Oxymorphone Extended-Release Tablets (Opana ER) For the Management of Chronic Pain A Practical Review for Pharmacists

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Key words: oxymorphone, opioid, chronic pain, opioid rotation, opioid switching

INTRODUCTION

Whether in a dedicated pain-management clinic or in a community pharmacy, pharmacists can provide valuable education and treatment recommendations to patients and clinicians. Pain programs, jointly managed by pharmacists, nurse practitioners, specialists in behavioral medicine and functional restoration, and specialty pain physicians, can enhance the satisfaction of patients and health care professionals, improve clinical outcomes, and minimize the need for secondary pain referrals.1 Pharmacists who become knowledgeable in pain pharmacotherapy can facilitate safe, effective, and cost-beneficial equianalgesic opioid conversions in primary care settings.2

Long-acting (LA) opioids are recommended for moderate-to-severe chronic cancer and non-cancer pain.3,4 In their most recent evidence review, the American Pain Society and American Academy of Pain Medicine concluded that there is insufficient evidence to recommend that LA opioids be used in place of short-acting opioids for chronic non-cancer pain, but they acknowledge that LA opioids might provide more consistent pain control, improve adherence, and reduce the risk of addiction or abuse.4 Additional research is needed to evaluate these proposed advantages.5

Differences among opioids influence individual patient response and tolerability, risks and benefits in specific disease states, the likelihood of drug interactions, and ease of monitoring. Differences among patients with respect to genetic factors, age, sex, and the prior use of opioids also contribute to variability of response to individual opioids.6 Consequently, when selecting LA opioids, clinicians cannot reliably predict how a given patient will respond. Patients with chronic pain usually require consecutive trials of several LA opioids before they find one that provides adequate analgesia with acceptable tolerability.7-9 For this reason, it is essential to have multiple LA opioids from which to choose.

In 2006, the FDA approved extended-release oxymorphone HCl (Opana ER, Endo) for the control of moderate-to-severe chronic pain. At that time, morphine (MsContin, Purdue); Oramorph SR, Xanodyne; oxycodone (OxyContin, Purdue); methadone (Dolophine, Roxane); and transdermal fentanyl (Duragesic, Ortho-McNeil-Janssen) were the only LA opioids approved in the U.S., and they remain the primary alternatives to oxymorphone ER today. Some pain specialists do not consider LA tramadol (Ultram, PriCara) to be an equivalent alternative to these drugs because of its predominantly non-opioid mechanism of action10 and relatively weak analgesic potency, compared with other more potent opioids.

LA hydromorphone (Palladone, Purdue) was withdrawn from the U.S. market in 2005 because of a potentially fatal interaction with alcohol.11 A new formulation (Exalgo, Covidien) has received FDA approval.12,13 Transdermal buprenorphine (e.g., Transtec, Butrans, or Norspan in Europe) is being studied for the management of chronic pain. It will probably represent another LA opioid choice if it receives FDA approval.14 Tapentadol (Nucynta, PriCara) combines mu-opioid receptor agonism with norepinephrine reuptake inhibition. It is available as an immediate-release (IR) tablet, and a long-acting preparation is being investigated.15 Tapentadol is featured in this month’s Drug Forecast column on page 330.

A Schedule II controlled substance (CII), oxymorphone ER is a selective mu-opioid agonist that is embedded in an agglomerated hydrophilic matrix to provide sustained activity over a 12-hour dosing interval.17 This article describes the agent’s pharmacology, pharmacokinetics, efficacy and safety, and clinical considerations of significance to pharmacists, clinicians, and members of P&T committees.

