

# Implications of the Extended-Release/Long-Acting Opioid REMS for Managed Care

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**E**xtended-release and long-acting (ER/LA) opioid formulations are designed to deliver stable plasma concentrations over the dosing interval and provide chronic pain patients with the convenience of regular and less frequent dosing intervals, especially at night.<sup>1</sup> But higher doses and a long duration of action increase the risk of overdose when ER/LA formulations are misused, especially by opiate-naïve persons.<sup>2</sup> In the United States, the use of ER/LA opioid analgesics has increased steadily since the first ER opioid formulation, MS Contin (morphine), was approved by the FDA in 1987. A nationwide survey of outpatient retail pharmacies found that the number of prescriptions for ER/LA opioid analgesics more than doubled over the last decade, increasing from 9.3 million prescriptions in 2000 to 22.9 million in 2009. ER/LA formulations account for only a small portion, 9%, of the opioid analgesic prescriptions during this period. The volume for immediate-release (IR) formulations increased from 164.8 million in 2000 to 234 million in 2009.<sup>3</sup> Since 2010, the number of prescriptions for opioid analgesics has stabilized.<sup>4</sup>

A confluence of factors may have contributed to the increase in use of ER/LA opioids, including aggressive promotion from the pharmaceutical industry, efforts to address under-treatment of pain, and underestimation of the risk of opiate addiction during treatment of chronic pain.<sup>5,6</sup> The liberal increase of opioid analgesic prescribing over the past 20 years has been accompanied by an epidemic of prescription opioid misuse, abuse, and overdose. The earliest sign of the impending public health crisis was an upswing in abuse, diversion, and addiction reported in 2000 with Oxycontin (oxycodone), which had received FDA approval only 4 years earlier.<sup>6</sup> Between 2000 and 2009, the epidemic accelerated as opiate usage increased. Since 2010, the volume of opioid prescriptions has stabilized and rates of prescription opioid diversion,

## Abstract

The intent of the Risk Evaluation and Mitigation Strategy for extended-release/long-acting (ER/LA) opioid analgesics is to reduce harm by teaching prescribers how to safely use opioid analgesics. Key concepts include appropriate selection of doses and formulations for individual patients, avoidance of drug interactions that contribute to opioid toxicity, and anticipation and management of adverse effects. Abuse-deterrent opioid formulations have the potential to reduce opiate abuse and overdose, but they create unique challenges for managed care organizations.

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For author information and disclosures, see end of text.

abuse, and deaths have plateaued.<sup>4</sup> In response to the epidemic, the FDA implemented a Risk Evaluation and Mitigation Strategy (REMS) for ER/LA opioid analgesics. This article explores how the ER/LA opioid REMS impacts managed care clinicians, and applies REMS principles to the treatment of chronic pain patients in managed care.

### ER/LA Opioid Analgesic REMS

In 2011, the Office of National Drug Control Policy (ONDCP) released the national prescription drug abuse plan to combat the prescription drug abuse epidemic in the United States.<sup>7</sup> The plan, which focuses on opioid analgesics, has 4 components: education, tracking and monitoring, proper disposal, and enforcement. The key educational element of the plan is the FDA's ER/LA opioid REMS. In 2007, legislation granted the FDA the authority to require pharmaceutical companies to develop and implement REMS programs.<sup>2</sup> In 2009, the FDA started planning a classwide REMS to replace earlier voluntary Risk Minimization Action Plans for individual opiates like oxycodone and fentanyl. Meetings were held with stakeholders, including pharmaceutical companies, other government agencies, patient advocacy groups, and organizations representing prescribers, pharmacists, and insurance providers. The process culminated in the approval of the ER/LA opioid REMS in 2012.<sup>2</sup> **Table 1**<sup>8-24</sup> summarizes the ER/LA opioids affected by the REMS.

