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Evaluation of the Extended-Release/Long-Acting Opioid Prescribing Risk Evaluation and Mitigation Strategy Program by the US Food and Drug Administration
A Review

James Heyward, MPH; Lily Olson, BA; Joshua M. Sharfstein, MD; Elizabeth A. Stuart, PhD; Peter Lurie, MD, MPH; G. Caleb Alexander, MD, MS

IMPORTANCE Extended-release/long-acting (ER/LA) opioids have caused substantial morbidity and mortality in the United States, yet little is known about the efforts of the US Food and Drug Administration (FDA) and drug manufacturers to reduce adverse outcomes associated with inappropriate prescribing or use. This review of 9739 pages of FDA documents obtained through a Freedom of Information Act request aimed to investigate whether the FDA and ER/LA manufacturers were able to assess the effectiveness of the ER/LA Risk Evaluation and Mitigation Strategy (REMS) program by evaluating manufacturer REMS assessments and FDA oversight of these assessments.

OBSERVATIONS The REMS program was implemented largely as planned. The FDA's goal was for 60% of ER/LA prescribers to take REMS-adherent continuing education (CE) between 2012 and 2016; 27.6% (88 316 of 320 000) of prescribers had done so by 2016. Audits of REMS programs indicated close adherence to FDA content guidelines except for financial disclosures. Nonrepresentative cross-sectional surveys of self-selected prescribers suggested modestly greater ER/LA knowledge among CE completers than noncompleters, and claims-based surveillance indicated slowly declining ER/LA prescribing, although the contribution of the REMS to these trends could not be assessed. The effectiveness of the REMS program for reducing adverse outcomes also could not be assessed because the analyses used nonrepresentative samples, lacked adequate controls for confounding, and did not link prescribing or clinical outcomes to prescribers' receipt of CE training. Although the FDA had requested studies tracking adverse outcomes as a function of CE training, the FDA concluded that these studies had not been performed as of the 60-month report in 2017.

CONCLUSIONS AND RELEVANCE Five years after initiation, the FDA and ER/LA manufacturers could not conclude whether the ER/LA REMS had reduced inappropriate prescribing or improved patient outcomes. Alternative observational study designs would have allowed for more rigorous estimates of the program's effectiveness.

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Invited Commentary
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Author Affiliations: Center for Drug Safety and Effectiveness, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland (Heyward, Olson, Sharfstein, Alexander); Office of Public Health Practice and Training, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland (Sharfstein); Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland (Stuart); Center for Science in the Public Interest, Washington, DC (Lurie); Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland (Alexander); Division of General Internal Medicine, Johns Hopkins Medicine, Baltimore, Maryland (Alexander).

Corresponding Author: G. Caleb Alexander, MD, MS, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 N Wolfe St, Room W6035, Baltimore, MD 21205 (galexan9@jhmi.edu).

In 2016, an estimated 2.1 million Americans had prescription opioid use disorder.[1] In 2017, almost 50 000 individuals in the United States died of opioid overdoses, the most of any year on record.[2,3] More than 40% of these deaths involved a prescription opioid, and most people who used heroin and illicit fentanyl reported that their first opioid was a prescription opioid.[4,5]

Extended-release/long-acting (ER/LA) opioids, such as long-acting formulations of oxycodone and morphine, accounted for almost one-third of opioid volume (morphine milligram equivalents) dispensed in 2016 in the United States.[6] Although ER/LA drugs can be clinically useful among appropriately selected patients, they have also been widely oversupplied, are commonly used nonmedically, and account for a disproportionate number of fatal overdoses.[7-9]

In June 2012, because ER/LA opioids were associated with greater risk of addiction, unintentional overdose, and death than their immediate-release counterparts, the US Food and Drug Administration (FDA) mandated a Risk Evaluation and Mitigation Strategy (REMS) for ER/LA products "to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics."[10] The REMS required ER/LA manufacturers to deliver voluntary REMS-adherent continuing education (CE) to prescribers, with content based on an FDA blueprint for safe ER/LA prescribing.[11] Extended-release/long-acting opioid manufacturers were also required to develop medication guides to inform patients about risks associated with ER/LA opioids and to monitor and annually report on prescriber knowledge and behavior, as well as patient access and safety.