PHARMACOLOGY AND PHARMACOKINETICS

Oxymorphone has selective affinity for the mu-opioid receptor, whereas oxycodone has weaker mu-receptor affinity and greater kappa-receptor affinity.18 Oxymorphone has lower protein binding (10% to 12%) compared with morphine (30% to 35%) or oxycodone (45%).19 Its highly lipophilic properties facilitate its transit across the blood-brain barrier.17

The pharmacokinetic profile of oxymorphone ER is predictable, linear, and dose-proportional.17,19 The technology used in the ER formulation, TIMERx (Penwest Pharmaceuticals), maintains steady plasma levels over a 12-hour period.17,19 With a half-life of 9 to 11 hours,17 oxymorphone ER maintains a low fluctuation index of less than 1 after achieving steady state, as do its two metabolites.17,18 Oxymorphone is metabolized primarily via hepatic glucuronidation17 to one active metabolite (6-OH-oxymorphone) and to one inactive metabolite (oxymorphone-3-glucuronide). It is neither metabolized by

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cytochrome P-450 (CYP) enzymes nor inhibited or induced by CYP substrates. Consequently, oxymorphone ER, along with morphine and hydromorphone, lacks significant potential for CYP-mediated drug interactions and is unaffected by genetic factors influencing these enzymes. By contrast, oxycodone, fentanyl, methadone, buprenorphine, and other opioids are metabolized by CYP enzymes and therefore have the potential for clinically important pharmacokinetic interactions with other drugs that share this metabolic pathway. Interestingly, the CYP 3A4 enzyme alone is responsible for the metabolism of more than 50% of currently available drugs.

The absence of CYP-mediated metabolism is also advantageous because genetic variations in the activity of CYP enzymes have been associated with altered opioid metabolism. For example, codeine and hydrocodone are metabolized by CYP 2D6 to more active metabolites (morphine and hydromorphone, respectively). Some patients who are poor CYP 2D6 metabolizers (i.e., 5% to 10% of Caucasians) or ultra-rapid CYP 2D6 metabolizers (i.e., 1% to 7% of Caucasians) may experience reduced efficacy or an increase in adverse events (AEs) because of a reduced or accelerated production of metabolites. A small portion of oxycodone undergoes CYP 2D6 metabolism to oxymorphone, and increased AEs have been reported for poor CYP 2D6 metabolizers.

Although oxymorphone ER has minimal potential for pharmacokinetic interactions, its use with sedatives, tranquilizers, hypnotics, phenothiazines, and other central nervous system (CNS) depressants can produce additive effects. Hence, as with other opioids, vigilance is required in preventing pharmacodynamic interactions during therapy with oxymorphone ER.

Pharmacists can help prevent medication errors, particularly those that result in drug interactions. Patients receiving opioid therapy for chronic pain may have complex medical problems, often requiring the involvement of their primary care physician, a pain specialist, and one or more medical or surgical specialists. Although each prescriber has an obligation to be aware of all of a patient’s prescription and over-the-counter medications, the pharmacist is in a unique position to monitor the patient’s medications from all sources.

Pharmacists must recognize and be vigilant in guarding against potential drug interactions, redundancy, misuse, or evidence of abuse and must take action to advise prescribers and caution patients accordingly. In this regard, pharmacists can be most successful by developing a collegial, cooperative relationship with the prescribing physician.

**CLINICAL TRIAL PROGRAM**

The clinical trial program for oxymorphone ER has included more than 2,000 opioid-naive and opioid-experienced patients with chronic cancer pain and non-cancer pain. The duration of treatment ranged from two weeks to two years. Collectively, the trials demonstrated that oxymorphone ER was an effective, generally well-tolerated 12-hour opioid agent in controlling chronic pain.

In long-term, open-label trials of cancer and non-cancer pain, analgesic effects were maintained over time, and in patients with osteoarthritis and low back pain, the effects were accompanied by improvements in functional outcomes.

**Use of Oxymorphone ER in Opioid-Naive Patients**

In clinical trials, individualized gradual titration improved the tolerability of oxymorphone ER in opioid-naive patients with moderate-to-severe chronic low back pain. These patients underwent a flexible, tailored, open-label, dose-titration period consisting of oxymorphone ER 5 mg every 12 hours, titrated at increments of 5 and 10 mg every three to seven days. A well-tolerated mean dose of approximately 40 mg in 205 of 325 patients (63%) was achieved. These responders (n = 205) entered a randomized, double-blind, placebo-controlled 12-week period. Rescue medication, consisting of oxymorphone IR, was used to manage breakthrough pain and to prevent withdrawal symptoms in patients switching from oxymorphone ER to placebo for the double-blind treatment period.