The REMS requires drug manufacturers to develop educational materials and initiatives to train prescribers in the appropriate use of opioid analgesics, as well as educational materials for patients on the appropriate use and disposal of opiate analgesics.<sup>25</sup> The REMS contains 2 components of patient education: a patient counseling document for clinician use, and a specific medication guide for each formulation. Although pharmacists are not the intended audience, they will likely play a key role in implementing the patient education component of the REMS.<sup>26</sup> Pharmacist-delivered patient education to chronic pain patients has demonstrated a reduction in adverse effects and increased patient satisfaction, and may reduce pain.<sup>27,28</sup>

In response to the FDA requirement for a shared response, pharmaceutical companies formed a consortium, the REMS Program Companies, to fund development of continuing education (CE) programs by independent providers. An FDA blueprint outlines the required content for 2- to 3-hour CE programs aimed at opioid prescribers.<sup>29</sup> Continuing education programs that

meet the requirements of the FDA blueprint are available at [www.er-la-opioidrems.com](http://www.er-la-opioidrems.com). The FDA established a performance goal for prescriber participation in these CE programs, expecting 60% of the 320,000 active schedule-II controlled-substance prescribers to begin participating in these programs within 4 years.<sup>25</sup> Follow-up surveys will assess whether the REMS has negatively impacted access to opioid analgesics for legitimate patients.<sup>2</sup> Proposed metrics for evaluating the effectiveness of REMS education include prescribing formulations to opiate-naïve patients when those formulations are intended only for opiate-tolerant patients, filling prescriptions for ER/LA opioids early, the incidence of urine drug screening, use of ER/LA formulations for acute pain, high daily doses, and overlapping of opioid and benzodiazepine prescriptions.<sup>30,31</sup>

The FDA did not require prescriber education to be mandatory, out of concern that it might burden the healthcare system, impede patient access to LA opiates, and require registration of prescribers that would duplicate the existing Drug Enforcement Administration (DEA) registration system.<sup>2</sup> The number of stakeholders involved makes the inclusion of mandatory requirements complicated. The REMS is estimated to affect approximately 700,000 DEA-registered prescribers of schedule II opioid analgesics, 4 million patients receiving ER/LA opioid analgesics, 20 pharmaceutical companies (including generics), and 30 products.<sup>32</sup> Although prescriber education is not mandatory now, the ONDCP plan recommends passing legislation that requires mandatory training about appropriate opioid use as part of the DEA registration application process.<sup>33</sup>

The decision by the FDA to limit the opiate REMS to ER/LA formulations is controversial. These formulations account for only a small portion of opioid prescription volume, but a disproportionate number of emergency department (ED) admissions for nonmedical use of opioids.<sup>34</sup> Critics argue that failing to include IR formulations could imply that they are safer, and could lead to a preference for prescribing IR formulations.<sup>35</sup> Others consider the ER/LA opioid REMS a first step in the implementation of a REMS that includes all opioids. Although IR formulations are currently exempt, a REMS for the rapid-onset opiates, specifically transmucosal fentanyl, has more stringent requirements, including enrollment of wholesalers, prescribers, pharmacies, and patients, and access only through a restricted distribution program.<sup>36</sup>

Education is not the only component of the ER/LA opioid REMS. Additional FDA actions include labeling changes to strengthen warnings about abuse and addic-

