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Original Research Article

Frequency of Early Refills for Opioids in the United States

David M. Kern , PhD,* M. Soledad Cepeda, MD, PhD,* Maribel Salas, MD, DSc,[†,‡] Syd Phillips, MPH,[§] Matthew H. Secrest, MSc,[¶] and Gregory P. Wedin, PharmD[‖]

*Janssen Research & Development, LLC, Titusville, New Jersey; [†]Daiichi-Sankyo, Clinical Safety and Pharmacovigilance, and Epidemiology, Basking Ridge, New Jersey; [‡]University of Pennsylvania Perelman School of Medicine, CCEB/CPeRT, Philadelphia, Pennsylvania; [§]IQVIA Epidemiology & Drug Safety, Seattle, Washington; [¶]IQVIA Epidemiology & Drug Safety, Cambridge, Massachusetts; [‖]Upsher-Smith Laboratories, LLC, Pharmacovigilance & Risk Management, Maple Grove, Minnesota, USA

Correspondence to: David M. Kern, PhD, Janssen Research and Development, LLC, 1125 Trenton Harbourton Rd, Titusville, NJ 08560, USA. Tel: 484-433-1192; Fax: 609-730-7927; E-mail: dkern2@its.jnj.com.

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Abstract

Objective. Refilling an opioid prescription early is an important risk factor of prescription opioid abuse and misuse; we aimed to understand the scope of this behavior. This study was conducted to quantify the prevalence and distribution of early refills among patients prescribed opioids. **Methods.** We conducted a retrospective cohort study utilizing dispensed prescription records. Patients filling one or more prescription opioids were identified and followed for one year. Early refills were defined as having a second prescription filled ≥15% early relative to the days' supply of the previous prescription for the same opioid (according to the National Drug Code [NDC]). The distribution of the number of early refills and patient characteristics were assessed. **Results.** A total of 60.6 million patients met the study criteria; 28.8% had two or more opioid prescriptions for the same opioid during follow-up. Less than 3% of all patients receiving an opioid had an early refill. Approximately 10% of those with two or more opioid prescriptions for the same drug had an early refill. For patients with multiple fills (N = 1.5 million with extended-release long-acting [ER/LA] opioids; N = 17.1 million with immediate-release short-acting [IR/SA] opioids), early refills were more common among patients with an ER/LA opioid (18.5%) compared with an IR/SA opioid (8.7%). Three-quarters of patients with an early refill had only one (70.9% and 78.4% for ER/LA and IR/SA, respectively). **Conclusion.** Refilling an opioid prescription with the same opioid early is an infrequent behavior within all opioid users, but more common in ER/LA users. Patients who refilled early tended to do so just once.

Key Words: Opioids; Substance Abuse; Early Refills; REMS; Education; Continuing; Opioid Abuse

Background

With the increase in opioid abuse and deaths due to overdose in recent decades [1–4], 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, to support national efforts to address the opioid crisis and to ensure that the benefits outweigh the risks when opioid products are prescribed. The primary goal of the REMS Program was to reduce adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioids. The ER/LA Opioid Analgesics REMS was expanded to include immediate-release and short-acting (IR/SA) opioid analgesics and was renamed the "Opioid Analgesic REMS" on September 18, 2018 [5, 6]. This study was conducted to support the ER/LA Opioid Analgesics REMS program.

Prescription drugs are implicated in the increased rates of opioid overdose [7]. Prior work has found that refilling an opioid prescription early is a more important risk factor of prescription opioid abuse than nonopioid substance abuse, dose escalation, number of pharmacies where an opioid was filled, and all other variables assessed [8]. Early refills of an opioid are also associated with risk factors of opioid misuse [9]. Due to the risk of opioid abuse and misuse associated with refilling opioid prescriptions early, it is vital to understand the scope of this behavior. We conducted a study to quantify the frequency of this behavior and assess whether it is common enough to justify future studies examining the reasons for this action. In this study, we estimate the number of patients with at least one early refill of an opioid and describe the distribution of the number of early refills in a given year.

