ORIGINAL RESEARCH

Abuse-Deterrent Opioids: A Survey of Physician Beliefs, Behaviors, and Psychology

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ABSTRACT

Objective: Evaluate beliefs and behaviors pertaining to abuse-deterrent opioids (ADFs).
Design: Survey in 2019 by invitation to all licensed physicians.
Setting: Commonwealth of Kentucky.
Participants: 374 physicians.
Methods: Descriptive statistics, and hypothesis test that early adopter prescribers would have greater endorsement of opioid risk management.
Results: Of all prescribers, 55% believed all opioid analgesics should have ADF requirements (15% were unsure); 74% supported mandating insurance coverage. Only one-third considered whether an opioid was ADF when prescribing, motivated by patient family diversion (94%) and societal supply reduction (88%). About half believed ADFs were equally effective in preventing abuse by intact swallowing, injection, chewing, snorting, smoking routes. Only 4% of OxyContin prescribers chose it primarily because of ADF properties. Instead, the most common reason (33%) was being started by another prescriber. A quarter of physicians chose not to prescribe ADFs because of heroin switching potential. Early adopters strongly believed ADFs were effective in reducing abuse (PR 3.2; 95% CI 1.5, 6.6) compared to mainstream physicians. Early-adopter risk-management practices more often included tools increasing agency and measurement: urine drug screens (PR 2.0; 1.3, 3.1), risk screening (PR 1.3; 0.94, 1.9). While nearly all respondents (96%) felt that opioid abuse was a problem in the community, only 57% believed it was a problem among patients in their practice. Attribution theory revealed an externalization of opioid abuse problems that deflected blame from patients on to family members.
Conclusions: The primary motivator for prescribing ADFs was preventing diversion by family members, not patient-level abuse concerns.

Keywords: Abuse-deterrent formulations (ADF); Drug abuse; Opioids; Epidemiology; Pain management; Survey

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Key Summary Points

Why carry out this study?

Decisions by physicians and other practitioners directly impact which patients receive "abuse-deterrent formulations" (ADF) opioids versus a traditional formulation.

Identification of factors that influence prescribing ADFs is critical in informing clinical guidelines and policymaking.

What was learned from this study?

The decision to prescribe an ADF opioid was rarely their tamper-deterring properties.

The motivation to write for ADFs was more about diversion by family members and broad societal concerns, and less related to individual patient characteristics.

Physicians who were early adopters to new medicines might have more restrictive pain management practices, having an impact on early REMS assessments for new opioid analgesics.

INTRODUCTION

One response to societal concerns about prescription opioid abuse has been the development and approval of opioid analgesic products designed to be harder to tamper with or manipulate, with the intention of reducing abuse by non-oral routes [1]. These so-called "abuse-deterrent formulations" (ADFs) are intended to make certain types of abuse, such as crushing to snort or dissolving to inject, more difficult or less rewarding [2–4]. Despite the stated intent of the technology and enduring concern about opioid analgesic prescribing, ADF utilization remains low. ADFs comprise only 8.2 out of 1000 adult opioid recipients in

Kentucky, and about twice that rate in Florida [5]. As the healthcare community works to improve its stewardship of opioid analgesics, there has been considerable academic and regulatory debate about the role of ADFs in pain management [2, 3, 6–13]. The academic and regulatory discussions have three generally unresolved issues: whether ADFs can prevent overdose deaths during therapy, whether ADFs prevent iatrogenic addiction over longer periods of time, and if societal ADF availability has been partially responsible for the dramatic increases in overdose from heroin and unregulated fentanyl.

In the clinical setting, decisions by physicians and other practitioners directly impact which patients receive ADF opioids versus a traditional formulation. The identification of factors that influence ADF prescribing is critical in informing clinical guidelines and policymaking. Nearly all dispensed ADFs are extended-release opioids, a class of medications that have been relegated to second- or third-line therapy through clinical guidelines, state laws, and insurer requirements.

Studies on ADF utilization are limited. In February 2021, the only ADFs available in the United States were extended-release opioids, a class of medications that have additionally been targeted for prescribing reduction by myriad non-pharmaceutical interventions. Extended-release opioid prescribing has declined dramatically from its peak in 2010 [14]; in 2019 they comprised only 9% of all opioid analgesic prescriptions, with ADFs only representing 2% [15]. Extended-release oxycodone formulations comprised 78% of the ADF market [5] with OxyContin® and Xtampza® with the largest shares [16]. In one study from New York City, 14% of oxycodone 80 mg recipients discontinued opioid use, while 40% switched to a different opioid after the reformulation of OxyContin 80 mg in 2010 [17]. Another early extended-release ADF was EMBEDA® (morphine sulfate and naltrexone hydrochloride extended-release), which was discontinued in 2019 [18], while others were approved but never launched. Further characterization of ADF use in clinical practice bears scrutiny, especially investigations

that shed light on why these opioid formulations are (or are not) prescribed.

A few studies have examined prescriber perceptions about properties intended to deter abuse [19]. In a 2010 survey of physicians, board certification in pain medicine and higher in-practice opioid use were associated with willingness to prescribe tamper-resistant opioids [20]. A 2014 survey reported that half of respondents believed that ADFs were "less addictive" than traditional formulations [21]. Perceptions about tamper-deterrent properties were also assessed among people who use drugs nonmedically prior to the advent of modern ADFs [22]. However, no recent survey that we are aware of has probed ADF-prescribing motivations.

After an elapsed decade for market maturity and changes to opioid prescribing norms, there is a need to better understand the drivers of ADF utilization. ADF utilization is strongly influenced by health insurance plan coverage [23], and they generally have higher costs than traditional formulations at the retail level [24, 25] and to the healthcare system [26]. Some states have legislation which requires third-party payers to have reimbursement parity between ADFs and traditional formulations. These and other undescribed factors silently impact which patients receive ADF opioids. Beyond clinical care, patient selection has a strong influence on how ADFs are evaluated in real-world data. If patients at higher risk for opioid abuse or overdose are preferentially placed on these newer medications, observational studies evaluating abuse in the community that compare ADFs to non-ADFs could be subject to a channeling bias or "confounding by indication" [27–29]. Therefore, there is a pressing need to understand the clinical decision-making process regarding ADF opioids.

The objective of our study was to assess physician experiences with prescribing ADF opioids, with an intent to inform the design of observational epidemiologic studies evaluating ADF effectiveness. We sought to answer fundamental questions about ADF prescribing: What factors influence a practitioner's decision to prescribe an ADF opioid versus a traditional formulation? How do state laws and health insurance coverage limit the use of ADF opioids? What are the perceived barriers to ADF prescribing?

