ORIGINAL ARTICLE

Impact of the extended-release/long-acting opioid analgesics risk evaluation and mitigation strategy on prescribing practices

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ABSTRACT

Objective: *To assess the impact of extended-release (ER)/long-acting (LA) opioid prescriber training on prescribing behaviors.*

Design: *Retrospective cohort study.*

Setting: *Prescriber training was evaluated from June 1, 2013 through December 31, 2016. The full study period was 2 years longer, from June 1, 2012 through December 31, 2017, to include data for all prescribers' 1-year pretraining and post-training periods.*

Participants: *24,428 prescribers who wrote ER/LA opioid prescriptions for eligible patients, with a record of training from the partner continuing education provider between June 1, 2013 and December 31, 2016.*

Intervention: *ER/LA opioid prescriber training. Main outcome measures: Prescribing behaviors 1-year before (pretraining) and after (post-training) prescribers completed training, specifically the proportion of opioid-nontolerant patients receiving ER/LA opioids indicated for opioid-tolerant patients and for patients receiving ≥100 morphine equivalents dose daily, and the proportion of concomitant users of central nervous system depressant drugs.*

Results: *The differences in the proportion of opioid-nontolerant patients receiving ER/LA opioids indicated for opioid-tolerant patients and for patients receiving ≥100 morphine equivalents dose daily were −0.69 percent (95 percent confidence interval [CI]: −1.78 percent, 0.40 percent) and −0.23 percent (95 percent CI: −1.18 percent, 0.68 percent), respectively. The differences in the proportion of concomitant users of central nervous system depressant drugs were −0.94 percent (95 percent CI: −1.39 percent; −0.48 percent) for benzodiazepines, 0.06 percent (95 percent CI: −0.13 percent; 0.25 percent) for antipsychotics, −0.41 percent (95 percent CI: −0.69 percent; −0.13 percent) for hypnotics/sedatives, and 0.08 percent (95 percent CI: −0.40 percent; 0.57 percent) for muscle relaxants.*

Conclusions: *While prescribers showed some changes in prescribing behavior after completing training, training was not associated with clinically relevant changes in prescribing behaviors.*

INTRODUCTION

Opioid analgesics used for the management of acute and chronic pain have come under intense scrutiny over the last several decades because of increases in opioid use, misuse, abuse, and deaths attributable to opioid overdose.[1-3] To support national efforts to address the opioid crisis and to ensure that the benefits outweigh the risks when opioid products are prescribed, the United States Food and Drug Administration (US FDA) approved the extended-release and long-acting (ER/LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) on July 9, 2012.[4] The goal of the

ER/LA Opioid Analgesics REMS Program (*termed* REMS Program) was to reduce adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioids. Although the REMS Program was expanded to include immediate-release and short-acting (IR/SA) opioid analgesics and renamed the "Opioid Analgesic REMS" on September 18, 2018,[5] the focus of this paper is on activities that took place under the ER/LA Opioid Analgesics REMS.

One central component of this REMS Program is the delivery of accredited continuing education (CE) activities to educate prescribers on safe and effective ER/LA opioid prescribing. The FDA outlined the recommended content of REMS-compliant accredited CE activities in a Blueprint for Prescriber Education (*FDA Blueprint*).[6] FDA Blueprint topics included general ER/LA opioid information, specific risks of ER/LA opioids, contraindications, drug–drug interactions, patient assessment for treatment, patient management and counseling, titration, dose modification, and discontinuation. The FDA Blueprint described in detail how to evaluate patients for opioid tolerance (some ER/LA opioids are appropriate only for opioid-tolerant patients) and concurrent use of central nervous system (CNS) depressants (which, when taken with ER/LA opioids, may lead to respiratory depression, sedation, coma, and death).[6] While ER/LA opioid prescribers were not required to complete training, it was encouraged.[7]

To meet the requirements of the REMS Program, ER/LA opioid manufacturers voluntarily formed a consortium referred to as the REMS Program Companies (RPC). The RPC supported CE delivery by providing unrestricted educational grants to CE providers in accordance with Accreditation Council for Continuing Medical Education (ACCME) standards for commercial support. CE providers then created REMS-compliant accredited CE activities (hereafter referred to as *training*) independently of the RPC using the FDA Blueprint.[6]

Previous studies of the effectiveness of the ER/LA Opioid Analgesics REMS found lower rates of overdose, abuse, misuse, and major medical outcomes including hospitalization and death following implementation of the REMS Program.[8-10] Decreases in ER/LA opioid prescription volume[9,11] and in off-label prescribing to opioid nontolerant patients and patients taking concomitant benzodiazepines[9] were also reported after the REMS Program implementation. However, these previous studies were ecologic studies comparing periods before and after implementation of the REMS Program among patients whose providers may or may not have completed REMS-compliant accredited CE activities. As a result, previous studies of REMS Program effectiveness were not able to distinguish between the impact of the REMS Program and concomitant efforts to address opioid abuse and misuse, such as state-run prescription-monitoring programs,[12-14] changes to insurance adjustment policies,[15] media campaigns,[16] non-REMS educational initiatives,[17] and other state and local public health interventions.

To evaluate the impact of the REMS Program in changing ER/LA opioid prescribing behaviors, we conducted a study among prescribers who completed training using data from an outpatient prescriptions database. REMS Program effectiveness was evaluated by calculating differences in three inappropriate prescribing behaviors between 1-year periods before (pretraining) and after (post-training) prescribers completed training. Three inappropriate prescribing behaviors were selected as they increase the risk of adverse events and were outlined in the FDA Blueprint.[6] First, we assessed the difference in the proportion of patients (post-training minus pretraining) who were opioid-nontolerant among those who received an ER/LA opioid indicated for use in only opioid-tolerant patients. Second, we evaluated the difference in the proportion of patients who were opioid-nontolerant among those who received ≥100 morphine equivalent dose (MEQs) daily of ER/LA opioids. Finally, we evaluated the difference in the proportion of patients who concomitantly used CNS depressants, ie, benzodiazepines, antipsychotics, hypnotic/sedatives, and muscle relaxants, among those prescribed any ER/LA opioid.

METHODS

Accredited REMS-compliant CE activities

As outlined in the FDA Blueprint (page 2),[6] REMS-compliant accredited CE activities were designed such that prescribers who completed the training would:

- Understand how to assess patients for treatment with ER/LA opioid analgesics.
- Be familiar with how to initiate therapy, modify dose, and discontinue the use of ER/LA opioid analgesics.

- Be knowledgeable about how to manage ongoing therapy with ER/LA opioid analgesics.

- Know how to counsel patients and caregivers about the safe use of ER/LA opioid analgesics, including proper storage and disposal.

- Be familiar with general and product-specific drug information concerning ER/LA opioid analgesics.

The FDA Blueprint outlined specific messages to be included in training activities to meet each of the goals. The FDA placed no restrictions on the format of CE delivery, though the training was required to meet the standards of the ACCME.[18] The format and nature of training thus varied and included interactive and didactic web-based activities and live symposia. Prescribers who wished to complete a training program were able to search for training by activity type, location, and date on the ER/LA Opioid Analgesics REMS website.

For the purposes of this study, a CE provider agreed to partner with the RPC to provide information on prescribers who participated in their REMS-compliant accredited CE activities. The CE provider offered a curriculum with multiple formats, including live, virtual, and on-site activities for participants. Live sessions were integrated within a meeting (part of a full-day meeting consisting of at least six sessions, and organized as one or two concurrent tracks), or presented as symposia (single topic with no other concurrent sessions occurring).

Data sources

The IQVIA Longitudinal Prescriptions (LRx) database was used for all analyses. The LRx database contains Health Insurance Portability and Accountability Act (HIPAA)-compliant data on de-identified electronic dispensed prescriptions records reimbursed by cash, Medicare, Medicaid, and other third-party transactions, ie, those from commercial insurers, from retail pharmacies, long-term care facilities, and traditional and specialty mail-order pharmacies in the US. Only data from retail pharmacies were used in this study. LRx data on age, sex, and three-digit ZIP code for dispensings of ER/LA opioids were used. Prescriber National Provider Identifier (NPI) numbers were available for each dispensed prescription in the LRx database. A separate IQVIA database was used to identify prescriber specialty (Appendix 2), age, sex, and US census division from the prescriber's NPI number. The IQVIA (formerly IMS Health) LRx database has been used in numerous studies of prescription patterns.[19-22]

The CE provider who partnered with the RPC for this study provided the NPI numbers of prescribers who participated in their training and the dates of training completion exclusively for the purpose of this study in accordance with an agreement between the RPC and the CE provider.

Study period and population

Prescriber training was evaluated from June 1, 2013 through December 31, 2016. The full study period was 2 years longer, from June 1, 2012 through December 31, 2017, to include data for all prescribers' 1-year pretraining and post-training periods.

We first identified a patient cohort with ≥1 dispensed prescription in the LRx database for an ER/LA opioid (Appendix 1) during the study period. Among these patients, we excluded those who: (1) used pharmacies that did not have a constant supply of data to the LRx database throughout the study period; (2) had no medication dispensings recorded in the LRx database prior to the study period; or (3) had unknown age or sex.

Among the prescribers who wrote ER/LA opioid prescriptions for the remaining eligible patients, we excluded those with no record of training from the partner CE provider between June 1, 2013 and December 31, 2016 to create a cohort of trained prescribers. Where more than one CE completion date was provided by the partner CE provider, the first date of completion was considered the training date. Patients who did not receive an ER/LA opioid during the study period from a prescriber trained by the partner CE provider were excluded.

Self-controlled pre-/post-analysis

To analyze changes in inappropriate prescribing behaviors before and after training, a pre-/post-analysis was performed. Comparisons were made between two periods: A 1-year *pretraining* period defined as the 365 days prior to and including the prescriber's training date and a 1-year *post-training* period defined as the 365 days following the training date.

We first calculated the difference between pre-training and post-training periods in the proportion of patients who were opioid-nontolerant among those prescribed an ER/LA opioid indicated for only opioid-tolerant patients (Appendix 1, Table A2). For each trained prescriber, we identified patients who received ER/LA opioids indicated for only opioid-tolerant patients from the prescriber in his/her pretraining or post-training period. Opioid tolerance was evaluated among these patients at the first ER/LA opioid prescription indicated for opioid-tolerant patients within the pre- or post-training period. Using the FDA's definition,[6] we considered patients to be opioid-tolerant if they received ≥60 MEQs daily from any prescriber (not just the trained prescriber) each day for ≥ 7 days in the 1-30 days prior to receiving the ER/LA opioid indicated for opioid-tolerant patients. Patients who did not meet the FDA's definition of opioid tolerance were considered opioid-nontolerant.

We also calculated the difference between pre-training and post-training periods in the proportion of opioid-nontolerant patients among patients prescribed ≥100 MEQs of ER/LA opioids daily (Appendix 3). In this analysis, opioid tolerance was assessed for patients who received an ER/LA opioid ≥ 100 MEQs daily from a trained prescriber in the prescriber's pre- or post-training period at the date of first ER/LA opioid prescription ≥ 100 MEQs daily during the pre- or post-training period. Opioid tolerance was calculated according to the FDA's definition, as above.[6]

Finally, we calculated the difference between pre- and post-training periods in proportion of patients who were concomitant users of CNS depressants (Appendix 1) among those prescribed any ER/LA opioid. For each trained prescriber, we identified patients who received ≥1 ER/LA opioid prescription from the prescriber in his/her pre- or post-training period. These patients were considered concomitant users of CNS depressants if they had ≥1 overlapping day of CNS depressant use and ER/LA opioid use during the pre- or post-training period, where the CNS depressant was dispensed 1-90 days *before* the ER/LA opioid. Patients with 0 overlapping days of CNS depressant use and ER/LA opioid use were not considered concomitant users (Appendix 4). Concomitant use was evaluated separately for four categories of CNS depressants: Benzodiazepines, antipsychotics, hypnotics/sedatives, and muscle relaxants (Appendix 1). These categories were chosen to represent a diversity of CNS depressants and include those clearly referenced in the FDA Blueprint,[6] eg, benzodiazepines, as well as those that were only inferred, eg, antipsychotics.

Statistical analyses

Demographic characteristics of patients and prescribers (age, sex, and US census division derived from three-digit ZIP code [New England, Middle Atlantic, East North Central, West North Central, South Atlantic, East South, Wet South, Mountain, Pacific, and other]) were assessed as well as prescriber specialty and patient pay type (cash, Medicare, Medicaid, and commercially insured). Counts and proportions of patients who were opioid-nontolerant and who concomitantly used CNS depressants and ER/LA opioids were derived for the pretraining and post-training periods. *Crude differences* in proportions were calculated as post-training minus pretraining so that negative values indicated improvements in prescribing behavior. Ninety-five percent confidence intervals (CIs) and p-values for the crude differences in proportions between pre- and post-training periods were also calculated.