Outcome measures included pain intensity, as measured by a 100-mm Visual Analogue Scale (VAS) and by patient and physician global ratings of treatment. No functional outcome measures were assessed. The Adjective Rating Scale (ARS) for Withdrawal and the Clinical Opiate Withdrawal Scale (COWS) were administered to ensure that between-group differences were not a result of withdrawal by patients who switched from oxymorphone ER to placebo.

Patients given oxymorphone ER were significantly more likely than placebo patients to complete the double-blind treatment period (68% vs. 47% respectively; P < 0.001) and were significantly less likely to stop treatment owing to a lack of efficacy (11% vs. 35%, respectively; P < 0.001). Discontinuations attributed to AEs occurred with similar frequency in the two groups (oxymorphone ER, 8.6%; placebo, 8%). Only one patient receiving oxymorphone ER and two patients receiving placebo discontinued treatment because of withdrawal symptoms.

Patients who received oxymorphone ER in the double-blind period exhibited consistent statistically significant improvement in VAS-rated pain intensity relative to placebo-treated patients (P < 0.001). Before enrollment into the study, most patients (87%) had rated their previous pain regimen as poor or fair. After the trial, 97% of patients and 87% of physicians rated oxymorphone ER as good, very good, or excellent.

In an open-label, six-month study of opioid-naive patients with osteoarthritis, a similar flexible, individualized titration period resulted in a stable, effective, and tolerable dose of oxymorphone ER in 94 of 126 patients (75%). Mean (SD) average pain intensity significantly declined from 6.2 (1.3) at screening to below 2.5 (1.6) at the end of titration, on a 10-point pain intensity scale. Measures of general activity, work, enjoyment of life, walking ability, sleep, mood, and relations with others also showed significant improvement. Sixty of the 94 patients (64%) completed the titration phase successfully. Analgesia and improvements in measures of function were maintained, and the mean daily dose of oxymorphone ER remained stable for the duration of the study. Rates of discontinuation resulting from AEs were low during the titration and maintenance phases (16% and 17%, respectively).

**Use of Oxymorphone in Opioid-Experienced Patients**

The safety and efficacy of oxymorphone ER in opioid-experienced patients were assessed in a pivotal two-period study. Opioid-experienced patients with moderate-to-severe chronic low back pain who were following a stable opioid pain regimen
Oxymorphone therapy.

Stipation, nausea, headache, and somnolence) were typical of ER as excellent or very good. The most common AEs (continuation of therapy in 53% of placebo patients and in 11% of oxymorphone patients, but discontinuations resulting from AEs were similar (for oxymorphone ER, 10%; for placebo, 11%). Opioid withdrawal, as measured on the ARS and the COWS, was infrequent but nonetheless was the most common occurrence leading to discontinuation by the placebo patients (7%).

Continuation of the individually titrated dose of oxymorphone ER over the next 12 weeks maintained relief of chronic low back pain with little change, as measured via the VAS. Before entering the trial, only 14% of patients had rated their pain regimen as excellent or very good. After the dose-titration period, 72% of patients and 68% of physicians rated oxymorphone ER as excellent or very good. The most common AEs (constipation, nausea, headache, and somnolence) were typical of opioid therapy.

