Oxymorphone has been available for more than 50 years, long enough that there are few practitioners around who can remember a time when it was not part of the acute pain-management armamentarium. But new formulations that can make its analgesic effects more immediate or more sustained, combined with its inherent potency, merit a review of the evidence behind oxymorphone so that clinicians can determine its utility for individual patients.

Oxymorphone (14-hydroxydihydromorphinone) is a semisynthetic mu opioid agonist that was first approved by the US FDA in 1959. Oxymorphone has a greater analgesic potency than morphine and, until recently, has been available only as a parenteral injection and in suppository form. Recently, immediate-release (IR) and long-acting extended-release (ER) oral formulations (Orpana, Endo Pharmacueticals) of this drug were developed that make oxymorphone a new option for treating moderate to severe pain, which, as defined by the World Health Organization 3-step ladder, corresponds to the highest rung, or step 3. Clinical trials in both malignant and nonmalignant pain demonstrate the drug’s utility as a new addition to the pantheon of step 3 options. As a newly rediscovered potent analgesic in the list of step 3 opioids, it is important to critically review its pharmacology and pharmacoeconomics to determine its proper place in pain management.

Formulations
It is available in oral, intravenous, and suppository forms. The oral form is now available in an IR and ER form. Both are available as tablets. Drug release from the ER form is based on a
controlled-release technology that involves the rate of penetration of water entering a hydrophilic matrix with subsequent expansion of the gel coating (TIMERx, Penwest Pharmaceuticals Co).2 The matrix consists of locust bean gum and xanthan gum. The fluctuation index, or more simply, the rate of drug release, of the ER form of oxymorphone is comparable to known fluctuation indices with other long-acting opioids such as morphine ER and oxycodone ER.

The antinociceptive effects of oxymorphone are mediated through the mu opioid and delta opioid receptors.3 Oxymorphone has a higher binding affinity to mu-opioid receptors than morphine does (Ki 15 vs morphine Ki 38). Oxymorphone binds to delta receptors4 with a much greater affinity than morphine (Ki 145 vs morphine 500). Oxymorphone is also characterized as a delta agonist. This is similar to hydromorphone.4 In contrast to hydromorphone, however, oxymorphone has little kappa receptor activity.3

An example of an opioid with a high affinity for the kappa opioid receptor is oxycodone. Quantitatively, oxymorphone5 has 10-fold less affinity for the kappa receptor than the mu or delta receptor. The advantages of delta affinity may be 2-fold. Agonist actions at the delta receptors potentiate mu-mediated analgesic effects. They also may lessen the development of tolerance. The lesser affinity for the kappa opioid receptor could explain the decreased sedation seen in previous studies compared with morphine. However, this phenomenon has not been substantiated by recent trials. There is no information on whether oxymorphone binds to sigma receptors.
Pharmacology/Routes of Administration

Oxymorphone can be administered orally, intravenously, subcutaneously, intrathecally, and rectally.

Oral Administration

Pharmacology of IR oxymorphone. In healthy volunteers, the single dose and steady-state pharmacokinetic profiles of oxymorphone IR tablets were linear and dose-proportional across the accepted dose range from 5 to 20 mg.6 The oral bioavailability of oxymorphone is approximately 10%.7 This is the lowest of the oral step 3 opioids. This fact has 2 major implications for clinicians. First, the timing of administration in relation to meals is critical. Ideally, the medication is taken at least 1 hour before meals. If oxymorphone is taken in the presence of a fatty meal, the uptake of the drug may be further reduced, resulting in dose failure.

If oxymorphone is taken in the presence of a fatty meal, the uptake of the drug may be further reduced, resulting in dose failure.

Second, when taken in the presence of alcohol, the bioavailability increases dramatically and can result in relative overdose. So, the clinician must explicitly instruct the patients not to drink any alcohol while on this medication and it would be inappropriate for a patient who drinks regularly.

In healthy volunteers, the half-life ranges from 7.2 to 9.4 hours.8 The half-life of IR oxymorphone is definitely longer than that of morphine, hydromorphone, and oxycodone. Time to peak concentration is 30 minutes, which is equivalent to oral morphine. Protein binding of oxymorphone is 20% to 40%, which is an important consideration in low-protein disease states.8 The half-life is influenced by the route of administration (vide infra).

