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Review Article

ER/LA Opioid Analgesics REMS: Overview of Ongoing Assessments of Its Progress and Its Impact on Health Outcomes

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Conflicts of interest: All of the authors are employees of companies that sponsor the ER/LA opioid analgesics REMS and market ER/LA opioid analgesics.

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Abstract

Objective. Opioid abuse is a serious public health concern. In response, the Food and Drug Administration (FDA) determined that a risk evaluation and mitigation strategy (REMS) for extended-release and long-acting (ER/LA) opioids was necessary to ensure that the benefits of these analgesics continue to outweigh the risks. Key components of the REMS are training for prescribers through accredited continuing education (CE), and providing patient educational materials.

Methods. The impact of this REMS has been assessed using diverse metrics including evaluation of prescriber and patient understanding of the risks associated with opioids; patient receipt and comprehension of the medication guide and patient counseling document; patient satisfaction with access to opioids; drug utilization and changes in prescribing patterns; and surveillance of ER/LA opioid misuse, abuse, overdose, addiction, and death.

Results and Conclusions. The results of these assessments indicate that the increasing rates of opioid abuse, addiction, overdose, and death observed prior to implementation of the REMS have since leveled off or started to decline. However, these benefits cannot be attributed solely to the ER/LA opioid analgesics REMS since many other initiatives to prevent abuse occurred contemporaneously. These improvements occurred while preserving patient access to opioids as a large majority of patients surveyed expressed satisfaction with their access to opioids.

Key Words. Opioid Abuse; REMS; Opioids; Epidemiology

Introduction

The increase in abuse of opioids over the last decade has resulted in a public health concern about addiction, overdose, and death [1–3]. In response to these safety concerns, the Food and Drug Administration (FDA) determined that a single, shared system Risk Evaluation and Mitigation Strategy (REMS) was necessary for

extended-release and long-acting (ER/LA) opioids [4]. The FDA approved the ER/LA opioid analgesics REMS (hereafter referred to as the "REMS") on July 9, 2012. ER/LA opioid analgesics are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment, and for which alternative treatment options are inadequate. The goal of the REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioids, while maintaining access to these medications for those patients who need them for effective pain management [4].

This REMS is distinctive in its structure and the public health importance of its outcomes. The manufacturers of ER/LA opioids (currently 24 companies), referred to as the REMS program companies (RPC), are collaborating to operationalize this complex national program [5]. The RPC includes a diverse array of branded and generic companies, both large and small. A unique aspect of this REMS is that it is a prototype for the use of accredited continuing education (CE) to meet a REMS training requirement. Use of accredited CE required the RPC to meet regulatory requirements for the REMS established by FDA, while remaining in compliance with the Accreditation Council for Continuing Medical Education standards for commercial support for continuing education training courses. The result is that the content and delivery of CE is independent from the RPC.

Prescriber education in the form of accredited CE has been made available through unrestricted educational grants to CE providers. The content of these CE training courses is directed by the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics (FDA Blueprint) [6]. Additionally, the RPC created and the FDA revised patient educational materials including a one-page medication guide that is provided by a pharmacy with each dispensing of an ER/LA opioid and a one-page patient counseling document (PCD) to be used by health care providers when counseling patients [5]. The impact of these interventions is assessed annually using a variety of outcomes from numerous studies.

The goal of this article is to provide an overview of the progress of the REMS activities and general findings of the various studies conducted to assess the effectiveness of the REMS after 36 months of operation. The main outcomes and results of the primary analysis will be highlighted here. It is planned that further details on individual assessments will be provided in future publications.

Methods

To assess the impact of the REMS, the RPC is measuring a variety of outcomes on a yearly basis. These include the number of prescribers completing a REMS-compliant CE activity; results of independent audits of REMS-compliant CE training courses; evaluation of the knowledge and behaviors of prescribers; assessment of receipt and comprehension of the medication guide and patient counseling document by patients; patient satisfaction with their access to opioids; evaluation of drug utilization and prescribing patterns through claims databases; and surveillance monitoring for misuse, abuse, overdose, addiction, and death associated with ER/LA opioids utilizing various programs, including RADARS (R) Poison and Treartment Center data, as well as NAVIPPRO (R) Treatment Center data.