Because prescribers who prescribe more ER/LA opioids may react differently to training than prescribers who prescribe fewer ER/LA opioids, we conducted stratified analyses to attempt to control for prescriber ER/LA opioid prescription volume.[23] We grouped prescribers into five categories based on their ER/LA opioid prescription counts in the 1-year pretraining period: 0, 1-150, 151-500, 501-1,000, and >1,000 ER/LA opioid prescriptions. Differences in proportions were evaluated within each pretraining ER/LA opioid prescription volume category. Wald tests were used to evaluate the homogeneity of the differences in proportions across pretraining ER/LA opioid prescription volume categories.[23] *Weighted differences* in proportions with weights corresponding to the sum of patients in each pretraining ER/LA opioid prescription category were calculated alongside 95 percent CIs.[23] p-Values for the weighted differences in proportions were derived from the Cochran-Mantel-Haenszel test.[24] We excluded the category of 0 ER/LA opioid prescriptions from all stratified analyses as the differences in proportions within this category were indeterminate. Weighted differences in proportions were calculated as post-training minus pretraining, so that negative differences indicated improvements in prescribing behavior.

All analyses used SAS version 9.4 (SAS Institute Inc., Cary, North Carolina).

Ethics

This research was reviewed and approved by Quorum Review (#33115/1), an appropriately constituted research ethics board, in accordance with pertinent authorities.

RESULTS

Characteristics of prescribers

A total of 24,428 prescribers were identified (Table 1), of whom the plurality were 41-64 years old (N = 10,146, 41.5 percent), followed by ≥ 65 years old (N = 4,607, 18.9 percent); age was unknown for 32.9 percent of prescribers. The majority of prescribers were female (N = 14,027, 57.4 percent). Of the nine US census divisions,[25] most prescribers were from the Pacific (N = 6,989, 28.6 percent) or South Atlantic (N = 5,591, 22.9 percent) divisions. Primary care physicians represented the majority of prescribers (N = 10,292, 42.1 percent), followed by nurse practitioners (N = 7,048, 28.9 percent), and physician assistants (N = 7,048, 11.1 percent).

Characteristics of patients of prescribers

A total of 2.65 million patients of prescribers were identified (Table 2). These patients were mostly female (N = 1.64 million, 62.0 percent) and predominantly aged > 40 years (47.8 percent were 41-64 years; 26.9 percent were ≥ 65 years). Geographically, patients were most commonly from the Pacific and South Atlantic divisions (N = 689,282, 26.1 percent and N = 576,215, 21.8 percent, respectively), with other regions representing 15.0 percent (N = 396,937, New England) or fewer patients.[6] Most prescriptions were paid by third-party, eg, commercial insurance (N = 1.76 million, 66.6 percent), followed by Medicare Part D (N = 587,347, 22.2 percent).

Difference in the proportions of patients who were opioid-nontolerant among patients prescribed an ER/LA opioid indicated for opioid-tolerant patients

A total of 15,451 patients in the pretraining period and 13,725 patients in the post-training

Table 1. Demographic characteristics and specialty of prescribers of ER/LA opioids in the LRx database between June 1, 2013 and December 31, 2016

	Prescribers (N = 24,428)	
	N	**Percent**
Age		
≤18 years	0	0.0
19-40 years	1,646	6.7
41-64 years	10,146	41.5
≥65 years	4,607	18.9
Unknown	8,029	32.9
Sex		
Female	14,027	57.4
Male	10,380	42.5
Unknown	21	0.1
US census division		
Division 1—New England	2,989	12.2
Division 2—Middle Atlantic	3,193	13.1
Division 3—East North Central	2,270	9.3
Division 4—West North Central	351	1.4
Division 5—South Atlantic	5,591	22.9
Division 6—East South Central	608	2.5
Division 7—West South Central	1,618	6.6
Division 8—Mountain	790	3.2
Division 9—Pacific	6,989	28.6
Other geographic location*	29	0.1
Specialty		
Primary Care Physician	10,292	42.1
Nurse Practitioner	7,048	28.9
Physician Assistant	2,708	11.1
Other prescriber	2,256	9.2
Pediatrician	930	3.8
Surgeon	289	1.2
Emergency Medicine Physician	252	1.0

Table 1. Demographic characteristics and specialty of prescribers of ER/LA opioids in the LRx database between June 1, 2013 and December 31, 2016 (continued)

	Prescribers (N = 24,428)	
	N	Percent
Anesthesiologist	148	0.6
Rheumatologist	86	0.4
Pain Physician	77	0.3
Neurologist	72	0.3
Oncologist	69	0.3
Hospice and Palliative Medicine Physician	18	0.1
Dentist	14	0.1

ER/LA, extended-release/long-acting; N, number.
*Other geographic location includes locations that are part of the FDA's regulatory authority, but are not covered by US census divisions, such as Puerto Rico.

were prescribed ER/LA opioids indicated for use only in opioid-tolerant patients by a trained prescriber (Table 3). Approximately the same proportions of patients were opioid-nontolerant in each period—65.9 percent in the pretraining period and 65.2 percent in the post-training period. Homogeneity of the differences in proportions of opioid-nontolerant patients across categories of pretraining ER/LA opioid prescription volumes was supported by Wald tests (Table S1, Supplementary Data). The crude difference in the proportion of opioid-nontolerant patients prescribed an ER/LA opioid indicated for opioid-tolerant patients was –0.69 percent (95 percent CI: –1.78 percent, 0.40 percent), slightly attenuated relative to the weighted difference of –2.82 percent (95 percent CI: –3.93 percent; –1.70 percent; Table 3).

Difference in the proportions of patients who were opioid-nontolerant among patients prescribed ≥100 MEQs daily of ER/LA opioids

A total of 3,677 patients in the pretraining period and 3,281 in the post-training period were prescribed ≥100 MEQs daily of ER/LA opioids by a trained prescriber (Table 4). The proportions of

Table 2. Demographic and pay type characteristics of patients of ER/LA opioid prescribers in the LRx database between June 1, 2013 and December 31, 2016

	Patients (N = 2,645,656)	
	N	Percent
Age		
≤18 years	48,871	1.8
19-40 years	621,033	23.5
41-64 years	1,264,340	47.8
≥65 years	711,412	26.9
Sex		
Female	1,639,490	62.0
Male	1,006,166	38.0
US census division		
Division 1—New England	396,937	15.0
Division 2—Middle Atlantic	243,996	9.2
Division 3—East North Central	286,657	10.8
Division 4—West North Central	32,398	1.2
Division 5—South Atlantic	576,215	21.8
Division 6—East South Central	101,144	3.8
Division 7—West South Central	189,159	7.1
Division 8—Mountain	129,669	4.9
Division 9—Pacific	689,282	26.1
Other geographic location*	199	0.0
Pay type		
Cash	177,722	6.7
Medicaid	115,328	4.4
Medicare	2,687	0.1
Medicare Part D	587,347	22.2
Third-party, eg, commercial insurance	1,762,572	66.6

ER/LA, extended-release/long-acting; N, number.
*Other geographic location includes locations that are part of the FDA's regulatory authority, but are not covered by US census divisions, such as Puerto Rico.

Table 3. Proportions of patients who were opioid non-tolerant prescribed ER/LA opioids indicated for use in opioid-tolerant patients in the LRx database between June 1, 2012 and December 31, 2017

	Pretraining (N = 15,451)	Post-training (N = 13,725)	Pretraining period versus post-training period			
			Difference[¶], percent	95 percent CI		p-Value
	N opioid-nontolerant (percent)	N opioid-nontolerant (percent)		Lower bound, percent	Upper bound, percent	
Pretraining ER/LA opioid prescription volume category*						
0 prescriptions	0 (–)	900 (91.6)	–	–	–	–
1-150 prescriptions	6,450 (70.4)	5,165 (67.4)	–3.05	–4.46	–1.65	<0.0001
151-500 prescriptions	1,801 (59.4)	1,473 (56.5)	–2.96	–5.54	–0.37	0.0249
501-1,000 prescriptions	1,059 (58.9)	790 (58.4)	–0.50	–3.97	2.98	0.7781
>1,000 prescriptions	874 (59.2)	624 (55.4)	–3.79	–7.62	0.05	0.0529
Total[†]	10,184 (65.9)	8,952 (65.2)	–0.69	–1.78	0.40	0.2170
Weighted difference[‡]			–2.82	–3.93	–1.70	<0.0001

CI, confidence interval; ER/LA, extended-release/long-acting; N, number.
*Based on a prescriber's ER/LA opioid prescription volume in the 1-year pretraining period.
†Includes patients in the 0 pretraining ER/LA opioid prescriptions category.
‡Weighted differences are weighted to the average distribution of patients into pretraining ER/LA opioid prescription volume categories between pre- and post-training periods. This analysis excludes patients in the 0 pretraining ER/LA opioid prescriptions category.
¶Pretraining minus post-training.

patients prescribed ≥100 MEQs daily of ER/LA opioids who were opioid-nontolerant between training groups were similar at 4.2 percent (pretraining period) and 3.9 percent (post-training period). Wald tests supported the assumption of homogeneity of the difference in opioid-nontolerant patients across pretraining ER/LA opioid prescription volume categories (Table S2, Supplementary Data). The crude and weighted differences in the proportion of opioid-nontolerant patients who were prescribed ≥ 100 MEQs daily of ER/LA opioids were similar at –0.23 percent (95 percent CI: –1.16 percent, 0.70 percent) and –0.25 percent (95 percent CI: –1.18 percent, 0.68 percent), respectively (Table 4).

Concomitant use of central nervous system (CNS) depressants

The numbers of patients prescribed ER/LA opioids from a trained prescriber—the denominator of all concomitant CNS depressant use analyses—were 55,411 for the pretraining period and 52,299 for the post-training period. The assumption of homogeneity of the differences in the proportion of patients who concomitantly used CNS depressants was supported by Wald tests for all CNS depressant types except muscle relaxants (Tables S3-S5, Supplementary Data). The crude differences in the proportion of concomitant ER/LA opioid and CNS depressant users before and after training were (Table 5): –0.94 percent (95 percent CI: –1.39 percent; –0.48 percent) for benzodiazepines, 0.06 percent (95 percent CI: –0.13 percent; 0.25 percent) for antipsychotics, –0.41 percent (95 percent CI: –0.69 percent; –0.13 percent) for hypnotics/sedatives, and 0.08 percent (95 percent CI: –0.40 percent; 0.57 percent) for muscle relaxants. The weighted differences were: –0.54 percent (95 percent CI: –1.01 percent, –0.08 percent) for benzodiazepines; 0.13 percent (95 percent –0.07 percent, 0.33 percent) for antipsychotics; –0.22 percent (95 percent CI: –0.50 percent, 0.07 percent) for hypnotics/sedatives; and 0.81 percent (95 percent CI: 0.32 percent, 1.31 percent) for muscle relaxants (Table 5).

Table 4. Proportions of patients prescribed ≥100 MEQ daily of ER/LA opioids who were opioid-nontolerant in the LRx database between June 1, 2012 and December 31, 2017

	Pretraining (N = 3,677)	Post-training (N = 3,281)	Pretraining period versus post-training period			
			Difference[¶], percent	95 percent CI		p-Value
	N opioid-nontolerant (percent)	N opioid-nontolerant (percent)		Lower bound, percent	Upper bound, percent	
Pretraining ER/LA opioid prescription volume category*						
0 prescriptions	0 (–)	2 (8.3)	–	–	–	–
1-150 prescriptions	73 (3.9)	61 (3.6)	–0.32	–1.59	0.94	0.6176
151-500 prescriptions	35 (3.9)	32 (3.8)	–0.09	–1.94	1.76	0.9212
501-1,000 prescriptions	23 (4.3)	17 (4.4)	0.06	–2.62	2.75	0.9624
>1,000 prescriptions	22 (5.1)	17 (4.5)	–0.60	–3.55	2.36	0.6939
Total[†]	153 (4.1)	129 (3.9)	–0.23	–1.16	0.70	0.6280
Weighted difference[‡]			–0.25	–1.18	0.68	0.6005

CI, confidence interval; ER/LA, extended-release/long-acting; N, number; MEQ, morphine equivalent dose.
*Based on a prescriber's ER/LA opioid prescription volume in the 1-year pretraining period.
†Includes patients in the 0 pretraining ER/LA opioid prescriptions category.
‡Weighted differences are weighted to the average distribution of patients into pretraining ER/LA opioid prescription volume categories between pre- and post-training periods. This analysis excludes patients in the 0 pretraining ER/LA opioid prescriptions category.
¶Pretraining minus post-training.