**Table 1.** Extended-Release and Long-Acting Opioids Affected by REMS<sup>8-24</sup>

Generic Name, Brand Name, and Manufacturer	Dosage Form and Interval Strengths	Strengths Only for Opioid-Tolerant <sup>a</sup>	Abuse-Deterrent Label	Generic Available	Alcohol Dose-Dumping
Buprenorphine: CIII					
Butrans Purdue Pharma	Patch every week 5 to 20 mcg/h	7.5, 10, 15, 20 mcg/h	No	No	No
Fentanyl: CII					
Duragesic Janssen	Patch every 3 days 12 to 100 mcg/h	All strengths	No	Yes	No
Hydrocodone: CII					
Hysingla ER Purdue Pharma	ER tab every 24 h 20 to 120 mg	80, 100, 120 mg	Yes	No	No
Zohydro ER Pernix	ER cap every 12 h 10 to 50 mg	>40 mg/dose or 80 mg/day	No <sup>b</sup>	No	Yes
Hydromorphone: CII					
Exalgo Mallinckrodt	ER tab every 24 h 8 to 32 mg	All strengths	No <sup>b</sup>	Yes	No
Methadone: CII					
Dolophine Roxane	IR tab every 8 to 12 h 5 to 10 mg	--	No	Yes	No
Morphine: CII					
Avinza Pfizer	ER cap every 24 h 30 to 120 mg	90, 120 mg	No	Yes	Yes
Embeda (morphine/ naltrexone) Pfizer	ER cap every 12 to 24 h 20/0.8 mg to 100/4 mg	100/4 mg	Yes	No	Yes
Kadian Actavis	ER cap every 24 h 10 to 200 mg	100, 130, 150, 200 mg	No	Yes	No
MS Contin Purdue Pharma	ER tab every 8 to 12 h 15 to 200 mg	100, 200 mg	No	Yes	No
Oxycodone: CII					
Oxycontin Purdue Pharma	ER tab every 12 h 10 to 80 mg	60, 80 mg	Yes	No	No
Oxymorphone: CII					
Opana ER Endo Pharm	ER tab every 12 h 5 to 40 mg	--	No <sup>b</sup>	No	Yes
Oxymorphone ER	ER tab every 12 h 5 to 40 mg	--	No	NA	Yes
Targiniq ER Purdue Pharma	ER tab every 12 h 10 mg/5 mg to 80 mg/40 mg	--	Yes	No	No
Tapentadol: CII					
Nucynta ER Janssen	ER tab every 12 h 50 to 250 mg	--	No <sup>b</sup>	No	Yes

CII indicates controlled substance schedule II; CIII, controlled substance schedule III; ER, extended release; IR, immediate release; REMS, Risk Evaluation and Mitigation Strategy.

<sup>a</sup>Opioid tolerance is defined as at least 1 week of therapy at a dose of oral morphine 60 mg/day, transdermal fentanyl 25 mcg/hour, oral oxycodone 30 mg/day, oral hydromorphone 8 mg/day, oral oxymorphone 25 mg/day, or an equianalgesic dose of another opioid.

<sup>b</sup>Exalgo, Nucynta ER, and Opana ER have physical barriers, but did not receive abuse-deterrent formulation labeling from the FDA.

■ **Table 2.** ER/LA Opioid Formulations With Abuse-Deterrent Indications<sup>10-13,46</sup>

ER/LA Product	Abuse Deterrent Mechanism	FDA Indication	Form of Abuse Affected
Hydrocodone			
Hysingla ER	Hard polymer turns into viscous gel with hydration	Expected to deter intranasal and intravenous abuse, reduce intranasal abuse and oral abuse when chewed	Gel resists injection; less drug liking with intranasal abuse or chewing
Zohydro ER	Inactive beads immediately form a viscous gel when crushed and dissolved in liquids or solvents	Pending human abuse liability studies	Gel resists injection
Morphine			
Embeda	Co-formulated with sequestered naltrexone	Expected to reduce oral and intranasal abuse	Crushing releases naltrexone; less drug liking with crushed oral and intranasal
Oxycodone			
Oxycontin	Hard polymer turns into viscous gel with hydration	Expected to make abuse via injection difficult and to reduce intranasal abuse	Gel resists injection; less drug liking with intranasal abuse

ER/LA indicates extended-release/long-acting.