Importance of Slow, Individualized Titration

Outcomes are typically less successful for patients whose opioid doses are titrated on a fixed-dose schedule. More recent guidelines for the use of opioids in chronic non-cancer pain recommend individualized, flexible titration to minimize AEs and premature discontinuation of therapy.4

This was the case in two earlier trials of oxymorphone ER.26,29 In a two-week dose-ranging study,28 opioid-naïve and opioid-experienced patients with moderate-to-severe osteoarthritis of the knee or hip received initial doses of oxymorphone ER 10 mg twice daily or 20 mg twice daily during week 1, followed by 40 mg twice daily or 50 mg twice daily during week 2. In a fixed-dose, double-blind, placebo-controlled and active comparator-controlled trial,29 opioid-naïve and opioid-experienced patients with moderate-to-severe osteoarthritis pain initiated oxymorphone ER 20 mg or 40 mg twice daily.29 In the two trials combined, 225 of 521 patients (43.2%) receiving oxymorphone ER discontinued therapy because of AEs.

By contrast, a pooled analysis of two clinical trials of oxymorphone ER in patients with chronic low back pain confirmed the value of flexible titration.30,31 Of 575 patients, 348 (60.5%) completed titration to an effective, well-tolerated oxymorphone ER dose.30 Only 106 patients (18.4%) stopped therapy because of AEs. These results were consistent with outcomes for other LA opioids titrated during a flexible, individualized dosing schedule. For example, in a randomized, open-label trial by Rouch et al.,31 68% of LA opioid-naïve patients (266 of 392) completed the opioid dose titration phase to effective and generally well-tolerated doses of either once-daily morphine sulfate ER (Avinza, King) or twice-daily oxycodone CR (OxyContin, Purdue).

After titration, the proportion of patients discontinuing double-blind treatment with oxymorphone ER (54 of 175 patients, or 30.8%) was nearly identical to the discontinuation rate reported in a systematic review of randomized controlled trials that evaluated other LA opioids in patients with chronic non-cancer pain (209 of 698 patients, or 29.9%).32

ROLE OF THE PHARMACIST

When initiating oxymorphone ER or other opioid agents, pharmacists can help patients understand essential information, such as instructions for taking medications. They can also advise patients about how to distinguish between AEs that are likely to resolve over time and those indicating the need for a medication switch, a dose reduction, or another intervention. Some patients who experience inadequate analgesia or bothersome AEs find it more convenient and less costly to consult with their pharmacist rather than their physician. However, relationship building between patients and physicians is an important component of clinical care and may improve physician decision making and patient outcomes.

Pharmacists are often placed in the position of managing over-the-counter treatments that are complementary to or fundamental adjuncts to prescription therapy, such as a bowel regimen during chronic opioid therapy. Informing patients that the cause of opioid-induced constipation is impaired intestinal motility, pharmacists can recommend a stimulant laxative, but they should emphasize that a stool softener in the absence of a stimulant is ineffective and that bulk-forming laxatives may

### Table 1 Conversion Ratios of Daily Oral Opioid Doses to an Equivalent Dose of Oxymorphone Extended Release

<table>
<thead>
<tr>
<th>Approximate Equivalent Daily Oral Dose (mg)</th>
<th>Oral Conversion Ratio</th>
</tr>
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<tbody>
<tr>
<td>Oxymorphone</td>
<td>1.0</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>0.5</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>0.5</td>
</tr>
<tr>
<td>Methadone†</td>
<td>0.5</td>
</tr>
<tr>
<td>Morphine</td>
<td>0.333</td>
</tr>
</tbody>
</table>

† It is extremely important to closely monitor all patients who are switched from methadone to other opioid agonists. The conversion ratio of methadone to other opioid agonists may vary widely as a function of previous exposure, because methadone has a long half-life and tends to accumulate in the plasma.17

Data from Opana ER, prescribing information.17
lead to intestinal obstruction. Elderly patients and those with complex medical conditions may also need to be steered away from osmotic laxatives and enemas, which raise the risk of dehydration, electrolyte imbalances, and renal dysfunction.

Ultimately, programs that optimize the relationship between patients and pharmacists may provide an opportunity to improve health care and reduce costs. Research suggests that pharmacist-intervention programs can improve pain management, reduce drug interactions and other AEs, enhance patient compliance, and identify unaddressed patient needs. For example, patients with chronic disease who participated in a primary care pharmacist-intervention program were significantly more likely than nonparticipants to address non-compliance with therapy and untreated conditions and to receive necessary medications. Costs were lower among program participants, although not significantly.

