale abuse of the proprietary oxycodone hydrochloride formulation OxyContin, an abuse-deterrent formulation (ADF) was introduced in 2010. Although the reformulation produced an immediate drop in abuse rates, a definite ceiling effect appeared over time, beyond which no further decrease was seen.

OBJECTIVE To examine the factors that led to the initial steep decline in OxyContin abuse and the substantial levels of residual abuse that have remained relatively stable since 2012.

DESIGN, SETTING, AND PARTICIPANTS We used data from the ongoing Survey of Key Informants' Patients program, part of the Researched Abuse, Diversion and Addiction-Related Surveillance system that collects and analyzes postmarketing data on misuse and diversion of prescription opioid analgesics and heroin. For our survey study, patients with a *DSM-V* diagnosis of opioid use disorder and primary drug of abuse consisting of a prescription opioid or heroin (N = 10 784) at entry to 1 of 150 drug treatment programs in 48 states completed an anonymous structured survey of opioid abuse patterns (surveys completed from January 1, 2009, through June 30, 2014). A subset of these patients (n = 244) was interviewed to add context and expand on the structured survey.

MAIN OUTCOMES AND MEASURES In addition to key demographic measures, past-month abuse of opioids was the primary measure in the structured surveys. In the interviews, the effect of the introduction of the ADF on drug-seeking behavior was examined.

RESULTS Reformulated OxyContin was associated with a significant reduction of past-month abuse after its introduction (45.1% [95% CI, 41.2%-49.1%] in January to June 2009 to 26.0% [95% CI, 23.6%-28.4%] in July to December 2012; $P < .001$; $\chi^2 = 230.83$), apparently owing to a migration to other opioids, particularly heroin. However, this reduction leveled off, such that 25% to 30% of the sample persisted in endorsing past-month abuse from 2012 to 2014 (at study end [January to June 2014], 26.7% [95% CI, 23.7%-29.6%]). Among the 88 participants who indicated experience using pre-ADF and ADF OxyContin, this residual level of abuse reflects the following 3 phenomena: (1) a transition from nonoral routes of administration to oral use (38 participants [43%]); (2) successful efforts to defeat the ADF mechanism leading to a continuation of inhaled or injected use (30 participants [34%]); and (3) exclusive use of the oral route independent of formulation type (20 participants [23%]).

CONCLUSIONS AND RELEVANCE Abuse-deterrent formulations can have the intended purpose of curtailing abuse, but the extent of their effectiveness has clear limits, resulting in a significant level of residual abuse. Consequently, although drug abuse policy should focus on limiting supplies of prescription analgesics for abuse, including ADF technology, efforts to reduce supply alone will not mitigate the opioid abuse problem in this country.

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Rapid entry of abuse-deterrent formulations (ADFs) of extended-release opioid drugs in the analgesic market reflects an effort to curb epidemic levels of prescription opioid abuse in this country.¹⁻³ For the reader unfamiliar with the concept of ADFs of opioid analgesics, those who use these medications for nontherapeutic or recreational reasons often chew the pill to release the drug quickly or more commonly crush it for inhalation or solubilize it for injection. The goal of most ADFs is to impose mechanical barriers that make crushing or chewing the pill difficult. Alternatively, some ADFs (eg, Suboxone) incorporate an opioid antagonist (naloxone hydrochloride) that blocks the effects of the parent opioid (in this case, buprenorphine hydrochloride), making the drug unsuitable for obtaining a high, even if crushed into a powder.⁴

The proprietary oxycodone hydrochloride formulation OxyContin was introduced in the mid-1990s as a long-acting, sustained-release opioid analgesic, but it very quickly became one of the most commonly abused opioids, particularly by those who injected and inhaled it, because of its large reservoirs of the active drug (oxycodone).⁵⁻⁸ In an effort to blunt this abuse profile, the manufacturer (Purdue Pharma, Inc) reformulated OxyContin and released an ADF in 2010. This reformulation, which makes crushing and solvent extraction difficult, has been shown to be highly effective in reducing the abuse of OxyContin⁹⁻¹³ based on a number of systematic studies (eg, reports to poison control, overdose deaths, and past-month abuse among recreational users or treatment seekers). This ADF earned the company the first-ever allowance by the US Food and Drug Administration to change the label to emphasize its abuse-deterrent properties.¹⁴ However, most studies have not investigated specific changes in drug-seeking behavior, such as whether ADF OxyContin discouraged abuse entirely, shifted preferences to other drugs, or altered the routes of administration.