Prior assessments of the ER/LA REMS have been funded by opioid manufacturers and identified declines in ER/LA misuse. However, these declines were self-reported by clinicians[12,13] and reflected population-level trends rather than direct comparisons of CE completers and noncompleters. Pre-post analyses by CE providers, which were also funded by manufacturers, suggested that CE completers had moderately greater ER/LA knowledge immediately after and 2 months after CE training. Completers also reported increased patient communications and education relating to prescribing of ER/LA opioids, as well as greater monitoring of ER/LA drug adherence and misuse.[14] However, a May 2016 FDA advisory committee noted methodological concerns regarding these studies.[15] Other reports have suggested low prescriber awareness of the ER/LA REMS,[16] and some researchers have expressed skepticism about the objectivity and effectiveness of these programs.[17,18]

To evaluate the FDA's ER/LA REMS, we obtained previously unavailable documents through a Freedom of Information Act (FOIA) request. The analysis focused on FDA and manufacturer assessments of the REMS, including how well such assessments could assess REMS effectiveness.

Methods

FOIA History and Additional Data Sources

A FOIA request was submitted to the FDA in September 2012 requesting annual assessments submitted by ER/LA manufacturers (REMS Program Companies [known collectively as the RPC]), FDA responses to those assessments, and other correspondence between the FDA and ER/LA manufacturers. In May and June 2018, the FDA provided 5963 pages of REMS materials; after appeal, an additional 3776 pages of documents were obtained. A search of the peer-reviewed literature and FDA.gov were conducted for additional information about the REMS program, and a transcript and slide presentation from a May 3-4, 2016, advisory committee meeting examining the ER/LA REMS program were reviewed.

Analysis

Based on a prior analysis of the REMS program for transmucosal immediate-release fentanyl products[19] as well as a 2013 Office of Inspector General (OIG) report,[20] we structured the present analysis around the annual REMS assessments submitted by the RPC, which in turn were focused on 8 elements unique to the ER/LA REMS that were agreed on by the FDA and ER/LA manufacturers (**Table 1**). We focused on the following: (1) how each of the 8 REMS elements was studied over time, (2) what the results were for each assessment element, (3) whether the FDA concluded that the RPC provided enough information to evaluate the REMS effectiveness on that element, and (4) what the response of the FDA was to these assessments. We also assessed the program evaluation measures used by the RPC using criterion standard methods of program evaluation[21-23] as well as our own expertise.

Two of us (J.H. and L.O.) performed document coding and primary analysis. The team aggregated and archived the 9739 pages of documents, centrally storing source documents to facilitate access. The source documents were indexed, coding each document based on the annual assessment to which it corresponded, which assessment element it evaluated, and whether it was a manufacturer-submitted assessment, an FDA review of such an assessment, or related correspondence. Quantitative assessment information provided by the RPC regarding each of the 8 REMS elements (eg, number of REMS-participating prescribers and results of pharmacist and patient knowledge assessments) was extracted. We also noted what numeric goals were agreed on by drug manufacturers and the FDA and whether the outcomes met those goals. In addition, qualitative information was extracted from the FDA's responses to each RPC assessment, and communications between the RPC and the FDA were tracked.

We used grounded theory and the constant comparative approach to organize and interpret the information and core themes pertinent to our 4 main outcomes.[24] We met frequently to review findings from the iterative review of the source documents and to build consensus regarding the analysis and interpretation of results, structuring our synthesis according to the 4 primary outcomes of interest. Disagreements were resolved based on consensus among the study team. The study was exempted from review by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board because it only involved the evaluation of publicly available documents.

Observations

Prespecified Assessment Elements

Table 1 lists the 8 elements that the FDA used to evaluate the REMS, and eTable 1 in the Supplement summarizes the times when each was assessed. At 36 months and 48 months, the FDA assessed whether or not sufficient data had been provided by ER/LA opioid manufacturers to evaluate a given element. At these times, the FDA concluded that only 2 of 8 elements, enrollment targets and educational program audits, could be fully evaluated. **Table 2** summarizes FDA-identified deficiencies at 36 months and 48 months that prevented the FDA from fully evaluating the remaining 6 elements as well as the FDA's recommendations regarding how these deficiencies could be addressed.