The recommended dosing has been every 6 hours, which is longer than most IR opioids. Steady-state conditions are achieved after 3 to 4 days. Oxymorphone is subject to hepatic first-pass effects and is renally excreted. Oxymorphone undergoes extensive hepatic metabolism via conjugation with glucuronic acid to create oxymorphone 3-glucuronide and the keto group is reduced to form 6-OH-oxymorphone. There are no published studies on the relationship between sex, age, and metabolism.

Pharmacology of ER oxymorphone. In healthy volunteers, the ER form of oxymorphone has a lower Cmax and an elevated Cmin, which is consistent with decreased dose fluctuations. This is characteristic of long-acting opioids.8,9 The time to maximum concentration was 3.0 hours (range 1–12 hours). Steady state was achieved after 3 days of dosing. A reduced fluctuation in oxymorphone concentration during the dosing interval keeps oxymorphone blood levels more centered within the theoretical “therapeutic window.” The fluctuation index of ER oxymorphone compares favorably with that of other long-acting compounds. In clinical studies with other formulations (ie, Cmax of 12 and 24 hours), differences in pharmacokinetic variables (eg, fluctuations in plasma morphine concentration and time to maximum concentration) have not been shown to translate into differences in extent of pain relief or the incidence or severity of adverse effects.

Intravenous and Subcutaneous Administration

After intravenous administration of oxycodone, onset of action is rapid; initial effects are usually perceived within 5 to 10 minutes. Its duration of action is approximately 3 to 6 hours.10 After an intravenous dose, the steady-state volume of distribution was 3.08 ± 1.14 L/kg in healthy male and female subjects. This is very low in comparison to morphine or fentanyl. The half-life after intravenous dosing is 1.5 hours.10 Onset of action after subcutaneous or intramuscular injection is within 10 to 15 minutes. There is no information about the bioavailability after subcutaneous administration.

When taken in the presence of alcohol, the bioavailability increases dramatically and can result in relative overdose.

Intrathecal Administration

Oxymorphone has been administered via epidural and intrathecal routes. No information exists regarding peak cerebrospinal fluid levels or regarding the appropriate dose conversions from intravenous or oral forms to epidural and intrathecal doses.

The reported duration of action of oxymorphone seems to be shorter than that of morphine.11 For epidural block, oxymorphone is approximately 3 times as potent as morphine.

One report12 associated intrathecal oxymorphone with the development of leg edema. Five of the 23 patients who had intrathecal infusions of opiates for longer than 24 months developed leg and feet edema. Three of the 5 patients were receiving oxymorphone at doses ranging from 6 to 13 mg/d. The mechanism of this edema was postulated to be the result of opioid-induced vasodilatation.

Rectal Administration

Oxymorphone suppositories are absorbed well. Rectal administration results in a lower and more delayed peak analgesia and a longer duration of action than intramuscular administration. After rectal administration, onset of action usually occurs within 15 to 30 minutes. Analgesia is maintained for 3 to 6 hours after rectal administration. It is important to remember that the presence of stool may alter absorption markedly and unexpectedly, resulting in delays in onset or dose failure.

Biotransformation of Oxymorphone

Oxymorphone is metabolized by uridine diphosphate glucuronosyltransferase (UGT) enzymes, enzymes 1A3 and 2B7, with UGT 2B7 being the predominant enzyme.1 At the 3 position,
oxymorphone undergoes conjugation to create oxymorphone 3-glucuronide.

Another potential area of biotransformation is via the cytochrome P450 (CYP450) system. The CYP450 system has well-known implications in the biotransformation of many opioids, such as oxycodone and methadone.

