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# New Therapeutics Bulletin

*Opana® ER Extended-  
Release Tablets*

*(oxymorphone HCl) CII*

## **INSIDE:**

**Background Information on Pain Management and Use of Opana (oxymorphone HCl) Tablets CII and Opana ER (oxymorphone HCl) Extended-Release Tablets CII**

**Answers to Patients' Questions About Pain Management and Use of Opana (oxymorphone HCl) Tablets CII and Opana ER (oxymorphone HCl) Extended-Release Tablets CII**

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## Introduction

Pain is a universal affliction experienced by everyone at some time and to some degree. Pain is characterized as either acute or chronic; chronic pain may be intermittent or persistent. *Intermittent* pain is episodic and may occur in waves or patterns. *Persistent* pain is continuous, lasting 12 hours or longer every day. Pain that flares up or breaks through the relief provided by pain medication taken around the clock is called *breakthrough* pain.<sup>1</sup>

The approach to pain management has changed considerably in recent decades. Whereas pain was once considered as little more than a symptom for which treatment was secondary to identifying and treating the underlying cause, today pain is also recognized as a condition in itself that needs to be assessed and treated.<sup>2</sup> Controversies about the use of opioids in pain management have engendered advocacy groups among both patients and health care professionals who seek to overturn earlier points of view and to ensure that patients are provided the relief that they deserve. Even with growing acknowledgement of the need for pain management, attitudes among both clinicians and the public have been slow to change, with the result that an estimated 50 million Americans continue to suffer unduly.<sup>3</sup>

State and national organizations have issued guidelines and models for treating pain, and progress has been made in providing access to opioid medications. However, even patients who are taking opioids continue to experience the significant impact of pain on their lives and relationships. In a recent survey of such patients, 97% reported a physical or social hardship as a direct result of their pain; most (93%) reported more than one negative effect. They listed these occurrences: difficulty walking or moving, inability to sleep, feelings of depression, inability to concentrate, loss of appetite, and inability to drive. Further, half reported the loss of a job or chance for promotion, while 52% cited strained relationships with family or friends.<sup>4</sup>

One of the major obstacles in advancing the proper use of opioids is the fear of addiction and abuse, which is felt by both physicians and patients.<sup>2,5</sup> Such fears are based largely on misunderstanding and misuse of terminology.<sup>6</sup> It is important to distinguish between addiction and conditions such as tolerance, physical dependence, and pseudo-addiction, which are defined in Table 1.

## Learning Objectives

After reading this article, the pharmacist should be able to:

1. Discuss the complexities of using opioids as maintenance therapy for chronic pain.
2. Describe the implementation of opioid therapy for the management of moderate to severe chronic pain in a manner that minimizes the risks of drug diversion, addiction, and side effects.
3. Discuss the pharmacology, pharmacokinetics, and proper use of Opana ER (oxymorphone HCl) extended-release tablets.
4. List key counseling points for patients regarding opioid safety.
5. Fulfill professional and legal responsibilities when dispensing Schedule II drugs.

Table 1.

## Pain Management Lexicon

Term	Definition
Tolerance	A state of adaptation in which exposure to a drug induces changes that result in a decrease of one or more of the drug's effects over time.
Physical dependence	A state of adaptation manifested by withdrawal symptoms that are specific to a drug class and that may be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.
Addiction	A primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestation. A compulsive disorder characterized by behaviors that include one or more of the following: loss of control over drug taking, drug craving, compulsive use, and ongoing drug use despite harm.
Pseudoaddiction	A term used to describe patient drug-seeking behaviors that may occur because pain is undertreated.

Source: Reference 6.

It is not uncommon for patients taking an opioid to develop physical dependence; in fact, most patients taking opioids around the clock develop some dependence for 1 to 2 weeks. However, dependence is distinctly different from addiction, which is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. The term pseudoaddiction is used to describe behavior of a patient who is focused on obtaining medication because of poor pain control rather than drug craving. The apparently excessive drug-seeking behavior ceases when the patient's pain is effectively treated.<sup>6</sup>

Such fears of addiction seem to be largely unfounded. In patients receiving opioids for the treatment of pain, who have no history of substance abuse, the prevalence of addiction appears to be low.<sup>7</sup> A recent literature review reported a minimal risk of addiction among patients with chronic pain who are being treated with opioids.<sup>8</sup>

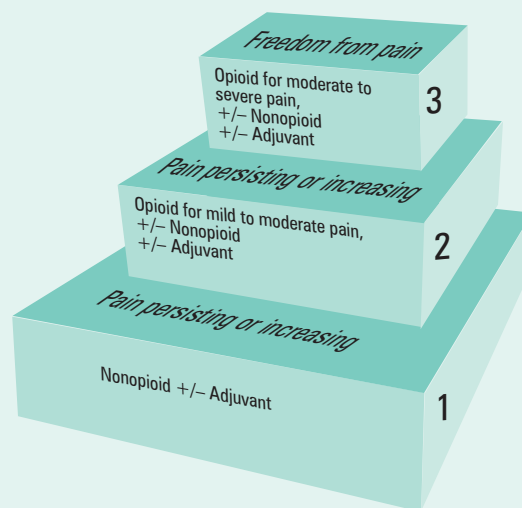
## Pharmacologic Management of Pain

Pain management is particularly challenging for people with chronic pain. There is widespread agreement today on the approach to pain relief as promulgated by the World Health Organization, known as the "Pain Ladder" (see Figure).<sup>9</sup> While the Pain Ladder was originally developed for patients with cancer pain, most experts today endorse the approach for noncancer chronic pain as well.

The Pain Ladder emphasizes administering the right analgesic, in the right dose, and on the right schedule to maximize

Figure.