In addition to reporting survey results, we tested one a priori hypothesis. Consistent with previous research [30], we hypothesized that early prescribers of new opioid medicines could be identified, and that early adopter status would be associated with more intensive opioid risk management practices. In our earlier study of national dispensing patterns, we noticed that new opioid analgesics were initially prescribed in locations that hosted phase III clinical trials for that product, tertiary care and teaching hospitals, and well-established advanced pain management clinics with multi-state catchment areas [30]. The hypothesis is also consistent with our previous analysis, where we found that early high-dispensing locations for new branded opioids was geographically concentrated and sometimes corresponded to phase 3 clinical trial sites [31], a phenomenon reported in a much earlier study [32] but given little attention until recently [33].

Finally, we situated the survey results using a relevant model from social psychology known as "attribution theory" [34–36]. Attribution theory is well established and explains the thinking processes for how individuals respond to observed phenomena by developing causal explanations. It has been previously applied to physician decision-making [37–39], including for opioids [40]. Applied here, it means that ADF perceptions are influenced by physicians trying to understand the causes of opioid abuse based on knowledge of their environment, and their role within it. In attribution theory, "locus of causality" describes the tendency of an individual to attribute *internal* or *external* causes in situations where etiology is ambiguous [39, 40]. In our study, the phenomenon being assessed by physicians is widespread problems with opioid abuse (e.g., the problem that ADFs purport to ameliorate). In clinical care, we conceptualize "internal" as within a given patient–physician encounter, such as patient demeanor, history, and clinical investigations. "External" is any factor outside that specific encounter, including the patient's family members, the healthcare system, and society

more broadly. This attribution style is important because it can predict motivational states such as empowerment (e.g., to prescribe ADFs), which formed the basis of a post hoc hypothesis test to assess the belief model's applicability.

METHODS

Summary

We conducted a cross-sectional survey of controlled substance prescribers in Kentucky, querying perceptions of experience prescribing ADFs. Descriptive statistics are reported, along with one a priori hypothesis test and a post hoc analysis.

Questionnaire Development

Literature searches in the summer of 2019 for validated questionnaires regarding ADF prescribing behaviors returned no results. Novel questionnaire development was undertaken with input from the FDA and informed by the team's experience. The questionnaire and code book are publicly available [41]. The instrument contained seven sections:

1. Perceptions of ADF opioids: Familiarity with ADFs, whether all opioids should be ADFs, route-specific deterrence.
2. Experiences prescribing brand name opioid medications: ADF prescribing frequency, factors influencing prescribing decisions.
3. Communication with patients and pharmacists about ADF opioids: patient requests/ recommendations from pharmacists for ADF prescriptions, requests/recommendations to substitute non-ADFs for ADFs.
4. Third-party payer requirements for ADF opioids: prior authorization requirements, third-party coverage mandate legislation.
5. Perceptions of opioid misuse/abuse: Extent of drug abuse in community and practice, deterrence by route of administration, interventions that are perceived to be effective.
6. Practice setting: Respondent gender, medical specialty, years in practice, location (county), practice setting, practice volume.

7. Opportunity to provide additional thoughts on survey topics: Free text.

Questions were mostly structured as multiple-choice questions, with opportunities for free text clarification. Four-point scales, with an option for unsure, were the primary construct based on our experience with earlier successful surveys in this population [42–44]. Coding conventions are provided in Appendix Section 2.

Respondents were asked specifically about the five ADF opioids commercially available at the time of survey: EMBEDA®, Hysingla® ER, MorphaBond® ER, OxyContin®, and Xtampza® ER. With the exception of an eligibility screening question which asked if the respondent prescribed opioid analgesics, all questions were voluntary. Reasons for prescribing or not prescribing an ADF were also queried. The questionnaire was designed to provide a comprehensive and nuanced view of ADF prescribing decisions.

The final questionnaire and codebook (including skip patterns) have been publicly archived [41]. The questionnaire and recruitment methodology were reviewed by the White House Office of Management and Budget (OMB) for compliance with the Paperwork Reduction Act. Requested changes were made, and the final survey is registered as OMB Control Number 0910-0847. Study data were collected and managed using REDCap electronic data capture tools [45, 46] hosted at the University of Kentucky. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources.

Definitions

Early adopter status was defined by any positive response to the following prompts: "I prescribe

new medications before others do" or "I like being able to share with colleagues about new medications I've prescribed" or "I like the variety of prescribing new medications." Instead of a single question, these constructs probed different dimensions of what it means to be an early adopter. Pairwise correlation was assessed by the Pearson product-moment correlation coefficient.

Sampling Frame and Recruitment

The sampling frame was all physicians who resided and held active medical licensure in Kentucky in 2019. Physicians were recruited in partnership with the Kentucky Board of Medical Licensure (KBML). The initial e-mail invitations were sent from KBML with a note encouraging participation on November 19, 2019, and two reminder e-mails sent 1 and 2 weeks following the initial request. Responses were collected over a 4-week period, November 19, 2019 to December 16, 2019. Participants were informed that their response to the survey was anonymous; neither the researchers nor the KBML will know who did, or did not, respond to the survey; and the research team would not attempt to identify or contact respondents. No incentive was offered for survey completion. Statistics on the numbers of e-mails sent and delivered were provided by the KBML.

Survey Completion Analysis

Incomplete questionnaires are an anticipated concern with online surveys. Before analyzing response content, we first conducted an analysis of missing data and survey completion. There were 686 responses to the survey, of which 480 met criteria for opioid prescribing eligibility. Analysis of incomplete surveys was conducted by examining drop-off in responses during the initial questions; time-to-abandonment metadata suggested the bulk of attrition occurred in the first few minutes of the survey. Sequential response analysis confirmed that attrition stabilized after the seventh question, leading to the exclusion of incomplete surveys with seven or fewer questions answered. Our analysis

yielded an analytic sample of $n = 374$, summarized in Fig. 1. Residual non-response was not associated with ADF familiarity (χ^2 7.6, 4 df, $p = 0.11$), and therefore for the intent of this analysis is assumed to be random. Details are provided in Appendix Section 1.