Element 1: Enrollment Targets

The REMS goal was for 60% of 320 000 ER/LA opioid prescribers to take a REMS-adherent CE course between 2012 and 2016; 27.6% (88 316 of 320 000) of prescribers had done so by 2016. Audits of the REMS program indicated close adherence to FDA content guidelines except for financial disclosures. The REMS CE did not achieve this enrollment goal even by the end of the evaluation period. At 12 months, 1147 prescribers had enrolled; at 24 months, 19 805 prescribers had enrolled. At 36 months, that number had climbed to 37 512 prescribers, or 46.9% of the 80 000 prescribers who were to have been reached by that point. At 48 months and 60 months, 41.8% (66 881 of 160 000) and 46.0% (88 316 of 192 000), respectively, of the target number of prescribers were reported as having enrolled. The RPC and FDA both noted these persistently low enrollment numbers during annual assessments. The RPC responded to this finding by citing high numbers of completers failing to take posttraining evaluation, confusion among participants about what training was REMS adherent, and competition from other opioid CE (eExhibit 1 in the Supplement). After the 24-month report, the RPC committed to creating a communications campaign for health care

Table 1. Assessments Used by the US Food and Drug Administration (FDA) to Evaluate Extended-Release/Long-Acting (ER/LA) Opioid Risk Evaluation and Mitigation Strategy (REMS)

Measure	Goal	Outcomes	Did the FDA Deem Manufacturer-Submitted Data Sufficient to Assess Measure?[a]	
			36-mo Review	48-mo Review
Enrollment targets	Train 60% of ER/LA prescribers within 4 y of first CE	No. of prescribers enrolled	Yes	Yes
Educational program audits	Have uniform adherence to FDA blueprint and ACCME-adherent disclosure of commercial support	Proportion of adherent programs based on sample of 10% of total No. of programs based on continuing medical education accrediting bodies	Yes	Yes
Health care professional awareness of ER/LA opioid risks	Convey risks of improper ER/LA prescribing and use; target of 80% comprehension of key risk messages	Knowledge of ER/LA opioid information and reported prescribing comparing CE completers with noncompleters; knowledge retention 6-12 mo after CE completion	No	No
Patient awareness of ER/LA opioid risks	Counsel patients about risks of improper ER/LA use; goal of 70% comprehension regarding safe ER/LA opioid use	Patient understanding of ER/LA opioid risks and reported interaction with prescribers	No	No
Surveillance for adverse events	Reduce misuse, abuse, overdose, addiction, and death stemming from inappropriate ER/LA opioid use; no target reduction specified	Emergency department visits for adverse drug events; intentional/unintentional exposures using poison control databases; rates of people in substance abuse programs abusing ER/LA drugs; mortality rates from drug poisonings; and surveys of abuse in adolescents and adults	No	No
ER/LA opioid use	Reduce the overall volume of ER/LA drugs prescribed; no target reduction specified	Trends in ER/LA drugs dispensed; trends in prescribing by prescriber specialty; switches from ER/LA drugs to comparator products	No	No
ER/LA prescribing	Reduce ER/LA opioid prescribing to inappropriate patients; no target reduction specified	Monthly volume of prescriptions in opioid-tolerant and opioid-naive patients; starting doses; and early refills before and during REMS implementation	No	No
ER/LA access	Maintain patient access to ER/LA drugs; no target satisfaction rate specified	Prescriptions stratified by prescriber type; patient/prescriber perceptions of ER/LA opioid access	No	No

Abbreviations: ACCME, Accreditation Council for Continuing Medical Education; CE, continuing education.

[a] At 36 months and 48 months, the FDA noted whether they were able to evaluate each element based on the data provided by ER/LA manufacturers; such analyses were not performed at 12 months and 24 months, while the 60-month report was excluded from this table because many REMS goals were changed at 60 months.

professionals to raise awareness of CE (eExhibit 2 in the Supplement), but this campaign had not been implemented as of the 60-month report.

Element 2: Educational Program Audits

The FDA audited a random sample of at least 10% of manufacturer-funded CE programs per year to monitor adherence to the FDA blueprint and disclosure of commercial support in accord with Accreditation Council for Continuing Medical Education guidelines. The FDA reported results of the first audits at 24 months; between 24 months and 60 months, 69.0% (20 of 29) to 90.0% (18 of 20) of audited programs met all requirements for REMS-adherent CE. The remainder, between 10.0% (2 of 20) and 31.0% (9 of 29) of programs depending on the time point, were nonadherent because of failure to disclose financial support or inability to resolve financial conflicts of interest. In its reports, the RPC maintained that commercial support disclosure issues were important but did not materially alter educational content. In its reviews, the FDA requested that the identified disclosure deficiencies be addressed; however, the FDA did not institute systemwide policy changes to address these lapses.

Element 3: Health Care Professional Awareness of ER/LA Risks

The FDA and ER/LA opioid manufacturers attempted to assess whether the ER/LA REMS increased health care professional awareness of ER/LA opioid risks. Two cross-sectional prescriber surveys, first administered 3 years after REMS implementation, assessed knowledge, attitudes, and practices (eTechnical Appendix in the Supplement). The FDA and ER/LA opioid manufacturers set a threshold for adequate comprehension of 80% of items answered correctly within each of 6 survey subdomains. Both CE completers and noncompleters closely approached or exceeded the target comprehension rate for most survey domains at all times.