The purpose of the present study was to perform such investigations using a mixed-methods approach, including structured surveys of 10 784 individuals entering treatment for opioid use disorder in 1 of more than 150 drug treatment programs in the United States and detailed qualitative interviews with a subset of these patients (n = 244). Because ADF OxyContin is the first effective reformulation in what promises to be a long succession of similar products, evidence regarding its effect on abuse behaviors could shape the role of future ADFs in addressing the prescription opioid abuse epidemic in the United States.

Methods

Study Sample

This report used data from the ongoing nationwide Survey of Key Informants' Patients (SKIP) program, a key element of the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) system, a comprehensive series of programs that collect and analyze postmarketing data on the misuse and diversion of prescription opioid analgesics and heroin. The SKIP program consisted of key informants from more than 150 public and privately funded treatment centers in 48 states, with a fair distribution among the 4 census areas (Midwest, 28.5%; Northeast, 16.9%; South, 31.7%; and West, 22.9%) and along the urban-rural

continuum (urban, 52.5%; suburban/rural, 47.5%). Key informants were asked to recruit clients older than 18 years who were entering their substance abuse treatment program with a primary diagnosis of opioid abuse, as defined by *DSM-V* criteria. All study protocols were approved by the institutional review board of Washington University, St Louis. Surveys were anonymous, and a cover sheet to the survey was used to obtain informed consent. Completion of the survey acted as acknowledgment of consent. Surveys did not ask any identifying data.

Clients were asked to complete an anonymous paper survey centered on opioid abuse patterns and related behaviors. We attained an 82.0% response rate. The survey packet included a \$20 Walmart gift card and a self-addressed stamped envelope that, after survey completion, was used by the respondent to mail the survey (identified by a unique case number) directly to Washington University. The SKIP questions centered on patterns of abuse of prescription opioids and heroin, with historical information obtained concerning drug use behaviors and mental and physical health. The SKIP data for this study were analyzed from January 1, 2009, through June 30, 2014.

A subset of respondents indicated by a mail-in postcard provided with the SKIP survey that they were willing to give up their anonymity and participate in the interview-based Researchers and Participants Interacting Directly (RAPID) program. The purpose of the RAPID program was to supplement and add context to the structured SKIP survey by establishing a 2-way exchange of information with participants in which questions were developed, administered, and answered within a short period. The RAPID participants completed an online survey with direct quantitative questions based on SKIP analyses and prior literature on the topic as well as open-ended, qualitative questions to explain responses to quantitative questions in greater detail. Participants were followed up when necessary through e-mail exchanges to clarify or to provide further insight to responses or to answer supplemental questions that may have arisen from the online questionnaire. The collection period for this RAPID interview, developed specifically to gather more understanding of the effects of ADF OxyContin, was from May 1 through June 30, 2014; 244 of 439 treatment clients consented to participate in this study (response rate, 55.6%) during this 3-month period. Participants in the RAPID program were compensated with a \$20 Walmart gift card.

Statistical Analysis

The SKIP and RAPID programs gathered sociodemographic variables (eg, sex, current age, and race/ethnicity). In addition, the SKIP respondents were asked to identify all opioid compounds (buprenorphine, fentanyl, heroin, hydrocodone, hydromorphone hydrochloride, methadone hydrochloride, morphine sulfate, oxycodone, oxymorphone hydrochloride, tapentadol hydrochloride, and tramadol hydrochloride) used for nontherapeutic/recreational purposes in the month before entering treatment, stratified by the formulation and, when applicable, the product name. Unlike prior reports on this topic using SKIP data, our sample included heroin and prescription opioid abusers because of the high levels of concurrent use of both drugs (82.3% of heroin users also had past-month abuse of prescription opioids). The RAPID participants were asked

Table. Comparison of SKIP and RAPID Demographic Data

Characteristic	SKIP (n = 11 782) ^a	RAPID (n = 244) ^b
Male sex	50.6	46.4
Age, mean (SEM), y	34.1 (0.1)	35.9 (0.6)
Race/ethnicity		
White	78.4	90.4
Nonwhite	21.6	9.6

Abbreviations: RAPID, Researchers and Participants Interacting Directly; SKIP, Survey of Key Informants' Patients.