Methods

Study Overview

This was a retrospective cohort study utilizing outpatient dispensed prescription records. Patients were identified based on having at least one prescription dispensed for an ER/LA or IR/SA opioid and were followed for one year to identify early refill events. Early refills were estimated for each patient as a second prescription for an opioid filled $\geq$15% early relative to the days' supply of the previous prescription for the same opioid with the same national drug code (NDC). Additional measures, such as the distribution of the number of early refills and patient characteristics (age, sex, and geographic region), were assessed. Analyses were stratified by opioid type: any opioid, ER/LA opioids, and IR/SA opioids.

Study Data Source

This study used the IQVIA LRx database, which contains electronic dispensed prescription records at the anonymized patient level collected from retail, long-term care (LTC), specialty, and mail-order pharmacies for ~252 million individuals. In this paper, we present data obtained from the retail channel. Through agreements with a variety of data contributors, the warehouse represents dispensed prescriptions for 93% of the retail pharmacy channel in the United States, including those reimbursed by cash, Medicare, Medicaid, and other third-party transactions (e.g., commercial insurance).

The database includes de-identified patient longitudinal prescription claims data, such as age, sex, three-digit ZIP codes, dispensed drug (through NDC), molecule, form, strength, quantity, and days' supply. The database contains data for >252 million unique de-identified patients and 1 million physicians. All data are Health Insurance Portability and Accountability Act (HIPAA) compliant to protect patient privacy.

Study Period and Population

The enrollment period was from January 1, 2016, to December 31, 2016. Patients included in the study had at least one prescription claim for any opioid during the enrollment period. The first prescription claim for an opioid during this time was the index prescription; the date of the index prescription was defined as the index date. Patients were followed for one year from the index date, resulting in a study period of January 1, 2016, through December 31, 2017, during which early refills were assessed. Patients were required to have continuous eligibility in LRx for the duration of the study period. Patients with unknown age and sex were excluded.

Early Refills

An early refill was defined as two consecutive prescription claims for the same individual and the same opioid (with the same NDC) with the number of days between prescriptions $\geq$15% less than the days' supply of the first prescription (Figure 1). Previously published studies used a threshold for early refills of 10%, but the published studies reported that patients may frequently get refills three days early on a 30-day prescription within the course of usual clinical practice [10–12].

A patient could have any number of early refills over the course of follow-up for any number of opioid analgesics, including opioids that were not the index prescription. No period of time was required between early refills for the next prescription to be an early refill event (i.e., a single prescription could participate in two early refill events, acting as the second prescription, then as the first). For each patient, we collected information on all early refills during the one-year follow-up period. For each early refill, we gathered information on opioid molecule, opioid type (ER/LA vs IR/SA) and days' supply.

The following outcomes for early refills were captured overall and stratified by opioid type: 1) the number and proportion of patients who had one or more early refills of any opioid; 2) the distribution of the number of early refills among patients who had one or more early refills of an opioid; 3) the distributions of age, sex, and geographic region (based on US Census division) of patients with two or more opioid claims, one or more early refills, and an unusually high number of early refills (five or more, the threshold informed by preliminary results).

Statistical Analysis

Descriptive statistics were evaluated. No formal statistical tests for comparisons between groups were conducted, and no adjustments were made for covariates or confounding variables. The study population characteristics were described using frequency and percentage distributions for categorical variables and mean and SD for continuous and count variables. We calculated 95% confidence intervals (CIs) according to the Clopper-Pearson

Figure 1. Example of the early refill period for a 30-day prescription of an opioid. The early refill window starts on the fill date and extends to 85% of the days' supply (30 * 0.85 = 25.5 days). A second prescription filled during this window would be considered an early refill.