### Pain Ladder From the World Health Organization



Source: Reference 9. Reprinted with permission from the World Health Organization.

pain relief and minimize adverse effects. It is a comprehensive approach to pain management that specifies the use of<sup>9</sup>:

- Nonopioids or mild analgesics for mild pain
- Low-dose opioids (such as codeine) alone or in combination for moderate pain that is not controlled by nonopioids alone

- Strong opioids as drugs of choice for severe pain, alone or in combination

Numerous organizations have endorsed the use of opioids to relieve moderate to severe pain. A watershed document published in 2001 recommended the use of opioids as the most effective way to treat many patients' pain, stating "often the only treatment option that provides significant relief."<sup>10</sup> That consensus statement, which was endorsed by 21 health organizations, also urged that while preventing drug abuse is an important goal, it should not hinder patients' ability to receive the care they need and deserve.<sup>10</sup> The Federation of State Medical Boards (FSMB) has issued a "Model Policy for the Use of Controlled Substances for the Treatment of Pain" which stresses the necessity of using opioid analgesics for treating pain.<sup>5</sup> That initiative, which is meant to be a template for state policies, also contains the statement that "the undertreatment of pain will be considered a departure from the acceptable standard of practice."<sup>5</sup>

Across the country, many states have adopted policies that recognize the legitimate use of controlled substances. As of March 2006, 28 states had adopted a version of the FSMB policy in whole or in part, and an additional four states had developed their own policies that contain similar criteria for enlightened pain management.<sup>11</sup>

The goals of managing chronic pain should be to decrease pain to the maximum extent possible without unmanageable side effects, to improve overall functioning, and to reduce psychological distress.<sup>12,13</sup> The key to optimizing pain management with opioids is individualized titration combined with attempts to reduce adverse effects.<sup>14</sup> Today's accepted strategy is to individualize the treatment regimen for opioid use, considering these factors for each patient<sup>15</sup>:

- Previous experience with an opioid
- Degree of opioid tolerance (both to analgesia and side effects)
- Age, general condition, and medical status
- Concurrent nonopioids and other medications
- Type and severity of pain
- The balance between pain control and adverse reactions
- Risk factors for abuse, addiction, or diversion, including a prior history of abuse, addiction, or diversion

Most patients with persistent pain should receive opioids on a consistent schedule, once the dosage has been determined by titration. Regular around-the-clock dosing of opioids has been shown to prevent recurrence of severe pain for many patients.<sup>14</sup> A number of long-acting opioid preparations have been developed for use in around-the-clock treatment (Table 2). In addition to relieving pain, the benefits of long-acting analgesic medications include decreased sleep disturbances,

increased control over one's own pain management, independence from caregivers, and enhanced medication compliance.<sup>16</sup> Some patients may require a supplemental dose of a short-acting opioid for use as a "rescue medication" to provide adequate pain relief.<sup>14</sup>

Table 2.

## Oral Opioids Used to Treat Moderate to Severe Pain

Agent	Comments
Morphine sulfate	Numerous short-acting formulations available as branded and generics Sustained-release preparations: Oramorph <sup>®</sup> SR, Kadian <sup>®</sup> , Avinza <sup>®</sup> , MS Contin <sup>®</sup>
Hydromorphone	No long-acting formulations are marketed Short-acting form marketed as Dilaudid <sup>®</sup> Slightly shorter acting than morphine
Methadone	Intrinsically long-acting, requires up to 10 days to reach steady state May cause excessive sedation with repetitive dosing Marketed as Dolophine <sup>®</sup>
Levorphanol	Intrinsically long-acting May cause excessive sedation with repetitive dosing Marketed as Levo-Dromoran <sup>®</sup>
Oxycodone	Numerous short-acting formulations available as branded and generics Controlled-release preparation: OxyContin <sup>®</sup> Used in lower doses in combination with nonopioids for less severe pain (e.g., Percocet <sup>®</sup> )
Oxymorphone	Sustained-release preparation: Opana <sup>®</sup> ER Immediate-release preparation: Opana <sup>®</sup>
Codeine	Used for less severe pain No long-acting dosage form available
Fentanyl	Transdermal patch for sustained release: Duragesic <sup>®</sup> and generics Oral transmucosal fentanyl citrate available for breakthrough pain: Actiq <sup>®</sup> Oral buccal fentanyl citrate for breakthrough pain: Fentora <sup>®</sup>

Source: Reference 14.

Patients' responses to opioids vary considerably.<sup>15</sup> When a patient's pain no longer responds sufficiently to the current medication and/or the patient is bothered by side effects, it is common in clinical practice to rotate opioids (i.e., switch a patient from one opioid to another to reduce adverse effects and/or increase pain relief). Evidence is accumulating that interindividual differences in analgesic responsiveness play a role.<sup>14</sup> Further, initial tolerance is somewhat drug-specific; cross-tolerance among the opioid analgesics is incomplete, so that a patient who no longer responds optimally to one opioid may obtain better pain relief from a different opioid.<sup>14</sup>

Other medications are often given along with an opioid to increase analgesia, reduce adverse effects, or to reduce the need to increase the opioid dosage. Nonopioids such as acetaminophen, salicylate, and other nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in this way. Other agents may include caffeine, the antihistamine hydroxyzine, a central stimulant such as dextroamphetamine, or a phenothiazine such as methotrimeprazine. Tricyclic antidepressants (e.g., amitriptyline, imipramine, nortriptyline, desipramine) and anticonvulsants (e.g., gabapentin, phenytoin, carbamazepine, valproate sodium, clonazepam) are often used adjunctively with opioids for neuropathic pain.<sup>14</sup>

## Opana<sup>®</sup> ER (oxymorphone HCl) Extended-Release Tablets CII

Opana ER is a new option for patients with moderate to severe chronic pain requiring around-the-clock opioid therapy.

Oxymorphone has been available since 1959 in a parenteral dosage form.<sup>17</sup> Now, two oral formulations are available: Opana ER, an extended-release, long-acting form, and Opana, an immediate-release, short-acting form.