Analytic Methods

Quantitative assessment was assessed by six survey sections: (1) Respondent characteristics were analyzed using descriptive statistics, with a focus on practice settings and clinical experience; (2) Beliefs about opioid misuse/abuse problems in the community and in-practice were analyzed descriptively to provide context for further responses; (3) To analyze beliefs about ADFs we combined Agree and Strongly Agree and compared across medical specialty and practice setting; (4) Prescribing decisions were analyzed using descriptive statistics, combining Some influence and Great Influence categories; (5) Patient preferences; and (6) Communications with pharmacists were reported using dichotomous (yes/no) outcomes.

Quantitative analyses of across-group differences were analyzed using two-sided χ^2 or Fisher exact tests. Free text responses of ADF beliefs (Section 3 in the list above) were reviewed for thematic concordance with the concepts queried in the quantitative survey. We extracted exemplary responses to complement quantitative survey responses and allow us to represent respondents' beliefs with greater nuance and fidelity. In reporting verbatim text, we utilize italics for our added emphasis to highlight the relevant concept.

A Priori Hypothesis Testing

The early adopter hypothesis was tested using prevalence ratios (PR) and 95% confidence intervals, comparing self-described early adopters to mainstream prescribers. Prevalence ratios are a relative metric, and are calculated by dividing the proportion of beliefs in two populations. We tested for differences in perceptions of ADF effectiveness, ADF prescribing behaviors, and opioid risk management practices.
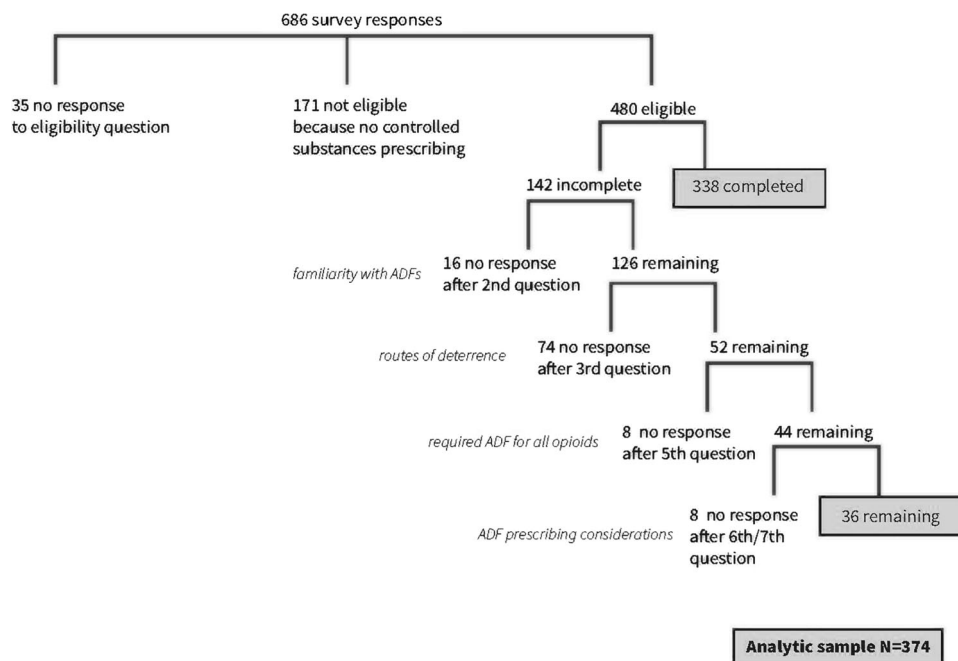
Fig. 1 Study participant flow diagram accounting for survey completion. *Shaded boxes* indicate the final analytic sample. *ADF* abuse-deterrent formulation

Post Hoc Analysis

We also conducted a post hoc analysis test to evaluate if attribution theory is an appropriate belief model to explain ADF beliefs among physicians, using likelihood ratio Chi-squared tests. Beliefs about opioid misuse/abuse problems in the community and in-practice were analyzed descriptively to provide context for further responses. In our post hoc analysis, we separately analyzed physician specialties that treat the consequences of individual level drug use harm (e.g., emergency medicine, psychiatry, addiction medicine). We computed prevalence ratios (PR) and 95% confidence intervals, comparing these specialties against all others.

Responses were analyzed using Stata MP (version 16, College Station, TX, USA). All code used in the analysis is available in the Appendix in the form of a Jupyter Notebook. The notebook was also used for quality control, with all underlying numbers for figures and results provided in Appendix Sections 3 and 4, respectively.

Ethics Review

This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. The project was reviewed by the University of Kentucky Medical Institutional Review Board (Protocol # 47958). A cover letter containing elements of informed consent was presented on the first screen of the survey using language approved by OMB; consent to participate was implied by participants who accessed the survey questionnaire. No identifying information or linkages to either respondent e-mail addresses or Internet protocol (IP) addresses were retained.

RESULTS

Respondent Characteristics

E-mails were delivered to 7631 physicians, with 686 respondents, for a response proportion of 9.0%. After accounting for eligibility and attrition, the analytic sample was *n* = 374 (Fig. 1).

This sample included representation across a spectrum of practice experience and setting. The respondents were 59% male ($n = 221$), reflecting historical professional trends in Kentucky. About 10% of respondents did not complete questions about personal and professional characteristics ($n = 38$). Years in practice were evenly distributed through the career-span, from less than 5 years (11%) to longer than 35 years (17%). Respondents ($n = 336$) were evenly distributed in practice settings, with major groups being: 16% hospital-based practice, 13% emergency departments, 12% academic practice, 12% large group private practice, 11% small group private practice (five or fewer clinicians), 10% solo practice, and 8% hospital inpatient service. Respondents were mostly in active clinical practice, with half seeing 50–100 patients per week, with 13% at higher volumes. The most common specialties were: family medicine (19%), internal medicine (13%), emergency medicine (13%), obstetrics and gynecology (7%), general surgery (5%), orthopedic surgery (5%), and pain medicine (3%). We received responses from 61 out of 120 Kentucky counties. As expected, the three most common counties of practice included the cities of Louisville, Lexington, and southern Cincinnati suburbs, combining for 41% of the sample.

Physician Beliefs

The most common route of administration for misuse/abuse was believed to be swallowing intact (40%), followed by injection (18%), snorting (11%), chewing (8%) and smoking (1%), with 27% unsure. Eight-out-of-ten prescribers said they were familiar with ADFs (Fig. 2a). A quarter believed that ADFs were effective in preventing abuse by *all* routes, and about a third were unsure (Fig. 2b). The greatest uncertainty (46%) was whether ADFs deterred smoking of tablets.