Table 1. Counts of patients with at least one early refill, overall and by opioid type

	Any Opioid			ER/LA Opioids			IR/SA Opioids		
		95% CI			95% CI			95% CI	
	Value	Upper	Lower	Value	Upper	Lower	Value	Upper	Lower
No. of patients with ≥1 opioid prescription	60,566,417			2,277,537			60,290,650		
No. of patients with ≥2 opioid prescriptions*	17,441,494			1,489,575			17,140,940		
% of those with ≥1 prescription	28.8	28.8	28.8	65.4	65.3	65.5	28.4	28.4	28.4
No. of patients with ≥1 early refill	1,667,264			275,636			1,483,810		
% of those with ≥1 prescription	2.8	2.8	2.8	12.1	12.1	12.1	2.5	2.5	2.5
% of those with ≥2 prescriptions*	9.6	9.6	9.6	18.5	18.4	18.6	8.7	8.6	8.7

CI = confidence interval; ER = extended-release; IR = immediate-release; LA = long-acting; LRx, Longitudinal Prescriptions (database); NDC = National Drug Code; SA = short-acting.

*For the same NDC during the patient follow-up period. The repeated NDC does not need to be the index NDC, but it must be from the same class.

method for binomial distributions. All analyses used SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethics

This study complied with all applicable laws, regulations, and guidance regarding patient protection including patient privacy. This was a database study; no individual patients were identified or enrolled. IQVIA has established HIPAA-compliant operating policies and procedures for extracting, translating, loading, and removing all personal health information (de-identifying) before depositing data in the IQVIA databases. The use of LRx was reviewed by the New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subjects research.

Results

Number of Patients with Early Refills

There were 60.6 million patients who met the study eligibility criteria (Table 1), and the clear majority (99.5%) of patients had an index prescription for an IR/SA opioid, while many fewer (3.8%) indexed on an ER/LA opioid. Patients who filled both IR/SA and ER/LA opioids during the study period were included in each group; therefore, the proportion of IR/SA and ER/LA users sums to greater than 100%. The proportion of patients who had at least two opioid prescriptions for the same NDC in the year of follow-up was 28.8%, which was more common for ER/LA-treated patients than IR/SA-treated patients (65.4% vs 28.4%).

Early refills occurred in 2.8% of all opioid-treated patients and 9.6% of those with at least two opioid prescriptions for the same NDC. Early refills in patients with multiple opioid fills were more common among patients who indexed with an ER/LA opioid (18.5%) compared with an IR/SA (8.7%).

Distribution of Early Refills

Among the 1.7 million patients with an early refill, a total of 2.6 million early refills were observed (mean = 1.6 early refills per patient among those with at least one) (Table 2). There was little difference in the number of early refills with respect to opioid type. Most patients had only one early refill over the one-year follow-up (70.9–78.4%).

After noting how rapidly the frequency of early refills decreased with each additional early refill, we chose to consider five early refills to be the threshold for an "abnormally high" number of early refills, which accounted for 3.4% (N = 56,981) of patients who filled an opioid early (Table 2). Early refillers who indexed on ER/LA opioids were more likely to have an abnormally high number of early refills than those who indexed on IR/SA opioids (3.5% vs 2.6%, respectively).

Table 2. Distribution of early refills, overall and by opioid type

	Any Opioid				ER/LA Opioids				IR/SA Opioids			
			95% CI				95% CI				95% CI	
	No.	%	Upper	Lower	No.	%	Upper	Lower	No.	%	Upper	Lower
No. of early refills	2,590,106				442,304				2,147,802			
Average per patient with ≥1 early refill	1.6				1.6				1.4			
SD per patient with ≥1 early refill	1.7				1.7				1.5			
No. of patients with ≥1 early refill by number of early refills	1,667,264				275,636				1,483,810			
1	1,245,069	74.7	74.6	74.7	195,446	70.9	70.7	71.1	1,164,009	78.4	78.4	78.5
2	250,631	15.0	15.0	15.1	48,993	17.8	17.6	17.9	198,903	13.4	13.4	13.5
3	79,332	4.8	4.7	4.8	15,072	5.5	5.4	5.6	58,373	3.9	3.9	4.0
4	35,251	2.1	2.1	2.1	6,449	2.3	2.3	2.4	23,514	1.6	1.6	1.6
≥5	56,981	3.4	3.4	3.4	9,676	3.5	3.4	3.6	39,011	2.6	2.6	2.7