Opana ER is a new alternative for Steps 2 and 3 of the Pain Ladder.<sup>17</sup> It offers an additional rotational option for addressing patient variation in responsiveness to pain medications and optimizing the balance between adverse effects and analgesic efficacy.<sup>18</sup> This formulation provides long-acting, true 12-hour analgesia for long-term treatment of moderate to severe chronic pain.<sup>16</sup>

Differences between Opana ER and other long-acting oral opioids are illustrated in Table 3. The primary distinction is its significantly longer half-life and lower bioavailability.<sup>15,19-22</sup>

### Description

Oxymorphone is a semisynthetic  $\mu$ -opioid agonist analgesic that is structurally more closely related to hydromorphone than to morphine.<sup>17</sup> Oxymorphone is several times more potent than morphine with a more rapid onset of action.<sup>23</sup> It is available as a hydrochloride salt, which makes it water soluble.<sup>15,17</sup>

This opioid agonist differs from morphine by substitution of a ketone group, which makes it more lipid soluble, conferring greater potency and a more rapid onset of action. Its moderate lipid solubility facilitates rapid penetration into the neurovascular membranes of the brain and spinal cord.<sup>23</sup>

Opana ER utilizes the proprietary TIMERx-N controlled-release system from Penwest Pharmaceuticals. This technology controls the rate of penetration of water into the hydrophilic

Table 3.

### Differentiation of Long-Acting Oral Opioids

	Oxymorphone ER	Oxycodone CR	Morphine CR
Brand name(s)	Opana <sup>®</sup> ER	OxyContin <sup>®</sup>	Avinza <sup>®</sup> , Kadian <sup>®</sup> , MS Contin <sup>®</sup>
Oral bioavailability (%)	10	60–87	<40
T <sub>max</sub> (hr)			4.4
Single dose	2.5–4	2–3	
Multiple doses	1.3–3.5	3	
Half-life (hr)	9–11	4.5	2–4
CYP metabolism	None	CYP 2D6 and 3A4 substrate	None
Pregnancy category	C	B	C
Dosing	Every 12 hours	Every 12 hours	Every 12–24 hours

CR = continuous release; CYP = cytochrome P450; ER = extended release; SR = sustained release; T<sub>max</sub> = time to maximum effect.

Source: References 15 and 19–22.

matrix, which gels and slowly releases drug through the matrix over the 12-hour dosing period.<sup>17</sup>

As with other opioid agonists, the precise mechanism of analgesic action of oxymorphone is not known. However, it is generally related to its binding to specific central nervous system (CNS) opioid receptors throughout the brain and spinal cord. While opioid receptors also have been identified within the peripheral nervous system, the role of these receptors in analgesia is unknown.<sup>15</sup> Oxymorphone has a higher binding affinity for  $\mu$ -opioid receptors than morphine.<sup>17</sup>

## Approved Indications

Opana ER is indicated for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. It is not intended for dosing “as needed” for analgesia; nor is it intended for pain in the immediate postoperative period (12–24 hours following surgery) for patients not previously taking opioids or for postoperative pain that is mild or not expected to persist.<sup>15</sup>

Immediate-release Opana is indicated for the relief of moderate to severe acute pain where the use of an opioid is appropriate.<sup>24</sup> The half-life of this formulation is longer than that of morphine, hydromorphone, and oxycodone.<sup>15</sup>

*Note: The following information applies to Opana ER unless the immediate-release Opana is specifically named.*

## Pharmacokinetics

**Absorption.** The absolute oral bioavailability of oxymorphone is approximately 10%. Steady-state levels are achieved

after 3 days of multiple doses. Dose proportionality has been established for all four dosage strengths of the ER formulation for both peak plasma levels and extent of absorption (area under the plasma concentration–time curve) (Table 4).<sup>25</sup>

**Distribution.** Oxymorphone is not extensively bound to human plasma proteins; binding is in the 10% to 12% range.<sup>15</sup>

**Metabolism.** Oxymorphone is metabolized primarily in the liver, forming both active and inactive metabolites. Its two major metabolites are oxymorphone-3-glucuronide and 6-OH-oxymorphone. Mean plasma concentration is 90 times higher than the parent compound for the former, and essentially the same at steady-state for the latter.<sup>15</sup>

**Elimination.** Oxymorphone is extensively metabolized; less than 1% of the dose is excreted unchanged in the urine. On average, 33% to 38% of the administered dose is excreted as the glucuronide metabolite, and 0.25% to 0.62% is excreted as 6-OH-oxymorphone in people with normal liver and kidney function.<sup>15</sup>

## Dosage and Administration

Clinicians should individualize treatment, using nonopioid analgesics, opioids indicated for “as needed” use and/or combination products, and chronic opioid therapy in a progressive plan of pain management such as those outlined by the World Health Organization, the American Pain Society, and the FSMB’s Model Policy as discussed previously in this New Therapeutics Bulletin.<sup>15</sup>

A primary consideration when planning the dosage regimen for Opana ER is the patient’s prior experience with opioid analgesics. Those who have never taken an opioid should be started at the lowest dose (5 mg every 12 hours).<sup>15</sup> If patients are

Table 4.

### Pharmacokinetics of Opana ER

Dosage Regimen	Dosage (mg)	C <sub>max</sub> <sup>a</sup> (ng/mL)	AUC <sup>a</sup> (ng • hr/mL)	T <sub>1/2</sub> <sup>a</sup> (hr)
Single dose	5	0.27 ± 0.13	4.54 ± 2.04	11.30 ± 10.81
	10	0.65 ± 0.29	8.94 ± 4.16	9.83 ± 5.68
	20	1.21 ± 0.77	17.81 ± 7.22	9.89 ± 3.21
	40	2.59 ± 1.65	37.90 ± 16.20	9.35 ± 2.94
Multiple dose <sup>b</sup>	5	0.70 ± 0.55	5.60 ± 3.87	NA
	10	1.24 ± 0.56	9.77 ± 3.52	NA
	20	2.43 ± 1.35	19.28 ± 8.32	NA
	40	4.47 ± 1.91	36.98 ± 13.53	NA

<sup>a</sup>Mean ± SD.

<sup>b</sup>Results after 5 days of dosing every 12 hours.

AUC = area under the plasma concentration–time curve; C<sub>max</sub> = peak plasma concentration; NA = not applicable; SD = standard deviation; T<sub>1/2</sub> = half-life.

Source: Reference 25.

Table 5.