^a Data analyzed from January 1, 2009, through May 1, 2014.

^b Data collected from May 1 through June 30, 2014.

about their lifetime abuse of OxyContin, including formulations used, routes of administration, and the effect of the introduction of ADF OxyContin on their opioid abuse patterns. We used χ^2 tests for trend to measure differences in abuse rates over time in the SKIP sample as a function of half-year intervals (mean number of respondents, 991; range, 594-1335), with simple χ^2 goodness-of-fit tests to analyze differences in the routes of administration from the RAPID sample. Counts from the direct question-and-answer sets were used to analyze the RAPID data, with open-ended responses for those substances used to replace OxyContin undergoing dual review and coding with no discrepancies. We analyzed data from the SKIP and RAPID data sets using commercially available software (SPSS Statistics, version 22; IBM).

Results

Demographics

The Table summarizes the gross demographic features of those participating in the SKIP (n = 10 784) and RAPID (n = 244) programs. The RAPID subset, although much smaller, was similar to the larger SKIP sample with the exception that more participants in the SKIP sample were nonwhite. However, in both groups, most of the participants were white and in their early fourth decade of life at the time of completion of the survey, with an even distribution of men and women.

Impact of ADF and Residual Abuse

Figure 1 shows the past-month abuse of OxyContin for the 1.5 years before and 4 years after introduction of the ADF. Approximately 45% of those entering treatment in 2009 and 2010 indicated that they had used OxyContin for nontherapeutic/recreational purposes in the 30 days before entering treatment (in January to June 2009, 45.1% [95% CI, 41.2%-49.1%]). On the introduction of the ADF, the number of abusers declined sharply and significantly (to 26.0% [95% CI, 23.6%-28.4%] in July to December 2012; $\chi^2 = 230.83$; $P < .001$) but reached a plateau at 25% to 30% of new patients entering treatment, with no further decreases from 2012 to 2014 (at study end [January to June 2014], 26.7% [95% CI, 23.7%-29.6%]).

To better understand this residual abuse, we interviewed the 153 RAPID participants (62.7%) who indicated any lifetime abuse of the original formulation of OxyContin. They were asked

whether the ADF influenced the drugs they chose to use for non-therapeutic/recreational purposes. The results are shown in Figure 2A. Similar to the residual rates of OxyContin abuse seen in the SKIP data above, 51 respondents (33.3%) indicated that the ADF had no effect on drug selection and continued to abuse OxyContin, whereas a separate 51 respondents (33.3%) indicated that they replaced OxyContin with other drugs as a result of the ADF. Just 5 respondents (3.3%) indicated that the ADF influenced their decision to stop abusing drugs altogether. The remaining 46 respondents (30.1%) indicated that they did not use OxyContin enough to change their choice of drug.

Route of Administration

Eighty-eight RAPID participants indicated experience in using both formulations of OxyContin to "get high"; subsequent interviews with this subset shed light on the effects of ADF on the routes of OxyContin administration (Figure 2B). Data showed 3 distinct groups of abusers. Thirty-eight respondents (43%) indicated that they switched from primarily injecting/inhaling the drug to swallowing it whole, whereas 30 respondents (34%) reported that they were able to defeat the ADF formulation and continued to inject or to inhale the drug as the primary route. The remaining 20 respondents (23%) primarily swallowed the previous formulation of OxyContin, and the ADF had no effect on their continued oral use. When asked to identify all routes of administration used for original and reformulated OxyContin, significantly more individuals selected oral routes after the introduction of the ADF than before (80.7% [95% CI, 72.1%-89.4%] vs 55.4% [95% CI, 44.5%-66.3%]; $\chi^2 = 12.22$; $P < .001$). The opposite was observed for nonoral routes, which declined significantly (92.8% [95% CI, 87.1%-98.5%] vs 50.6% [95% CI, 39.6%-61.2%]; $\chi^2 = 36.36$; $P < .001$) but were still used at least once by a large part of the sample. The following comments are representative responses to the reformulation from participants in the RAPID program.