About half of prescribers (55%) believed that all opioid analgesics should be required to have abuse-deterrent properties and marketing statements approved by the FDA (Fig. 2c). About 15% were unsure. We provide exemplary free text responses that provide context and nuance in the prescribers' own words. When asked to elaborate, many strong supporters spontaneously reframed the issue as a question: "Why not if the technology exists?" and "Why should we not try to prevent abuse?" Among supporters, we found a belief that ADFs were not an imposition to patients: "It is a common-sense safety mechanism. It in no way harms or inconveniences patient using narcotics appropriately." Some respondents also invoked corporate responsibility: "Pharmaceutical companies should put more effort and money to fight the opioid epidemic."

In contrast, some free text responses displayed concerns about patient cost that were often paired with questioning effectiveness: "These formulations are abused at the same rate as other opioids in my community and are a waste of time and money." and "Unfortunately, unless the technology to do abuse-deterrent drugs improves, they are not currently effective enough to justify the cost." The belief that ADFs are a technical solution to a societal problem was encapsulated by one respondent in the extreme: "Excessively burdensome, expensive, using a bazooka to kill a gnat." While infrequently mentioned, one clinical rationale for opposing universal ADFs was: "Immediate-release opiates need to be able to be crushed and dissolved to be continuously effective for my hospice patients as they decline and cannot tolerate full tablets." Another physician also warned: "If abuse-deterrent formulations were mandatory for all opioids, then we would help further escalate the opioid crisis in our country." Quantified response to cost considerations are illustrated in Fig. 3 and described in the next section.

Support for a universal ADF labeling requirement was highest in medical specialties where negative consequences of opioid addiction manifest: emergency medicine (χ^2 5.1, 1 *df*, $p = 0.02$) and addiction/psychiatry (χ^2 2.7, 1 *df*, $p = 0.11$). Among practice settings, respondents in hospital-based clinic supported ADF labeling disproportionately more (χ^2 4.6, 1 *df*, $p = 0.03$).

Three-quarters (73.6%) supported state legislation mandating third-party coverage for ADFs. Some supporters of ADF reimbursement parity framed their belief in terms of societal
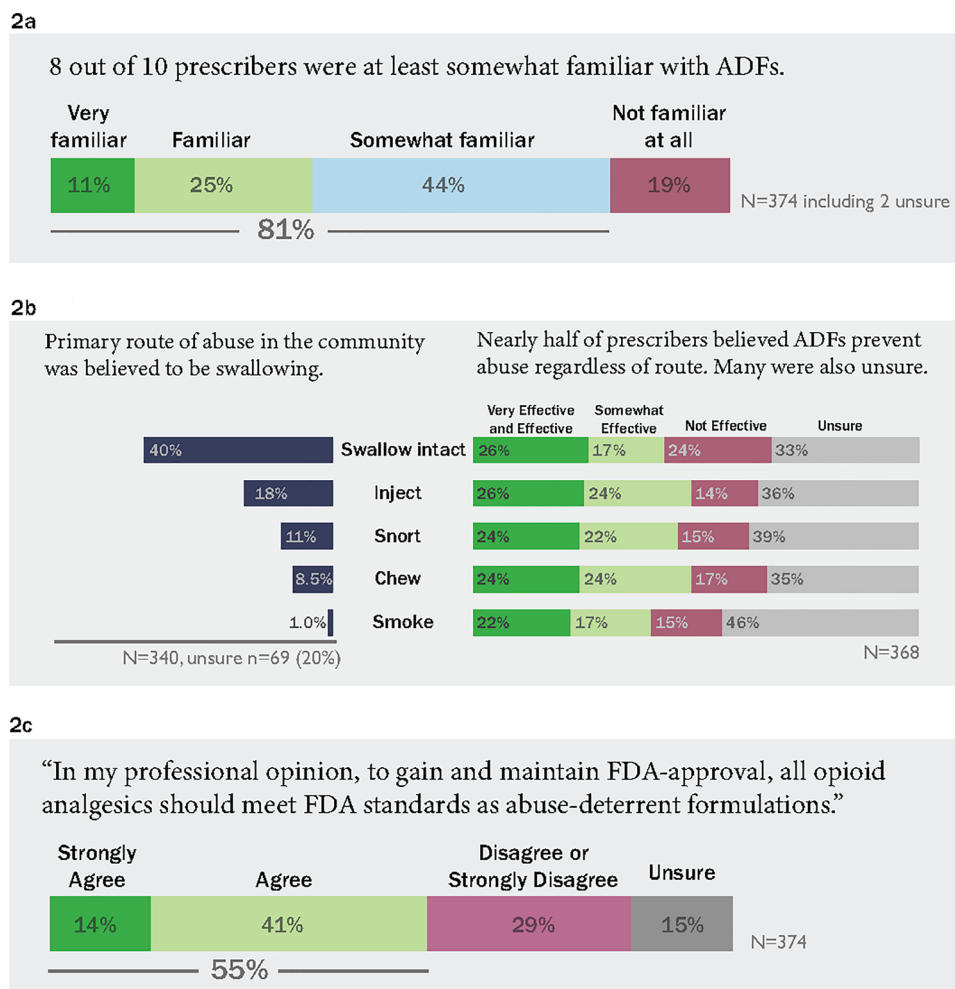
2a

8 out of 10 prescribers were at least somewhat familiar with ADFs.

Very familiar	Familiar	Somewhat familiar	Not familiar at all
11%	25%	44%	19%

N=374 including 2 unsure

———— 81% ————

2b

Primary route of abuse in the community was believed to be swallowing.

Nearly half of prescribers believed ADFs prevent abuse regardless of route. Many were also unsure.

		Very Effective and Effective	Somewhat Effective	Not Effective	Unsure
40%	Swallow intact	26%	17%	24%	33%
18%	Inject	26%	24%	14%	36%
11%	Snort	24%	22%	15%	39%
8.5%	Chew	24%	24%	17%	35%
1.0%	Smoke	22%	17%	15%	46%

N=340, unsure n=69 (20%)   N=368

2c

"In my professional opinion, to gain and maintain FDA-approval, all opioid analgesics should meet FDA standards as abuse-deterrent formulations."