The first type of prescriber survey was initiated at 36 months and was based on a cross-sectional comparison of CE completers with noncompleters. Completers were contacted by CE providers, and a comparison group of randomly selected ER/LA prescribers who had not completed CE was recruited from an Intercontinental Medical Statistics (IMS) Health database. Therefore, no baseline data were available for CE completers before CE completion nor was follow-up information available for any survey respondent at

Table 2. US Food and Drug Administration (FDA) 36-Month and 48-Month Feedback on Nonevaluable Risk Evaluation and Mitigation Strategy (REMS) Assessment Elements[a]

Assessment Element	FDA Comment	FDA Recommendation
36 mo[b]		
Health care professional awareness of ER/LA opioid risks	No information about which CE providers were used to recruit participants. No verification of adherence for self-reported CE completers. No response rate provided. No comparison between CE completers and noncompleters was performed.	Compare characteristics of survey participants with target population for each survey; propose methods to standardize survey results to targeted population (FDA correspondence, p 887)
Patient awareness of ER/LA opioid risks	No comparison of respondents with nonrespondents was performed.	Compare characteristics of survey participants with target population for each survey; propose methods to standardize survey results to targeted population (FDA correspondence, p 904)
Surveillance for adverse events	Submitted data unable to show whether the REMS is reducing serious adverse events. Studies do not directly examine associations between REMS CE participation and clinical practice or patient outcomes.	Explore feasibility of pre-post study enrolling clinicians who participated in REMS CE and those who did not (FDA correspondence, p 914)
ER/LA opioid use	Decreasing trend in select ER/LA prescriptions began before REMS implementation and was accompanied by decreased immediate-release opioids. Additional data are needed on patient access.	Consider study assessing patient-level use (FDA correspondence, p 915)
ER/LA opioid prescribing	Appropriateness of opioid prescriptions and use cannot be ascertained and should be assessed using additional data sources.	Consider studies tracking prescribing behavior of clinicians before and after REMS CE training by comparing against prescribers who did not participate (FDA correspondence, p 915)
ER/LA opioid access	Information submitted does not address whether patient access has been an issue. Surveys alone are not sufficient for this purpose.	Submit concept paper for alternate approach to evaluating consequences of the REMS on patient access (FDA correspondence, p 916)
48 mo[c]		
Health care professional awareness of ER/LA opioid risks	No verification of REMS adherence among self-reported CE completers. One-third of control group reported completing REMS-compliant CE. Prescriber specialty self-reported, and other prescriber characteristics not collected. Generalizability of REMS CE group to target population not verified. CE completers and noncompleters not comparable.	Collect prescriber characteristics across all CE providers; consider other designs like randomized or self-controlled experiment to adjust for observed and unobserved characteristics across groups (48-mo review, p 22)
Patient awareness of ER/LA opioid risks	Patient sample not representative of target population for race, income, educational level, or payer type. Low number of Medicare and Medicaid participants and caregivers.	Use another data source that is representative of target population (48-mo review, p 57)
Surveillance for adverse events	Decline in opioid-related adverse events is likely not attributable to the REMS but rather to other policy changes. Poor generalizability, relying too much on commercially insured and not enough on Medicaid. Unclear if cohorts are comparable across periods.	Describe national trends in prescription opioid overdoses using electronic health care data that are not dependent on payer type (48-mo review, p 65)
ER/LA opioid use	Same concerns noted as in 36-mo report. Cross-sectional, aggregated use data insufficient to assess REMS consequences. Concept paper describing study examined changes in opioid prescribing behavior and patient outcomes under review.	Design studies that use more appropriate data resources and innovative methods (48-mo review, p 72)
ER/LA opioid prescribing	Limitations in definition of opioid tolerance used in claims data. Relying on claims data or prescription data may overestimate the number of patients classified as "opioid tolerant."	Use a data source that captures patients' complete medications so that opioid tolerance can be properly identified; do not rely solely on claims data (48-mo review, p 80)
ER/LA opioid access	No evaluation of patient access submitted with this assessment. The FDA is deliberating about new studies designed to measure access that use focus groups and surveys of clinicians and patients. The FDA has numerous concerns with the studies proposed.	Return feedback pending internal deliberations (48-mo review, p 81)

Abbreviations: CE, continuing education; ER/LA, extended-release/long-acting.

[a] See the Methods section and Table 1 for a complete list of REMS assessment elements.