Oxymorphone ER was studied in a randomized, open-label, parallel-group study examining the effects on CYP2C9 or CYP3A4 metabolic activities in healthy subjects. Oxymorphone ER exhibited minimal potential for causing metabolic drug-drug interactions mediated by CYP2C9 or CYP3A4.13 This fact is extremely important in patients who are on other medications that are dependent on the P450 cytochrome system for metabolism. For example, methadone (Topics in Pain Management, vol. 23, no. 5) is extremely dependent on metabolism by CYP2B6. If other drugs occupy the P450 system, an overdose can result. Making sure that the patient takes only medications that are independent of that system will prevent this issue from arising. Other examples of P450-dependent pain medications include fluoxetine, sertraline, fluvoxamine, duloxetine, carbamazepine, alprazolam, triazolam, desipramine, and nortriptyline. Extra caution needs to be taken with patients on methadone while on these medications.

**Patients who are on antidepressant therapy may benefit from oxymorphone’s lack of interaction.**

Patients who are on antidepressant therapy may benefit from oxymorphone’s lack of interaction. Oxymorphone has the advantage of not being metabolized by P450.

**Elimination of Oxymorphone**

Less than 2% of the parent compound is excreted in the urine. For oxymorphone 3-glucuronide, 33% to 38% is excreted in the urine in patients with normal renal and hepatic function, and its area under the curve (AUC) is 90 times higher than that for oxymorphone. After a 10-mg oral dose, 49% was excreted in the urine during a 5-day period. Of this, 82% was excreted in the first 24 hours after administration. The recovered drug-related products contained oxymorphone (1.9%), the glucuronic acid conjugate of oxymorphone (44.1%), the 6(β)-carbinol product produced by 6-keto reduction of oxymorphone (0.3%), and the conjugates of 6(β)-carbinol (2.6%) and 6(α)-carbinol (0.1%). There is no published information on its metabolism in any other extrahepatic sites.

**Effects of Kidney Disease**

Oxymorphone accumulates in renal failure. A pharmacokinetic study evaluated the pharmacokinetics of oxycodone and the excretion of oxycodone and its metabolites, noroxycodone and oxymorphone, in 10 uremic patients undergoing renal transplantation. In all 10 patients, the mean elimination half-life of oxymorphone (a metabolite of oxycodone) was prolonged. The dosing interval should be increased, as with any opioid that depends on renal excretion.

**Effects of Liver Disease**

Data regarding hepatic extraction and clearance of oxymorphone are not available. One would expect bioavailability to vary in pathologic conditions where hepatic blood flow and liver metabolic function are impaired. In the setting of hepatic insufficiency, it is important to increase the dosing interval if this medication is chosen.

**Drug Interactions**

In vivo drug-drug interactions involving oxymorphone have not been studied.13 The potential for drug interactions exists for opioids at both CYP450 system and the glucuronidation pathways. Very little has been published about the potential for pharmacokinetic drug interactions with oxymorphone.13 Oxymorphone ER did not induce or inhibit CYP activity in healthy adults during steady-state administration. This differs from methadone, which is a substrate for CYP2B6, or oxycodone, which is dependent on CYP2D6. Cimetidine can potentiate opioids, presumably by altering hepatic blood flow and/or extraction ratio.

Barbiturates, phenytoin, and rifampicin induce hepatic metabolism. Monoamine oxidase inhibitors delay metabolism and increase the number of adverse effects. Phenothiazines, including promethazine and chlorpromazine, potentiate opioids.

**Adverse Effects**

Overall, the adverse effects that have been observed with oxymorphone are similar to those seen with potent mu agonists. Beaver et al14 demonstrated that the occurrence of adverse effects was qualitatively and quantitatively similar for intramuscular oxymorphone and morphine, and oral oxymorphone and intramuscular morphine. When administered via patient-controlled analgesia (PCA), oxymorphone was demonstrated to cause more nausea and vomiting but less sedation when compared with morphine.15,16 Therefore, it is not a good choice for intravenous PCA.

Quality-of-life studies with the use of oxymorphone demonstrate it to be as good as, or better than, the use of morphine. The American Academy of Pediatrics has not yet rated the safety of oxymorphone in breast-feeding. Available evidence suggests that there are insufficient data to establish safety during breast-feeding; so, caution is advised.