Strongly Agree	Agree	Disagree or Strongly Disagree	Unsure
14%	41%	29%	15%

N=374

———— 55% ————

Fig. 2 Eight-out-of-ten prescribers said they were familiar with ADFs. **a** Physician familiarity of abuse-deterrent formulations. The most common route of administration for misuse/abuse was believed to be swallowing intact (40%), followed by injection (18%), snorting (11%), chewing (8%) and smoking (1%), with 27% unsure. A quarter believed that ADFs were effective in preventing abuse by all routes, and about a third were unsure. **b** Physician beliefs about routes of deterrence. The greatest uncertainty (46%) was whether ADFs deterred smoking of tablets. **c** Physician opinion on regulatory requirement

responsibility: "*Society created problem* and epidemic requires all parties involved to take accountability for creating it and responsibility for working to reduce the problem." This contextual perspective led to support for *any* measures to prevent abuse: "If it helps prevent even one addiction then it is worth it." Concisely stated: "I will support any effort to deter opioid abuse." Another common theme for supporting pay parity was patient cost, eloquently stated: "You can't ask people to buy that which they can't afford."

In contrast, some physicians opposed to third-party payer requirements for parity in ADF reimbursement couched comments in terms of practice autonomy: "Legislation never helps, only hinders. Keep government out of medicine!" and "Least government is best government." Increasing scrutiny on pain management manifested: "Too many problems with state mandates by people who have no damn clue what they are doing and don't care about the real end result." Simply stated: "Doctors prescribe not legislators." Some
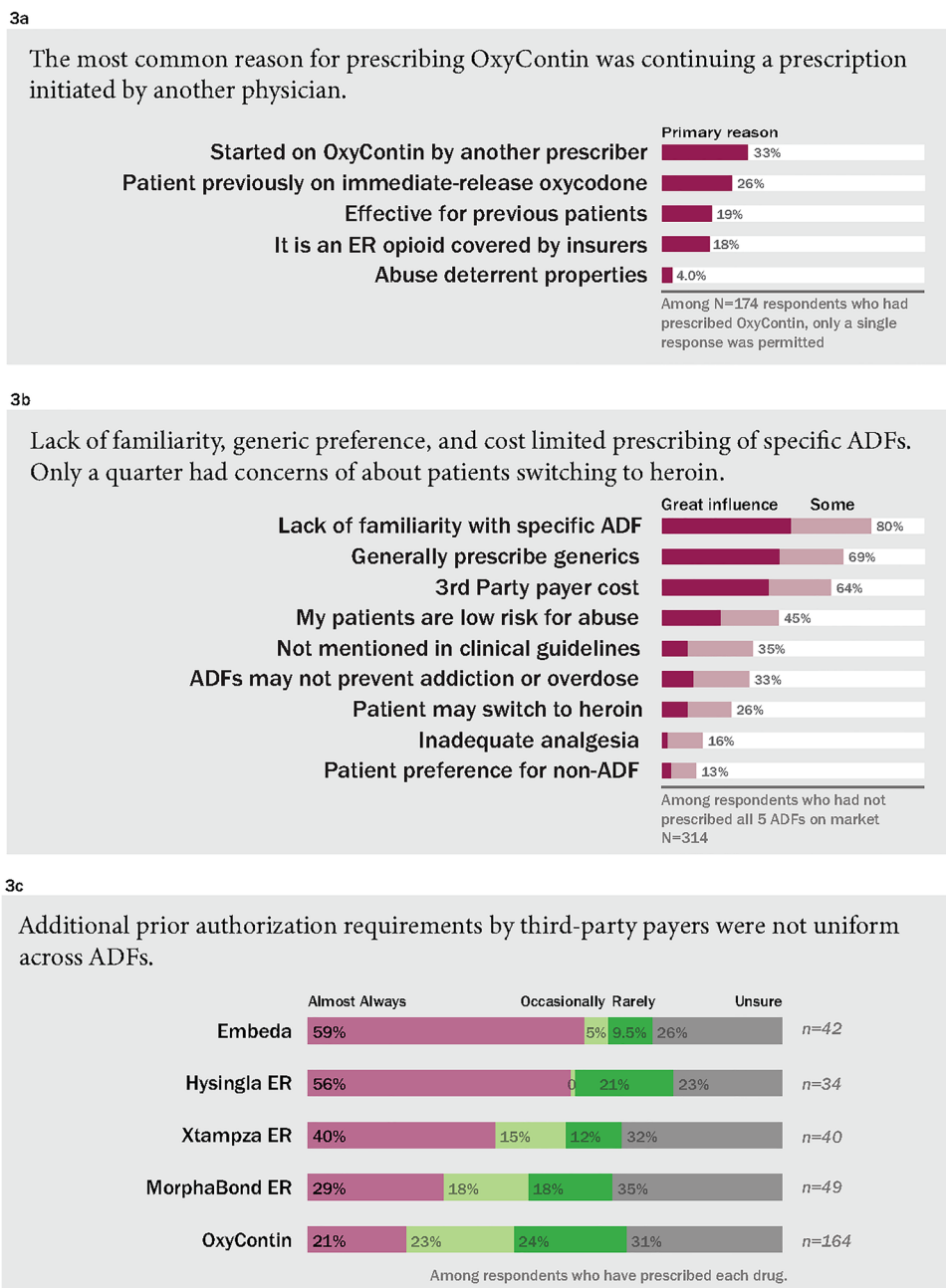
3a

The most common reason for prescribing OxyContin was continuing a prescription initiated by another physician.

Primary reason

Started on OxyContin by another prescriber	33%
Patient previously on immediate-release oxycodone	26%
Effective for previous patients	19%
It is an ER opioid covered by insurers	18%
Abuse deterrent properties	4.0%

Among N=174 respondents who had prescribed OxyContin, only a single response was permitted

3b

Lack of familiarity, generic preference, and cost limited prescribing of specific ADFs. Only a quarter had concerns of about patients switching to heroin.

Great influence   Some

Lack of familiarity with specific ADF	80%
Generally prescribe generics	69%
3rd Party payer cost	64%
My patients are low risk for abuse	45%
Not mentioned in clinical guidelines	35%
ADFs may not prevent addiction or overdose	33%
Patient may switch to heroin	26%
Inadequate analgesia	16%
Patient preference for non-ADF	13%

Among respondents who had not prescribed all 5 ADFs on market N=314

3c

Additional prior authorization requirements by third-party payers were not uniform across ADFs.

	Almost Always		Occasionally	Rarely	Unsure	
Embeda	59%		5%	9.5%	26%	n=42
Hysingla ER	56%		0	21%	23%	n=34
Xtampza ER	40%	15%	12%		32%	n=40
MorphaBond ER	29%	18%	18%		35%	n=49
OxyContin	21%	23%	24%		31%	n=164

Among respondents who have prescribed each drug.