DISCUSSION

In this study, we evaluated the effectiveness of the ER/LA Opioid Analgesics REMS in improving prescriber behavior of 24,428 prescribers (out of approximately 320,000 in the US during the same time period)[9,26] by comparing inappropriate prescribing behaviors before and after prescribers completed REMS-compliant accredited CE activities. One behavior we studied was prescribing ER/LA opioids that should be used only in opioid-tolerant patients to opioid-nontolerant patients. A related behavior we studied was prescribing ER/LA opioids ≥ 100 MEQs daily to opioid-nontolerant patients. The final behavior was prescribing any ER/LA opioid to patients concomitantly taking CNS depressants. These behaviors were selected for our study of REMS Program effectiveness as they increase the risk of potentially serious adverse events, eg, overdose, respiratory depression, and were clearly outlined in the FDA Blueprint[6] that guided REMS-compliant accredited CE activity content. If training is effective in improving prescribing behavior, inappropriate prescribing would be expected to decline after training as measured by decreases in the proportion of opioid-nontolerant patients or decreases in the proportion of patients concomitantly using CNS depressants. We conducted an analysis stratified by pretraining ER/LA opioid prescription volume to address the potential for training to have different effects among prescribers who write different volumes of ER/LA opioid prescriptions.

We observed no clinically relevant decreases in the proportion of opioid-nontolerant patients among those prescribed ER/LA opioids indicated for use in only opioid-tolerant patients in both crude and weighted analyses. The slight difference observed in the weighted analysis of –2.82 percent (95 percent CI: –3.83 percent, –1.70 percent) was not clinically relevant when considered in the context of the high proportion of opioid-nontolerant patients in the post-training period (65.2 percent).

Nor did we observe clinically relevant benefits of prescriber training in the crude or weighted analyses of patients who were opioid-nontolerant among those prescribed ≥100 MEQs daily of ER/LA opioids.

Table 5. Proportions of patients prescribed CNS depressants concomitantly with any ER/LA opioid in the LRx database between June 1, 2012 and December 31, 2017

	Pretraining (N = 55,441)	Post-training (N = 52,299)	Pretraining period versus post-training period			
			Difference†, percent	95 percent CI		p-Value
	N concomitant users (percent)	N concomitant users (percent)		Lower bound, percent	Upper bound, percent	
Benzodiazepines						
Total	10,110 (18.2)	9,052 (17.3)	–0.94	–1.39	–0.48	<0.001
Weighted difference*			–0.54	–1.01	–0.08	0.0227
Antipsychotics						
Total	1,426 (2.6)	1,375 (2.6)	0.06	–0.13	0.25	0.5670
Weighted difference*			0.13	–0.07	0.33	0.1895
Hypnotics/sedatives						
Total	3,310 (6.0)	2,910 (5.6)	–0.41	–0.69	–0.13	0.0040
Weighted difference*			–0.22	–0.50	0.07	0.1438
Muscle relaxants						
Total	11,351 (20.5)	10.757 (20.6)	0.08	–0.40	0.57	0.7360
Weighted difference*			0.81	0.32	1.31	0.0011

CI, confidence interval; CNS, central nervous system; ER/LA, extended-release/long-acting; N, number.
*Weighted differences are weighted to the average distribution of patients into pretraining ER/LA opioid prescription volume categories between pre- and post-training periods. This analysis excludes patients in the 0 pretraining ER/LA opioid prescriptions category.
†Pretraining minus post-training.

The proportions of patients who received ER/LA opioids ≥ 100 MEQs daily who were opioid-nontolerant were low in both pre- and post-training periods at 4.2 percent and 3.9 percent, respectively, implying prescribers are largely adhering to good prescribing practices for these opioids. However, it is particularly important that patients receiving ≥100 MEQs daily of ER/LA opioids are opioid-tolerant, as the risk of opioid-related overdose is dose-dependent.[27] As a result, we would consider a clinically relevant reduction in inappropriate prescribing to be one that lowers the proportion of opioid-nontolerant patients to well below 4 percent.

Finally, we did not observe a clinically relevant impact of training in reducing prescribing of ER/LA opioids to patients concomitantly using CNS depressants. While two CNS depressant categories showed decreases in the crude analyses (benzodiazepines and hypnotics/sedatives), these crude differences in proportion were small in magnitude and attenuated in the weighted analyses.

Our conclusion is that REMS-compliant accredited CE activities do not appear to produce clinically relevant reductions in inappropriate prescribing behaviors. This is in contrast to previous ecologic studies of REMS Program effectiveness as assessed by opioid prescription volume and adverse opioid-related events such as overdose, addiction, and death.[8-11] However, these previous ecologic studies all relied on comparisons between periods before and after REMS Program implementation conducted among all patients, regardless of the training status of the provider. It is therefore possible that the observed benefit of the REMS Program in these studies in fact resulted from other efforts that overlapped in time with the REMS Program implementation.

REMS Program effectiveness studies based on prescriber questionnaires also have suggested that

the REMS Program is largely effective.[28,29] These analyses found that correct responses to knowledge questions are significantly improved immediately and two months after training[28] and that prescribers commonly implement changes to their clinical practice following CE activities.[29] Although we acknowledge the potential benefit of the REMS Program on short-term prescriber knowledge and prescriber-reported behavior, we suggest that the results of our study based on observed prescriber behavior are more relevant to patient health than survey-based REMS assessments.

These results are consistent with the broader CE literature. CE interventions are generally considered effective in improving physician performance and patient outcomes[30]; however, the effects of CE interventions are often small, inconsistent, and can vary according to format.[30-33] In particular, programs that are shorter and less interactive are typically less effective.[30,32,33] In this study, the live training provided by the partner CE provider often occurred in the context of a full day of meetings or symposia, and the average duration was 3.5 to 4 hours. Limited evidence suggests that physicians may not benefit or may only modestly benefit from self-directed learning[34] in which individuals are responsible for taking the initiative to pursue CE activities. It may also be that prescribers who seek out optional training are those least likely to benefit from it, eg, because they are more knowledgeable about or sensitive to the potential harms of opioids than the general prescriber population. Less traditional CE activities that are more interactive and which tailor to the individual needs of the prescriber, eg, adaptive learning, may be more effective in promoting clinically relevant benefits to prescriber behavior.

Our study contains several notable strengths. Our study leveraged prescriber training data from a partner CE provider, which permitted us to evaluate differences in prescribing behavior for the same prescriber before and after training. This robust study design better controls for time-varying trends than ecologic analyses, which may be biased by secular changes in prescriber volume, prescriber specialty, or any other extraneous factors that may influence observed prescriber behavior over time. Furthermore, we conducted stratified analyses to address the potential for heterogeneous effects of the REMS Program on prescribers with different levels of familiarity and comfort with opioid prescribing as evinced through pretraining ER/LA opioid prescription volume. By and large, the effects of the crude and weighted analyses were similar: The REMS Program did not consistently impact prescribers differently based on how frequently they prescribed ER/LA opioids.

Nevertheless, our study contains some potential limitations. As with all studies based on secondary healthcare databases, measurement error is a potential concern. In the context of this study, patients considered opioid-nontolerant may have received opioids not captured by the LRx database, or patients may have been administered opioids in-hospital. However, these concerns may have impacted our findings for both pre- and post-training periods. Our study also identified prescribers trained by a single CE provider. Since the CE provider ultimately determines the nature and format of the REMS-compliant accredited CE activities, our results may not be generalizable to other CE providers or other CE programs and formats. Furthermore, as another consequence of studying only a single CE provider, prescribers may have received training from another CE provider prior to the training date we assigned. Thus, our observed effects may not directly correspond to the effects of the training that serves as the foundation for this analysis. A prescriber may also have received other opioid-related education not related to the REMS Program, though this may have happened in both pre- and post-training periods.

Additionally, our study allowed for double-counting of patients across prescribers without adjustment and did not account for the clustering of patients who received ER/LA opioids from the same prescriber. Our study also did not consider differences stratified by other prescriber characteristics such as prescriber specialty or geographic region, limiting our ability to detect confounding by these specialty features. While our study design attempted to reduce the impact of secular trends, it is still possible that our results reflect some secular changes to prescriber behaviors that result from non-REMS Program interventions, such as state and local laws, health system policies, and prescription monitoring programs.[35] A major limitation of our work is that prescribing behaviors were assessed among patients who received an ER/LA opioid. According to this design, we are unable to detect when prescribers decide to prescribe an alternative to ER/LA opioids in consideration of safe ER/LA opioid use—we only observed treatment episodes involving ER/LA opioids. Future studies may improve upon our design by reporting changes in

prescribing behavior overall among patients with an indication for analgesia. We evaluated inappropriate prescribing behaviors using only available pharmacy claims data; inpatient data were not included and all prescriptions dispensed to the patient might not be included in the LRx database. It may be that prescribers were prescribing appropriately, by weighing the risks and benefits of ER/LA opioid treatment appropriately according to clinical information to which we do not have access, such as inpatient opioid administrations or prescriptions dispensed by pharmacies not included in the LRx database. Finally, it may be true that changes in prescribing practices are implemented gradually, perhaps in a subset of existing or new patients, which may have had an impact on the magnitude of the observed change. This potential could be investigated in future studies of the long-term impact of the REMS Program.

In summary, completion of REMS-compliant accredited CE activities was not associated with clinically relevant changes in prescribing behaviors in our self-controlled analysis of prescribers who completed training. Reasons for the lack of observed effectiveness may relate to the format of the accredited CE activities and the limited duration over which they take place.

The Appendix referenced in this article is available at: https://doi.org/10.5055/jom.2023.0764-Appendix.

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REFERENCES

1. Guy JG, Zhang K, Bohm MK, et al.: Vital signs: Changes in opioid prescribing in the United States, 2006-2015. *MMWR Morb Mortal Wkly Rep.* 2017; 66(26): 697-704.

2. Jones CM, Mack KA, Paulozzi LJ: Pharmaceutical overdose deaths, United States, 2010. *JAMA.* 2013; 309(7): 657-659.

3. Okie S: A flood of opioids, a rising tide of deaths. *N Engl J Med.* 2010; 363(21): 1981-1985.

4. United States Food and Drug Administration: Risk evaluation and mitigation strategy (REMS) for opioid analgesics. Available at *http://er-la-opioidrems.com/IwgUI/rems/home.action.* Accessed July 25, 2018.

5. United States Food and Drug Administration: FDA takes important steps to encourage appropriate and rational prescribing of opioids through final approval of new safety measures governing the use of immediate-release opioid analgesic medications. Available at *https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm620935.htm.* Accessed January 17, 2019.

6. United States Food and Drug Administration: Introduction for the FDA blueprint for prescriber education for extended-release and long-acting opioid analgesics. Available at *https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM515636.pdf.* Accessed July 25, 2018.

7. United States Food and Drug Administration: Prescriber letter #3: FDA-required REMS program for serious drug risks. Available at *https://www.accessdata.fda.gov/drugsatfda_docs/rems/ERLA_2017-05-26_Prescriber_Letter_3.pdf.* Accessed August 8, 2018.

8. Bucher Bartelson B, Le Lait MC, Green JL, et al.: Changes in misuse and abuse of prescription opioids following implementation of extended-release and long-acting opioid analgesic risk evaluation and mitigation strategy. *Pharmacoepidemiol Drug Saf.* 2017; 26(9): 1061-1070.

9. Cepeda MS, Coplan PM, Kopper NW, et al.: ER/LA opioid analgesics REMS: Overview of ongoing assessments of its progress and its impact on health outcomes. *Pain Med.* 2017; 18(1): 78-85.

10. Esposito D, Desai V, Cepeda MS, et al.: Incidence of opioid overdose and death among patients using ER/LA opioid analgesics before and after implementation of the class-wide REMS. Presented at: American Academy of Pain Medicine Annual Meeting, March 16-19, 2017, Orlando, FL.

11. Divino V, Cepeda MS, Coplan P, et al.: Assessing the impact of the extended-release/long-acting opioid analgesics risk evaluation and mitigation strategies on opioid prescription volume. *J Opioid Manag.* 2017; 13(3): 157-168.

12. Reifler LM, Droz D, Bailey JE, et al.: Do prescription monitoring programs impact state trends in opioid abuse/misuse? *Pain Med.* 2012; 13(3): 434-442.