tion risk, specifying more clearly who should receive ER/LA opioids, and requiring postmarketing safety studies. In 2013, all ER/LA opioid analgesics received a new indication specifying use “for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate.”<sup>37</sup> This differs dramatically from indications in early labeling, such as “for the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days.”<sup>34</sup> A classwide black box warning was added for neonatal opioid withdrawal syndrome (NOWS; also referred to as neonatal abstinence syndrome [NAS] in the medical literature) as a consequence of the substantial increase in chronic opiate use during pregnancy.<sup>38,39</sup> Between 2004 and 2013, newborn intensive care unit admissions for NAS increased from 7 cases per 1000 admissions to 27 cases per 1000 admissions.<sup>39</sup> Infants with NAS have high rates of medical complications, including respiratory complications and low birth weight, prolonged hospitalization, and high resource utilization.<sup>39,41</sup> Manufacturers are now required to complete postmarketing studies to estimate the incidence of misuse, abuse, addiction, overdose, and death during long-term treatment of chronic pain with ER/LA opioid analgesics (results expected in 2018).<sup>42</sup> Another requirement is a clinical trial to evaluate the risk of opioid-induced hyperalgesia during long-term treatment of chronic pain (results expected in 2017). FDA actions outside of the REMS include the rescheduling of all hydrocodone products to schedule II controlled substances, facilitating rapid approval of naloxone as an antidote for

opiate overdose, providing incentives for the development of new non-opioid analgesics, and facilitating the development of abuse-deterrent formulations (ADFs).<sup>7,33,43</sup>

### Abuse-Deterrent Opioid Formulations

In April 2015, the FDA released long-awaited guidance to the pharmaceutical industry on requirements for approval of ADFs.<sup>44</sup> The guidance has 4 categories of data required for ADF labeling claims: *in vitro* manipulation and extraction studies (Category 1); pharmacokinetic studies (Category 2); clinical abuse potential studies (Category 3); and postmarketing comparison studies (Category 4).<sup>44</sup> The guidance does not require all new opioids to be ADFs; rather, a new product’s abuse-deterrent properties will be evaluated against the range of available abuse-deterrent and non-abuse-deterrent products, including generics.<sup>44</sup> Guidance on generic ADFs is still pending.<sup>45</sup> ADF mechanisms address specific forms of abuse. When mixed with water, some formulations (Hysingla ER, Zohydro ER [hydrocodone], Oxycontin [oxycodone]) become a gel that is difficult to draw into a syringe for injection.<sup>9,12</sup> Another mechanism involves sequestration of an opiate antagonist, either naloxone or naltrexone, that diminishes the desired opiate effects if the formulation is crushed for oral or intranasal administration.<sup>9,13</sup> **Table 2**<sup>10-13,46</sup> summarizes the properties of ER/LA opioids that were approved by the FDA as ADFs. Other ER/LA formulations that have tamper-resistant properties, but did not meet FDA requirements for ADF labeling, include Exalgo (hydromorphone), Nucynta (tapentadol), and Opana ER (oxymorphone).<sup>47</sup>

When the Oxycontin ADF (oxycodone) was approved in 2010, the FDA withdrew approval for generic versions of the original formulation. Without evidence of the effectiveness of Opana ER (oxymorphone) to be labeled as an ADF, generic versions of the drug were allowed to remain on the market.<sup>9</sup> These regulatory decisions created major budgetary issues for patients and payers, because currently available ADFs are brand-only. In the managed care setting, this leads to access barriers, including prior approval need, non-coverage, and higher-tiered co-pays.<sup>34</sup> Legislation has been proposed or passed in a number of states mandating coverage of ADFs and requiring their inclusion on formularies and the lowest co-pay tier.<sup>48</sup> The systematic implementation of risk management strategies that include the compulsory use of opiate-abuse screening tools, such as the Opioid Risk Tool or the SOAPP-R, could be valuable in identifying and stratifying patients who may benefit from an ADF in managed care.<sup>49</sup>