CI = confidence interval; ER = extended-release; IR = immediate-release; LA = long-acting; LRx = Longitudinal Prescriptions (database); NDC = National Drug Code; SA = short-acting.

Table 3. Patient demographics of opioid users with at least two fills, stratified by early refills

	Any Opioid								
	≥2 Opioid Prescriptions			≥1 Early Refills			≥5 Early Refills		
		95% CI			95% CI			95% CI	
	%	Upper	Lower	%	Upper	Lower	%	Upper	Lower
Age									
≤18 y	2.2	2.2	2.2	1.7	1.7	1.7	0.6	0.6	0.7
19–40 y	23.4	23.4	23.4	19.0	18.9	19.0	18.5	18.2	18.8
41–64 y	50.0	50.0	50.0	54.2	54.1	54.3	64.0	63.6	64.4
≥65 y	24.4	24.4	24.4	25.1	25.0	25.2	16.8	16.5	17.1
Sex									
Male	43.0	42.9	43.0	43.9	43.8	43.9	44.7	44.3	45.1
Female	57.0	57.0	57.1	56.1	56.1	56.2	55.3	54.9	55.7
US Census division									
New England	3.8	3.8	3.8	3.3	3.3	3.3	2.1	2.0	2.2
Middle Atlantic	9.4	9.4	9.4	9.1	9.1	9.2	10.0	9.7	10.2
East North-Central	17.4	17.3	17.4	15.7	15.6	15.7	10.1	9.9	10.4
West North-Central	5.6	5.6	5.6	6.4	6.3	6.4	6.8	6.6	7.0
South Atlantic	19.4	19.4	19.4	17.3	17.2	17.4	14.8	14.5	15.1
East South-Central	9.6	9.6	9.6	9.2	9.2	9.3	16.2	15.9	16.5
West South-Central	11.8	11.8	11.8	11.9	11.8	11.9	11.6	11.3	11.8
Mountain	8.3	8.3	8.3	9.5	9.4	9.5	8.5	8.3	8.8
Pacific	13.3	13.3	13.3	15.7	15.7	15.8	17.2	16.9	17.6
Other	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Missing	1.5	1.5	1.5	2.0	2.0	2.0	2.6	2.5	2.8

CI = confidence interval.

Patient Characteristics

Opioid-treated patients with at least five early refills were older than those with one or more early refills, who were in turn older than patients with at least two opioid prescriptions overall, irrespective of early refill status (Table 3). The proportion of patients older than 40 years was 80.9% for those with five or more early refills, 79.3% for patients having any number of early refills, and 74.4% for the overall population of opioid users having at least two fills. This trend was driven by IR/SA patients as the ER/LA patient age distributions were similar across the various subgroups.

In general, patients in the IR/SA opioid-treated cohort were younger than those in the ER/LA cohort at every stage of opioid treatment (Table 4). For instance, 25.8% of IR/SA patients with at least two prescriptions were 40 years or younger vs 12.1% of ER/LA patients. And for patients with five or more early refills, 21.2% of IR/SA patients were 40 years or younger vs 16.4% of ER/LA patients.