The pharmacist’s observation of patients’ use of over-the-counter medications may prompt interventions to increase the quality of opioid prescribing. One important area of concern is the use of short-acting combination opioids for chronic pain. The most frequently prescribed opioids for chronic pain are combination products that contain acetaminophen, which is hepatotoxic at doses of 4 g/day or greater.

Pharmacists should be aware that combination opioids, when used for chronic pain, pose risks for undertreatment of pain and acetaminophen toxicity. Clinical trials of oxymorphone ER in opioid-experienced patients found that most patients who were switched from combination opioids had been taking the maximum dose of these products and reported low satisfaction with pain relief. Patients with undertreated pain may be tempted to self-medicate with over-the-counter medications containing acetaminophen in addition to their combination opioid, thereby risking liver toxicity. Patients may further increase their exposure if they are also using other nonprescription drugs, such as pain, cold, and allergy products.

In addition to alerting patients to the danger of over-the-counter medications containing acetaminophen, pharmacists can help identify the inappropriate concomitant use of prescription and nonprescription agents. They might suggest that the physician consider substituting either a short-acting opioid that does not include aspirin or acetaminophen or, if appropriate, a long-acting opioid.

**SWITCHING TO OXYMORPHONE ER**

Patients with chronic pain may have to endure switching to three or four opioids before they discover one that offers effective analgesia with tolerable AEs. Patients may feel perplexed when the efficacy or tolerability of an opioid wanes over time, so that rotation to a different opioid becomes necessary. Pharmacists must often explain why switching and rotation are sometimes necessary. Some of these reasons include:

- development of tolerance.
- emergence of drug interactions when new medications are added.
- changes in hepatic or renal drug clearance, leading to intolerable side effects.
- differences in the patient’s response that may be related to age, sex, and genetic variability.

Although genetic and other factors (e.g., renal or hepatic function) do influence the patient’s response to opioids in general, in a combined analysis of a cohort with chronic low back pain who completed initial titration to oxymorphone ER, age, sex, and previous opioid experience had no impact on the effectiveness and tolerability of oxymorphone ER. However, completing this step was more challenging in several patient subgroups. Patients 65 years of age or older experienced more opioid-related AEs than younger patients and were more likely to discontinue treatment as a result. Similar proportions of opioid-naive and opioid-experienced patients completed titration; however, patients who took hydrocodone/acetaminophen (e.g., Vicodin, Abbott) as their previous opioid were more likely to complete the titration phase successfully than patients who had previously used oxycodone.

Among patients switching from oxycodone, the success rate was higher among men (56.4%) than women (53%) and among patients 65 years of age or younger (47.8%) compared with those 65 years of age or older (33.3%). The initial starting dose of oxymorphone ER might have been lower than needed in women and in older patients because (1) oxycodone blood levels are 25% higher in women than in men; (2) they are 15% higher in older patients than in younger patients; and (3) conversion tables do not give sex or age recommendations based on pharmacokinetic differences in subpopulations.

Two studies suggest that patients who were successfully switched from hydrocodone to oxymorphone ER likely entered the study with undertreated pain. More than half of the hydrocodone-experienced patients required a daily dose of oxymorphone ER 65 mg or greater, which is more than the maximum dose of their presstudy combination agent, hydrocodone/acetaminophen, consisting of approximately 120 mg of hydrocodone and 4 g of acetaminophen. Patients previously taking oxycodone CR, with no dose maximum, might have entered the study with more satisfactory pain control and with less motivation to switch to oxymorphone ER.

Alternatively, differences in the pharmacokinetics of oxycodone CR and oxymorphone ER could have contributed to a perceived lack of efficacy with oxymorphone ER, compared with oxycodone CR, which undergoes biphasic release with absorption peaks at 0.6 and 6.9 hours after the dose is given. Patients experience a rapid onset of effect with the first peak and then continuous analgesia thereafter.