Fig. 3 Reasons for not prescribing abuse-deterrent formulation. Percentages in **b** represent the total among respondents report some or great influence. In **c**, ten respondents who had prescribed OxyContin did not respond to the question. *ADF* abuse-deterrent formulation

respondents also wanted more community-based scientific evidence: "More unbiased evidence needed." and "Would need to see the data that it's highly efficacious." Distrust of the pharmaceutical industry was evident: "Money should be spent addressing addiction issues and not coming up with new opioids. We have opioids that work, new medications in this class only benefit the drug companies." and "Talk about a waste of time and just another avenue that pharmaceutical companies are trying to create to increase revenue streams." Yet, there

was also explicit support for capitalism: "I think government should allow companies to function in a free market without interference."

Prescribing Decisions

Only about one-third ($n = 130$) of prescribers considered whether an opioid was an ADF when making a prescribing decision. Among them, concern about diversion by the patient's family was ubiquitously (93.8%) cited as a reason to preferentially prescribe an ADF, encapsulated by one physician: "Frail, elderly cancer patients are vulnerable to younger family members trafficking and use." At the time of survey development, OxyContin was the most commonly prescribed ADF opioid nationally, leading us to probe specific motivations. When OxyContin prescribers ($n = 174$) were asked why they chose this product, only 4% cited its ADF properties primarily (Fig. 3a). Instead, the most common reason for prescribing OxyContin (33%) was that the patient had been started on it by another prescriber.

Among those who had not prescribed ADFs on the market, the most common reason (80%) was lack of familiarity about specific ADFs (Fig. 3b). Nearly half (45%) felt their patients were low risk for opioid abuse or misuse.

Interestingly, concerns that ADFs might push patients to heroin manifest in different ways among ADF prescribers and non-prescribers. For physicians who did not prescribe an ADF, heroin transition was cited by a quarter (26%) of respondents as a reason for *not prescribing* (Fig. 3b). On the other hand, among those who already prescribed ADF opioids, 80% said that their decision *to prescribe* was influenced by preventing switching to heroin. Considered together across the population, the same medications could be perceived as a retardant or an accelerant of illicit opioid use.

External Communications

Only 9.6% of respondents recalled a specific request for an ADF by a patient. Among those who did ($n = 33$), patient reasons for requesting an ADF were their own medical history (58%),

belief that ADFs were safer alternatives to non-ADF opioids (36%), concern about diversion by others (24%), with write-in responses: advertising, preferred dosing schedule, and inadequate analgesia with other formulations.

Among ADF prescribers, a quarter (25.4%) recalled a patient asking for a non-ADF instead. The most common stated reasons were cost and inadequate pain control. Side effects were also noted by patients "Reported EMBEDA made her sick", as well as "Fear of abuse and stigma." Interestingly, a preference against *generic* ADF extended-release oxycodone was given as: "They wanted a trademark."

Very few prescribers (2.3%) reported requests to switch a traditional formulation to an ADF by a pharmacist. A similarly low (3.8%) proportion reported being contacted by a pharmacist to switch an ADF to a non-ADF, mostly due to cost: In nearly every instance, patient cost led prescribers to capitulate.

ADF prescribing decisions were influenced by societal factors and the healthcare system, including prior authorization requirements by insurers (Fig. 3c). Among respondents who considered whether the opioid was an ADF when prescribing ($n = 117$), the public health impact of reducing the supply of abusable drugs was a motivating factor (87.9%), stated by a physician as: "Remove the abuse potential *from the streets*." Anecdotal influences by colleagues was found to have some (46%) but not great (6%) influence. Conversely, information from pharmaceutical sales representatives and medical liaisons were stated to have little or no influence by 8-out-of-10 prescribers. About 59% were influenced by abuse-deterrence technology being innovative.

Early Adopters

To test our a priori hypothesis, we identified prescribers who considered themselves quick to adopt pharmaceutical innovation (e.g., "I prescribe new medications before others"). One-in-five prescribers ($n = 81/374$) self-identified as early adopters. The three questions used to ascertain early adopter status had pairwise correlation coefficients of 0.11 to 0.14.

Early adopters were disproportionately in early or late career (less than 15 or 35 + years of practice). There were no differences in patient load or practice setting. Among medical specialty, emergency medicine and general surgery were less likely to be early adopters, and hematology/oncology and obstetrics/gynecology were more likely to be early adopters (Appendix Section 4 for details).

Members of the early adopter phenotype tended to believe ADFs were very effective in reducing misuse/abuse of opioids (PRR 3.2; 95% CI 1.5, 6.6) compared to traditional prescribers, and more supportive (PRR 1.3; 1.1, 1.4) of legislation for ADFs to be covered by insurance. They were generally more supportive that all opioids should be ADFs (PRR 1.5; 0.90, 2.6). Early adopters appeared somewhat more likely to prescribe non-OxyContin ADFs (PRR 1.4; 0.90, 2.2), but the association was less strong for ADFs as a composite class (PRR 1.1; 0.88, 1.4). Reinforcing construct validity, early adopters were twice as likely (PRR 2.0; 1.5, 2.5) to consider prescribing ADFs explicitly because they were innovative. Early adopter opioid risk management practices were also influenced by an appreciation for clinical tools that increased physician agency and returned empirical information. Early adopters were twice as likely to vehemently endorse urine drug screens (PRR 2.0; 1.3, 3.1) and use of opioid risk screening tools (PRR 1.3; 0.94, 1.9), for example. Conversely, early adopters were no more likely than traditional prescribers to endorse strategies that operated through fiat: pill counts, lock-in programs, and prescribing limits. Kentucky's longstanding prescription drug monitoring program was endorsed positively by early adopters and traditional prescribers equally.

Attribution Theory

That prescribing of ADFs could be explained by attribution theory seemed plausible, as the descriptive results suggest. Most respondents differentiated between opioid problems at the community level versus inside the medical setting. While nearly all respondents (96%) felt that opioid misuse/abuse was a problem in their community, only 57% agreed that it was a problem among patients in their practice. Emergency department physicians were more likely than those from other practice settings to say opioids were a problem among their patients, prevalence ratio [PR] 3.4 (95% CI 1.7, 6.8). One respondent summarized: "I practice emergency medicine, I prescribe short courses of opiates and *see the results of opioid abuse on a regular basis*." This statement reinforces our application of attribution theory whereby physicians in certain specialties are pre-disposed to having an internal locus of causality when it comes to opioid abuse.