The Oxycontin ADF (oxycodone) had both intended and unintended consequences. As intended, abuse and overdose deaths with Oxycontin (oxycodone) decreased.<sup>50-54</sup> However, residual abuse persists, due to successful efforts to circumvent the ADF mechanism and continued abuse by the oral route.<sup>51</sup> Some abusers switched to other prescription opioids (buprenorphine, fentanyl, hydromorphone, oxymorphone) and heroin.<sup>52,55</sup> Since 2010, overall utilization of Oxycontin (oxycodone) has decreased, even after accounting for the removal of generic formulations.<sup>56</sup> There has been a flattening in the number of prescriptions for opioid analgesics, as well as in the abuse and diversion of prescription opioid analgesics.<sup>4</sup> But these changes have been accompanied by a dramatic increase in heroin abuse and mortality.<sup>4,57</sup> The experience with reformulated Oxycontin (oxycodone) indicates that ADFs are just one of many tools necessary to deal with illicit and prescription opioid abuse.

### ER/LA REMS Prescriber Education

The FDA Blueprint for Prescriber Education is a comprehensive outline of concepts and principles that clinicians should utilize to prescribe ER/LA opioid analgesics safely.<sup>29</sup> Some of the core competencies are<sup>29</sup>:

- selecting initial doses and formulations that are appropriate for opiate-naïve patients
- converting patients from one opioid product to another safely
- understanding the general characteristics and toxicities of specific ER/LA opioids, especially unique opioids such as methadone

- managing drug-drug interactions of ER/LA opioids
- anticipating and managing opioid adverse effects

### Selecting Doses and Formulations

The risk of serious toxicity or overdose is increased in the first few weeks of opioid therapy, especially with ER/LA formulations.<sup>58,59</sup> In a cohort study of Veterans Administration patients with chronic pain, the overall risk of unintentional overdose was 2.3-fold higher with an LA opioid than with a short-acting opioid.<sup>59</sup> During the first 2 weeks of therapy, overdose risk was 5-fold higher with an LA opioid. The American Society of Interventional Pain Physicians (ASIPP) recommends short-acting opioids for initial therapy of chronic non-cancer pain (CNCP).<sup>60</sup> Tolerance to respiratory depression with opioids develops slowly and may be incomplete.<sup>61</sup> This may explain why overdose risk is high early in therapy but can also persist long-term.<sup>61,62</sup>

Lower initial doses are recommended for opiate-naïve patients.<sup>60</sup> In the VA cohort study, initial greater than 50-mg morphine-equivalent dose (MED) doubled the risk of overdose compared with 20 mg or less.<sup>59</sup> Higher strengths of some ER/LA opioids are not indicated for use in opiate-naïve patients (see Table 1).<sup>8,24</sup> Transdermal fentanyl patches and Exalgo (hydromorphone) are indicated only for opioid-tolerant patients.<sup>14,15</sup> Opioid tolerance is defined as at least 1 week of therapy at a dose equivalent to oral morphine 60 mg/day.<sup>29</sup> A patient's status as opioid-naïve or opioid-tolerant is not always clear-cut. For example, codeine is metabolized to morphine by the CYP 2D isoenzyme to produce analgesia. Patients who have a genetic polymorphism as a poor metabolizer or who are treated with a strong CYP 2D6 inhibitor will obtain little to no analgesia from codeine and should not be considered opioid-tolerant.<sup>60,63,64</sup>

In patients with CNCP, the risk of opioid overdose appears dose-related. Most epidemiologic studies suggest substantial increases in risk at MEDs of 100 mg/day or greater.<sup>65-67</sup> Based on these data, guidelines from various state agencies and medical boards call for maintaining patients on lower doses of opioids and may recommend pain specialist consultation for higher doses.<sup>68,69</sup> In Washington, an inter-agency group of state public payers adopted voluntary opioid dosing guidelines that recommend pain-specialist consultation for patients receiving 120 mg/day MED or greater.<sup>70</sup> After adoption of the guideline, there was a 27% decline in the average dose of LA opioids, a 35% reduction in patients receiving 120 mg MED/day or more, and a 50% reduction in overdose