By contrast, oxymorphone ER’s TIMERx technology enables steady drug release throughout the 12-hour dosing interval. It is possible that oxycodone CR–experienced patients who switched to oxymorphone ER did not believe that they were receiving comparable analgesia because they did not experience an initial rapid onset of effect. Whether the absence of a rapid-onset phase is a disadvantage for oxymorphone ER is debatable, because this phase can be associated with increased euphoria and abuse potential.

**ADVERSE EVENTS AND SAFETY CONSIDERATIONS**

As previously mentioned, one of the most common AEs observed in clinical trials of oxymorphone ER is constipation. Pharmacists should be aware that failure to include an effective bowel regimen during chronic opioid therapy produces...
constipation and myriad associated signs and symptoms that augment pain. Lack of a bowel regimen can be debilitating and can lead to poor adherence with treatment, impair quality of life, and create complications such as hemorrhoids, impaction, ileus, and rectal prolapse.\(^\text{58}\) The pivotal trials with oxymorphone ER that demonstrated favorable tolerability incorporated an effective bowel regimen as part of the study protocol.\(^\text{25,27,28}\) This is an area in which pharmacists can assist in the patient’s pain-management plan.

As with other opioids, oxymorphone ER should not be taken with alcohol. The package labeling for the drug includes a boxed (black-box) warning for patients not to consume alcoholic beverages, or prescription or nonprescription medications containing alcohol, while they are receiving oxymorphone ER. In pharmacokinetic studies, there was a significant rise in maximum drug concentration when 40% alcohol was ingested with oxymorphone.\(^\text{\text{52}}\) However, the area under the concentration (AUC) versus time curve did not change, indicating no change in overall drug exposure. This is important because in vitro, the TIMERx delivery system does not release oxymorphone more rapidly (i.e., no dose dumping occurs) in solutions of up to 40% ethanol. The rapid absorption of oxymorphone ER occurring with alcohol coadministration in vivo may be a result of increased splanchnic blood flow.

Vigilance in identifying opioid abuse or the diversion of opioids is a duty of prescribers and pharmacists. Urine monitoring of oxymorphone is facilitated by the drug’s lack of metabolites, which can be mistaken for other prescribed opioids. Oxymorphone tablets may contain up to 1% oxycodone, depending on the method of production, but urine testing by liquid chromatography or tandem mass spectrometry usually reports more than 99\% oxymorphone.\(^\text{\text{51}}\) Interpretation of urine monitoring tests is more complicated when the prescribed opioid has metabolites that are identical to other prescription opioids. For example, codeine produces morphine and hydrocodone, morphine produces hydromorphone, oxycodone produces oxymorphone, and hydrocodone produces hydromorphone.\(^\text{\text{5,43,47–49}}\)

Although pharmacists are valuable in detecting and preventing drug abuse and diversion, a survey conducted by the National Center on Addiction and Substance Abuse indicated that fewer than 50\% of pharmacists receive training in this area.\(^\text{\text{50}}\) Checking the legitimacy of a prescription is an essential first step; the pharmacist should evaluate the prescription itself, the patient, licensing information about the prescribing physician, and the state’s prescription drug-monitoring programs if applicable. The pharmacist should also be aware of other ongoing drug-diversion programs in the jurisdiction.

Errors included in a written prescription may call into question its legitimacy, but mistakes alone do not mean that a prescription is forged or fraudulent. A forged prescription may be attributed to a fictitious physician, or the script might contain errors in a physician’s name, address, telephone number, or license number. The drug name might be misspelled, or a drug may be ordered in an unavailable dose or an unusual quantity. There might be refill orders for a Schedule II controlled substance (CII). The pharmacist should check for evidence of tampering, such as photocopying; an absence of safety features, such as watermarks; obscured, unclear, or obliterated content; erasures; and correction fluid or tape.

Pharmacists should be alert for suspicious patient behavior, such as impatience, anxiety, or hostility. One red flag might be an insured patient who pays with cash, because insurers usually have systems in place to identify redundant prescriptions.\(^\text{\text{50}}\) A simple safeguard against diversion is to request identification and to telephone the patient when a third party arrives to pick up medication for a patient said to be “too sick to come in.”