13. Centers for Disease Control and Prevention: State prescription drug laws. Available at *www.cdc.gov/drugoverdose/policy/laws.html*. Accessed April 24, 2017.

14. Bureau of Justice Assistance: Program performance report, prescription drug monitoring program. Available at *https://www.bja.gov/Publications/PDMP_PPR_Jan-Dec13.pdf*. Accessed April 24, 2014.

15. Mercer Inc: State Medicaid interventions for preventing prescription drug abuse and overdose: A report for the national association of Medicaid directors. Available at *http://medicaid-directors.org/publications/state-medicaid-interventions-for-preventing-prescription-drug-abuse-and-overdose/*. Accessed April 24, 2017.

16. United States Department of Health and Human Services: Prevention programs & tools. Available at *https://www.hhs.gov/opioids/prevention/prevention-programs-tools/index.html*. Accessed February 25, 2019.

17. Davis CS, Carr D: Physician continuing education to reduce opioid misuse, abuse, and overdose: Many opportunities, few requirements. *Drug Alcohol Depend.* 2016; 163: 100-107.

18. Accreditation Council for Continuing Medical Education: The ACCME accreditation requirements. Available at *https://www.accme.org/sites/default/files/2019-01/626_20190125_Accreditation_Requirements_Document.pdf*. Accessed March 25, 2019.

19. Olfson M, King M, Schoenbaum M: Benzodiazepine use in the United States. *JAMA Psychiatry.* 2015; 72(2): 136-142.

20. Olfson M, King M, Schoenbaum M: Treatment of young people with antipsychotic medications in the United States. *JAMA Psychiatry.* 2015; 72(9): 867-874.

21. King M, Essick C: The geography of antidepressant, antipsychotic, and stimulant utilization in the United States. *Health Place.* 2013; 20: 32-38.

22. Schumock GT, Stayner LT, Valuck RJ, et al.: Risk of suicide attempt in asthmatic children and young adults prescribed leukotriene-modifying agents: A nested case-control study. *J Allergy Clin Immunol.* 2012; 130(2): 368-375.

23. Greenland S, Rothman KJ, Lash TL: Introduction to stratified analysis. In Seigafuse S, Bierig L (eds.): *Modern Epidemiology.* Philadelphia, PA: Lippincott Williams & Wilkins, 2008: 258-282.

24. Balding D, Cressie N, Fitzmaurice G, et al. (eds.): *Introduction to Categorical Data Analysis.* Hoboken, NJ: John Wiley & Sons, Inc., 2018.

25. United States Census Bureau: Census regions and divisions of the United States. Available at *http://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf*. Accessed February 26, 2019.

26. Heyward J, Olson L, Sharfstein JM, et al.: Evaluation of the extended-release/long-acting opioid prescribing risk evaluation and mitigation strategy program by the US food and drug administration: A review. *JAMA Intern Med.* 2020; 180(2): 301-309.

27. Dowell D, Haegerich TM, Chou R: CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA.* 2016; 315(15): 1624-1645.

28. Alford DP, Zisblatt L, Ng P, et al.: SCOPE of pain: An evaluation of an opioid risk evaluation and mitigation strategy continuing education program. *Pain Med.* 2016; 17(1): 52-63.

29. Chatterjee P, Finnegan T, Grimes C, et al.: Interim analysis of practice changes following participation in online and live ER/LA opioid CME/CE programs from the CO*RE collaborative (P1. 221). Presented at: American Academy of Neurology, April 22-28, 2017, Boston, MA.

30. Cervero RM: Effectiveness of continuing medical education: Updated synthesis of systematic reviews. Available at *https://www.accme.org/sites/default/files/652_20141104_Effectiveness_of_Continuing_Medical_Education_Cervero_and_Gaines.pdf*. Accessed December 7, 2022.

31. Mansouri M, Lockyer J: A meta-analysis of continuing medical education effectiveness. *J Contin Educ Health Prof.* 2007; 27(1): 6-15.

32. Bloom BS: Effects of continuing medical education on improving physician clinical care and patient health: A review of systematic reviews. *Int J Technol Assess Health Care.* 2005; 21(3): 380-385.

33. Marinopoulos SS, Dorman T, Ratanawongsa N, et al.: Effectiveness of continuing medical education. *Evid Rep Technol Assess (Full Rep).* 2007; 149(1): 1-69.

34. Murad MH, Coto-Yglesias F, Varkey P, et al.: The effectiveness of self-directed learning in health professions education: A systematic review. *Med Educ.* 2010; 44(11): 1057-1068.

35. Duensing K, Twillman R, Ziegler S, et al.: An examination of state and federal opioid analgesic and continuing education policies: 2016–2018. *JPR.* 2020; 13: 2431-2442.

Impact of the extended-release/long-acting opioid analgesics risk evaluation and mitigation strategy on prescribing practices

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APPENDIX 1: DRUGS OF INTEREST

The following tables list the drugs included in the analyses. Prior to study initiation, all drug lists were reviewed and approved by the REMS Program Companies (RPC) Metrics Subteam. Each table contains the following columns:

- Grouping: The drug group and method of action
- Generic name: The generic name of each drug included
- Marketed drug name: The marketed drug name of each drug included
- Dosage form code: The code for each drug form that was included in analyses

Table A1 lists the REMS ER/LA opioid analgesics included in analyses.

Table A1. REMS extended-release/long-acting (ER/LA) opioid analgesics*

Grouping	Generic name	Marketed drug name	Dosage form Code
FDA approved abuse-deterrent opioids	Hydrocodone bitartrate	Hysingla ER	T24A
	Morphine sulfate	Arymo ER	TBEA
		MorphaBond ER	T12A
	Morphine-naltrexone	Embeda	CPCR
	Oxycodone	Xtampza ER	C12A
	Oxycodone HCl	OxyContin	T12A
Other ER/LA opioid analgesics	Buprenorphine	Buprenorphine	PTWK
		Butrans	PTWK
	Buprenorphine HCl	Belbuca	FILM
	Fentanyl	Duragesic	PT72
		Fentanyl	PT72
	Hydrocodone bitartrate	Zohydro ER	C12A
			CP12

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Table A1. REMS extended-release/long-acting (ER/LA) opioid analgesics* (continued)			
Grouping	**Generic name**	**Marketed drug name**	**Dosage form code**
Other ER/LA opioid analgesics	Hydromorphone HCl	Exalgo	T24A
		Hydromorphone HCl ER	T24A
		Hydromorphone hydrochloride	T24A
	Methadone HCl	Dolophine	TABS
		Methadone HCl	CONC
			SOLN
			TABS
	Methadone HCl	Methadone HCl intensol	CONC
		Methadose	CONC
			TABS
		Methadose sugar-free	CONC
	Morphine sulfate	Kadian	CP24
		Morphine sulfate CR	TBCR
		Morphine sulfate ER	CP24
			TBCR
		MS contin	TBCR
		Oramorph SR	TB12
			TBCR
		Avinza	CP24
		Morphine sulfate ER	CP24
	Oxycodone HCl	Oxycodone HCl	TB12
		Oxycodone HCl CR	TB12
		Oxycodone HCl ER	T12A
			TB12
	Oxycodone w/ acetaminophen	Xartemis XR	TBCR
	Oxymorphone HCl	Opana ER	TB12
		Opana ER (crush resistant)	T12A
		Oxymorphone hydrochloride	TB12
	Tapentadol HCl	Nucynta ER	TB12

*As of December 12, 2017, the following ER/LA opioid drugs were not present in the LRx database: Targiniq ER, Troxyca ER, Vantrela ER. For most drugs not present in the LRx, this was usually because they were not yet been launched/were not yet commercially available.

Table A2 lists the ER/LA opioids indicated only for opioid-tolerant patients. In the analysis of opioid tolerance restricted to ≥100 morphine milligram equivalents (MMEs), only the doses for these medications ≥100 MMEs were used.

Table A2. REMS extended-release/long-acting (ER/LA) opioids indicated for use among patients who are opioid-tolerant

Grouping	Generic name	Marketed name	Dosage form code	Dose
FDA-approved abuse-deterrent opioids	Morphine sulfate	MorphaBond ER	T12A	100 mg
	Morphine-naltrexone	Embeda	CPCR	100 mg
Other ER/LA opioid analgesics	Fentanyl	Duragesic	PT72	Any
		Fentanyl	PT72	Any
	Hydromorphone HCl	Exalgo	T24A	Any
		Hydromorphone HCl ER	T24A	Any
		Hydromorphone HCl	T24A	Any
	Morphine sulfate	Kadian	CP24	100-200 mg
		Morphine sulfate CR	TBCR	100-200 mg
		Morphine sulfate ER	CP24	100 mg
			TBCR	100-200 mg
		MS contin	TBCR	100 mg
		Oramorph SR	TB12	100 mg
			TBCR	100 mg
		Avinza	CP24	90-120 mg
		Morphine sulfate ER	CP24	90-120 mg

Table A3 lists the IR/SA opioids included in all analyses. Note that carisoprodol with aspirin and codeine was included in Table A2 (IR/SA opioids) and Table A6 (CNS depressants). To mitigate confusion, especially when assessing concomitant use of opioids with CNS depressants, it was removed from Table A6 CNS depressant list).

Table A3. Immediate-release/short-acting (IR/SA) opioid analgesics

Grouping	Generic name	Marketed drug name	Dosage form code
Immediate-release/short-acting opioids*	Acetaminophen w/ codeine	Acetaminophen/codeine	SOLN
			TABS
		Acetaminophen/codeine #2	TABS
		Acetaminophen/codeine #3	TABS
		Acetaminophen/codeine #4	TABS
		Acetaminophen/codeine Pho	TABS
		Acetaminophen-codeine	TABS
		Capital/codeine	SUSP
		Cocet	TABS
		Cocet plus	TABS
		Codeine phosphate/ acetaminophen	TABS
		Codeine/acetaminophen	TABS
		Tylenol/codeine #3	TABS
		Tylenol/codeine #4	TABS
	Acetaminophen-caffeine-dihydrocodone	Acetaminophen/caffeine/ dihydrocodone	CAPS
			TABS
		Panlor DC	CAPS
		Panlor SS	TABS
		Trezix	CAPS
		Zerlor	TABS
	Acetaminophen-codeine and dietary management drug	Theracodeine-300	MISC
	Aspirin-caffeine-dihydrocodeine bitartrate	Aspirin-caffeine-dihydrocodone	CAPS
		Synalgos DC	CAPS
		Synalgos-DC	CAPS
	Codeine phosphate	Codeine phosphate	SOLN
	Codeine sulfate	Codeine sulfate	SOLN
			TABS
	Fentanyl	Subsys	LIQD

Table A3. Immediate-release/short-acting (IR/SA) opioid analgesics (continued)			
Grouping	**Generic name**	**Marketed drug name**	**Dosage form code**
Immediate-release/short-acting opioids*	Fentanyl citrate	Abstral	SUBL
		Actiq	LPOP
		Fentanyl citrate oral	LPOP
		Fentora	TABS
		Lazanda	SOLN
		Onsolis	FILM
	Hydrocodone-acetaminophen	Anexsia	TABS
		Co-gesic	TABS
		Hycet	SOLN
		Hydrocodone bitartrate/AC	SOLN
			TABS
		Hydrocodone/acetaminophen	SOLN
			TABS
		Hydrocodone-acetaminophen	TABS
		Hydrogesic	CAPS
		Liquicet	SOLN
		Lorcet	TABS
		Lorcet 10/650	TABS
		Lorcet HD	TABS
		Lorcet plus	TABS
		Lortab	LIQD
			SOLN
			TABS
		Lortab 5	TABS
		Margesic H	CAPS
		Maxidone	TABS
		Norco	TABS
		Polygesic	CAPS
		Stagesic	CAPS
		Verdrocet	TABS
		Vicodin	TABS
		Vicodin ES	TABS
		Vicodin HP	TABS
		Xodol	TABS
		Zamicet	SOLN
		Zolvit	SOLN
		Zydone	TABS

Table A3. Immediate-release/short-acting (IR/SA) opioid analgesics (continued)			
Grouping	**Generic name**	**Marketed drug name**	**Dosage form code**
Immediate-release/short-acting opioids*	Hydrocodone-ibuprofen	Hydrocodone/ibuprofen	TABS
		Ibudone	TABS
		Reprexain	TABS
		Vicoprofen	TABS
		Xylon	TABS
	Hydromorphone HCl	Dilaudid	LIQD
			TABS
		Hydromorphone HCl	LIQD
			SUPP
			TABS
	Meperidine HCl	Demerol	SOLN
			TABS
		Meperidine HCl	SOLN
			TABS
		Meperitab	TABS
	Meperidine HCl-sodium chloride	Meperidine HCl-NS	DEVI
			SOLN
		Meperidine hydrochloride/ sodium chloride	SOLN
	Meperidine w/ promethazine	Meperidine HCl/promethazine	CAPS
	Morphine sulfate	Morphine sulfate	SOLN
			SUPP
			TABS
	Oxycodone HCl*	Oxaydo	TABA
		Oxecta	TABA
		Oxycodone HCl	CAPS
			CONC
			SOLN
			TABS
		Roxicodone	SOLN
			TABS
	Oxycodone with acetaminophen	Endocet	TABS
		Magnacet	TABS
		Oxycodone/acetaminophen	CAPS
			SOLN
			TABS
		Percocet	TABS
		Primalev	TABS
		Primlev	TABS

Table A3. Immediate-release/short-acting (IR/SA) opioid analgesics (continued)			
Grouping	**Generic name**	**Marketed drug name**	**Dosage form code**
Immediate-release/short-acting opioids*	Oxycodone with acetaminophen	Roxicet	TABS
		Tylox	CAPS
		Xartemis XR	TBCR
		Xolox	TABS
	Oxycodone-aspirin	Endodan	TABS
		Oxycodone/aspirin	TABS
		Percodan	TABS
	Oxycodone-ibuprofen	Combunox	TABS
		Oxycodone/ibuprofen	TABS
	Oxymorphone HCl	Opana	TABS
		Oxymorphone hydrochloride	TABS
	Tapentadol HCl	Nucynta	TABS
*As of December 12, 2017, the following IR/SA opioid drug was not present in the LRx database: RoxyBond. For most drugs not present in the LRx, this was usually because they had not yet been launched/were not commercially available.			