mortality.<sup>70</sup> Under-treated pain might be an unintended consequence of this strategy if access to specialty care is not widely available.<sup>71</sup> In March 2015, HHS announced an initiative to reduce the opioid overdose epidemic within several years by focusing on improving opioid prescribing practices and increasing access to naloxone and medication-assisted treatment of opioid addiction.<sup>43</sup> To improve opioid prescribing practices, the CDC is developing chronic pain treatment guidelines that can be converted into standardized clinical decision support tools.

Patients transitioning from one opioid to another are also at risk for toxicity.<sup>72</sup> Relying solely on data from equianalgesic dosing tables can lead to inappropriately high initial doses. In these tables, opioid potency may be derived from single-dose or acute pain studies that are not applicable to chronic pain patients.<sup>73</sup> In addition, they do not account for patient factors, primarily incomplete cross-tolerance between opioids, and wide inter-individual variability in potency.<sup>72</sup> The potency data in equianalgesic dosing tables from different sources varies widely.<sup>74,75</sup> Therefore, it is safest to start the new opioid at a low dose and provide an IR opioid to manage withdrawal symptoms or pain during the dosing conversion process.<sup>72</sup> Alternatively, a 25% to 50% dosage reduction should be applied to the equianalgesic dose.<sup>72</sup>

### Methadone

Methadone appears to carry a higher risk of overdose and death than other ER/LA opioids.<sup>76,77</sup> Treatment of chronic pain with methadone accelerated in the 1990s, in large part because of its low acquisition cost. But methadone is a difficult drug to use safely.<sup>76</sup> It has a long and variable half-life (range: 5 to 59 hours), which can account for accumulation of drug, resulting in increased risk of respiratory depression persisting long beyond the duration of pain relief (4 to 6 hours).<sup>16</sup> Providing adequate patient education is critical because patients who experience incomplete pain relief at the prescribed dose risk respiratory depression if they exceed the recommended dose and/or interval. This is of particular concern early in therapy, because it may take 3 to 7 days to achieve steady-state plasma levels after starting methadone.<sup>16</sup> Incomplete cross-tolerance and inappropriate reliance on data from equianalgesic dosing tables may also play a role in methadone mortality.<sup>76,78</sup> To compound factors, the equianalgesic dose ratio for methadone may be different for low and high doses.<sup>73</sup> (A methadone safety guideline coauthored by the American Pain Society provides specific dosing recom-

mendations and titration intervals for opiate-naïve and opiate-tolerant patients.<sup>78</sup>)

Methadone can prolong the QT interval and has an established risk of causing torsades de pointe.<sup>16</sup> In the FDA's Adverse Event Reporting System, methadone accounts for a disproportionate number of cases of QT interval prolongation or torsades, second only to dofetilide.<sup>79</sup> Cardiac monitoring is recommended at baseline, to exclude patients who already have QT-interval prolongation, as well as periodically after methadone is started, to detect methadone-induced QT-interval prolongation.<sup>60,78</sup> In addition, monitoring is indicated if coadministration of another QT interval-prolonging drug is necessary. The cost of cardiac monitoring, education of prescribers and patients about safe use, and management of drug interactions offsets the low acquisition cost of methadone. The ASIPP recommends that methadone be considered a second-line agent for CNCP, to be used after other opioids have failed and only by clinicians with training and experience in using it.<sup>60</sup>

### Drug Interactions

The risk of polypharmacy is high in chronic pain patients receiving ER/LA opiates, due to the use of non-opiate analgesic adjuncts for pain, drugs to manage opiate adverse effects, and drugs to manage other health problems.<sup>80,81</sup> These all contribute to the risk of drug interactions in these patients.