In many of these assessments, outcomes from July 2010 through June 2012 were compared to those from July 2013 through August or December 2014. The first period reflects the pre-implementation period of the REMS as a baseline, and the second period reflects the active period after full implementation of the REMS. The transition year (July 2012–June 2013) reflects the period when the REMS was being established.

Results

Educational Training Courses

Education for prescribers of ER/LA opioid analgesics is provided through accredited CE training courses supported by unrestricted educational grants from the RPC [5]. The CE training courses must include the full content of the FDA Blueprint, as well as a knowledge assessment covering all sections of the FDA Blueprint, in order to be considered "REMS-compliant." The content is directed toward prescribers of ER/LA opioid analgesics, but is also relevant for other healthcare professionals (e.g., pharmacists) involved in the care of patients with pain.

Over 500 RPC-funded REMS-compliant CE training courses were conducted by CE providers in 2013 and 2014. A performance goal of 80,000 ER/LA opioid prescribers having completed training within 2 years of the first training becoming available (March 1, 2013) was established by the FDA. There are approximately 320,000 active ER/LA opioid prescribers in the United States (unpublished data from IMS). To count towards the goal, FDA required that a prescriber had to take a REMS-compliant CE activity, complete the post-training evaluation, and endorse that they had prescribed an ER/LA opioid in the past year.

The REMS is designed by the FDA to include prescribers of ER/LA opioids who completed REMS-compliant training, either funded by RPC or funded by non-industry sources as long as the courses cover the content defined in the FDA Blueprint and are independent of the influence of commercial sponsors. As of February 28, 2015, approximately 143,126 participants participated in a REMS-compliant CE activity, of which approximately 82,131 completed the post-test evaluation, of which 37,512 endorsed that they had prescribed an ER/LA opioid in the past year. Therefore

37,512 trained prescribers count toward the REMS performance goals. In addition, over 100,000 health care providers completed a CE training course on safe opioid prescribing sponsored by the National Institute on Drug Abuse (NIDA), but these completers did not count towards the performance goals because the NIDA course covered some but not all of the content in the FDA Blueprint. Other ER/LA opioid prescribers completed opioid CE training courses mandated by their state licensing boards, such as the State of Utah that requires opioid prescribers to take a state-mandated training, but would not count towards the REMS performance goals because the training course does not cover all FDA Blueprint content. This impacts the reach of the REMS since these prescribers are unlikely to also complete a REMS-complaint CE course, thus diluting the eligible "pool" of target prescribers for REMS-compliant education. The existence of such non-REMS-compliant CE courses may contribute to overall knowledge of the topic and improvements in associated health outcomes.

Prescriber Knowledge of the Safe Use and Appropriate Prescribing of ER/LA Opioids

A survey of ER/LA opioid prescribers was conducted to assess knowledge and behaviors relating to the safe use and appropriate prescribing of ER/LA opioids, as described in the REMS educational materials and FDA Blueprint, and to compare the knowledge of prescribers who completed and those who did not complete a REMS-compliant CE training courses. The most recent survey was conducted from February 2015 to April 2015. The aim was to survey 600 prescribers, half of whom completed a CE training course and half that did not. Completers of a REMS-compliant CE training course were recruited from a list of prescribers who had completed a REMS-compliant CE activity, while a target sample of opioid prescribers without REMS-compliant CE training was recruited from a list of all ER/LA opioid prescribers obtained from IMS Health. For the latter sample, a total of 11,284 e-mail invitations were sent and the survey closed after 8 weeks when the desired number of prescribers was achieved.

A total of 612 prescribers completed the survey: 301 recruited from a list of prescribers who had completed a REMS-compliant CE activity and 311 from a list of all ER/LA opioid prescribers obtained from IMS. The majority of respondents (80% or more) from both groups answered at least 72% of the questions correctly. The questions answered correctly by less than 80% of respondents were related to the concepts of opioid tolerance, conversion between different opioid products, and product-specific information regarding indications and usage.

Prescribers who completed the REMS-compliant education programs had higher knowledge scores and they reported using the PCD more often.