Table A4 lists nonsteroidal anti-inflammatory drugs (NSAIDs) included in analyses.Table A5 lists tramadol formulations included in analyses.Table A6 lists the central nervous system depressants-benzodiazepines, antipsychotics, hypnotics/sedatives, and muscle relaxants-included in analyses.

Table A4. Prescription non-steroidal anti-inflammatory drugs (NSAIDs)			
Grouping	**Generic name**	**Marketed drug name**	**Dosage form code**
NSAIDS	Celecoxib	Celebrex	CAPS
		Celecoxib	CAPS

Table A5. Tramadol formulations			
Grouping	**Generic name**	**Marketed drug name**	**Dosage form code**
Immediate-release/short-acting opioids	Tramadol HCl	Rybix ODT	TBDP
		Synapryn fusepaq	SUSR
		Tramadol HCl	TABS
		Ultram	TABS
	Tramadol-acetaminophen	Tramadol HCl-acetaminophen	TABS
		Tramadol hydrochloride/AC	TABS
		Ultracet	TABS
Tramadol ER	Tramadol HCl	Conzip	CP24
		Ryzolt	TB24
		Tramadol HCl ER	CP24
			TB24
		Ultram ER	TB24

Table A6. Central nervous system (CNS) depressants			
Grouping	**Generic name**	**Marketed drug name**	**Dosage form code**
Benzodiazepines	Alprazolam	Alprazolam	TABS
		Alprazolam ER	TB24
		Alprazolam intensol	CONC
		Alprazolam ODT	TBDP
		Alprazolam XR	TB24
		Niravam	TBDP
		Xanax	TABS
		Xanax XR	TB24
	Chlordiazepoxide HCl	Chlordiazepoxide HCl	CAPS
	Clorazepate dipotassium	Clorazepate dipotassium	TABS
		Tranxene T	TABS
	Diazepam	Diazepam	CONC
			SOLN
			TABS
		Diazepam intensol	CONC
		Valium	TABS
	Lorazepam	Ativan	TABS
		Lorazepam	CONC
			TABS
		Lorazepam intensol	CONC
	Oxazepam	Oxazepam	CAPS
Antipsychotics	Aripiprazole	Abilify	SOLN
			TABS
		Abilify discmelt	TBDP
		Abilify maintenance	PRSY
			SRER
		Aripiprazole	SOLN
			TABS
		Aripiprazole ODT	TBDP
	Aripiprazole lauroxil	Aristada	PRSY
	Asenapine maleate	Saphris	SUBL
	Brexpiprazole	Rexulti	TABS

Table A6. Central nervous system (CNS) depressants (continued)			
Grouping	**Generic name**	**Marketed drug name**	**Dosage form code**
Antipsychotics	Carbamazepine (antipsychotic)	Equetro	CP12
	Cariprazine HCl	Vraylar	CAPS
			CPPK
	Chlorpromazine	Thorazine	SUPP
	Chlorpromazine HCl	Chlorpromazine HCl	SOLN
			TABS
	Clozapine	Clozapine	TABS
		Clozapine ODT	TBDP
		Clozaril	TABS
		Fazaclo	TBDP
		Versacloz	SUSP
	Fluphenazine decanoate	Fluphenazine decanoate	SOLN
	Fluphenazine HCl	Fluphenazine HCl	CONC
			ELIX
			SOLN
			TABS
	Haloperidol	Haloperidol	TABS
	Haloperidol decanoate	Haldol decanoate 100	SOLN
		Haldol decanoate 50	SOLN
		Haldol decanoate-100	SOLN
		Haldol decanoate-50	SOLN
		Haloperidol decanoate	SOLN
	Haloperidol lactate	Haldol	SOLN
		Haloperidol	CONC
		Haloperidol lactate	SOLN
	Iloperidone	Fanapt	TABS
		Fanapt titration pack	TABS
	Loxapine	Adasuve	AEPB
	Loxapine succinate	Loxapine	CAPS
		Loxapine succinate	CAPS
		Loxitane	CAPS
	Lurasidone HCl	Latuda	TABS

Table A6. Central nervous system (CNS) depressants (continued)			
Grouping	**Generic name**	**Marketed drug name**	**Dosage form code**
Antipsychotics	Molindone HCl	Moban	TABS
		Molindone hydrochloride	TABS
	Olanzapine	Olanzapine	SOLR
			TABS
		Olanzapine ODT	TBDP
		Zyprexa	SOLR
			TABS
		Zyprexa zydis	TBDP
	Olanzapine pamoate	Zyprexa relprevv	SUSR
	Paliperidone	Invega	TB24
		Paliperidone ER	TB24
	Paliperidone palmitate	Invega sustenna	SUSP
		Invega trinza	SUSP
	Perphenazine	Perphenazine	TABS
	Pimavanserin tartrate	Nuplazid	TABS
	Prochlorperazine	Compazine	SUPP
		Compro	SUPP
		Prochlorperazine	SUPP
	Prochlorperazine edisylate	Prochlorperazine edisylat	SOLN
	Prochlorperazine maleate	Compazine	TABS
		Prochlorperazine maleate	TABS
	Quetiapine fumarate	Quetiapine fumarate	TABS
		Quetiapine fumarate ER	TB24
		Seroquel	TABS
		Seroquel XR	TB24
	Risperidone	Risperdal	SOLN
			TABS
		Risperdal M-tab	TBDP
		Risperidone	SOLN
			TABS
		Risperidone M-tab	TBDP
		Risperidone ODT	TBDP

Table A6. Central nervous system (CNS) depressants (continued)			
Grouping	**Generic name**	**Marketed drug name**	**Dosage form code**
Antipsychotics	Risperidone microspheres	Risperdal consta	SUSR
	Thioridazine HCl	Thioridazine HCl	TABS
	Thiothixene	Navane	CAPS
		Thiothixene	CAPS
	Trifluoperazine HCl	Trifluoperazine HCl	TABS
	Ziprasidone HCl	Geodon	CAPS
		Ziprasidone HCl	CAPS
	Ziprasidone mesylate	Geodon	SOLR
Hypnotics/sedatives	Amobarbital sodium	Amytal sodium	SOLR
	Butabarbital sodium	Butisol sodium	ELIX
			TABS
	Chloral hydrate	Chloral hydrate	SYRP
		Somnote	CAPS
	Dexmedetomidine HCl	Dexmedetomidine HCl	SOLN
		Precedex	SOLN
	Dexmedetomidine HCl in sodium chloride	Precedex	SOLN
	Doxepin HCl (SLEEP)	Silenor	TABS
	Eszopiclone	Eszopiclone	TABS
		Lunesta	TABS
	Mephobarbital	Mebaral	TABS
		Mephobarbital	TABS
	Pentobarbital sodium	Nembutal	SOLN
		Nembutal sodium	SOLN
		Pentobarbital sodium	SOLN
	Phenobarbital	Phenobarbital	ELIX
			TABS
	Phenobarbital sodium	Luminal	SOLN
		Phenobarbital sodium	SOLN
	Ramelteon	Rozerem	TABS
	Secobarbital sodium	Seconal	CAPS
		Seconal sodium	CAPS

Table A6. Central nervous system (CNS) depressants (continued)			
Grouping	**Generic name**	**Marketed drug name**	**Dosage form code**
Hypnotics/sedatives	Suvorexant	Belsomra	TABS
	Tasimelteon	Hetlioz	CAPS
	Zaleplon	Sonata	CAPS
		Zaleplon	CAPS
	Zolpidem and dietary management drug	Gabazolpidem-5	MISC
		Sentrazolpidem PM-5	MISC
	Zolpidem tartrate	Ambien	TABS
		Ambien CR	TBCR
		Edluar	SUBL
		Intermezzo	SUBL
		Zolpidem tartrate	SUBL
			TABS
		Zolpidem tartrate ER	TBCR
		Zolpimist	SOLN
Muscle relaxants	Baclofen	Baclofen	TABS
		ED baclofen	TABS
		First-baclofen 1	SUSP
		First-baclofen 5	SUSP
		Gablofen	SOLN
			SOSY
		Lioresal intrathecal	SOLN
	Carisoprodol	Carisoprodol	TABS
		Soma	TABS
	Carisoprodol w/ aspirin	Carisoprodol/aspirin	TABS
	Carisoprodol-dietary management drug	Prazolamine	MISC
	Chlorzoxazone	Chlorzoxazone	TABS
		Lorzone	TABS
		Parafon forte DSC	TABS
	Cyclobenzaprine HCl	Amrix	CP24
		Cyclobenzaprine HCl	TABS
		Cyclobenzaprine HCl ER	CP24

Table A6. Central nervous system (CNS) depressants (continued)			
Grouping	**Generic name**	**Marketed drug name**	**Dosage form code**
Muscle relaxants	Cyclobenzaprine HCl	Cyclophene	CREA
		Fexmid	TABS
		Flexeril	TABS
	Cyclobenzaprine HCl w/ liniment	Cyclobenzaprine comfort P	KIT
	Cyclobenzaprine HCl w/ MSM	Tabradol rapidpaq	SUSP
	Cyclobenzaprine HCl-electrode device and pads	Cyclotens starter pak	KIT
	Cyclobenzaprine HCl-electrode pads	Cyclotens refill pak	KIT
	Cyclobenzaprine-capsaicin-menthol	Cyclobenzaprinepax	THPK
		Flexepax	THPK
	Cyclobenzaprine-dietary management drug	Tabradol	SUSR
		Therabenzaprine-60	MISC
		Therabenzaprine-90	MISC
		Therabenzaprine-90-5	MISC
	Cyclobenzaprine-gabapentin	Cyclo/Gaba10/300 pack	THPK
	Dantrolene sodium	Dantrium	CAPS
		Dantrium Iv	SOLR
		Dantrolene sodium	CAPS
		Revonto	SOLR
		Ryanodex	SUSR
	Metaxalone	Metaxall	TABS
		Metaxalone	TABS
		Skelaxin	TABS
	Metaxalone-capsaicin	Metaxall CP	KIT
	Metaxalone-diclofenac sodium	Lorvatus pharmapak	KIT
	Methocarbamol	Methocarbamol	SOLN
			TABS
		Robaxin	SOLN
			TABS
		Robaxin-750	TABS

Table A6. Central nervous system (CNS) depressants (continued)			
Grouping	**Generic name**	**Marketed drug name**	**Dosage form code**
Muscle relaxants	Orphenadrine citrate	Norflex	SOLN
			TBCR
		Orphenadrine citrate	SOLN
		Orphenadrine citrate CR	TB12
			TBCR
		Orphenadrine citrate ER	TB12
	Orphenadrine w/ aspirin and caffeine	Norgesic forte	TABS
		Orphenadrine compound Ds	TABS
		Orphenadrine/ASA/caffeine	TABS
	Tizanidine and liniment	Tizanidine comfort pac	MISC
	Tizanidine HCl	Tizanidine HCl	CAPS
			TABS
		Tizanidine hydrochloride	TABS
		Zanaflex	CAPS
			TABS

APPENDIX 2: PROVIDER SPECIALTIES

Table A7 lists the 15 provider specialty groups, and corresponding specialties, used in this study.