While we did not query patients directly, physicians reported that patients' own medical histories drove the few who requested an ADF ($n = 33$) to do so based on their own medical history (58%).

In the context of attribution theory, among patients who requested an ADF, it is worth noting that this expression of the locus of causality was internal, e.g., based on their own past. Stated another way, these patients seemed to take responsibility for their own individual risk of opioid misuse. In contrast, physicians who considered ADFs often perceived the risk as external (e.g., family members and societal). However, this question was not asked in a way that would allow generalization to all patients.

Only about one-third ($n = 130$) of prescribers considered whether an opioid was an ADF when making a prescribing decision. Among them, concern about diversion by the patient's family was ubiquitously (93.8%) cited as a reason to preferentially prescribe an ADF, encapsulated by one physician: "Frail, elderly cancer patients are vulnerable to younger family members' trafficking and use." Turning back to attribution theory, the externalization of opioid abuse is clearly evident. As previously reported, removing abuse potential "from the streets" as a motivation for prescribing an ADF also suggests an external locus of causality.

Therefore, we proceeded to assess the belief model's applicability with a novel post hoc analysis. We hypothesized that medical specialties with an internal locus of causality (e.g., seeing patient-level abuse consequences) would minimize the practical logistical barriers to ADF

prescribing. This hypothesis is anticipated by the "empowerment" dimension of attribution theory, which states that those with an internal locus of causality are more likely to feel empowered to overcome obstacles [37]. We examined if physicians who saw the individual consequences of opioid abuse (emergency medicine and addiction/psychiatry) would be less likely to see third-party payer (insurance) considerations as an ADF prescribing impediment. Physicians in these specialties were much more likely to say that third-party considerations had "No influence" on ADF prescribing, 28.6% versus 7.3% (χ^2 8.6, 3 df, $p = 0.03$). They were also much less likely to say third-party payer considerations had "Great influence," 14.3% versus 36.8%.

An alternate interpretation of the findings could arise from less frequent use of ER opioids in emergency medicine and addiction/psychiatry. However, we found that physicians in these specialties prescribed most ADFs at similar frequencies as other specialties: EMBEDA (χ^2 1.2, 4 df, $p = 0.88$), Hysingla ER (χ^2 2.6, 4 df, $p = 0.62$), MorphaBond ER (χ^2 1.9, 4 df, $p = 0.58$), Xtampza (χ^2 2.1, 4 df, $p = 0.55$). The exception was OxyContin, which was prescribed less frequently (χ^2 12.4, 4 df, $p = 0.01$). Since physicians in these two specialties were less likely to prescribe OxyContin (but not other ADFs), we reanalyzed the hypothesis test by restricting to prescribers of non-OxyContin ADFs. The association with minimizing third-party barriers still held (χ^2 9.1, 3 df, $p = 0.03$). These findings provide a more nuanced view of attribution theory, but show that the underlying psychological observations are not solely due to prescribing variation.

DISCUSSION

Through this study, we offer detailed insight into beliefs and behaviors regarding abuse-deterrent opioids. Our results reveal two phenomena that have not been described previously. First, the decision to prescribe an extended-release was less often due to ADF properties and more often a passive continuation of OxyContin started by another

prescriber. Second, the motivation to write for ADFs was more about diversion by family members and broad societal concerns, and less related to individual patient characteristics. These observations should lead us to reconsider our conceptual model of why ADFs are prescribed, as less an individual patient-level decision and instead as a response to societal concerns. The subtle shift of focus away from the patient, and towards society, offers clues about possible underlying psychological processes and may explain the two following sets of observations in our survey. While we did not set out to formally test a belief model, we did ask questions about problems with opioid abuse in the community and practice settings, and perceptions about ADFs. Our application of the belief model ties these observations together, but the findings stand independent of a psychological explanation.

First, in free text responses, we found consistent externalization of opioid-abuse problems beyond the doctor–patient encounter. Among physicians who considered whether an opioid had abuse-deterrent properties when prescribing, diversion by family members was the top reason for considering them, by 94% of respondents. In free text replies, physicians made explicit mention of a responsibility to get opioids "off the streets" and that "society created [the] problem."

Our interpretation, based on attribution theory, is as follows: Since the decision to prescribe an opioid has already been made, the patient has provided enough credible signals to convince the physician that opioid abuse is not likely to be a problem in this particular encounter (internal). Yet, broad societal concerns with opioids are impossible to ignore, and in the decision to prescribe an ADF, the physician deflects away from the patient by attributing the blame for opioid abuse problems to external parties (family members).

Second, many physicians felt that opioid abuse was more a problem in their community rather than their practice. This is epitomized by a family medicine physician in small group practice with more than 25 years of experience. They wrote, "I live in KY. Abuse is rampant," but selected "Disagree" when shown the statement

"Misuse/abuse of prescription opioids is a problem among patients in my practice." We found that nearly half of physicians felt their patients were low risk for opioid abuse. In contrast, emergency department physicians were three times more likely to say that opioid abuse is a problem among their patients. The latter physicians were more supportive of a universal ADF labeling requirement.

Our interpretation is that internal/external locus of causality for the cause of opioid problems may help explain support for ADFs. Physicians who treat the individual consequences of drug abuse minimized the external barriers to ADF prescribing in the form of third-part payer considerations. These observations suggest that enthusiasm for ADFs is highest among physicians who have observed the immediate personal consequences of opioid abuse. Considering these two sets of observations together, physicians appeared to use an externally influenced heuristic [47]: If societal opioid abuse is believed to be a problem, but their past experience was that their patients did not exhibit problems with opioids, then the justification for using an ADF is concern about diversion by family members. Psychological belief models provide novel insights for opioid prescribing and new directions for research in pain management. Future studies would do well to further probe these psychological constructs, since this element of our analysis admittedly post hoc and exploratory. In particular, it may be beneficial to link attribution style with motivational states, such as empowerment [37]. The belief model suggests that empowered physicians may feel they have the ability to overcome insurance barriers, for example, which we found evidence to support. Expressions of practice autonomy could be intertwined with political leanings. We further posit that ADF prescribing is a two-step mental process, where first a decision to prescribe an opioid is made, and then whether to select an ADF is secondary. For example, it is unclear how consistently ADFs are prescribed by the same physician, and the attendant interactions between individual level and societal perceptions. We are currently preparing to test these concepts in more detail in an upcoming physician survey.