[b] The FDA recommendations are from the following FDA correspondence: US Food and Drug Administration. Division of Risk Management review of the ER/LA 36-month REMS assessment report. Submitted June 29, 2019 (obtained under the Freedom of Information Act [FOIA] from the FDA; requested as FDA FOIA 2012-7093 September 2012; received May 2018).

[c] The FDA recommendations are from the following 48-month review: US Food and Drug Administration. Review of the fifth (48 month, May 11, 2014, through May 9, 2015) Risk Evaluation and Mitigation Strategy (REMS) Consolidated Assessment Report for Extended-Release and Long-Acting (ER/LA) opioid analgesic products. Submitted August 10, 2017 (obtained under the FOIA from the FDA; requested as FDA FOIA 2012-7093 September 2012; received January 2019).

subsequent times. The survey was mailed to an unspecified number of prescribers identified through CE providers and to 11 881 prescribers identified through IMS Health. The survey was closed once a target of 600 prescribers (300 CE completers and 300 noncompleters) was achieved. The CE completers consistently scored modestly higher than noncompleters on almost all questions about key ER/LA opioid risks at all survey times, although both groups scored at or near the target threshold. In its 36-month review, the FDA noted that the lack of comparability between CE completers and noncompleters limited the interpretation of the results.

The 48-month survey used the same sampling methods as the 36-month survey. Of the 9124 CE completers and 11 092 noncompleters invited to participate, 631 complete responses were received. The overall scores and differences in ER/LA prescribing knowledge between the 2 groups were similar to the 36-month results. For example, the mean difference in overall scores among completers and noncompleters was 4.9% (84.6% vs 79.7%) at 36 months and 5.0% (85.0% vs 80.0%) at 48 months (**Table 3**). At 48 months, one-third (32.6% [108 of 331]) of the IMS Health–derived sample, a proxy for CE noncompleters, self-reported prior

Table 3. Understanding of Key Risk Messages Regarding Extended-Release/Long-Acting (ER/LA) Opioids Stratified by Completion of Continuing Education (CE)[a]

Variable	Prescribers, % (95% CI)							
	36-mo Report				48-mo Report[b]			
	Completed CE		Absolute Difference	*P* Value	Completed CE		Absolute Difference	*P* Value
	No (n = 179)	Yes (n = 301)			No (n = 223)	Yes (n = 300)		
Patients should be assessed for treatment with ER/LA opioid analgesic therapy	87.7 (85.6-89.9)	91.5 (89.9-93.0)	3.8 (6.4-1.1)	.005	86.68	90.88	4.20	<.01
Prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics	74.6 (73.1-76.1)	80.1 (79.0-81.1)	5.5 (7.4-3.6)	<.001	77.81	79.14	1.33	.26
Management of ongoing therapy with ER/LA opioid analgesics is important	84.3 (82.9-85.6)	86.2 (85.2-87.2)	1.9 (3.6-0.3)	.02	83.83	86.88	3.05	<.01
It is important to counsel patients and caregivers about the safe use of ER/LA opioid analgesics	89.2 (87.9-90.4)	92.0 (91.1-93.0)	2.9 (4.5-1.3)	<.001	90.15	93.74	3.59	<.01
Prescribers must be familiar with general information concerning ER/LA opioid analgesics	78.9 (76.6-81.2)	87.7 (86.4-89.1)	8.8 (11.3-6.4)	<.001	78.30	85.15	6.85	<.01
Prescribers must be familiar with product-specific drug information concerning ER/LA opioid analgesics	50.9 (47.1-54.8)	60.2 (57.5-62.9)	9.3 (13.9-4.7)	<.001	54.16	64.85	10.69	<.01
Overall score	79.7 (78.6-80.9)	84.6 (83.8-85.4)	4.9 (6.2-3.5)	<.001	79.95	84.94	4.99	<.01

[a] Data derived from cross-sectional survey comparing posttest knowledge of self-reported CE completers with knowledge of noncompleters, samples derived from separate source populations, and no CIs reported for survey data within the 48-month report.

[b] Exact numbers corresponding to percentages not available in the 48-month report.

REMS-adherent ER/LA CE training in a survey question. These reports could not be validated by the FDA or ER/LA opioid manufacturers. Compared with the overall population of ER/LA opioid prescribers, allopathic and osteopathic physicians who responded to the survey were underrepresented, and pain management specialists were overrepresented; no such comparisons of responders with nonresponders were available at other times. In its 48-month review, the FDA requested that the RPC discontinue the survey because the comparison between prescribers recruited from IMS Health and those recruited from CE providers was not meaningful, and the survey was discontinued after 60 months.