Patient Understanding of Risks Associated with ER/LA Opioids, Medication Guide and Patient Counseling Document Use and Satisfaction with Access to Opioids

A survey of commercially-insured patients identified through the HealthCore Integrated Research Database^{SM} (HIRD) was conducted to assess receipt and comprehension of the medication guide and patient counseling document as well as patient understanding of the risks associated with ER/LA opioids. Patient satisfaction with their ability to access, obtain and fill their opioid prescriptions was also measured.

Patient respondents who filled at least one prescription for ER/LA opioids between September 2013 and August 2014 were recruited from a commercial health insurance plan database. To obtain the desired 400 responders, 2,441 patients were contacted and the desired number of participants was achieved within 3 weeks.

A total of 423 adult patients completed the survey. The mean age was 50 years, 60% were female, and all geographic regions of the U.S. were represented. The participants were more often females and slightly older than the patients on ER/LA opioids in the HIRD database; the geographic distribution was similar.

Nearly all respondents (99%) reported that they received or read the medication guide, of whom 98% reported understanding more than half of the information. A smaller proportion of respondents reported that they received the PCD (46%). Knowledge of safe use was high, as 74% of respondents had a score above 80% on the assessment of understanding of risks of taking ER/LA opioids.

Factors predicting high knowledge scores included a self-reported understanding of the PCD (odds ratio [OR] = 2.5, 95% confidence intervals [CI] 1.1 to 5.7), having a pain specialist prescribe the ER/LA opioids (OR = 2.4, 95% CI 1.3 to 4.3), being a female (OR = 2.3, 95% CI 1.3 to 4.1), and having completed a college degree (OR = 1.9, 95% CI 1.0 to 3.4).

The questions with a level of understanding less than 80% were related to the need to store ER/LA opioids away from other household medications, never splitting or crushing tablets, and the need to inform a healthcare provider in case of fever when using opioid patches.

In terms of patients' ability to obtain their medications, 71% of respondents reported satisfaction with their access to ER/LA opioids. However, the sample was selected from patients prescribed ER/LA opioids, so access findings may not be generalizable to patients with chronic pain not prescribed opioids.

Opioid Abuse Rates in Substance Abuse Treatment Center Programs

Opioid abuse rates before and after implementation of the REMS were compared by conducting repeated cross-sectional studies employing two sources of data, the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System [7] and the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO®) [8,9]. These systems capture self-reported information from patients entering private or public substance abuse treatment programs.

The rates of abuse were calculated as the number of cases of abuse of ER/LA or immediate release (IR) opioids in the past 30 days per 100,000 U.S. population for the 3-digit ZIP codes covered by the RADARS or NAVIPPRO programs. Poisson regression was utilized to compare average rates before and after the REMS.

Both systems showed a decrease in the rates of ER/LA opioids abuse after REMS implementation. In the RADARS System, there was a 47.0% decrease, (95% CI – 60.0 to – 29.8) and in the NAVIPPRO System there was a 20.4% reduction (95% CI – 25.4 to – 15.2). The decrease in the rates of IR opioid abuse was 12.1% (95% CI – 27.3 to 6.3) in the RADARS System and 18.2% (95% CI – 22.8 to – 13.3) in the NAVIPPRO System. The decrease in the ER/LA opioid group was statistically significantly larger than the decrease in the IR opioid group in the RADARS System but not in the NAVIPPRO System (Table 1).

Opioid Abuse and Overdose in Poison Center Programs

The risk of opioid abuse and overdose before and after implementation of the REMS was evaluated through surveillance using the RADARS System Poison Center Program. Poison center data collected through the RADARS System provide an estimate of change in abuse and overdose associated with opioids. Anonymized data were obtained about individuals from the general population and healthcare providers seeking advice regarding potential toxic exposures, including prescription opioids [7]. The two outcomes of interest were opioid abuse and any opioid exposures resulting in the designation of major medical outcome, hospitalization or death.

There was a 44.0% decrease (95% CI – 50.6 to – 36.6) in rates of ER/LA opioid abuse reported to US poison centers in the active period compared with the pre-implementation period, whereas there was a smaller decrease of 30.9% (95% CI – 36.4 to – 24.9), observed for IR opioids. The decrease for the ER/LA opioid group was statistically significantly larger than that for the IR opioids (Table 1).