**Cytochrome P450 (CYP) interactions.** A retrospective cohort analysis of claims data estimated that 5.7% of chronic pain patients are exposed to a major CYP-mediated drug interaction.<sup>82</sup> These interactions are estimated to increase the cost of care by approximately \$600 per month, with the increase primarily driven by interactions between CYP 3A4 inhibitors and oxycodone or fentanyl.<sup>83</sup> Most often, CYP interactions that cause opioid toxicity occur when a CYP inhibitor is added to therapy. However, they can also occur when a CYP inducer is discontinued.<sup>82</sup>

Inhibitors of CYP 3A4 can substantially increase exposure to fentanyl and oxycodone. Case reports describe delirium and respiratory depression after coadministration of fentanyl with moderate to strong CYP 3A4 inhibitors such as clarithromycin, diltiazem, fluconazole, and itraconazole.<sup>84-87</sup> In studies of healthy volunteers, the mean area under the curve for oxycodone has been increased substantially (2.4- to 3.6-fold) by strong inhibitors of CYP 3A4, including voriconazole, ritonavir, lopinavir-ritonavir, and itraconazole.<sup>88-90</sup> Case reports

describe improved pain control and an increase in oxycodone toxicity when voriconazole is coadministered.<sup>91,92</sup>

Despite decades of research, the metabolism of methadone is not completely understood. Methadone is often described as a substrate of CYP 3A4, and clinicians are warned about interactions with CYP 3A4 inhibitors and inducers.<sup>16</sup> However, thorough pharmacokinetic studies indicate that methadone is not substantially metabolized by CYP 3A4.<sup>93-94</sup> S-methadone, the enantiomer that is responsible for QT-interval prolongation, is primarily metabolized by CYP 2B6.<sup>95,96</sup> Exposure to methadone is increased by CYP 2B6 inhibitors such as clopidogrel and reduced by CYP 2B6 inducers such as efavirenz.<sup>95,97</sup>

**Benzodiazepines.** Although benzodiazepines do not usually cause respiratory depression when used alone, they augment respiratory depression with opioids.<sup>61</sup> Benzodiazepines were a factor in 31% of opioid-related deaths in the United States in 2011. Between 2006 and 2011, there was a 14% annual increase in opioid-analgesic poisoning deaths that involved benzodiazepines.<sup>98</sup> For chronic pain patients, coadministration of benzodiazepines with opioids raises additional concerns about driving safety, because benzodiazepines can increase psychomotor impairment with opioids.<sup>99</sup> The ASIPP, American Pain Society, and American Academy of Neurology discourage coadministration of benzodiazepines and opioids to patients with CNCP.<sup>60,78</sup>

**Alcohol.** Ingestion of alcohol enhances central nervous system depression with opioids, increasing the risk of respiratory depression.<sup>61</sup> The Drug Abuse Warning Network reported that alcohol was involved in 19% of opioid-related ED visits and 22% of opioid-related deaths in 2010.<sup>100</sup> Although all opiates have a pharmacodynamic interaction with alcohol, some ER/LA opioid formulations also have a pharmacokinetic interaction in which alcohol causes rapid release of the opiate, a phenomenon called “dose-dumping.” In pharmacokinetic studies enrolling healthy volunteers, ingestion of some ER opiate formulations with alcohol led to higher peak concentrations of the opiate, with effects that were highly variable. Mean increases in opioid exposure were 2-fold for Embeda (morphine/naltrexone), 2.4-fold for Zohydro ER (hydrocodone), 70% for Opana ER (oxymorphone), and 48% for Nucynta ER (tapentadol) 100 mg.<sup>11,13,17</sup> In some patients, peak levels increased as much as 5-fold for Embeda (morphine/naltrexone), 3.9-fold for Zohydro ER (hydrocodone), 2.7-fold for Opana ER (oxymorphone), and 4.4-fold for Nucynta ER (tapentadol) 100 mg. For Avinza (morphine), the concern about dose-dumping

is based on an in vitro study.<sup>8</sup> Prescribers of ER/LA opioid analgesics should screen and intervene early for patients prone to alcohol abuse or problem drinking; counsel patients about the risks of drinking alcohol; and avoid formulations that are susceptible to dose-dumping in patients who are likely to drink.<sup>60,69</sup>