A second type of prescriber survey, conducted by email and US mail, assessed knowledge retention of CE completers 6 to 12 months after training. Again, no baseline data were available for participants before CE completion, and there was no comparison group of individuals who did not complete the training in this survey. Results were reported in the 36-month and 48-month reports. Although no response rate was reported at 36 months, 588 of 6955 invited prescribers (8.5%) participated at 48 months. At both 36 months and 48 months, more than 80% of items related to safe ER/LA opioid prescribing were answered correctly by at least two-thirds of respondents for 4 of the 6 domains examined (**Table 4**). In its 48-month review, the FDA noted limited demographic data on responders in this survey, but the FDA approved continuation of the survey with additional demographic measures.

Element 4: Patient Awareness of ER/LA Risks

The FDA and ER/LA opioid manufacturers sought to understand whether patients who received medication guides were more knowledgeable about their medications than those who did not receive guides. Patients who had filled at least 1 ER/LA opioid prescription in the year before data collection with commercial, Medicare, and (beginning with the 48-month assessment) Medicaid health coverage were sent notification letters with a web link and telephone number. The survey assessed knowledge of safe ER/LA opioid use and its association with self-reported receipt of counseling and education, including receipt of a medication guide. Results were first reported in the 24-month assessment, and an overall score of 80% was identified as the threshold for acceptable understanding.

At the 24-month assessment, 413 of the 1923 patients who were contacted responded to the survey, yielding a response rate of 21.5%. At the 36-month assessment, 423 of the 2441 patients who were contacted responded to the survey, yielding a response rate of 17.3%. At the 48-month assessment, 485 patients of the 14 041 patients who were contacted responded to the survey, yielding a response rate of 3.5%. At the 60-month assessment, the response rate was 3.4%, with 443 responses received from the 12 911 patients who were contacted. Respondents consistently displayed overall high knowledge of the risks of ER/LA opioids (eTable 2 in the Supplement); however, respondents were more likely to be well educated and white than the general population of ER/LA opioid users. In its 48-month

Table 4. Prescriber Understanding of Safe Use Questions Regarding Extended-Release/Long-Acting (ER/LA) Opioids 6 to 12 Months After Completion of Continuing Education[a]

Variable	Prescribers Answering ≥80% of Questions Correctly, %[b]	
	36-mo Report (n = 328)	48-mo Report (n = 588)
Patients should be assessed for treatment with ER/LA opioid analgesic therapy	67.7	66.3
Prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics	17.4	50.9
Management of ongoing therapy with ER/LA opioid analgesics is important	84.5	86.6
It is important to counsel patients and caregivers about the safe use of ER/LA opioid analgesics	93.9	95.7
Prescribers must be familiar with general information concerning ER/LA opioid analgesics	67.7	82.1
Prescribers must be familiar with product-specific drug information concerning ER/LA opioid analgesics	35.1	22.4

[a] Data derived from cross-sectional survey, samples derived from separate source populations, and no CIs reported; this survey was not included in the 60-month report.

[b] Exact numbers corresponding to percentages not available.

review, the FDA said that "the survey respondents were not representative of the drug [ER/LA] use population for race, income, education level, and payer type" and requested that "future surveys should use another data source," but the FDA noted that these issues were still evident in their 60-month assessment, which used the same data source (eExhibit 3 in the Supplement).

Element 5: Surveillance for Adverse Events

The FDA and ER/LA opioid manufacturers attempted to assess whether the ER/LA REMS program led to fewer adverse events for patients prescribed ER/LA products. Beginning with the 24-month assessment, the REMS included surveillance data on adverse events from a variety of sources (eTable 3 in the Supplement), although ER/LA opioid manufacturers did not specify a target reduction in rates of ER/LA opioid adverse outcomes related to the REMS. Analyses were performed at a population level (ie, no differentiation between CE recipients and nonrecipients), tracking trends before and after REMS implementation, with trends for immediate-release opioids and benzodiazepines as control groups for select analyses.

Beginning with the 48-month report, medical examiner data demonstrated statistically significant decreases in fatal ER/LA opioid overdoses in Florida, Oregon, and Washington compared with before REMS initiation. The documents we reviewed did not contain a rationale for the selection of these states or results of analyses in other states. National analyses of Medicaid beneficiaries and commercially insured individuals at 48 months also revealed statistically significant declines in fatal ER/LA opioid overdoses after REMS initiation. Similar analyses were presented in the 60-month report.