Table A7. Provider specialty groups and corresponding specialties

Specialty group	Included specialties
Pain Physician	Pain Medicine
	Pain Medicine (Anesthesiology)
	Pain Medicine (Physical Medicine and Rehabilitation)
Primary Care Physician	Family Medicine
	General Practice
	General Preventive Medicine
	Geriatric Medicine (Family Medicine)
	Geriatric Medicine (Internal Medicine)
	Internal Medicine
	Internal Medicine/Family Medicine
	Internal Medicine/Preventive Medicine
Dentist	Dentist
	Dentistry/Endodontics
Surgeon	Colon and Rectal Surgery
	Female Pelvic Medicine and Reconstructive Surgery
	General Surgery
	Hand Surgery
	Hand Surgery (Orthopedics)
	Neurological Surgery
	Oral and Maxillofacial Surgery
	Orthopedic Surgery
	Orthopedic Surgery of the Spine
	Plastic Surgery
	Sports Medicine (Orthopedic Surgery)
	Surgical Critical Care (Surgery)
	Surgical Oncology
	Thoracic Surgery

Table A7. Provider specialty groups and corresponding specialties (continued)

Specialty group	Included specialties
Surgeon	Transplant Surgery
	Trauma Surgery
	Vascular Surgery
Emergency Medicine Physician	Emergency Medicine
Oncologist	Gynecological Oncology
	Hematology/Oncology
	Medical Oncology
	Radiation Oncology
Hospice and Palliative Medicine Physician	Hospice and Palliative Medicine
	Hospice and Palliative Medicine (Internal Medicine)
	Palliative Medicine
Nurse Practitioner	Advanced Registered Nurse
	Clinical Nurse Specialist
	Nurse Midwife
	Nurse Practitioner
	Registered Nurse
Physician Assistant	Physician Assistant
Neurologist	Neurodevelopmental Disabilities (Psychiatry and Neurology)
	Neurology
	Psychiatry/Neurology
Pediatrician	Adolescent Medicine (Internal Medicine)
	Adolescent Medicine (Pediatrics)
	Child and Adolescent Psychiatry
	Child Neurology
	Internal Medicine/Pediatrics
	Neonatal-Perinatal Medicine

Table A7. Provider specialty groups and corresponding specialties (continued)	
Specialty group	**Included specialties**
Pediatrician	Pediatric Allergy
	Pediatric Cardiology
	Pediatric Emergency Medicine
	Pediatric Endocrinology
	Pediatric Gastroenterology
	Pediatric Hematology/Oncology
	Pediatric Infectious Disease
	Pediatric Nephrology
	Pediatric Orthopedics
	Pediatric Otolaryngology
	Pediatric Pulmonology
	Pediatric Surgery
	Pediatrics
	Public Health and General Preventive Medicine
Rheumatologist	Rheumatology
Anesthesiologist	Anesthesiology
	Certified Nurse Anesthetist
	Critical Care Medicine (Anesthesiology)
Physical Medicine and Rehabilitation Physician	Physical Medicine and Rehabilitation
	Spinal Cord Injury Medicine
Other Prescriber	Abdominal Surgery
	Addiction Medicine
	Addiction Psychiatry
	Adult Reconstructive Orthopedics
	Aerospace Medicine
	Allergy
	Allergy and Immunology
	Anatomic/Clinical Pathology
	Behavioral Health and Social Services

Table A7. Provider specialty groups and corresponding specialties (continued)	
Specialty group	**Included specialties**
Other Prescriber	Blood Banking/Transfusion Medicine
	Cardiovascular Disease
	Clinical Cardiac Electrophysiology
	Clinical Neurophysiology
	Clinical Pathology
	Clinical Social Worker
	Critical Care Medicine (Internal Medicine)
	Dermatology
	Diabetes
	Diagnostic Radiology
	Endocrinology, Diabetes and Metabolism
	Forensic Pathology
	Forensic Psychiatry
	Gastroenterology
	Geriatric Psychiatry
	Gynecology
	Hematology (Internal Medicine)
	Hepatology
	Hospitalist
	Immunology
	Infectious Disease
	Internal Medicine/Psychiatry
	Interventional Cardiology
	Legal Medicine
	Maternal and Fetal Medicine
	Medical Genetics
	Medical Management
	Medical Toxicology (Preventive Medicine)
	Naturopathic Doctor
	Nephrology
	Neuroradiology

Table A7. Provider specialty groups and corresponding specialties (continued)	
Specialty group	**Included specialties**
Other Prescriber	Not Applicable
	Nuclear Medicine
	Nuclear Radiology
	Nutrition
	Obstetrics
	Obstetrics and Gynecology
	Occupational Medicine
	Ophthalmology
	Optometrist
	Orthopedic Trauma
	Other Specialty
	Otolaryngology
	Pharmaceutical Medicine
	Phlebology
	Podiatrist

Table A7. Provider specialty groups and corresponding specialties (continued)	
Specialty group	**Included specialties**
Other Prescriber	Proctology
	Psychiatry
	Pulmonary Critical Care Medicine
	Pulmonary Disease
	Radiology
	Reproductive Endocrinology and Infertility
	Selective Pathology
	Sleep Medicine
	Sports Medicine (Family Medicine)
	Student, Health Care
	Transitional Year
	Unspecified
	Urology
	Vascular and Interventional Radiology
	Vascular Medicine

APPENDIX 3: CONVERSION BETWEEN MORPHINE AND OTHER OPIOIDS

Table A8 summarizes the conversion factors between ER/LA opioids and morphine.

Table A8. Conversion factors between extended-release/long-acting (ER/LA) opioids and morphine

Grouping	Generic name	Marketed drug name	MG per unit	Conversion factor	Calculated morphine equivalent units
FDA-approved abuse-deterrent opioids	Hydrocodone bitartrate	Hysingla ER	20	1	20
			30	1	30
			40	1	40
			60	1	60
			80	1	80
			100	1	100
			120	1	120
	Morphine sulfate	Arymo ER	15	1	15
			30	1	30
			60	1	60
		MorphaBond ER	15	1	15
			30	1	30
			60	1	60
			100	1	100
	Morphine-naltrexone	Embeda	20	1	20
			30	1	30
			50	1	50
			60	1	60
			80	1	80
			100	1	100
	Oxycodone	Xtampza ER	9	1.5	13.5
			13.5	1.5	20.25
			18	1.5	27
			27	1.5	40.5
			36	1.5	54

Table A8. Conversion factors between extended-release/long-acting (ER/LA) opioids and morphine (continued)					
Grouping	**Generic name**	**Marketed drug name**	**MG per unit**	**Conversion factor**	**Calculated morphine equivalent units**
FDA-approved abuse-deterrent opioids	Oxycodone HCl	OxyContin	10	1.5	15
			15	1.5	22.5
			20	1.5	30
			30	1.5	45
			40	1.5	60
			60	1.5	90
			80	1.5	120
Other ER/LA opioid analgesics	Buprenorphine	Buprenorphine	0.84	85	71.4
			1.26	85	107.1
			1.68	85	142.8
			2.52	85	214.2
			3.36	85	285.6
		Butrans	0.84	85	71.4
			1.26	85	107.1
			1.68	85	142.8
			2.52	85	214.2
			3.36	85	285.6
	Buprenorphine HCl	Belbuca	0.075	30	2.25
			0.15	30	4.5
			0.3	30	9
			0.45	30	13.5
			0.6	30	18
			0.75	30	22.5
			0.9	30	27
	Fentanyl	Duragesic	0.9	100	90
			1.8	100	180
			3.6	100	360
			5.4	100	540
			7.2	100	720
		Fentanyl	0.9	100	90

Table A8. Conversion factors between extended-release/long-acting (ER/LA) opioids and morphine (continued)					
Grouping	**Generic name**	**Marketed drug name**	**MG per unit**	**Conversion factor**	**Calculated morphine equivalent units**
Other ER/LA opioid analgesics	Fentanyl	Fentanyl	1.8	100	180
			2.7	100	270
			3.6	100	360
			4.5	100	450
			5.4	100	540
			6.3	100	630
			7.2	100	720
	Hydrocodone bitartrate	Zohydro ER	10	1	10
			15	1	15
			20	1	20
			30	1	30
			40	1	40
			50	1	50
			10	1	10
			15	1	15
			20	1	20
			30	1	30
			40	1	40
			50	1	50
	Hydromorphone HCl	Exalgo	8	4	32
			12	4	48
			16	4	64
			32	4	128
		Hydromorphone HCl ER	8	4	32
			12	4	48
			16	4	64
			32	4	128
		Hydromorphone hydrochloride	32	4	128

Table A8. Conversion factors between extended-release/long-acting (ER/LA) opioids and morphine (continued)					
Grouping	**Generic name**	**Marketed drug name**	**MG per unit**	**Conversion factor**	**Calculated morphine equivalent units**
Other ER/LA opioid analgesics	Methadone HCl	Dolophine	5	3	15
			10	3	30
		Methadone HCl	10	3	30
			1	3	3
			2	3	6
			5	3	15
			10	3	30
		Methadone HCl intensol	10	3	30
		Methadose	10	3	30
			5	3	15
			10	3	30
		Methadose sugar-free	10	3	30
	Morphine sulfate	Kadian	10	1	10
			20	1	20
			30	1	30
			40	1	40
			50	1	50
			60	1	60
			70	1	70
			80	1	80
			100	1	100
			130	1	130
			150	1	150
			200	1	200
		Morphine sulfate CR	15	1	15
			30	1	30
			60	1	60
			100	1	100
			200	1	200

Table A8. Conversion factors between extended-release/long-acting (ER/LA) opioids and morphine (continued)					
Grouping	**Generic name**	**Marketed drug name**	**MG per unit**	**Conversion factor**	**Calculated morphine equivalent units**
Other ER/LA opioid analgesics	Morphine sulfate	Morphine sulfate ER	10	1	10
			20	1	20
			30	1	30
			50	1	50
			60	1	60
			80	1	80
			100	1	100
			15	1	15
			30	1	30
			60	1	60
			100	1	100
			200	1	200
		MS Contin	15	1	15
			30	1	30
			60	1	60
			100	1	100
			200	1	200
		Oramorph SR	15	1	15
			30	1	30
			60	1	60
			100	1	100
			15	1	15
			30	1	30
			60	1	60
			100	1	100
	Morphine sulfate beads	Avinza	30	1	30
			45	1	45
			60	1	60
			75	1	75
			90	1	90
			120	1	120

Table A8. Conversion factors between extended-release/long-acting (ER/LA) opioids and morphine (continued)					
Grouping	**Generic name**	**Marketed drug name**	**MG per unit**	**Conversion factor**	**Calculated morphine equivalent units**
Other ER/LA opioid analgesics	Morphine sulfate beads	Morphine sulfate ER	30	1	30
			45	1	45
			60	1	60
			75	1	75
			90	1	90
			120	1	120
	Oxycodone HCl	Oxycodone HCl	20	1.5	30
			40	1.5	60
		Oxycodone HCl CR	10	1.5	15
			20	1.5	30
			40	1.5	60
			80	1.5	120
		Oxycodone HCl ER	10	1.5	15
			15	1.5	22.5
			20	1.5	30
			30	1.5	45
			40	1.5	60
			60	1.5	90
			80	1.5	120
			10	1.5	15
			20	1.5	30
			80	1.5	120
	Oxycodone w/ acetaminophen	Xartemis XR	7.5	1.5	11.25
	Oxymorphone HCl	Opana ER	5	3	15
			7.5	3	22.5
			10	3	30
			15	3	45
			20	3	60
			30	3	90
			40	3	120

Table A8. Conversion factors between extended-release/long-acting (ER/LA) opioids and morphine (continued)					
Grouping	**Generic name**	**Marketed drug name**	**MG per unit**	**Conversion factor**	**Calculated morphine equivalent units**
Other ER/LA opioid analgesics	Oxymorphone HCl	Opana ER (crush resistant)	5	3	15
			7.5	3	22.5
			10	3	30
			15	3	45
			20	3	60
			30	3	90
			40	3	120
		Oxymorphone hydrochloride	5	3	15
			7.5	3	22.5
			10	3	30
			15	3	45
			20	3	60
			30	3	90
			40	3	120
	Tapentadol HCl	Nucynta ER	50	0.4	20
			100	0.4	40
			150	0.4	60
			200	0.4	80
			250	0.4	100

Table A9 summarizes the conversion factors between IR opioids and morphine and tramadol (ER and IR formulations/combinations) and morphine. Note: Same strengths with different conversion factors indicate different formulation/mode of administration, eg, film versus tab.