## Suggested Initial Dosage of Opana ER

Patient Experience	Initial Dosage of Opana ER	Comment
Opioid-naïve	5 mg every 12 hours	Titrate at 5–10 mg increments every 12 hours, every 3–7 days until adequate analgesia with minimal side effects is achieved
Converting from parenteral oxymorphone	10 times the total daily parenteral dose divided into two daily doses	For example, a patient with a total daily dose of 4 mg parenteral oxymorphone should start with 20 mg Opana ER every 12 hours
Converting from other oral opioids <sup>a</sup>	Multiply the total daily dose of the current opioid times the oral conversion ratio:	If a patient is taking more than one opioid, calculate the converted dose for each and add them to estimate the total daily oxymorphone dose
Hydrocodone	0.5	Adjust the dose of Opana ER gradually, preferably at 10 mg per dose increments every 3–7 days There is significant patient variation in the relative potency of different opioid drugs and formulations
Oxycodone	0.5	
Methadone	0.5	
Morphine	0.333	
Converting from Opana	One half the total daily oral Opana dose every 12 hours	

<sup>a</sup>The conversion ratios and approximate equivalent doses in this conversion table are to be used only for the conversion from current opioid therapy to Opana ER.

Source: Reference 15.

currently taking another opioid—oral or parenteral—the starting dose of Opana ER should be determined according to the conversion factors in Table 5.

Because there is considerable patient variability in response to opioid analgesics, patients should be closely monitored to ensure adequate pain relief and to minimize side effects.<sup>15</sup> Titration guidelines are listed in Table 5. Titration should be based on the amount of supplemental opioid use, pain severity, and the patient's ability to tolerate the opioid. In general, patients should be titrated to mild or no pain with the regular use of no more than two doses of supplemental analgesia (rescue medication) in any 24-hour period. Dose adjustments should aim for an appropriate balance between pain relief and opioid-related adverse events.<sup>15</sup>

As with other opioids, there is no ceiling dose for Opana ER; the maximum dose depends on each individual's response and tolerance of side effects.<sup>14</sup> Like other extended-release opioids, Opana ER has been pharmaceutically designed to yield analgesia for about 12 hours.

While most patients will receive symmetric dosing (i.e., the same dose twice a day) some may benefit from asymmetric dosing, with a different dose given in the morning than in the evening, tailored to the individual's pain and response pattern.<sup>15</sup>

Because food significantly increases the bioavailability of Opana ER, patients should take Opana ER tablets on an empty

stomach, at least 1 hour prior to or 2 hours after eating.<sup>15</sup> Opana ER tablets must be swallowed whole and are not to be broken, chewed, crushed, or dissolved. Such misuse can release a potentially fatal dose of oxymorphone.<sup>15</sup>

**Overdosage.** Acute overdosage with Opana ER—like all opioids—is characterized by respiratory depression, extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest, and death may occur. Primary treatment should aim to reestablish a patent airway and to provide assisted or controlled ventilation. The airway should be secured before attempting to eliminate unabsorbed drug through gastric emptying. The opioid antagonist naloxone HCl may be administered (usual initial adult dose 0.4–2.0 mg), preferably by the intravenous route; alternatively, the pure opioid antagonist nalmefene may be administered.<sup>15</sup> Repeat dosing may be necessary because the duration of action of these antagonists is considerably shorter than that of Opana ER.

**Cessation.** Because of the possibility of physical dependence on Opana ER, it should not be abruptly terminated. As with other opioids, Opana ER can be safely discontinued without development of withdrawal symptoms by slowly tapering the daily dose.<sup>15</sup>

## Efficacy

Opana ER has repeatedly been shown effective in relieving moderate to severe pain while improving functioning and quality of life.<sup>16,18,23</sup> According to the drug's distributor, Endo Pharmaceuticals, the clinical trial program for Opana and Opana ER was one of the most comprehensive ever conducted for an opioid analgesic, with more than 15 clinical trials enrolling more than 3,000 patients.<sup>26</sup> Studies on Opana ER were conducted among both opioid-naïve and opioid-experienced patients with chronic back pain, osteoarthritis, and cancer pain.

In a large, randomized, double-blind, placebo-controlled trial of 213 patients (aged 18–75 years) in 26 centers, opioid-experienced patients with moderate to severe chronic low back pain were randomized to receive oxymorphone ER (10–110 mg) or oxycodone continuous release (CR) 20–220 mg every 12 hours during a 7 to 15 day dose titration phase. Patients achieving an effective analgesic dose entered the double-blind treatment phase lasting 18 days, where they either continued receiving opioid therapy or received placebo. Both active agents were found to be effective for relieving pain in these patients.<sup>23</sup> Both were statistically superior to placebo in relieving pain: 61% of patients taking either active drug reported moderate to complete pain relief, compared with 28% for placebo ( $P = .0006$  and  $P = .0001$ , respectively).<sup>23</sup> During the first 4 days of the trial, when rescue medication use was unrestricted, those patients taking active agents required significantly less rescue medication than those on placebo (oxymorphone ER, 25.5 mg,  $P = .0068$ ; oxycodone CR, 24.4 mg,  $P = .0024$ ; placebo, 34.8 mg). Patients on either active medication reported significantly less interference with normal activities as indicated by their ratings on scales of general activity, mood, normal work, relations with other people, and enjoyment of life. This study demonstrated that oxymorphone ER was equianalgesic to oxycodone CR at half the milligram daily dosage.<sup>23</sup>

In a trial of opioid-naïve patients with moderate to severe chronic low back pain, oxymorphone ER was carefully titrated to a stable dose over a 4-week period, followed by a 12-week, double-blind, placebo-controlled, randomized withdrawal period. The majority of patients reach a stabilized dose of oxymorphone ER within 1 month. The mean stabilized daily dose was  $40.0 \pm 25.8$  mg.<sup>27</sup> Pain was measured using a 100-mm Visual Analog Scale, with the zero end labeled “no pain” and the 100-mm end labeled “worst pain imaginable.” The mean pain intensity score of patients who completed the titration period decreased significantly, from  $69.4 \pm 11.8$  mm at screening to  $22.7 \pm 2.7$  mm at stabilization ( $P < .0001$ ). Those who were then randomized to oxymorphone ER maintained their pain control, while those receiving placebo did not. This trial showed that the majority of patients with moderate to severe chronic low back pain who had

been suboptimally responsive to nonopioid medications can be titrated to a stable, effective, and well-tolerated dose of oxymorphone ER.<sup>27</sup>