The distribution of sex was largely similar for strata formed by opioid type (overall, IR/SA, and ER/LA) and

Table 4. Patient demographics stratified by opioid type and early refills

	ER/LA									IR/SA								
	≥2 Opioid Prescriptions			≥1 Early Refill			≥5 Early Refills			≥2 Opioid Prescriptions			≥1 Early Refill			≥5 Early Refills		
		95% CI			95% CI			95% CI			95% CI			95% CI			95% CI	
	%	Upper	Lower	%	Upper	Lower	%	Upper	Lower	%	Upper	Lower	%	Upper	Lower	%	Upper	Lower
Age																		
≤18 y	0.5	0.5	0.5	0.5	0.5	0.6	0.5	0.4	0.7	2.2	2.2	2.2	1.8	1.8	1.9	0.6	0.5	0.7
19–40 y	11.6	11.5	11.6	12.5	12.4	12.6	15.0	14.3	15.7	23.6	23.6	23.7	19.8	19.8	19.9	20.1	19.7	20.5
41–64 y	61.5	61.4	61.6	59.8	59.6	60.0	65.4	64.5	66.4	49.9	49.8	49.9	53.7	53.6	53.7	64.2	63.7	64.7
≥65 y	26.5	26.4	26.5	27.1	26.9	27.3	19.0	18.2	19.8	24.3	24.2	24.3	24.7	24.6	24.7	15.1	14.7	15.4
Sex																		
Male	44.3	44.2	44.3	44.4	44.2	44.6	49.5	48.5	50.5	42.9	42.9	43.0	43.8	43.8	43.9	43.7	43.2	44.2
Female	55.7	55.7	55.8	55.6	55.4	55.8	50.5	49.5	51.5	57.1	57.1	57.1	56.2	56.1	56.2	56.3	55.8	56.8
US Census division																		
New England	4.8	4.7	4.8	3.6	3.6	3.7	2.1	1.9	2.4	3.7	3.7	3.7	3.2	3.2	3.3	1.9	1.8	2.1
Middle Atlantic	11.3	11.2	11.3	10.8	10.7	10.9	13.0	12.3	13.6	9.3	9.3	9.3	8.9	8.9	8.9	9.2	8.9	9.5
East North-Central	15.0	14.9	15.0	13.6	13.5	13.8	11.4	10.8	12.0	17.4	17.4	17.4	15.8	15.8	15.9	9.6	9.3	9.9
West North-Central	5.3	5.2	5.3	6.8	6.7	6.9	7.3	6.8	7.9	5.6	5.6	5.6	6.3	6.3	6.3	6.4	6.2	6.6
South Atlantic	21.5	21.4	21.5	18.9	18.8	19.0	17.5	16.8	18.3	19.4	19.4	19.4	17.1	17.0	17.1	13.7	13.3	14.0
East South-Central	8.6	8.5	8.6	6.9	6.8	7.0	9.4	8.8	10.0	9.7	9.6	9.7	9.5	9.4	9.5	20.1	19.7	20.5
West South-Central	8.8	8.7	8.8	9.7	9.6	9.9	9.1	8.5	9.7	11.8	11.8	11.9	12.1	12.1	12.2	12.7	12.4	13.0
Mountain	9.4	9.3	9.4	10.6	10.4	10.7	9.3	8.7	9.9	8.3	8.3	8.3	9.4	9.3	9.4	7.4	7.2	7.7
Pacific	13.0	12.9	13.0	16.3	16.2	16.5	17.9	17.1	18.6	13.3	13.3	13.3	15.7	15.7	15.8	16.5	16.1	16.9
Other	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Missing	2.6	2.6	2.6	2.6	2.6	2.7	3.1	2.7	3.4	1.5	1.5	1.5	2.0	1.9	2.0	2.5	2.4	2.7

CI = confidence interval; ER/LA = extended-release long-acting; IR/SA = immediate-release short-acting.

early refill count (two or more opioid prescriptions overall, one or more early refills, and five or more early refills). In all strata, women slightly outnumbered men.