Additionally, a decrease in rates of major medical outcome, hospitalization or death, was observed for both ER/LA and IR opioids. The decrease from the pre-implementation to the active period was 24.9%, (95% CI – 29.3 to – 20.2) for ER/LA opioids and 12.5%, (95% CI – 15.0 to – 9.9) for IR opioids. The decrease for the ER/LA opioid group was statistically significantly larger than that for the IR opioids (Table 1).

Table 1 General findings of some of the studies conducted to assess the effectiveness of the REMS after 36 months of operation

	Mean rate before ER/LA opioids	Mean rate after ER/LA opioids	Percent change ER/LA opioids	Mean rate before IR opioids	Mean rate after IR opioids	Percent change IR opioids
Opioid abuse (poison center)	0.123	0.069	−44.0 (−50.6, −36.6)	0.276	0.191	−30.9 (−36.4, −24.9)
Major medical outcome, hospitalization, or death (poison center)	0.250	0.188	−24.9 (−29.3, −20.2)	1.220	1.068	−12.5 (−15.0, −9.9)
Opioid abuse in treatment center programs (RADARS)	1.987	1.053	−47.0 (−60.0, −29.8)	2.133	1.875	−12.09 (−27.3, 6.3)
Opioid abuse in treatment center programs (NAVIPPRO)	0.1415	0.1125	−20.4 (−25.4, −15.2)	0.2426	0.1985	−18.2 (−22.8, −13.3)
Opioid related mortality in state of Washington medical examiner database	1.930	1.355	−29.8 (−39.8, −18.1)	0.276	0.199	−28.1 (−50.8, 5.2)

Rates are per 100,000 persons.

Opioid Related Mortality in State Medical Examiner Database

Changes in mortality rates associated with prescription opioids before and after the REMS were evaluated based on the Washington State medical examiner database. Mortality data do not generally differentiate ER/LA opioids from IR opioids, since forensic toxicology tests can identify the active ingredient, but not the formulation associated with a fatality. Two categories of analgesic groups were evaluated: 1) all opioids at the ingredient level included in the REMS (excluding hydrocodone), and 2) as a non-ER/LA opioid comparator, hydrocodone, which was only available as IR combination products during the study period.

There was a 29.8% decrease in mortality rate (95% CI – 39.8 to – 18.1) in the active period compared to the pre-implementation period in the ER/LA opioid group. In the hydrocodone only group, a 28.1% decrease was observed (95% CI – 50.8 to 5.2), but was not statistically significant. The decrease for the ER/LA opioid group was not significantly different than that for the hydrocodone group (Table 1). Figure 1 depicts mean death rates over time in both groups in the State of Washington. Data from additional states are being sought for subsequent analyses.

Opioid Emergency Department Visits

The incidences of emergency department (ED) visits and hospitalizations for opioid overdose and poisoning between the pre-implementation period and the REMS active period were compared by conducting a cohort study using the HealthCore Integrated Research Database^{SM} (HIRD), as well as data obtained from U.S. Medicaid.

This study included patients who received at least one dispensing of an ER/LA opioid during one or more of the REMS study periods. Incidence rates were calculated by dividing the number of opioid overdose events observed during each REMS period by the total person-time at risk within that same period. Adjusted incidence rate ratios (IRR) were then calculated, comparing the pre-implementation period to the active period of the REMS.

Among commercially insured patients, 80,209 ER/LA opioid recipients were identified in the 24-month pre-implementation period compared to 43,730 recipients in the 13-month active period. In the Medicaid population, 3,488 ER/LA opioid recipients were identified in the pre-implementation period compared to 3,625 recipients in the active period.

Medicaid-insured patients had a much higher incidence of opioid overdose and poisoning events than commercially insured patients. In the commercially insured subjects, the incidence of these events during the pre-implementation period was 84.6 (95% CI 76.5 to 93.5) per 10,000 person-years. In contrast, the incidence was 244.6 (95% CI 182.7 to 320.7) per 10,000 person-years in the Medicaid population.