### Adverse Effects

Opioid-related adverse effects reduce the quality of life of chronic pain patients and can substantially increase the cost of care.<sup>101-103</sup> The management of these adverse events can contribute to polypharmacy and places patients at risk for further iatrogenic events.<sup>104</sup> Opioid-induced androgen deficiency and constipation are 2 examples of the adverse effects that clinicians should be prepared to manage.

**Androgen deficiency.** Opioids remain an often unrecognized cause of symptomatic androgen deficiency.<sup>105</sup> This risk appears greater with higher daily doses and LA formulations.<sup>106,107</sup> In men with back pain, long-term opioid use is associated with increased use of erectile dysfunction drugs and testosterone replacement therapy.<sup>104</sup> The diagnosis of androgen deficiency should be confirmed with 2 measurements of morning testosterone levels before considering testosterone replacement therapy.<sup>105</sup> In addition, clinicians need to consider the potential risk of myocardial infarction and stroke that may be associated with testosterone replacement when managing opioid-induced androgen deficiency.<sup>108</sup>

**Constipation.** Between 2006 and 2011, the frequency of constipation-related ED visits increased by more than 40% and the mean cost per patient rose from \$1474 to \$2306. Opioid-induced constipation (OIC) may have contributed to this increase.<sup>109</sup> More than 80% of opioid-treated chronic pain patients report suffering from constipation.<sup>101</sup> Unlike other effects of opioid analgesics, tolerance does not develop for constipation. OIC contributes to higher incremental healthcare costs and more ED visits for patients with chronic pain.<sup>103,104</sup> Proactive management of constipation is an opportunity for managed care clinicians to reduce costs and improve function and quality of life of opioid-treated patients. Stimulant laxatives are the mainstay of managing OIC but may not be adequate treatment for some patients.<sup>110</sup> The ASIPP encourages clinicians to manage constipation proactively by starting a bowel regimen before constipation becomes a problem. At present there are no professional guidelines for the appropriate use of new FDA-approved drugs for OIC, such as lubiprostone, methylnaltrexone, and

naloxegol.<sup>60</sup> Defining a role for these new drugs is a current challenge for managed care organizations (MCOs). Taking a systematic approach to managing expected opioid adverse effects, such as constipation, has the potential to identify patients who can benefit most from these new drugs.

### Challenges for Managed Care Organizations

A survey of MCO medical directors found that only 32% had a formal mechanism for identifying chronic pain patients and only 18% systematically used clinical practice guidelines in their approach to managing chronic pain.<sup>111</sup> Most MCOs relied on formulary management techniques, including monitoring the number of units dispensed (57%), tiered co-pays (56%), and prior authorization for specific formulations (54%). Different approaches can identify patients who may benefit the most from ADFs and other safety measures, such as the naloxone auto-injector.<sup>112</sup> The use of opiate risk management techniques such as abuse screening tools may help identify patients who will benefit from early initiation of ADFs when continued opioid therapy is necessary (ie, cancer pain management) as part of an overall risk management plan.<sup>113</sup> Identification of patients receiving high opioid doses, among other risk factors for overdose, should help determine which patients receive take-home naloxone.

### Conclusion

New data suggest that slow progress is being made in reducing harm from prescription opioids. The ER/LA opioid analgesic REMS and the development of ADF opioids are key elements in a long-overdue response to combat the prescription drug abuse epidemic. Major challenges for MCOs include identifying patients who can benefit the most from innovations such as ADFs and novel treatments for OIC. A systematic approach to chronic pain that incorporates elements of the ER/LA REMS provides MCOs with some of the necessary strategies to address these challenges.

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