Familiarity with the surrounding community can be helpful in identifying potential abusers. Increased vigilance is warranted in areas of frequent drug abuse, but prescribers should keep in mind that abusers sometimes travel outside their community to find a pharmacy with less experience in dealing with those who aim to engage in illegal activities. Asking why a patient is filling a prescription far from home is a legitimate action.

The patient’s relationship to the prescribing physician is also important. It is unusual for a physician to prescribe opioids to a person working in his or her office, and it is unethical to prescribe opioids to a family member.

A questionable prescription that appears to have been legitimately written by a physician may represent an honest mistake or an error in judgment, or it might have been written under duress. It is appropriate for the pharmacist to question the prescribing physician about the therapeutic need for the medication—is it for trauma, palliative care, or chronic pain? The pharmacist might also ask about the physician’s level of familiarity with the patient—is this the patient’s primary physician or a physician at a walk-in clinic?

When in doubt, the pharmacist should phone the physician, focusing on the specific reasons for concern. The pharmacist should also notify all prescribers if it is evident that a patient is receiving opioids from multiple prescribers. It is common for patients who are prescribed opioids on a long-term basis to enter into a patient-prescriber agreement typically including language stating that if a patient knowingly accepts or solicits opioids from another prescriber, this would result in termination of the agreement and the patient-provider relationship.

The pharmacist should ensure that any prescription written for a controlled substance complies with the requirements of the Controlled Substances Act. Prescriptions for Schedule II drugs must be received in writing (except in an emergency) and cannot be refilled. Schedule III and IV drugs can be prescribed in writing or by telephone and refilled up to five times within six months of the original prescription.\(^\text{\text{51}}\) However, state laws may differ from federal law and may impose additional limits, such as the quantity of medication or time permitted to elapse between writing and refilling prescriptions.

When there is a discrepancy between state and federal laws, the more restrictive legislation is observed. For example, Virginia sets no limit on the quantity for a Schedule II drug prescription and allows up to six months for the prescription to be filled. By contrast, New Hampshire limits the quantity to 100 dosage units and Hawaii requires Schedule II prescriptions to be filled within seven days.\(^\text{\text{52}}\) These differences may mean that a patient who travels out of state to see a specialist could return with a prescription that cannot be filled as written. Awareness of these potential differences can help prevent misunderstandings and reduce patient distress.

After a prescription is filled, pharmacists can help in moni-
toring the correct use of the drug. Signs of medication misuse and abuse may include multiple requests for early refills, lost prescriptions, and unauthorized dose escalations. Patients taking opioids on a long-term basis should be expected to refill the medication at regular intervals; a prolonged interval between the date on the prescription and the date filled or erratic filling frequency may suggest diversion, hoarding, or bingeing, but this situation may also legitimately reflect chronic pain with episodic flares and remissions. With proper safeguards and vigilance, pharmacists can substantially improve patient outcomes and reduce the likelihood of opioid misuse.

CONCLUSION

Oxymorphone ER is a valuable addition to the limited selection of LA opioids available to physicians in the U.S., providing a much-needed option for patients requiring pain management or opioid rotation. There is strong clinical evidence supporting its use for cancer pain, chronic low back pain, and other chronic non-cancer pain. This drug is generally well tolerated in opioid-naïve and opioid-experienced patients, providing 12-hour analgesia and maintaining its effects over time.

Oxymorphone ER has advantages over other opioids; it is associated with fewer drug interactions, and urine-monitoring results are easy to interpret. Despite these benefits, oxymorphone ER carries a risk of AEs common with other opioids and has the same potential for abuse or diversion. Moreover, a subphone ER carries a risk of AEs common with other opioids and results are easy to interpret. Despite these benefits, oxymorphone extends the oral opioid receptor-mediated pain relief in opioid-naïve patients with moderate to severe chronic pain.

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