Similar findings were observed in another trial, this one conducted among patients with moderate to severe chronic low back pain who were not obtaining adequate pain relief from another opioid.<sup>28</sup> In an open-label phase, patients were converted to an equianalgesic dose of oxymorphone ER and then titrated over a 4-week period to a stable dose of oxymorphone ER. Following stabilization of the oxymorphone ER dose, patients were then randomized to receive oxymorphone ER or placebo during the 12-week double-blind phase. Those patients receiving the active drug experienced continuous analgesic efficacy and rated oxymorphone ER higher than their previous opioid medication ( $P < .001$ ) in terms of satisfaction (very good to excellent) with their medication (72% vs 14%, respectively).<sup>28</sup>

Opana ER also was studied in patients with moderate to severe pain due to osteoarthritis. The subjects had taken acetaminophen, a conventional NSAID, a cyclooxygenase-2 inhibitor, or an opioid analgesic for at least 75 days of the 90 days prior to their screening visit but were not achieving adequate pain relief. This trial was a randomized, double-blind, parallel-group study comparing twice-daily dosing of oxymorphone ER 40 mg, oxymorphone ER 20 mg, or oxycodone CR 20 mg with placebo on measures of pain and functioning.<sup>18</sup> Of the 495 patients randomized, a total of 269 patients completed 4 weeks of treatment. Overall, both the 20-mg and 40-mg twice-daily doses of oxymorphone ER provided superior pain relief and functional improvement relative to placebo in these patients. The trial investigators noted that patients' improvement when taking oxymorphone ER was clinically meaningful, as reflected in their improved scores on the WOMAC Index of pain, stiffness, and physical functioning.<sup>18</sup> In this trial, 56% of patients receiving oxymorphone ER 40 mg, 48% receiving oxymorphone ER 20 mg, and 40% receiving oxycodone CR 20 mg discontinued treatment; most were for nonserious adverse events. Insufficient therapeutic response was cited by 7.4%, 4.1%, and 10.4%, respectively. Patients taking placebo also discontinued at a high rate (37%), with most due to inadequate analgesia. Patients taking oxymorphone ER had a greater incidence of nausea, vomiting, and pruritus than those taking oxycodone CR.<sup>18</sup>

Another trial was a fixed-dose, forced titration comparison of the analgesic efficacy of oxymorphone ER and placebo in patients with osteoarthritis of the hip or knee whose pain was refractory to treatment with acetaminophen, NSAIDs, or opioid analgesics.<sup>29</sup> The study confirmed a linear dose relationship for oxymorphone ER in the 2-week trial period—pain relief scores improved with higher doses. Decreases in pain intensity were accompanied by significant improvements in WOMAC Index

scores of pain, stiffness, physical functioning, and in the Short-Form 36 (SF-36) physical health scores. Adverse events in the oxymorphone ER group included nausea (39.4%), vomiting (23.7%), dizziness (22.6%), constipation (22.2%), somnolence (17.6%), pruritus (16.5%), and headache (15%). The majority of adverse events were mild or moderate. There were three serious adverse events (urinary retention, CNS depression, and pancreatitis) that the investigators believed might be related to the study medication.<sup>29</sup>

Oxymorphone ER also was shown to provide long-term effective relief of moderate to severe pain among osteoarthritis patients.<sup>16</sup> In a 52-week open-label extension trial, 12-hour dosing of oxymorphone ER (median daily dose 40 mg) proved effective in patients with persistent, poorly controlled, moderate to severe osteoarthritis-related pain. This trial included a rating of patients' global satisfaction with the medication; more than 80% of the patients in this year-long trial rated their global satisfaction as excellent, very good, or good.<sup>16</sup>

Patients with moderate to severe cancer pain also experienced excellent pain relief from Opana ER.<sup>30</sup> In a crossover trial, patients received oxymorphone ER or oxycodone CR. Pain relief among the patients taking oxymorphone ER was comparable to that provided by oxycodone CR. Relief was reflected in improved endpoints of peak pain intensity, amount of rescue analgesic, quality of life ratings, and Karnofsky performance status.<sup>30</sup>

## Adverse Effects

The most common adverse effects of opioids in general are sedation, nausea and vomiting, constipation, and respiratory depression. Other adverse effects that have been reported by patients taking these drugs include confusion, hallucinations, nightmares, urinary retention, multifocal myoclonus, dizziness, dysphoria, and hyperalgesia.<sup>14</sup>

In Opana ER clinical trials in subjects with moderate to severe chronic pain or postsurgical pain, the most common adverse reactions reported at least once by 10% or more of subjects are listed in Table 6. Other side effects reported by between 1% and 10% of subjects were: blurred vision, diarrhea, abdominal pain, dyspepsia, dry mouth, decreased appetite, fatigue, lethargy, weakness, pyrexia, dehydration, weight loss, edema, insomnia, anxiety, confusion, disorientation, restlessness, nervousness, depression, dyspnea, flushing, and hypertension.<sup>15</sup>

In clinical trials of immediate-release Opana, the most common adverse drug reactions reported by 10% or more of subjects were nausea and pyrexia (Table 6). Other side effects occurring in between 1% and 10% of subjects were: tachycardia, vomiting, constipation, dry mouth, abdominal distention, flatulence, increased sweating, dizziness, somnolence, headache,

Table 6.