**Oxymorphone in extended- and controlled-release formulations has some utility in treating nonmalignant low back pain, and the IR formulation has utility for postoperative pain.**
Clinical Utility for Nonmalignant Pain

Evidence indicates that oxymorphone in extended- and controlled-release formulations has some utility in treating nonmalignant low back pain and that the IR formulation has utility for postoperative pain.

Hale et al. conducted a multicenter, randomized, double-blind, placebo- and active-controlled trial comparing the analgesic efficacy and safety of oxymorphone ER with placebo and oxycodone controlled release (CR) in ambulatory patients with moderate to severe chronic low back pain requiring opioid therapy.

A total of 213 patients between the ages of 18 and 75 years were randomized to receive either oxymorphone ER (10–110 mg) or oxycodone CR (20–220 mg) every 12 hours during a 7- to 14-day dose-titration phase. Patients achieving effective analgesia at a stable opioid dose entered an 18-day double-blind treatment phase and either continued opioid therapy or received placebo. With stable dosing throughout the treatment phase, oxymorphone ER (average 80 mg/d) and oxycodone CR (average 150 mg/d) were superior to placebo for change from baseline in pain intensity measured on a visual analog scale (P = 0.0001). The mean daily dosage of rescue medication was significantly lower for patients receiving oxymorphone ER (25.5 mg; P = 0.0068) or oxycodone CR (24.4 mg; P = 0.0024) than for those receiving placebo (34.8 mg). Adverse events for the active drugs were similar; the most frequent were constipation and sedation. They concluded that oxymorphone ER and oxycodone CR were generally safe and effective for controlling lower back pain. Oxymorphone ER was equianalgesic to oxycodone CR at half the milligram daily dosage, with comparable safety.

To study oxymorphone’s utility for postoperative pain, Gimbel and Ahdieh conducted a double-blind, parallel group study in patients receiving primary total hip- or knee-replacement surgery in American Society of Anesthesiologists class I–III patients. There were 2 treatment phases, an 8-hour single-dose phase and a multiple-dose phase that extended the study to 48 hours.

During the 8-hour single-dose phase, patients received a single dose of oxymorphone IR 10, 20, or 30 mg; oxycodone IR 10 mg; or placebo. In the double-blind, parallel-group study, 3 oxymorphone IR doses were compared with placebo for efficacy and with oxycodone IR and placebo for safety in patients with acute moderate-to-severe postsurgical pain. All oxymorphone IR doses were superior in providing pain relief for 8 hours (P < 0.05), with a significant analgesic dose response (P = 0.001).

Table 1. A Cost Comparison of Various Step 3 Opiates

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxymorphone</td>
<td>Oral extended release tablet</td>
<td>5 mg: $2.28 per tablet; 10 mg: $4.14 per tablet</td>
</tr>
<tr>
<td></td>
<td>5 mg; 10 mg</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>Oral immediate-release tablet</td>
<td>15 mg: $0.18 per tablet; 30 mg: $0.31 per tablet</td>
</tr>
<tr>
<td></td>
<td>15 mg; 30 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral sustained-release tablet</td>
<td>15 mg: $0.75 per tablet; 30 mg: $1.43 per tablet</td>
</tr>
<tr>
<td></td>
<td>15 mg: 30 mg; 60 mg; 100 mg; 200 mg</td>
<td></td>
</tr>
<tr>
<td>Rectal suppository</td>
<td>10 mg; 20 mg; 30 mg</td>
<td>10 mg: $4.79 per suppository; 20 mg: $5.83 per suppository; 30 mg: $7.34 per suppository</td>
</tr>
<tr>
<td>Oral liquid</td>
<td>2 mg/mL; 4 mg/mL; 20 mg/mL</td>
<td>2 mg/mL: $38.56 per 500 mL; 4 mg/mL: $65.03 per 500 mL; 20 mg/mL: $116.78 per 240 mL</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Oral tablet</td>
<td>5 mg: $0.48 per tablet; 15 mg: $0.74 per tablet; 30 mg: $1.42 per tablet</td>
</tr>
<tr>
<td></td>
<td>5 mg; 15 mg; 30 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral sustained-release tablet</td>
<td>10 mg: $2.01 per tablet; 15 mg: $3.01 per tablet; 20 mg: $3.46 per tablet; 40 mg: $5.44 per tablet; 40 mg: $6.14 per tablet; 60 mg: $9.93 per tablet; 80 mg: $11.55 per tablet</td>
</tr>
<tr>
<td></td>
<td>10 mg; 15 mg; 20 mg; 30 mg; 40 mg; 60 mg; 80 mg</td>
<td>1 mg/mL: $25.20 per 500 mL; 20 mg/mL: $34.42 per 30 mL</td>
</tr>
<tr>
<td>Oral liquid</td>
<td>1 mg/mL; 2 mg/mL; 10 mg/mL</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>Oral liquid</td>
<td>1 mg/mL: $39.88 per 500 mL; 2 mg/mL: $69.07 per 500 mL; 10 mg/mL: $79.87 per 946 mL</td>
</tr>
<tr>
<td></td>
<td>1 mg/mL; 2 mg/mL; 10 mg/mL</td>
<td></td>
</tr>
<tr>
<td>Oral tablet</td>
<td>5 mg; 10 mg; 40 mg</td>
<td>5 mg: $0.08 per tablet; 10 mg: $0.15 per tablet; 40 mg: $0.33 per tablet</td>
</tr>
</tbody>
</table>