Among commercially insured patients, the IRR for opioid overdose for the active period versus the pre-implementation period was 0.83 (95% CI 0.70 to 0.99). Among Medicaid patients, the IRR for opioid overdose for the active period versus the pre-implementation period among all users was 0.81 (95% CI 0.59 to 1.18). Those rates were calculated after adjustment for potential confounders (e.g., use of sleep medication, alcohol abuse, psychiatric disorders and history of overdose). It is difficult to assign causal attribution to these results.

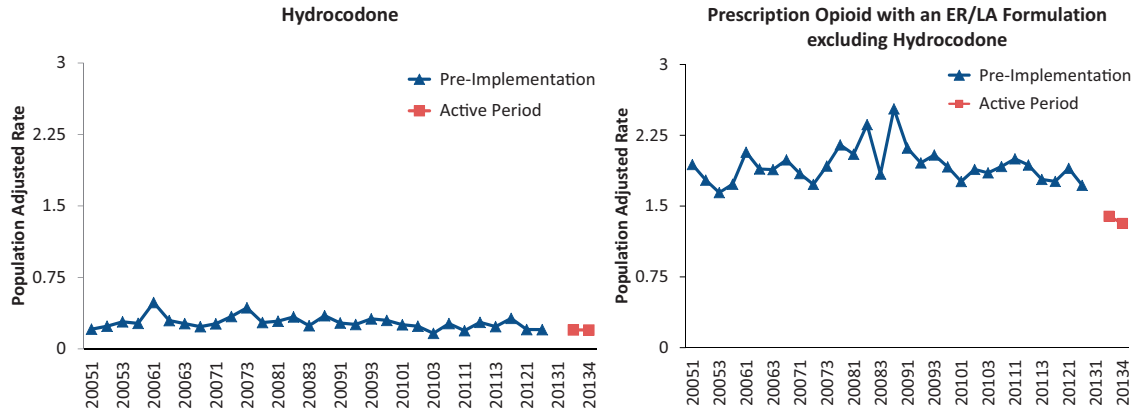

Figure 1 Washington State medical examiner mean death rates per 100,000 population for prescription opioids at the ingredient level included in the REMS (excluding hydrocodone) and hydrocodone from 2005 to 2013. There is a decrease in mortality rate in the active period compared to the pre-implementation period in the ER/LA opioid group. Horizontal lines represent 95% confidence intervals.

Table 2 Opioid prescription volume before and after REMS after 36 months of operation

	Before REMS	After REMS	% change (95% confidence interval)	*P* value
ER/LA opioids				
Overall ER/LA volume	5,575,834	5,336,053	−4.3 (−6.1, −2.4)	0.0001
Overall ER/LA volume by age (years)				
0–18	17,991	20,898	16.2 (−13.3, 47.8)	0.215
19–40	878,422	696,844	−20.7 (−25.7, −15.2)	0.0001
41–64	3,526,106	3,363,155	−4.6 (−6.7, −2.5)	0.0001
>=65	1,153,164	1,255,156	8.8 (6.4, 11.4)	0.0001
Overall IR volume	37,339,058	34,519,228	−7.6 (−14.5, −0.5)	0.033

Opioid Utilization Patterns

Opioid drug utilization patterns and changes in prescribing behaviors before and after implementation of the REMS were evaluated by conducting a drug-utilization study using data from two IMS Health prescription databases: National Prescription Audit™ (NPA™) and LifeLink™ patient-level longitudinal prescription (LRx). The resulting data set was representative of retail prescription activity among the U.S. population.

A statistically significant decrease of 4.3% was observed in ER/LA opioid prescription volume after REMS implementation. The average prescription volume per quarter for all ER/LA opioids in the pre-implementation period was estimated at 5.58 million, and decreased to 5.34 million in the active period. IR opioid prescription volume declined 7.6% during the same time periods, from 37.34 million prescriptions to 34.52 million (Table 2). The decrease in prescription volume was observed for patients between the ages of 19 and 64, but not for patients above 65. The largest decrease of 20.7% was observed in patients between 19–40 years of age (Table 2).

Changes in prescriber behavior were assessed by evaluating inappropriate prescribing of certain ER/LA opioids, defined as prescribing of ER/LA opioid products indicated only for opioid-tolerant patients to non-opioid-tolerant patients. Patients were classified as opioid-tolerant if they had received a daily morphine equivalent dose $\geq$60 mg in the week prior to receiving the ER/LA opioids of interest [10].