## Adverse Reactions Reported in Opana and Opana ER Clinical Trials by 10% or More of Subjects

Adverse Reaction	Opana	Opana ER
Nausea	x	x
Constipation		x
Dizziness		x
Vomiting		x
Pruritus		x
Somnolence		x
Headache		x
Increased sweating		x
Sedation		x
Pyrexia	x	

Source: References 15 and 24.

anxiety, sedation, confusion, hypoxia, pruritus, and hypotension.<sup>24</sup>

## Warnings and Precautions

**Warnings.** Opana and Opana ER contain oxymorphone, a Schedule II controlled substance with an abuse liability similar to that of other opioid analgesics. Oxymorphone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing Opana ER in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.<sup>15</sup>

Opana ER is intended for use in patients with moderate to severe pain who require a continuous, around-the-clock opioid analgesic for an extended period of time. It is not intended for dosing "as needed" for analgesia.<sup>15</sup>

Opana ER tablets are to be swallowed whole and must not be broken, chewed, dissolved, or crushed. Doing so leads to rapid release and absorption of a potentially fatal dose of oxymorphone.<sup>15</sup>

Patients must not consume alcoholic beverages or medications containing alcohol while taking Opana ER. Co-ingestion of alcohol with Opana ER may result in increased plasma levels and a potentially fatal overdose of oxymorphone.<sup>15</sup>

**Precautions.** Opana ER should be used with caution in elderly or debilitated patients and in those who are known to be sensitive to CNS depressants, such as those with cardiovascular, pulmonary, renal, or hepatic disease. It also should be used with caution in patients with<sup>15</sup>:

- Acute alcoholism

- Adrenocortical insufficiency (Addison's disease)
- CNS depression or coma
- Delirium tremens
- Kyphoscoliosis associated with respiratory depression
- Myxedema or hypothyroidism
- Prostatic hypertrophy or urethral stricture
- Severe impairment of pulmonary or renal function
- Moderate impairment of hepatic function
- Toxic psychosis
- Biliary tract disease, including acute pancreatitis

## Contraindications

Opana ER is contraindicated in any situation where opioids are contraindicated, such as patients with respiratory depression (in the absence of resuscitative equipment or in unmonitored settings) and in patients with acute or severe bronchial asthma or hypercarbia. Like all opioids, Opana ER is contraindicated in any patient who has or is suspected of having paralytic ileus. It is also contraindicated in patients with moderate or severe hepatic impairment. It should not be used in patients with a known hypersensitivity to oxymorphone HCl or to any of the other ingredients, or with known hypersensitivity to morphine analogs such as codeine.<sup>15</sup>

## Drug Interactions

In vitro studies suggest that oxymorphone is unlikely to react with any of the cytochrome P450 (CYP450) isoenzymes at normal analgesic concentrations, while producing only low levels of change at suprapharmacological concentrations in the activity of two CYP450 isoforms—CYP2C9 and CYP3A4. Clinical studies confirmed the in vitro results and showed no induction of CYP450 2C9 or 3A4 enzyme activity; therefore no dose adjustment for drug interactions mediated by CYP450 enzymes is needed.<sup>15,25</sup>

Many patients with chronic pain receive opioids concurrently with other medications, raising the possibility of drug-drug interactions that might compromise pain management. The lack of such interactions demonstrated for oxymorphone makes it a new option that may mitigate such polypharmacy-related challenges in patients with moderate to severe pain.<sup>25</sup>

## Safety

Oxymorphone ER was generally safe and well tolerated in clinical trials. Most of the adverse events experienced by patients in the trials were those typically associated with opioid therapy, and most were mild to moderate in severity.<sup>16,18,23</sup>

**Geriatric Use.** Plasma concentrations of oxymorphone are approximately 40% higher in people 65 years of age or older

than in younger subjects. Therefore elderly patients should receive smaller starting doses, and titration should proceed cautiously. Some adverse events (dizziness, somnolence, confusion, and nausea) occurred more frequently in people aged 65 years and older than in younger subjects.<sup>15,24</sup>

**Hepatic Impairment.** Greater plasma concentrations were seen in patients with hepatic disease than in those with normal liver function. For patients with mild hepatic impairment, Opana ER should be started with the lowest dose and titrated slowly while carefully monitoring for side effects. People with moderate or severe hepatic impairment should not take Opana or Opana ER.<sup>15,24</sup>

**Renal Impairment.** Clinical studies revealed an increase in bioavailability ranging from 57% to 65% in patients with moderate to severe renal impairment. These patients should be started cautiously with lower doses of Opana or Opana ER, and the medication should be titrated slowly while carefully monitoring patients for side effects.<sup>15,24</sup>

## How Supplied

Opana ER tablets are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets in four dosage strengths: 5 mg (pink), 10 mg (light orange), 20 mg (light green), and 40 mg (yellow).<sup>15</sup> Opana tablets are available in two dosage strengths: 5 mg (blue) and 10 mg (red).<sup>24</sup>

## Risk Management Program

Pain management faces another challenge in today's society: the need to balance the patients' access to pain relief as prescribed by their physicians with prevention of abuse and diversion of controlled substances such as opiate analgesics.<sup>31-33</sup> Maintaining this balance is an ongoing encumbrance for health care and law enforcement professionals alike.

Abuse of prescription drugs is a growing public health problem. The following statistics from the Drug Enforcement Administration (DEA) underscore the extent of the dilemma<sup>31</sup>:

- More new drug users abuse pain relievers (2.4 million) than marijuana (2.1 million) or cocaine (1.0 million).
- Six million Americans are currently abusing controlled substance prescription drugs—more than the number abusing cocaine, heroin, hallucinogens, and inhalants combined.
- Prescription opioid pain medications cause more drug overdose deaths than cocaine and heroin combined.
- Admissions for treatment of problems associated with prescription opiates increased by one third in the 2 years between 2002 (46,972) and 2004 (63,243).

To help ensure the safe use of opioid analgesics and minimize the risks of misuse, abuse, and diversion, Opana ER is being introduced with a program called the PROMISE Initiative (Partnership for Responsible Opioid Management through Information, Support, and Education). This program offers clinicians, pharmacists, and patients a range of information and continuing education (CE) opportunities through components such as<sup>34</sup>:

- The National Initiative on Pain Control—a CE program that utilizes interactive case-based workshops, live audio-conferences, live Web casts and on-demand Web-based programs, regional symposia, and CE-accredited newsletters.
- Support of independent educational Web sites, including:
  - PainEDU.org—for health care professionals who treat patients with pain.
  - PainKnowledge.org—an online resource for health care professionals developed by the National Initiative on Pain Control.
  - painACTION.com—for consumers and providers dealing with chronic pain.
- A Pain Management Resource Kit—practical tools to support the appropriate and responsible use of opioids, including:
  - Pain Assessment Inventory.
  - Screener and Opioid Assessment for Patients with Pain (SOAPP)—a tool to help clinicians assess the risk of medication misuse.
  - Tamper-evident prescription pads that help thwart alterations, forgery, and counterfeiting.
  - A Clinical Guide to Opioid Analgesia* handbook.
  - Educational materials for patients and caregivers on the use of oral opioids.