Significant pain intensity differences occurred by 45 minutes (20- and 30-mg doses; \( P < 0.05 \)). Discontinuation for lack of efficacy was 42% among placebo-treated patients and 27% among those treated with oxymorphone IR. Patients requiring rescue medication after 3 hours were allowed to receive additional study drug every 4 to 6 hours as needed during the multiple-dose phase (\( n = 164 \)). Analgesia was maintained for patients in all oxymorphone groups for 48 hours. The median dosing interval was greater than 9.5 hours for oxymorphone IR 30 mg and 7 hours or more for the other groups. Opioid-related adverse events, similar among groups, were generally mild or moderate. Oxymorphone IR 10, 20, or 30 mg provided significant dose-related pain relief compared with placebo and this relief was maintained over several days with a safety profile comparable to that of oxycodone IR.

**Clinical Utility for Cancer Pain**

Sloan et al\(^1\) conducted a pilot study comparing oxymorphone ER and oxycodone CR in patients (\( n = 86 \)) with moderate to severe cancer pain. This randomized, multicenter, double-blind, 2-period crossover study included adult outpatients with moderate or severe cancer pain who were first stabilized for 3 or more days on morphine CR or oxycodone CR. Those who attained stable analgesia for at least 3 days, defined as 3 or fewer rescue doses of opioid per day, entered the first 7-day treatment period (period 1) at the stabilized dose of the titrated medication with no dosage adjustments.

All patients who were treated for 7 days at their stabilized dose of either morphine CR or oxycodone CR were then crossed over to oxymorphone ER at an estimated equianalgesic dosage. They were treated for an additional 7 days (period 2).

During period 1 and period 2, the oral IR formulation of the study medication was available as rescue medication. Each dose of rescue medication was approximately 10% of the total daily dose of scheduled medication. Patients recorded assessments of analgesia, nausea, drowsiness, sleep quality, the use of regularly scheduled medications, and use of rescue medication.

Similar daily pain intensity scores during the last 2 days of the initial treatment phase (morphine CR or oxycodone CR) were compared with those during the last 2 days of the oxymorphone ER treatment phase. The comparison of scores indicates that equivalent analgesia was achieved after patients had been rotated to oxymorphone ER. This also suggests that the long-acting formulation can maintain drug levels in a stable fashion.

Patients taking oxymorphone ER needed less breakthrough medication than those taking morphine CR. The tolerability/safety profiles (eg, nausea, drowsiness, and somnolence) were similar between the 2 drugs. There were no significant differences in daily pain intensity scores between oxymorphone ER and either morphine or oxycodone.