Table A9. Conversion factors between immediate-release (IR/SA) opioids and tramadol and morphine

Grouping	Generic name	Marketed drug name	MG per unit	Conversion factor	Calculated morphine equivalent units
Immediate-release/short-acting opioids	Acetaminophen w/ codeine	Acetaminophen/codeine	2.4	0.15	0.36
			15	0.15	2.25
			30	0.15	4.5
			60	0.15	9
		Acetaminophen/codeine #2	15	0.15	2.25
		Acetaminophen/codeine #3	30	0.15	4.5
		Acetaminophen/codeine #4	60	0.15	9
		Acetaminophen/codeine phosphate	30	0.15	4.5
			60	0.15	9
		Acetaminophen-codeine	30	0.15	4.5
		Capital/codeine	2.4	0.15	0.36
		Cocet	30	0.15	4.5
		Cocet plus	60	0.15	9
		Codeine phosphate/ acetaminophen	30	0.15	4.5
		Codeine/acetaminophen	15	0.15	2.25
			30	0.15	4.5
			60	0.15	9
		Tylenol/codeine #3	30	0.15	4.5
		Tylenol/codeine #4	60	0.15	9
	Acetaminophen-caffeine-dihydrocodeine	Acetaminophen/caffeine/ dihydrocodeine	16	0.25	4
			16	0.25	4
			32	0.25	8
		Panlor DC	16	0.25	4
		Panlor SS	32	0.25	8
		Trezix	16	0.25	4
		Zerlor	32	0.25	8

Table A9. Conversion factors between immediate-release (IR/SA) opioids and tramadol and morphine (continued)					
Grouping	**Generic name**	**Marketed drug name**	**MG per unit**	**Conversion factor**	**Calculated morphine equivalent units**
Immediate-release/short-acting opioids	Acetaminophen-codeine and dietary management drug	Theracodeine-300	30	0.15	4.5
	Aspirin-caffeine-dihydrocodeine bitartrate	Aspirin-caffeine-dihydrocodeine	30	0.25	7.5
		Synalgos DC	30	0.25	7.5
		Synalgos-DC	30	0.25	7.5
	Butalbital-acetaminophen-caffeine w/ codeine	Butalbital/acetaminophen/caffeine/codeine	30	0.15	4.5
		Fioricet/codeine	30	0.15	4.5
	Butalbital-aspirin-caffeine w/ codeine	Asa/caff/butal/codeine	30	0.15	4.5
		Ascomp/codeine	30	0.15	4.5
		Butalbital compound/codeine	30	0.15	4.5
		Butalbital/aspirin/caffeine	30	0.15	4.5
		Fiorinal/codeine #3	30	0.15	4.5
	Butorphanol tartrate	Butorphanol tartrate	10	7	70
	Carisoprodol w/ aspirin and codeine	Carisoprodol/aspirin/codeine	16	0.15	2.4
	Codeine sulfate	Codeine sulfate	6	0.15	0.9
			15	0.15	2.25
			30	0.15	4.5
			60	0.15	9
	Fentanyl	Subsys	0.1	180	18
			0.2	180	36
			0.4	180	72
			0.6	180	108
			0.8	180	144
	Fentanyl citrate	Abstral	0.1	130	13
			0.2	130	26
			0.3	130	39
			0.4	130	52
			0.6	130	78
			0.8	130	104

Table A9. Conversion factors between immediate-release (IR/SA) opioids and tramadol and morphine (continued)					
Grouping	**Generic name**	**Marketed drug name**	**MG per unit**	**Conversion factor**	**Calculated morphine equivalent units**
Immediate-release/short-acting opioids	Fentanyl citrate	Actiq	0.2	130	26
			0.4	130	52
			0.6	130	78
			0.8	130	104
			1.2	130	156
			1.6	130	208
		Fentanyl citrate oral transmucosal	0.2	130	26
			0.4	130	52
			0.6	130	78
			0.8	130	104
			1.2	130	156
			1.6	130	208
		Fentora	0.1	130	13
			0.2	130	26
			0.3	130	39
			0.4	130	52
			0.6	130	78
			0.8	130	104
		Lazanda	0.8	160	128
			2.4	160	384
			3.2	160	512
		Onsolis	0.2	180	36
			0.4	180	72
			0.6	180	108
			0.8	180	144
			1.2	180	216
	Hydrocodone-acetaminophen	Anexsia	7.5	1	7.5
		Co-Gesic	5	1	5
		Hycet	0.5	1	0.5

Table A9. Conversion factors between immediate-release (IR/SA) opioids and tramadol and morphine (continued)					
Grouping	**Generic name**	**Marketed drug name**	**MG per unit**	**Conversion factor**	**Calculated morphine equivalent units**
Immediate-release/short-acting opioids	Hydrocodone-acetaminophen	Hydrocodone bitartrate/ acetaminophen	0.5	1	0.5
			0.67	1	0.67
			2.5	1	2.5
			5	1	5
			7.5	1	7.5
			10	1	10
		Hydrocodone/acetaminophen	0.5	1	0.5
			2.5	1	2.5
			5	1	5
			7.5	1	7.5
			10	1	10
		Hydrocodone-acetaminophen	5	1	5
			7.5	1	7.5
			10	1	10
		Hydrogesic	5	1	5
		Liquicet	0.67	1	0.67
		Lorcet	5	1	5
		Lorcet 10/650	10	1	10
		Lorcet HD	10	1	10
		Lorcet plus	7.5	1	7.5
		Lortab	0.5	1	0.5
			0.5	1	0.5
			0.67	1	0.67
			5	1	5
			7.5	1	7.5
			10	1	10
		Lortab 5	5	1	5
		Margesic-H	5	1	5
		Maxidone	10	1	10

Table A9. Conversion factors between immediate-release (IR/SA) opioids and tramadol and morphine (continued)					
Grouping	**Generic name**	**Marketed drug name**	**MG per unit**	**Conversion factor**	**Calculated morphine equivalent units**
Immediate-release/short-acting opioids	Hydrocodone-acetaminophen	Norco	5	1	5
			7.5	1	7.5
			10	1	10
		Polygesic	5	1	5
		Stagesic	5	1	5
		Verdrocet	2.5	1	2.5
		Vicodin	5	1	5
		Vicodin ES	7.5	1	7.5
		Vicodin HP	10	1	10
		Xodol	5	1	5
			7.5	1	7.5
			10	1	10
		Zamicet	0.67	1	0.67
		Zolvit	0.67	1	0.67
		Zydone	5	1	5
			7.5	1	7.5
			10	1	10
	Hydrocodone-ibuprofen	Hydrocodone/ibuprofen	2.5	1	2.5
			5	1	5
			7.5	1	7.5
			10	1	10
		Ibudone	5	1	5
			10	1	10
		Reprexain	2.5	1	2.5
			5	1	5
			10	1	10
		Vicoprofen	7.5	1	7.5
		Xylon	10	1	10

Table A9. Conversion factors between immediate-release (IR/SA) opioids and tramadol and morphine (continued)					
Grouping	**Generic name**	**Marketed drug name**	**MG per unit**	**Conversion factor**	**Calculated morphine equivalent units**
Immediate-release/short-acting opioids	Hydromorphone HCl	Dilaudid	1	4	4
			2	4	8
			4	4	16
			8	4	32
		Hydromorphone HCl	1	4	4
			2	4	8
			4	4	16
			8	4	32
			3	4	12
	Levorphanol tartrate	Levorphanol tartrate	2	11	22
	Meperidine HCl	Demerol	50	0.1	5
			100	0.1	10
		Meperidine HCl	10	0.1	1
			50	0.1	5
			100	0.1	10
		Meperitab	50	0.1	5
	Meperidine w/ promethazine	Meperidine HCl/promethazine	50	0.1	5
	Morphine sulfate	Morphine sulfate	2	1	2
			4	1	4
			20	1	20
			15	1	15
			30	1	30
			5	1	5
			10	1	10
			20	1	20
			30	1	30
	Oxycodone HCl	Oxaydo	5	1.5	7.5
			7.5	1.5	11.25
		Oxecta	5	1.5	7.5
			7.5	1.5	11.25

Table A9. Conversion factors between immediate-release (IR/SA) opioids and tramadol and morphine (continued)					
Grouping	**Generic name**	**Marketed drug name**	**MG per unit**	**Conversion factor**	**Calculated morphine equivalent units**
Immediate-release/short-acting opioids	Oxycodone HCl	Oxycodone HCl	5	1.5	7.5
			20	1.5	30
			1	1.5	1.5
			5	1.5	7.5
			10	1.5	15
			15	1.5	22.5
			20	1.5	30
			30	1.5	45
		Oxycodone hydrochloride	20	1.5	30
			1	1.5	1.5
		Roxicodone	1	1.5	1.5
			5	1.5	7.5
			15	1.5	22.5
			30	1.5	45
	Oxycodone w/ acetaminophen	Endocet	2.5	1.5	3.75
			5	1.5	7.5
			7.5	1.5	11.25
			10	1.5	15
		Magnacet	2.5	1.5	3.75
			5	1.5	7.5
			7.5	1.5	11.25
			10	1.5	15
		Oxycodone/acetaminophen	5	1.5	7.5
			1	1.5	1.5
			2.5	1.5	3.75
			5	1.5	7.5
			7.5	1.5	11.25
			10	1.5	15

Table A9. Conversion factors between immediate-release (IR/SA) opioids and tramadol and morphine (continued)					
Grouping	**Generic name**	**Marketed drug name**	**MG per unit**	**Conversion factor**	**Calculated morphine equivalent units**
Immediate-release/short-acting opioids	Oxycodone w/ acetaminophen	Percocet	2.5	1.5	3.75
			5	1.5	7.5
			7.5	1.5	11.25
			10	1.5	15
		Primalev	2.5	1.5	3.75
		Primlev	5	1.5	7.5
			7.5	1.5	11.25
			10	1.5	15
		Roxicet	5	1.5	7.5
		Tylox	5	1.5	7.5
		Xolox	10	1.5	15
	Oxycodone-aspirin	Endodan	4.84	1.5	7.26
		Oxycodone/aspirin	4.84	1.5	7.26
			4.88	1.5	7.32
		Percodan	4.84	1.5	7.26
	Oxycodone-ibuprofen	Combunox	5	1.5	7.5
		Oxycodone/ibuprofen	5	1.5	7.5
	Oxymorphone HCl	Opana	5	3	15
			10	3	30
		Oxymorphone hydrochloride	5	3	15
			10	3	30
	Pentazocine w/ naloxone	Pentazocine/naloxone HCl	50	0.37	18.5
		Talwin NX	50	0.37	18.5
	Pentazocine-acetaminophen	Pentazocine/acetaminophen	25	0.37	9.25
		Talacen	25	0.37	9.25
	Tapentadol HCl	Nucynta	50	0.4	20
			75	0.4	30
			100	0.4	40

Table A9. Conversion factors between immediate-release (IR/SA) opioids and tramadol and morphine (continued)					
Grouping	**Generic name**	**Marketed drug name**	**MG per unit**	**Conversion factor**	**Calculated morphine equivalent units**
Tramadol IR	Tramadol HCl	Rybix ODT	50	0.1	5
		Synapryn fusepaq	10	0.1	1
		Tramadol HCl	50	0.1	5
		Ultram	50	0.1	5
	Tramadol-acetaminophen	Tramadol HCl-acetaminophen	37.5	0.1	3.75
		Tramadol hydrochloride/ac	37.5	0.1	3.75
		Ultracet	37.5	0.1	3.75
Tramadol ER	Tramadol HCl	Conzip	100	0.1	10
			200	0.1	20
			300	0.1	30
		Ryzolt	100	0.1	10
			200	0.1	20
			300	0.1	30
		Tramadol HCl ER	100	0.1	10
			150	0.1	15
			200	0.1	20
			300	0.1	30
			100	0.1	10
			200	0.1	20
			300	0.1	30
		Ultram ER	100	0.1	10
			200	0.1	20
			300	0.1	30

APPENDIX 4: DECISION RULES TO OBTAIN DAY'S SUPPLY FOR CNS DEPRESSANTS

Concomitant use of drugs with CNS depressive properties was defined as ≥1 prescription claims for a CNS depressant within the 3 months prior to the dispensing of REMS ER/LA opioid drugs with days' supply that overlaps with REMS ER/LA opioid drug days' supply for at least 1 day.