The PROMISE program and its components may be accessed at <http://www.endopromise.com>.

## Implications for Pharmacists

In addition to familiarizing themselves with the federal and state requirements relevant to controlled substances, pharmacists also have a responsibility to protect their practices from becoming an easy target for drug diversion. One aspect of this is maintaining vigilance against forged or altered prescriptions.<sup>35</sup> The DEA lists these signs that a prescription may be forged<sup>35</sup>:

- The prescription looks “too good”—the handwriting is too legible.
- Quantities, directions, or dosages differ from usual medical usage.

- The prescription does not use standard abbreviations or has no abbreviations at all.
- The prescription appears to be photocopied.
- It is written in different handwriting or different-colored inks.
- Erasure marks are apparent.

Pharmacists are legally responsible for knowingly dispensing a prescription that was not issued “in the usual course of professional treatment.”<sup>35</sup> Here are some clues that the prescription may not have been issued for a legitimate medical purpose<sup>35</sup>:

- The prescription is being presented for a refill more frequently than is usual (e.g., a prescription that should last for a month is being refilled more often).
- The physician writes prescriptions for antagonistic drugs such as depressants and stimulants at the same time.
- The patient presents prescriptions written in the names of other people.
- Several people appear at the same time, or within a short time, with similar prescriptions from the same physician.
- Numerous people who are not regular patrons bring in prescriptions from the same physician.

Pharmacists can prevent these types of fraud and abuse by following a few simple rules<sup>35</sup>:

- Know the prescribing physician and his/her signature.
- Know the prescriber’s DEA registration number.
- Know your patients.
- Check the date of the prescription; is it being presented to you within a reasonable amount of time since it was written?
- If you are in doubt, require proper identification.
- If you believe that you have a forged, altered, or bogus prescription, do not dispense it. Call your local police.
- If you believe that you have discovered a pattern of prescription abuse, contact your State Board of Pharmacy or your local DEA office.

## Pharmaceutical Care Considerations

The pharmacist’s first duty, of course, is to dispense the correct medication to the correct patient in the correct amount and with the correct instructions. Because both Opana and Opana ER are available as 5-mg and 10-mg tablets, and because prescribing physicians may not yet be familiar with the medication, there is a risk of misprescribing and miscalculation. Whenever a prescription raises a doubt concerning the prescriber’s intention, the question must be clarified before the medication is dispensed.

# Opana<sup>®</sup> and Opana<sup>®</sup> ER at a Glance

	Opana Immediate-Release Tablets	Opana ER Extended-Release Tablets
<b>What It Is:</b>	Oxymorphone HCl, an immediate-release semisynthetic opioid analgesic	Oxymorphone HCl, an extended-release semisynthetic opioid analgesic
<b>How It Works:</b>	Opioid agonist Precise mechanism of analgesic action is unknown but may be related to its binding to central nervous system (CNS) opioid receptors	
<b>What It Does:</b>	Relieves moderate to severe pain	
<b>Indications:</b>	Relief of moderate to severe acute pain where the use of an opioid is appropriate	Relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time
<b>How Supplied:</b>	Tablets of 5 mg or 10 mg of oxymorphone HCl	Tablets of 5 mg, 10 mg, 20 mg, or 40 mg of oxymorphone HCl
<b>Dosage:</b>	Opioid-naïve patients: Starting dose 10–20 mg every 4–6 hours, depending on pain severity; may be started at 5 mg	Opioid-naïve patients: Starting dose 5 mg every 12 hours
	Opioid-experienced patients: See conversion recommendations in this New Therapeutics Bulletin or package insert Titrate to level that provides adequate analgesia with minimal side effects; there is no defined maximum dose	
<b>Most Common Adverse Events:</b>	Nausea, pyrexia	Nausea, constipation, dizziness (excluding vertigo), vomiting, pruritus, somnolence, headache, increased sweating, sedation
<b>Contraindications:</b>	Known hypersensitivity to oxymorphone HCl or to any other ingredients in Opana or Opana ER, or to morphine analogs such as codeine Respiratory depression except in monitored setting and in the presence of resuscitative equipment Patients with acute or severe bronchial asthma or hypercarbia Patients with paralytic ileus Patients with moderate or severe hepatic impairment Do not coadminister with ethanol or with other medications containing ethanol	
		Relief of pain in the immediate postoperative period (first 12–24 hours following surgery), or if the pain is mild or not expected to persist for an extended period of time
<b>Drug Interactions:</b>	Pharmacodynamic: Additive effects if used with alcohol, other opioids, illicit drugs that cause CNS depression, CNS depressants (general anesthetics, phenothiazines or other tranquilizers, sedatives, hypnotics)  Pharmacokinetic: Does not inhibit or induce any of the major cytochrome P450 enzymes at pharmacological doses	
<b>Use in Pregnancy:</b>	Pregnancy Category C; safety during pregnancy has not been established with regard to possible adverse effects on fetal development Crosses the placenta; may produce respiratory depression and psychophysiologic effects in neonates	

The important role of the pharmacist in ensuring that a patient realizes maximum benefit from any drug treatment was underscored in a study published in the *Archives of Internal Medicine* in September 2006. Researchers evaluated communication to patients about new prescriptions among family physicians, internists, and cardiologists. While physicians explained the purpose of the medication most of the time (87%), they failed to discuss adverse effects in 65% of new prescriptions and addressed dosing in just over half.<sup>36</sup>

The pharmacist can help to optimize opioid pain management by alerting patients to possible side effects and suggesting ways to counter them. For example, the pharmacist can advise patients of the potential for severe constipation when taking Opana ER and suggest that laxatives and/or stool softeners be used when initiating therapy with the medication.<sup>15</sup> If a patient experiences nausea, it is appropriate to suggest an antiemetic agent.<sup>14</sup> Opioids can cause drowsiness; advise patients that this side effect usually diminishes within the first several days.<sup>14</sup>