After the 36-month, 48-month, and 60-month reports, the FDA reported it was unable to assess if the REMS program was reducing ER/LA-related adverse events based on the data submitted by the RPC because of a lack of studies directly examining the association between participation in REMS training and changes in clinical practice or patient outcomes. The FDA suggested implementation of pre-post studies that enrolled both CE completers and noncompleters to examine the effectiveness of the REMS in terms of prescribing and patient safety. In its 60-month report, the FDA revised the goal of this assessment metric, reporting that "the goal of the surveillance data [was] not to assess the impact of the REMS…" but "to monitor the scope and trends in opioid misuse and abuse and the related outcomes of addiction, overdose, and death" (eExhibit 4 in the Supplement). Consequently, the FDA requested discontinuation of studies that either compared safety outcomes before and after the REMS or between ER/LA and immediate-release formulations. In effect, the FDA stopped assessing the REMS effectiveness on these measures.

Elements 6, 7, and 8: ER/LA Opioid Use, ER/LA Prescribing, and ER/LA Access

The FDA also sought to understand whether the ER/LA REMS program reduced inappropriate prescribing or changed access to medications. The FDA and ER/LA opioid manufacturers attempted to use national prescription claims databases and the aforementioned prescriber and patient surveys to assess these goals. No numeric targets for reducing inappropriate ER/LA opioid prescribing were specified, and the first results were reported at 36 months.

The FDA's 36-month review concluded that the data sources for prescribing behavior were inadequate to assess whether the REMS was meeting its goals. In making this conclusion, the FDA noted that the data lacked the clinical details needed to judge the appropriateness of opioid use. Nor was it possible to link trends in opioid use to the REMS program because of the lack of REMS participation data in the claims databases (eExhibit 5 in the Supplement). The FDA requested alternative studies incorporating more comprehensive patient medication histories and other clinical information. The FDA also noted that declining ER/LA prescribing predated the REMS and that the populations surveyed to ascertain patient access were not representative (eExhibit 6, eExhibit 7, and eExhibit 8 in the Supplement).

Retrospective commercial health claims studies attempting to evaluate the ER/LA REMS at 60 months revealed a statistically significant decrease in total mean quarterly ER/LA opioid prescription volume (the percentage change from preimplementation period to active period was −6.9%; 95% CI, −9.6% to −4.2%; $P < .001$ by t test), although the direction and magnitude of change varied among different age strata. The RPC also noted a larger 15.6% reduction in prescribing of immediate-release products, which were not subject to a REMS. Among the ER/LA drugs examined, between approximately one-quarter to one-half (27.2%-46.0%) of patients who received products indicated for opioid-tolerant patients lacked such tolerance according to claims-based measures.

The FDA also found analyses about changes to patient access to be unsatisfactory. The RPC assessed patient access to ER/LA drugs by comparing prescribing changes among prescribers for whom the REMS was "expected to have greater impact on prescribing" (eg, dentists) with clinicians who "would be relatively unaffected by the REMS" (eg, oncologists and hospice providers) (eExhibit 5 in the Supplement). Although the results of these analyses were redacted, the FDA in their 36-month review stated that these studies had proved not to be useful. The analyses of patient access based on prescription claims and surveys were discontinued after the

36-month report. Five years after initiation, the FDA concluded that as of the 60-month report in 2017, it was "unable to determine whether the REMS is meeting its goal because of the inability for the submitted surveillance data to inform whether the REMS has reduced addiction, unintentional overdose, and death" (eExhibit 9 in the Supplement).

Discussion

Based on the present review of FDA documents obtained via an FOIA request, the FDA's REMS program was largely implemented as planned, tens of thousands of physicians took CE courses approved through the REMS, and the courses generally included the content sought by the FDA. However, it is difficult to say whether the REMS program accomplished its goals. Were prescribers who took the REMS courses more aware of the risks of ER/LA opioids? Surveys suggested modestly greater ER/LA opioid knowledge among CE completers than noncompleters. However, these analyses consistently reflected small, self-selected, nonrepresentative prescriber populations without relevant baseline measures or adjustment for differences between responders and nonresponders.

Were patients who received new patient information more informed? Extended-release/long-acting opioid manufacturers conducted cross-sectional patient surveys to assess this question; the surveys showed reasonably high levels of patient understanding about key ER/LA opioid facts 6 to 12 months after receipt of REMS-adherent CE. However, the FDA concluded that the survey's design, response rate, and nonrepresentative sample precluded conclusions regarding the consequences of the ER/LA REMS, including medication guide receipt, on patient understanding of ER/LA opioid risks.