The days' supply values for a number of CNS depressants may not reflect patient behavior and, thus, may not be reliable indicators for the concomitancy analysis. This is true particularly for certain nonsolid oral CNS depressant forms and for certain PRN ("as needed") CNS depressants. For example, an injectable might have a days' supply of 1 day on the prescription claim when the injection lasts 30 days. Thus, to obtain an effective days' supply value for all relevant CNS depressant claims, the following decision rules were applied:

1. CNS depressant claims with a days' supply value of zero were not used in the analyses (the number of such claims was recorded)
2. For CNS depressants that were taken as needed (PRN), used the recorded days' supply value
3. For select CNS depressants, used a set days' supply value (based on clinical assessment)
4. For all remaining CNS depressant claims:
   a. Used the recorded days' supply value for solid oral form claims (or for any non-solid oral form claims that should be treated as solid oral form claims—based on clinical assessment).
   b. For non-solid oral form, claims with days' supply value of 1, used the recorded value of 1.
   c. For all remaining non-solid oral form claims (ODS = observed days' supply; ODur = observed duration [time between fills]; EDS = effective days' supply):
      i. If ODS–ODur≤(0.2*ODS), EDS = ODS
      ii. If (4*ODS)>ODS–ODur>(0.2*ODS), EDS = ODur
      iii. If -(4*ODS)<ODS–ODur<-(0.2*ODS), EDS = ODS
5. For all remaining CNS depressant claims, use the recorded days' supply value

SUPPLEMENTARY MATERIAL

Tables S1-S6 describe the counts and proportions of patients included in each pre-/post-analysis of prescribing behavior. Table A10 described the counts and proportions of patients who received ER/LA opioids indicated for use in only opioid-tolerant patients; Table A11 is on patients who received ER/LA opioids ≥100 MEQs daily. The concomitancy analyses are in Table A12 (benzodiazepines), Table A13 (antipsychotics), Table A14 (hypnotics/sedatives), and Table A15 (muscle relaxants).

Table S1. Counts and proportions of patients prescribed ER/LA opioids indicated for use in opioid-tolerant patients who were opioid-nontolerant in the pretraining and post-training periods, stratified by baseline ER/LA opioid prescription volume in the LRx database between June 1, 2012 and December 31, 2017

	Pretraining period		
	Opioid-nontolerant patients with index ER/LA opioid prescriptions indicated for use in opioid-tolerant patients (numerator)	**Patients with index ER/LA opioid prescriptions indicated for use in opioid-tolerant patients (denominator)**	**Proportion opioid-nontolerant among patients with index ER/LA opioid prescriptions indicated for use in opioid-tolerant patients, percent**
Baseline ER/LA opioid prescription volume category*			
0 prescriptions	0	0	-
1-150 prescriptions	6,450	9,150	70.5
151-500 prescriptions	1,801	3,029	59.5
501-1,000 prescriptions	1,059	1,797	58.9
>1,000 prescriptions	874	1,475	59.3
All categories	10,184	15,451	65.9
	Post-training period		
	Opioid-nontolerant patients with index ER/LA opioid prescriptions indicated for use in opioid-tolerant patients (numerator)	**Patients with index ER/LA opioid prescriptions indicated for use in opioid-tolerant patients (denominator)**	**Proportion opioid-nontolerant among patients with index ER/LA opioid prescriptions indicated for use in opioid-tolerant patients, percent**
Baseline ER/LA opioid prescription volume category*			
0 prescriptions	900	982	91.6
1-150 prescriptions	5,165	7,659	67.4
151-500 prescriptions	1,473	2,607	56.5
501-1,000 prescriptions	790	1,352	58.4
>1,000 prescriptions	624	1,125	55.5
All categories	8,952	13,725	65.2
Wald test statistic†	2.1		
p-Value	0.5571		

ER/LA, extended-release/long-acting.
*Based on a prescriber's ER/LA opioid prescription volume in the 1-year pretraining period.
†Excludes patients in the 0 baseline ER/LA opioid prescriptions category.

Table S2. Counts and proportions of patients prescribed ≥100 MEQ mg/day of ER/LA opioids who were opioid-nontolerant in the pretraining and post-training periods, stratified by baseline ER/LA opioid prescription volume in the LRx database between June 1, 2012 and December 31, 2017

	Pretraining period		
	Opioid-nontolerant patients with index ER/LA opioid prescriptions ≥100 MEQ daily dose (numerator)	**Patients with index ER/LA opioid prescriptions ≥100 MEQ daily dose (denominator)**	**Proportion opioid-nontolerant among patients with index ER/LA opioid prescriptions ≥100 MEQ daily dose, percent**
Baseline ER/LA opioid prescription volume category*			
0 prescriptions	0	0	-
1-150 prescriptions	73	1,838	4.0
151-500 prescriptions	35	878	4.0
501-1,000 prescriptions	23	530	4.3
>1,000 prescriptions	22	431	5.1
All categories	153	3,677	4.2
	Post-training period		
	Opioid-nontolerant patients with index ER/LA opioid prescriptions ≥100 MEQ daily dose (numerator)	**Patients with index ER/LA opioid prescriptions ≥100 MEQ daily dose (denominator)**	**Proportion opioid-nontolerant among patients with index ER/LA opioid prescriptions ≥100 MEQ daily dose, percent**
Baseline ER/LA opioid prescription volume category*			
0 prescriptions	2	24	8.3
1-150 prescriptions	61	1,672	3.6
151-500 prescriptions	32	822	3.9
501-1,000 prescriptions	17	386	4.4
>1,000 prescriptions	17	377	4.5
All categories	129	3,281	3.9
Wald test statistic†	0.1		
p-Value	0.9858		

ER/LA, extended-release/long-acting; MEQ, morphine equivalent.
*Based on a prescriber's ER/LA opioid prescription volume in the 1-year pretraining period.
†Excludes patients in the 0 baseline ER/LA opioid prescriptions category.

Table S3. Counts and proportions of patients prescribed ER/LA opioids prescribed concomitantly with benzodiazepines in the pretraining and post-training periods, stratified by baseline ER/LA opioid prescription volume in the LRx database between June 1, 2012 and December 31, 2017

	Pretraining period		
	Concomitant benzodiazepine use with ER/LA opioids (numerator)	**Prescribed ER/LA opioids (denominator)**	**Proportion concomitant among those prescribed ER/LA opioids, percent**
Baseline ER/LA opioid prescription volume category*			
0 prescriptions	0	0	-
1-150 prescriptions	6,309	29,849	21.1
151-500 prescriptions	2,106	12,205	17.3
501-1,000 prescriptions	953	7,081	13.5
>1,000 prescriptions	742	6,276	11.8
All categories	10,110	55,411	18.2
	Post-training period		
	Concomitant benzodiazepine use with ER/LA opioids (numerator)	**Prescribed ER/LA opioids (denominator)**	**Proportion concomitant among those prescribed ER/LA opioids, percent**
Baseline ER/LA opioid prescription volume category*			
0 prescriptions	461	4,127	11.2
1-150 prescriptions	5,530	26,348	21.0
151-500 prescriptions	1,785	11,284	15.8
501-1,000 prescriptions	737	5,657	13.0
>1,000 prescriptions	539	4,883	11.0
All categories	9,052	52,299	17.3
Wald test statistic†	4.9		
p-Value	0.1819		

ER/LA, extended-release/long-acting.
*Based on a prescriber's ER/LA opioid prescription volume in the 1-year pretraining period.
†Excludes patients in the 0 baseline ER/LA opioid prescriptions category.

Table S4. Counts and proportions of patients prescribed ER/LA opioids prescribed concomitantly with antipsychotics in the pretraining and post-training periods, stratified by baseline ER/LA opioid prescription volume in the LRx database between June 1, 2012 and December 31, 2017

	Pretraining period		
	Concomitant antipsychotic use with ER/LA opioids (numerator)	**Prescribed ER/LA opioids (denominator)**	**Proportion concomitant among those prescribed ER/LA opioids, percent**
Baseline ER/LA opioid prescription volume category*			
0 prescriptions	0	0	-
1-150 prescriptions	1,013	29,849	3.4
151-500 prescriptions	279	12,205	2.3
501-1,000 prescriptions	88	7,081	1.2
>1,000 prescriptions	46	6,276	0.7
All categories	1,426	55,411	2.6
	Post-training period		
	Concomitant antipsychotic use with ER/LA opioids (numerator)	**Prescribed ER/LA opioids (denominator)**	**Proportion concomitant among those prescribed ER/LA opioids, percent**
Baseline ER/LA opioid prescription volume category*			
0 prescriptions	53	4,127	1.3
1-150 prescriptions	965	26,348	3.7
151-500 prescriptions	256	11,284	2.3
501-1,000 prescriptions	63	5,657	1.1
>1,000 prescriptions	38	4,883	0.8
All categories	1,375	52,299	2.6
Wald test statistic†	2.9		
p-Value	0.4042		

ER/LA, extended-release/long-acting.
*Based on a prescriber's ER/LA opioid prescription volume in the 1-year pretraining period.
†Excludes patients in the 0 baseline ER/LA opioid prescriptions category.

Table S5. Counts and proportions of patients prescribed ER/LA opioids prescribed concomitantly with hypnotics/sedatives in the pretraining and post-training periods, stratified by baseline ER/LA opioid prescription volume in the LRx database between June 1, 2012 and December 31, 2017

	Pretraining period		
	Concomitant hypnotic/ sedative use with ER/LA opioids (numerator)	**Prescribed ER/LA opioids (denominator)**	**Proportion concomitant among those prescribed ER/LA opioids, percent**
Baseline ER/LA opioid prescription volume category*			
0 prescriptions	0	0	-
1-150 prescriptions	1,831	29,849	6.1
151-500 prescriptions	720	12,205	5.9
501-1,000 prescriptions	382	7,081	5.4
>1,000 prescriptions	377	6,276	6.0
All categories	3,310	55,411	6.0
	Post-training period		
	Concomitant hypnotic/ sedative use with ER/LA opioids (numerator)	**Prescribed ER/LA opioids (denominator)**	**Proportion concomitant among those prescribed ER/LA opioids, percent**
Baseline ER/LA opioid prescription volume category*			
0 prescriptions	130	4,127	3.1
1-150 prescriptions	1,574	26,348	6.0
151-500 prescriptions	669	11,284	5.9
501-1,000 prescriptions	287	5,657	5.1
>1,000 prescriptions	250	4,883	5.1
All categories	2,910	52,299	5.6
Wald test statistic†	3.2		
p-Value	0.3678		

ER/LA, extended-release/long-acting.
*Based on a prescriber's ER/LA opioid prescription volume in the 1-year pretraining period.
†Excludes patients in the 0 baseline ER/LA opioid prescriptions category.

Table S6. Counts and proportions of patients prescribed ER/LA opioids prescribed concomitantly with muscle relaxants in the pretraining period and post-training periods, stratified by baseline ER/LA opioid prescription volume in the LRx database between June 1, 2012 and December 31, 2017

	Pretraining period		
	Concomitant muscle relaxant use with ER/LA opioids (numerator)	**Prescribed ER/LA opioids (denominator)**	**Proportion concomitant among those prescribed ER/LA opioids, percent**
Baseline ER/LA opioid prescription volume category*			
0 prescriptions	0	0	-
1-150 prescriptions	4,361	29,849	14.6
151-500 prescriptions	3,049	12,205	25.0
501-1,000 prescriptions	1,941	7,081	27.4
>1,000 prescriptions	2,000	6,276	31.9
All categories	11,351	55,411	20.5
	Post-training period		
	Concomitant muscle relaxant use with ER/LA opioids (numerator)	**Prescribed ER/LA opioids (denominator)**	**Proportion concomitant among those prescribed ER/LA opioids, percent**
Baseline ER/LA opioid prescription volume category*			
0 prescriptions	581	4,127	14.1
1-150 prescriptions	4,356	26,348	16.5
151-500 prescriptions	2,798	11,284	24.8
501-1,000 prescriptions	1,521	5,657	26.9
>1,000 prescriptions	1,501	4,883	30.7
All categories	10,757	52,299	20.6
Wald test statistic†	22.9		
p-Value	<0.0001		

ER/LA, extended-release/long-acting.
*Based on a prescriber's ER/LA opioid prescription volume in the 1-year pretraining period.
†Excludes patients in the 0 baseline ER/LA opioid prescriptions category.