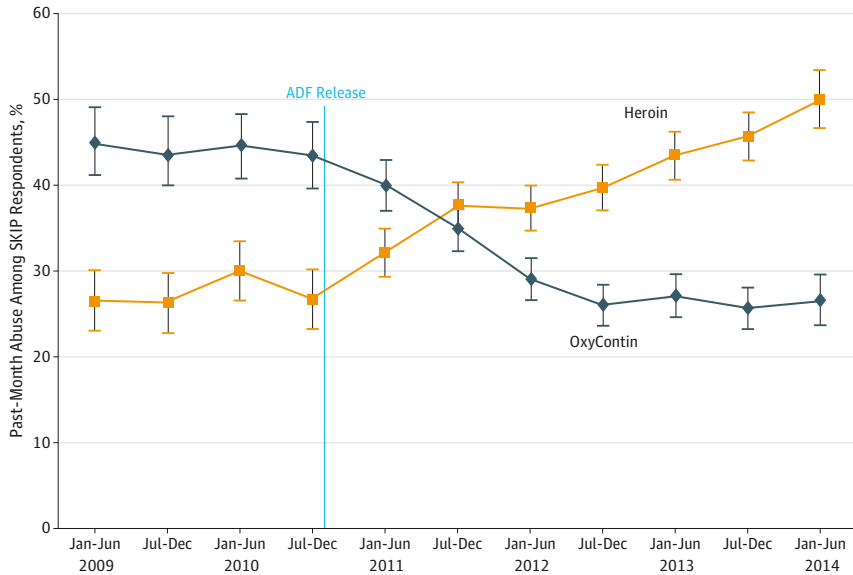
"With the new Oxy, I had to learn how to make it injectable."

"I was immediately familiar with how to get high from both the old and the new versions. I learned this by searching the Internet for information. I did research on how other drug addicts used the new formulation.... It was time consuming, but it worked."

Transitions to Other Drugs

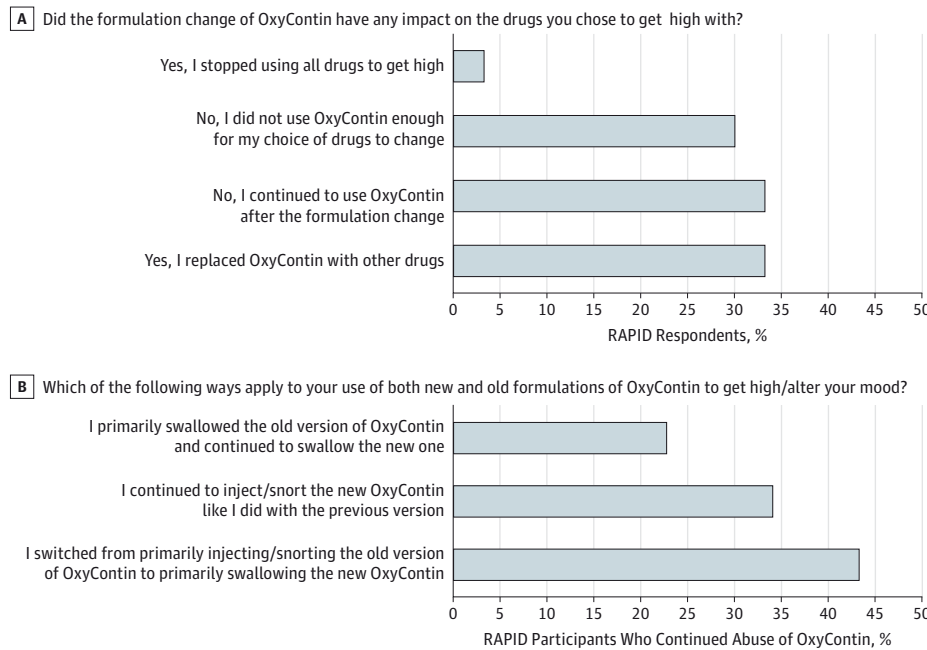
As mentioned above, 51 of 153 RAPID respondents indicated that the introduction of the ADF led them to shift drug choices. When participants were asked open-ended questions about the drugs with which they replaced OxyContin, 26 of 37 with codable responses (70%) indicated heroin. Far fewer participants shifted to other prescription opioids, and only 1 individual (2%) indicated that he or she replaced OxyContin with a nonopioid drug (crack/cocaine) (Figure 3). The past-month use of heroin in the SKIP population steadily and significantly increased during the 4 years after the introduction of the ADF ($\chi^2 = 224.98$; $P < .001$) (Figure 1). However, its rate of increase was greater during the year immediately after the introduction of the ADF (11.0% increase in 2011) than it was from 2012 through 2014 (mean change per half-year, 2.5%). Other than a slight increase in hydromor-

Figure 1. Respondents Who Endorsed Past-Month Use of OxyContin or Heroin Before and After the Introduction of an Abuse-Deterrent Formulation (ADF)



Respondents include 10 784 participants in the Survey of Key Informants' Patients (SKIP) program (mean number per half-year, 991). Data are presented in 6-month increments from January 1, 2009, through June 30, 2014, and are expressed as percentages (95% CI [error bars]), with a χ^2 test for trend significance of $P < .001$ during the study period. The ADF was released in August 2010. OxyContin is a proprietary formulation of oxycodone hydrochloride.