Individualization of dosage is essential to make optimal use of Opana ER.<sup>15</sup> To help patients understand this, the pharmacist should review the prescribing physician's dosage schedule, explaining the process of titration and emphasizing the need for frequent contact with the physician at the beginning of therapy. Explain that dosage is always individualized and that patients can obtain maximum pain relief by letting their doctor know if their pain is not being sufficiently relieved or if they are having side effects. Reassure patients that when using a long-acting medication such as Opana ER, it is not unusual to take an immediate-release medication in addition to handle breakthrough pain. These rescue medications may be over-the-counter products such as aspirin, acetaminophen, or ibuprofen, or they may be a prescription agent such as immediate-release Opana.<sup>15</sup>

Patients should be told not to adjust their dosage without consulting the prescribing physician.<sup>15</sup> Inform patients that they should not stop taking Opana ER abruptly; medication should be tapered gradually to avoid any withdrawal symptoms.<sup>15</sup> Any unused tablets should be destroyed by flushing them down the toilet.<sup>15</sup>

The pharmacist can provide a valuable service by addressing patients' concerns about addiction and making sure they understand the difference between physical dependence or tolerance, which are normal, and addiction. When patients complain that their pain relief from an opioid is not lasting as long as previously, they may be developing tolerance. Reassure them that most patients on long-term opioid therapy develop some degree of tolerance, and it may often be overcome by increasing the dose—*after checking with the prescribing physician*.<sup>14,15</sup> Patients should be told that Opana ER is a Schedule II drug with

abuse liability, and that they should protect it from theft and never give it to anyone else.<sup>15</sup>

Because Opana ER is a potent opioid, patients should be told to keep it in a secure place out of the reach of children and pets. Accidental consumption—especially by children—can result in overdose or death.<sup>15</sup>

As part of their role in the assessment and ongoing monitoring of patients taking opioids, pharmacists should encourage patients to report episodes of breakthrough pain and adverse experiences to their physician.<sup>15</sup>

## Summary

Challenges remain in overcoming obstacles to the use of opioids because of patients' unfounded fears of addiction and professionals' fear of regulatory action.<sup>5,11</sup> However, patients with moderate to severe pain have a better chance for obtaining relief today than in previous decades due to increasing acceptance of the use of opioids. Opana is a new oral opioid that is available in both immediate-release and extended-release (Opana ER) formulations. Opana ER has been proven generally safe and effective in a large number of patients with chronic low back pain, osteoarthritis pain, or cancer pain.

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## Answers to Common Questions About Pain Management and Opana<sup>®</sup> ER

### 1. My doctor prescribed Opana ER. What is it and how will it help?

Opana is an immediate-release, short-acting medicine used to treat moderate to severe pain that is expected to last for a few days and for breakthrough pain. Opana ER is an extended-release, long-acting form of the medicine for use around the clock for moderate to severe pain that is expected to last for an extended period of time. Both Opana and Opana ER contain oxycodone, which is derived from morphine. It is an opioid (formerly called a narcotic) analgesic that is used to treat moderate to severe pain.

### 2. Will I become addicted to the medicine?

Although there is a chance of abuse or addiction with opioids such as Opana ER, that is seldom a problem for people with moderate to severe pain who take their medication as prescribed. People with an *addiction* to opioids crave them and use them regularly for reasons other than pain relief. It is not unusual for people taking opioids for pain relief to need an increased dose over time to achieve relief; this is called *tolerance*. There is also a chance that you may become *physically dependent* on the drug, which means that withdrawal symptoms may occur if you suddenly stop taking it. Therefore, you should not stop taking your medication abruptly; your doctor can slowly reduce your dosage to avoid this condition. Neither tolerance nor physical dependence are addictive disorders and should not be confused with addiction.

### 3. How should I take Opana ER?

It is important to follow your prescription schedule precisely. If you have been prescribed the long-acting form, Opana ER, you will take it every 12 hours. Opana ER tablets must be swallowed whole; they are not to be broken, chewed, dissolved, or crushed, because doing so would release the entire 12-hour dose into your body at once, which is dangerous and could cause death. If you miss a dose of Opana ER, take it as soon as possible; if it is almost time for the next dose, skip the missed dose and go back to your regular dosing schedule. The short-acting form of Opana is usually taken every 4 to 6 hours as needed for pain. Both forms of Opana should be taken on an empty stomach, at least 1 hour before or 2 hours after eating.

### 4. What side effects might I expect?

Opana and Opana ER can cause trouble breathing; if your breathing slows down and if you have shallow breathing (little chest movement), or if you feel faint, dizzy, or confused, call your health care provider or get medical help right away. Opana ER may cause your blood pressure to drop, which can make you feel dizzy if you stand up too quickly. The most common side effects of Opana ER are nausea, constipation, dizziness, vomiting, itching, sleepiness, headache, increased sweating, and sedation. Except for constipation, these effects usually decrease in a few days with continued use. Talk to your doctor or pharmacist if you are bothered by these symptoms; they can change the dosage or take other steps to reduce side effects. For example, since constipation is a common occurrence with opioids, you may be advised to use a laxative while taking Opana ER. Because Opana and Opana ER can make you sleepy, you should not drive, operate heavy machinery, or take part in other possibly dangerous activities until you know how you will react to the medicine, usually after a week of therapy.

### 5. Is it safe to take Opana ER with other medicines?

Be sure to tell your doctor about all the medicines you take, including over-the-counter medicines, vitamins, and herbal supplements. Some drugs such as sleeping pills, anxiety medicines, antihistamines, or tranquilizers may cause serious problems when taken with Opana or Opana ER.

### 6. May I drink alcoholic beverages while taking Opana ER?

No. Drinking alcohol while taking Opana or Opana ER may increase the chance of dangerous side effects including overdose and death.

### 7. Is it safe to take Opana ER during pregnancy and while breast-feeding?

Opana and Opana ER have not been tested for safety in pregnancy. These medicines may harm your unborn baby or pass through your milk, so you should not take them if you are pregnant or breast-feeding.





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