Independent of any specific belief model, our findings have consequences for epidemiologic investigations. In observational studies using claims data that evaluate ADF effectiveness to deter abuse in the community, concerns about channeling have been articulated based on risk stratification (e.g., patients at greater risk for abuse put on ADFs instead of traditional formulations) [2, 27–29]. However, the results of our survey and the underlying cognitive processes they expose, suggest a lower need for emphasis on patient-level characteristics that may predispose for abuse or overdose outcomes. Only 4% of prescribers cited labeled abuse-deterrent properties of OxyContin as the primary reason for prescribing. This has practical implications because predictive models of opioid abuse in claims data often rely on previous drug problem diagnoses [48]; they are high specificity and low sensitivity [49]. Since prescribers are less likely to make ADF-prescribing decisions based on individual patient characteristics, our results suggest that epidemiologic investigations using administrative data to assess ADF effectiveness at preventing abuse and overdose may be less subject to misclassification bias than feared initially.

In terms of the descriptive findings, our results are somewhat different from a survey of primary care physicians in 2014 [21]. In that study, swallowing whole was considered to be the primary route of abuse in 66% of respondents, whereas in our study it was 40%. However, unsure or non-response was not reported in the earlier study; if we ignore unsure and missing values, the percent in our study rises to 50%. Conversely, in the earlier study 9% of prescribers believed that injection was the primary route of abuse, whereas in our study it was 18% (ignoring unsure and missing it rises to 22.5%). It is unclear whether these are sample artifacts or a shift in beliefs over time.

Another notable result was that more than half of respondents believed that ADFs were somewhat-to-very effective in preventing abuse by intact swallowing. No ADF on the market has labeling to support this belief. Perceptions of abuse deterrence effectiveness were fairly

similar across injection, chewing, snorting, and smoking routes, again without explicit support in approved labels. About a third of respondents were unsure about route-specific deterrence claims, even though route-specific claims are the cornerstone of the regulatory framework [4]. In combination, these observations suggest the need for communication channels that go beyond labeling.

Our analysis of early adopter prescribers supports research from other countries [30] and may influence ADF evaluation. In Australia, prescribing mirrored the adoption of new technology outside of health care, with prescribers who were driven by internal motivators being early adopters, whereas later uptake was primarily influenced by colleagues [50]. In England, 42% of new drugs were prescribed by only 10% of physicians [51], and in Spain, specialists were faster to adopt the use of new drugs, while many non-specialists never prescribed them [52]. An analysis from Denmark suggested that early adopter practices do not necessarily extend across therapeutic drug classes [53]. While common to studies of technology uptake and marketing, the early adopter phenomenon has received little attention in health services research recently. We document that early adopters of novel analgesics endorsed more opioid risk management practices. A common narrative has been that nonmedical opioid use increased in the United States because outpatient extended-release opioids became more widely used by those without formal pain management credentials or specialization [54–57]. From the findings of this survey and our previous work [31], we propose a complementary hypothesis that early adopters may have different approaches to opioid risk management. If confirmed by further investigation, this observation may impact the interpretation of FDA-mandated assessments of Risk Evaluation and Mitigation Strategies (REMS) that occur 18 months and 3 years after launch [58].

Beliefs about the interplay between heroin and ADFs revealed two distinct positions. For physicians who did not prescribe an ADF, heroin transition was cited by a quarter (26%) of respondents as a reason for not prescribing

(Fig. 3b). On the other hand, among those who already prescribed ADF opioids, 80% said that their decision to prescribe was influenced by preventing switching to heroin. Considered together, the same medications could be perceived as a preventative or an accelerant of illicit opioid use.

We note the following limitations of our analysis. The response proportion in this unincentivized study was low and similar to our previous surveys in Kentucky [42–44], but lower than other surveys conducted nationally with more targeted sampling by medical specialty [20, 21, 59]. However, our population-based sampling frame was notably different in that it included all licensed physicians in a state. Yet, we did not include advanced practice providers who are responsible for significant opioid prescribing, because our primary focus was on physicians. We also did not have a validated instrument by which to assess the early adopter phenotype, and thus we present these findings as hypotheses for further investigation. We chose to report univariate and bivariate statistics because our sample size was not powered for adjusted modeling. While we could not quantitatively model effect estimates using multivariable adjustment, scrutiny of free text responses suggested a saturation of viewpoints across sub-groups. We also did not query patients directly in conjunction with their prescribers to more carefully disentangle the relative decision influences from both parties; this kind of analysis could be used to further refine our initial model. Finally, although we took measures to assuage concerns, we cannot preclude the possibility of respondent desirability bias of a survey funded by a regulatory agency and disseminated through a licensing authority. We note that the responses provided by respondents were internally consistent and reflect a range of viewpoints and criticisms of the same government entities and believe that the industry-independent nature of this research has importance.

Finally, there are reasons for caution in extrapolating our conceptual model to all ADFs broadly. First, since most ADF opioids dispensed are also extended-release formulations, we must consider the decision-making model: A fully

rational initial prescribing decision may have as a first step assessing whether an extended-release drug is necessary (e.g., as opposed to immediate-release), and a second step as to whether that extended-release product should be an ADF. Our study did not have query with enough nuance to separate these concepts, especially in light of clinical guidelines that place strong cautions on extended-release opioids. It is also unclear how common this decision model is in practice, or if alternate pathways should be considered. Second, since OxyContin was the most widely used product with an ADF designation during the study period, the intense historical and negative publicity around OxyContin *specifically* may confer resistance to ADFs more *generally*. We were unable to disentangle such synecdoche effects because of the relatively low use of the other ADFs.

CONCLUSIONS

This study revealed that ADF prescribing is motivated less by patient-level abuse concerns, but more by reducing diversion by family members and start supply in society. Limited attention has been paid to the psychology of opioid prescribing and potential impacts on observational studies and clinical care. Future studies can refine our model by combining community-level overdose data, news media, and measures of public and professional sentiment to elucidate a more complete picture of the patient, prescriber and environment level factors.

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Compliance with Ethics Guidelines. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. The project was reviewed by the University of Kentucky Medical Institutional Review Board (Protocol # 47958). A cover letter containing elements of informed consent was presented on the first screen of the survey using language approved by OMB; consent to participate was implied by participants who accessed the survey questionnaire. No identifying information or linkages to either respondent e-mail addresses or internet protocol (IP) addresses were retained.

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Prior Presentation. At the request of the funder, parts of this research were presented at the Food and Drug Administration Advisory Committee meeting on September 10, 2020. Slides from that presentation are available at https://www.fda.gov/media/141975/download, and a transcript is available at https://www.fda.gov/media/144165/download.

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