Did the REMS change prescribing? No surveillance at any time contrasted prescribing patterns or other clinician-level or patient-level outcomes between CE completers and noncompleters, nor did analyses allow for the effectiveness of the REMS to be isolated from secular trends or a multitude of other factors that may have been associated with adverse outcomes.

Did REMS reduce adverse effects, including overdose? As with assessments of the association between REMS receipt and prescribing, ER/LA opioid manufacturers relied on population-level ecological trends to answer this question rather than comparing patient-level outcomes between prescribers who completed REMS-adherent CE and those who did not.

Extended-release/long-acting products have had an important role in driving the opioid epidemic,[8,9] and the ER/LA REMS was intended to be the FDA's primary tool "to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse."[10] Yet, more than 5 years after implementation, the FDA was unable to assess whether these outcomes were achieved. Although rigorously evaluating the REMS program presents challenges, experts in CE evaluation generally consider posttest-only designs, like the surveys used in the ER/LA REMS, to provide the lowest level of evidence regarding the effectiveness of educational interventions.[23,24] More sophisticated time series methods that allow modeling of trends, ideally with a comparison group, provide better evidence. A still more holistic evaluation would collect data prospectively, preferably with a comparison group (and clarity regarding who had been trained and who had not), and would connect educational objectives with prescribing behavior and clinical outcomes.[24] However, rather than seek more rigorous designs, the FDA instead changed the goal of REMS assessments to measure overall trends in safety and prescribing, abandoning efforts to directly quantify the ability of the REMS to change ER/LA prescribing behavior or the number of adverse events.

Previously, our group examined the structure and outcomes of the transmucosal immediate-release fentanyl REMS.[19] Although the transmucosal immediate-release fentanyl REMS is a much more restrictive, closed distribution system, that analysis (similar to the current one) suggested many opportunities for the FDA and ER/LA opioid manufacturers to strengthen the performance and ultimate effectiveness of the program through changes to the design and conduct of the program as well as its evaluation. The deficiencies in both programs are consistent with a 2013 OIG report,[20] which found that the FDA did not have the data to assess if REMS programs improve drug safety. The OIG recommended decreasing the reliance on survey data to evaluate REMS, working with manufacturers to promptly obtain additional data when early data suggest that the FDA will be unable to assess if the REMS is meeting its goals, and operating within a 60-day time window to review and return feedback on manufacturers' assessments.

The present analyses have implications for the conduct of future REMS programs. First, the FDA should establish and release a credible evaluation plan for REMS at the time of a program's adoption based on a validated, reproducible framework for CE program evaluation. For example, if the primary goal of the education is to change a behavior, then direct assessments of such behaviors should be included. A well-designed REMS program yielding timely information about ER/LA opioid use would have equipped the FDA and RPC to rapidly assess and adjust the CE training.[25] Second, risk management programs like the REMS should be designed to incorporate evolving information while not deviating unduly from the prespecified protocol. The structure of the ER/LA REMS posed potentially as long as a 1-year to 2-year cycle between when a problem would be identified to the FDA and when the FDA would next receive a report with data demonstrating the effectiveness or lack thereof of any remediation effort. Third, as we and others have called for (except in the case of any select redactions of highly sensitive proprietary information),[26,27] REMS assessments should automatically be made public given the strong overriding public interest in the issue.

Limitations

Our analysis has several limitations. First, some of the material that we requested was redacted, and we also did not have access to other documents, such as proprietary communications from ER/LA opioid manufacturers, that could shed additional light on the rationale for the REMS design. Second, as with all qualitative work, our results and interpretation may have been shaped by our own preconceptions. Given the nature of the documents we reviewed, we were unable to quantitatively assess concordance between our independent reviewers, although we attempted to maximize objectivity by using grounded theory and the constant comparative approach.[24] Third, our work does not include an analysis of the quality of the CE training programs.[17] In addition, our study focused

on the postapproval regulation of a single class of prescription opioids and may not be generalizable to other REMS programs.

Conclusions

Extended-release/long-acting opioids represent an important class of prescription opioids that account for disproportionate morbidity and mortality. In 2012, the FDA and ER/LA manufacturers implemented an REMS "to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse."[10] Despite a multitude of assessments, 5 years after initiation, the FDA and drug manufacturers could not assess whether the ongoing ER/LA REMS had accomplished this goal. Alternative observational study designs would have allowed for more rigorous estimates of the REMS effectiveness, improving the ability of the FDA and ER/LA manufacturers to critically evaluate and iteratively improve this important program.

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Concept and design: Heyward, Sharfstein, Alexander.
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