Figure 2. Effect of Abuse-Deterrent Formulation (ADF) of OxyContin in Subsamples of Respondents



A, Respondents include 244 participants in the Researchers and Participants Interacting Directly (RAPID) study, of whom 153 endorsed one of the set responses to the question. B, Respondents include the 88 of 244 participants in the RAPID study who endorsed continued abuse of OxyContin and one of the set responses to the question. OxyContin is a proprietary formulation of oxycodone hydrochloride.

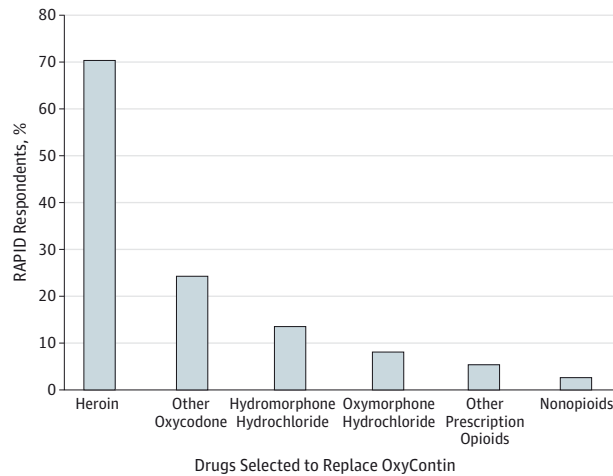
phone use, no other significant changes were observed in any other opioid classes included in the SKIP survey. Although 10 of the 26 RAPID participants (38%) indicated that the transition to heroin was motivated by a desire for a more intense high given tolerance to prescription opioids, by far the most common response (17 of 26 [65%]) was that heroin was the practical alternative because it was more readily available and cheaper than other opioid analgesics. The following quotations from RAPID participants illustrate this point.

“Price and heroin is more consistently available; also, once one leaves the stigma of prescription vs street drugs behind [as many addicts do], the question becomes more purely economic/pragmatic, ie, what will keep me from withdrawal right now?”

“Became easier to find heroin than good Oxys. Also, heroin was cheaper.”

“I heard heroin would get me higher and was cheaper, and when the Oxys changed, so did my choice of drug.”

Figure 3. Drugs Used to Replace OxyContin After the Introduction of the Abuse-Deterrent Formulation (ADF)



Data show the drugs used by the 51 participants in the Researchers and Participants Interacting Directly (RAPID) study sample in response to the question, "What drugs did you replace OxyContin with?" Because multiple drugs were used, percentages total more than 100. OxyContin is a proprietary formulation of oxycodone hydrochloride.

Discussion

The results of this study show that ADF OxyContin successfully reduced abuse of the active drug (ie, oxycodone), particularly in those who relied on tampering for injected or inhaled abuse. However, although survey responses indicated a time-related drop in the past-month abuse of OxyContin in the 12 to 18 months after the ADF's introduction, this steep decline leveled off such that a relatively large percentage (25%-30%) of those entering treatment with a diagnosis of opioid dependence from 2012 through 2014 persisted in abusing the new formulation. Based on results from our interviews in the RAPID sample, the initial decline in abuse appears to be related to a shift away from OxyContin to another opioid, particularly heroin, whereas the residual abuse appears to reflect the following 3 factors: (1) a sizeable percentage of OxyContin abusers simply changed their preferred route of administration from injected or inhaled to the oral route; (2) another sizeable percentage managed to defeat the ADF OxyContin mechanism and continued to inject or to inhale the drug; and (3) many abusers swallowed the pill and were not affected by the change in formulation. Thus, the ADF appears to have been effective in deterring at least some abuse, which led the US Food and Drug Administration to allow the manufacturer to include a discussion of abuse-deterrent properties in the package insert, the first for any such product.⁴