Patients in our study population of those who received at least two opioid prescriptions were geographically diverse. The distribution of patients by US Census division was representative of the 2017 projected US population [13]. For example, 19.4% and 17.4% of all patients with at least two fills for opioids in our study came from the South Atlantic and the East North-Central, compared with 19.9% and 14.4%, respectively, for the 2017 projected US population. Generally, patients in the Pacific and West North were slightly under-represented, while those in other regions were over-represented. The distributions of ER/LA and IR/SA patients by Census division were similar.

No obvious trends were discernable when comparing the geographic distributions of patients across early refill strata, with one exception. Patients with five or more early refills for an IR/SA opioid were more likely to be from the East South-Central division (20.1%) compared with patients with two or more opioid prescriptions overall (9.7%) or those with one or more early refills (9.5%).

Discussion

Our study identified a large number of patients with an opioid prescription and found that early refills among these patients were uncommon, with <3% of patients receiving an opioid with an early refill. However, this behavior occurred in approximately one in 10 patients who refilled their opioid prescription at least once. Early refills were more common within ER/LA opioid-treated patients. It was not the goal of this study to elucidate the reasons for early refills, though it could be that ER/LA opioid-treated patients are more likely to have multiple prescriptions because of an increased severity of the underlying disease and the additional prescriptions provide a greater opportunity for early refills.

When examining the subset of individuals who had an early refill, the majority refilled a prescription early just once during the year, and very few patients had an abnormally high number of early refills that would be indicative of a chronic, systematic behavior. Thus, early refills may be due to matters of convenience, such as filling a prescription early before a vacation.

Importantly, the opioid-treated patient population was largely representative of the projected 2017 US population. Because of this, in addition to the fact that the data source used in this study captures more than 90% of all retail prescriptions, it follows that conclusions about the frequency of early refills are generalizable to the US population.

Our study uncovered several differences between the strata under investigation, such as the observation that ER/LA opioid-treated patients were older than IR/SA opioid-treated patients. This observation supports the narrative that ER/LA patients may have had a higher incidence of progressive diseases and/or more poorly tolerated pain, as would be expected in an older population.

A related observation was that IR/SA opioid-treated patients with a record of an early refill were older than patients without early refills.

There were differences in patient geographic locations among patients with a high number of early refills when compared with patients without early refills, specifically the increased number of individuals from the East South-Central Census division. Comparing the trends we see in our study vs a map of opioid overdose death rates [14], we see that the two states with data in the East South-Central division (Kentucky and Tennessee) have high overdose, rates which is consistent with our findings that this region accounts for a high proportion of patients who have many early refills. However, when examining another division with high overdose rates, New England, there is not an over-representation of this division in the group of individuals with five or more early refills, reflecting no ecologic correlation between our findings for early refills and published rates of opioid overdose. One potential explanation for the differences in early refills by region is that there exist true differences in prescribing practices or patient needs geographically.

Several strengths of our study are noteworthy. We leveraged a large, electronic dispensed prescription records database with broad coverage in the United States, which allowed us to identify millions of patients geographically representative of the United States. Our choice of early refill metric was informed by the literature. Our stratification by opioid type allowed us to better contextualize early refills, and our comparison of demographic characteristics among various populations of interest supports the generalizability of our results.

Our study is subject to limitations, many of which are common to all database studies, such as the potential for selection bias and measurement error. We applied the threshold for early refills as the number of days between prescriptions $\geq$15% lower than the days' supply of the first prescription to all intended treatment durations, though the clinical relevance of refilling a seven-day prescription two days early and refilling a 30-day prescription five days early may not be comparable. Because we did not consider dispensed quantity in our estimation of early refills, we may also have classified early refills for prescriptions that were clearly intended for use as-needed (e.g., an IR/SA opioid prescription with a supply of 29 days and a quantity dispensed of five to 10 tablets or capsules; however, the days' supply of prescriptions that are prescribed as-needed is determined according to the maximum number of pills that could be taken each day, and such a large discrepancy between quantity and days' supply would be atypical). Consecutive prescriptions were assessed via NDCs. Prescriptions of the same ingredient but with different NDCs, for example, filling a branded and then generic drug, substituting the same drug from a different generic manufacturer, a change in package size, or other reasons, were not considered for early refills. This study only reflects prescribed opioids and does not capture opioids obtained by other means. The assessments in this report only consider retail pharmacies; however, the retail channel of the LRx captures 84.7% of morphine/opium noninjection products and 88.4% of codeine and combination noninjection products. We were unable to identify early refills that occurred across channels, that is, those that occurred in a nonretail setting. The indication for the prescribed opioid was not available from the data source, which may have added additional useful information. Further, our method for estimating early refills was insensitive to the expected duration of use of the opioids.