A decrease in the proportion of non-tolerant patients that should not be prescribed specific products or doses was observed for all products studied, although the difference was only statistically significant for ER hydromorphone. The proportion of non-tolerant patients dispensed ER hydromorphone decreased 8.8%. In addition, concomitant prescribing of benzodiazepines decreased 3.7% in the active period compared with the pre-implementation period.

Changes in prescribing behavior were also evaluated based on the specialty/profession of the prescribers. The average monthly volume of ER/LA opioid prescriptions remained stable for pain specialists and physical medicine and rehabilitation specialists. While there was a statistically significant decrease for almost all other prescribing specialties, the largest decrease was observed for dentists (48.5%) and emergency medicine specialists (25.5%). In contrast, a statistically significant increase was observed for nurse practitioners (33.7%) and physician assistants (31.2%). The increased prescribing by nurse practitioners and physician assistants was also observed for several comparator drugs, including antibiotics, IR opioids and celecoxib.

This phenomenon is consistent with a general trend toward greater prescribing by these healthcare professionals in recent years [11,12]. Celecoxib, an NSAID, was used as a comparator because it is commonly used to treat chronic pain and is only available by prescription.

Discussion

This report provides a summary of the results from the ER/LA Opioid Analgesics REMS to date and the assessment of its potential impact on public health. The findings suggest that the rapid increase in rates of opioid abuse or addiction, overdose, and death related to ER/LA analgesics opioids that was observed before the implementation of the REMS has leveled off and even started to decline. This finding for ER/LA opioids is in contrast to increases in deaths related to all opioids reported by the CDC, which also include immediate-release opioids, heroin and illicit fentanyl, with recent increases in fatalities with heroin and illicit fentanyl [13].

These improvements have taken place while seemingly preserving access to ER/LA opioids for the treatment of chronic pain, as a large majority of patients report that they are satisfied with their access to ER/LA opioids.

The ER/LA opioid REMS was introduced as part of a Presidential plan to prevent opioid abuse and its consequences that consisted of four components: education, monitoring, proper medication disposal, and enforcement [1,14]. Along with the implementation of this REMS, many other interventions targeting opioids in

general have occurred. These include prescribing and prescription monitoring standards at state and/or health system level [15,16], requirements from some states and/or health systems for prescriber opioid and/or pain management training [17], and the requirement by some healthcare systems and states that chronic pain patients be seen by pain specialists [18]. Also, abuse deterrent formulations of several ER/LA opioids have been introduced to the US market [19]. The decrease in opioid abuse, overdose, and death that occurred after the REMS was implemented suggests that these complimentary initiatives as a whole have been associated with decreases in abuse of ER/LA opioids, but cannot be causally attributed to the REMS. The findings of a plateau or even a decrease in opioid abuse and overdose due to prescription opioids have also been reported recently by other research groups [19,20].

The generalization of the findings of some of the studies conducted to assess the impact of the REMS could be limited to the commercially insured population. For example, to assess patient understanding of risks associated with ER/LA opioids, the receipt of the medication guide and the satisfaction with access to opioids, we surveyed commercially insured patients who were prescribed ER/LA opioids. The experience of uninsured patients or patients not prescribed opioids could be different. In addition, the patient survey did not include a pre-post evaluation so changes in patient satisfaction with access to opioids cannot be discerned. Similarly the opioid emergency department visit study results were predominately based on a commercially insured population, since only one state with a Medicaid population was included. Rates of opioid overdose were higher in the Medicaid than the commercially insured population.

The RPC continues to explore strategies to raise awareness of the REMS and REMS-compliant CE training courses and to further increase the number of healthcare professionals completing these programs.

In addition to this REMS, the manufacturers of branded ER/LA opioids are collaborating to fulfill recent class-wide post-marketing research requirements mandated by the FDA. Public comments on these research protocols have been received and as of summer 2015, the final protocols were approved by the FDA and some of the studies have been initiated [21]. These studies, in parallel with the continuous assessment of the REMS, will provide valuable information to better understand and improve the risk-benefit profile of ER/LA opioids as well as help understand the appropriate place of ER/LA opioids in treating chronic pain.

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