Contrary to other reports,^{15,16} our data demonstrate that the use of heroin increased markedly among our respondents as a direct result of the introduction of ADF OxyContin. However, the increases in the use of heroin during the past 4 years noted by other epidemiologic surveys^{17,18} cannot be related solely to the discontent with ADF OxyContin. Specifically, after a sharp rise in the year after the ADF's introduction (11.0%), past-

month heroin use continued to increase steadily, albeit at a somewhat slower pace (mean, 2.5% per half-year from 2012 through 2014) even when OxyContin abuse leveled off, suggesting some independence of these two phenomena. More important, other investigators¹⁹⁻²³ have shown that many prescription opioid abusers, no matter their drug of choice, are turning to heroin as a cheaper and far more accessible alternative. Our data suggest that the introduction of ADF OxyContin may have hastened this transition in some individuals. This change is a matter of considerable concern from a public health perspective given the toxicity of heroin in terms of overdose deaths, problems associated with injection and the transmission of infectious disease, crime, and so forth.

A fairly large percentage of OxyContin abusers reported they were able to defeat ADF OxyContin and continued to inject and to inhale it. However, given the highly sophisticated Internet websites that were noted by some of our RAPID participants, this finding should not be unexpected. With that stated, the work required to perform the extraction could ultimately become so significant that many abusers would conclude that the effect is not worth the effort and simply shift to a different route of administration or a different drug. In reality, this finding is the best possible outcome for any ADF. That is, all drugs intended for oral use need to be soluble in the gut, and thus it seems clear that ADFs will have little effect on those who simply take a drug orally, although pharmaceutical firms are using antagonists, for example, as one way to discourage even oral routes of abuse. Nevertheless, our data must not be misconstrued as evidence against the concept of ADFs because ADFs can be effective in reducing harmful abuse patterns. This finding greatly improves the risk-benefit ratio for opioids in the appropriate therapeutic treatment of pain.

One area not examined in our study and previous publications, most of which focus on abuse, is how ADFs might affect physician or patient acceptance. The argument can be made that ADFs should increase the use of these formulations by physicians because the potential for abuse would decrease. However, limited evidence for this argument exists, and we speculate that the focus on the ADF may evoke a reluctance to use OxyContin because of its obvious and now clearly defined potential for abuse.

Whether other, more improved ADFs currently under development might discourage any abuse or misuse of opioids remains to be determined. We hope that pharmaceutical firms can devise future ADFs that are even more tamper resistant than the current ADF OxyContin. In all probability, no perfect ADF exists that will discourage a small core of individuals from abusing any opioid with a potential for abuse. However, we can predict that as options to tamper with prescription opioids are reduced, some percentage of users will be discouraged from any nonmedical use of prescription opioids. The major concern, of course, remains that these formulations may cause some individuals to use heroin instead, but this change seems to be an unavoidable consequence involving a small number of vulnerable individuals. This consequence does not imply that efforts to reduce the heroin supply should cease; rather, as long as a demand exists, it will be met.

This study has important limitations. Our treatment-based sample has unknown generalizability to non-treatment-seeking or recreational users. Furthermore, people seek treatment for a variety of reasons (eg, family pressure, court

mandate), and individuals who seek treatment for different reasons may differ from our population in important ways. Moreover, some self-selection in the treatment centers that elected to participate in the SKIP and RAPID programs compared with those that did not may apply. In addition, we selected participants whose primary drug was an opioid. Other polysubstance abusers who only occasionally use opioids may react differently to the introduction of ADF OxyContin. We cannot ignore that the RAPID sample, which was limited to participants with an Internet connection and introduced potential bias, was much smaller than the SKIP sample and may have inaccurately captured results that a much larger sample may not. Finally, although some users who initially swallow their drugs will change to injected or inhaled routes, as noted in the literature,^{19,20,23}

our data give no indication as to whether ADF OxyContin curtailed such transitions—a potentially very important consequence of ADFs that should be examined in future studies.

Conclusions

Abuse-deterrent formulations have the intended purpose of curtailing abuse, but their effectiveness has clear limits, resulting in a significant level of residual abuse. Consequently, although drug abuse policy should focus on limiting supplies of prescription analgesics for abuse, including ADF technology, efforts to reduce supply alone will not mitigate the opioid abuse problem in this country.

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