Conclusions

Refilling an opioid prescription early is a relatively uncommon behavior. When limiting to patients who refilled an opioid at least one time, we found that nearly 10% of patients refilled early at least once within a one-year period, but those were primarily isolated events. Further research is warranted to explore the reasons for this behavior in order to understand whether it is a signal of opioid use disorder, due to pain treatment needs, or due to patient logistics. If deemed necessary by such research, efforts could be taken to use early refill information to identify these patients and bring about interventions and employ harm reduction strategies.

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References

1. Dart RC, Surratt HL, Cicero TJ, et al. Trends in opioid analgesic abuse and mortality in the United States. N Engl J Med 2015; 372(3):241–8.
2. Guy GP Jr, 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.
3. Hedegaard H, Minino AM, Warner M. Drug overdose deaths in the United States, 1999-2017. NCHS Data Brief 2018;(329):1–8.
4. Rudd RA, Seth P, David F, Scholl L. Increases in drug and opioid-involved overdose deaths—United States, 2010-2015. MMWR Morb Mortal Wkly Rep 2016;65(5051):1445–52.
5. US Food and Drug Administration. Opioid analgesic risk evaluation and mitigation strategy (REMS). 2019. Available at: https://opioidanalgesicrems.com/RpcUI/home.u (accessed July 2019).
6. US 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. 2018. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm620935.htm (accessed July 2019).
7. Paulozzi LJ, Strickler GK, Kreiner PW, Koris CM. Controlled substance prescribing patterns—prescription behavior surveillance system, eight states, 2013. MMWR Surveill Summ 2015; 64(9):1–14.

8. White AG, Birnbaum HG, Schiller M, Tang J, Katz NP. Analytic models to identify patients at risk for prescription opioid abuse. Am J Manag Care 2009;15(12):897–906.
9. Starrels JL, Becker WC, Weiner MG, Li X, Heo M, Turner BJ. Low use of opioid risk reduction strategies in primary care even for high risk patients with chronic pain. J Gen Int Med 2011;26 (9):958–64.
10. Katz N, Panas L, Kim M, et al. Usefulness of prescription monitoring programs for surveillance—analysis of Schedule II opioid prescription data in Massachusetts, 1996-2006. Pharmacoepidemiol Drug Saf 2010;19(2):115–23.
11. Pradel V, Delga C, Rouby F, Micallef J, Lapeyre-Mestre M. Assessment of abuse potential of benzodiazepines from a prescription database using 'doctor shopping' as an indicator. CNS Drugs 2010;24(7):611–20.
12. Pradel V, Frauger E, Thirion X, et al. Impact of a prescription monitoring program on doctor-shopping for high dosage buprenorphine. Pharmacoepidemiol Drug Saf 2009;18(1): 36–43.
13. US Census Bureau. American FactFinder. Annual estimates of the resident population: April 1, 2010 to July 1, 2017 2018. Available at: https://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml? pid=PEP_2017_PEPANNRES &prodType=table (accessed July 2019).
14. National Institutes of Health, National Institute on Drug Abuse. Opioid summaries by state 2019. Available at: https://www.drugabuse.gov/drugs-abuse/opioids/opioid-summaries-by-state (accessed July 2019).