**Pharmacoeconomics**

The cost of step 3 opiates varies widely. As listed in Table 1, the generics are an order of magnitude cheaper than oxymorphone. The issue for practitioners is to determine which patients are suitable candidates for this medication given the cost differential. Clearly, oxymorphone should not be the first-line step 3 medication considered. Although oxymorphone offers advantages in terms of its metabolism and lack of interaction with other cytochrome P450 inducers, its cost will be prohibitive for many patients.

**Conclusion**

Oxymorphone is a potent opioid whose antinociceptive effects are mediated predominantly through mu opioid and delta opioid receptors. Oxymorphone has limited bioavailability, is subject to hepatic first-pass effects, and is renally excreted. Oxymorphone undergoes extensive hepatic metabolism via conjugation with glucuronic acid. Oxymorphone exhibits minimal potential for causing metabolic drug-drug interactions mediated by CYP2C9 or CYP3A4. Unfortunately, oxymorphone accumulates in renal failure. The half-life of IR oxymorphone is longer than that of morphine, hydromorphone, or oxycodone. The long half-life of the IR formulation combined with the drug’s potency makes it an attractive option for sustained relief of breakthrough pain. In patients already receiving other step-3 opioids such as morphine and oxycodone, it may provide another option for opioid rotation. However, the cost of oxymorphone may be prohibitive for many patients.

**References**


An Act Relating to Pain Management” Passes the Washington State Legislature

New Law Faces Opposition Over Fixed-Threshold Opioid Dose

A new law passed the Washington State Legislature last year, unassumingly titled “An Act Relating to Pain Management.” It has set off a controversy over its unprecedented reach into how physicians and other practitioners can treat pain. In particular, one requirement is that practitioners must consult with a pain specialist before prescribing an opioid dose above 120 mg of morphine equivalent per day (MED) to a patient with nonmalignant chronic pain that is not getting better.

The law was championed by state and medical officials who say that it is a necessary step to both improve pain care and prevent deaths related to prescription pain medicines. It has been described as the first state law to require doctors to consult with a specialist if the patient’s opioid dose is being escalated.

But some advocates for patients with pain say that the wording of the bill—which takes effect July 1—threatens the access that patients and practitioners have to the limited number of pain-care specialists in the state by determining which cases must involve a specialist. Such a law, they say, will limit the ability of practitioners to seek consultations on cases that do not necessarily involve 120 mg, but which are complex nonetheless.

Each side includes highly regarded advocates for pain care, and each side is equally passionate in its insistence that the other is more likely to reduce access to pain care than to advance it. The law was written by legislators in collaboration with Alex Cahana, MD, professor and chief of the Division of Pain Medicine in the Department of Anesthesiology and Pain Medicine, University of Washington.

Each side includes highly regarded advocates for pain care, and each side is equally passionate in its insistence that the other is more likely to reduce access to pain care than to advance it.

Yet the American Pain Foundation (APF)—whose board of medical advisers includes some big names in pain medicine—is lobbying against the bill, saying that it is an ill-conceived approach that will limit access to pain care, that the dosage level set at 120 mg morphine equivalent is too limiting to practitioners,
and that there is no evidence that the 120-mg threshold dose before requiring consultation with a pain specialist will lead to a reduction in deaths.

The controversy continues as the state’s professional health-care boards and commissions establish dosing criteria and other details by June 30, 2011, the day before the new law takes effect. The law was written to leave many practice-related clinical details up to these boards to draft. (See excerpts from the draft rules on page 10.)

Meanwhile, officials in Ohio, Florida, Oregon, and other states are looking into similar laws in their jurisdictions, so Washington’s process is being watched nationwide, especially after an article in the New York Times over the summer put the issue in the national spotlight.

“**You have to understand that in the state of Washington, this is a state of emergency.**”

**New Law Is the Beginning of Measurement-Based Care**

“You have to understand that in the state of Washington, this is a state of emergency,” Cahana says. “We have close to 600 people last year who died from prescription drugs.”

Meanwhile, he said, some patients weren’t getting good pain care because there was no system of coordination between primary care providers and pain specialists. This bill, he said, comes with an initiative to develop relationships between pain specialists and those in primary care.

“I think our approach here is very simple,” Cahana said. “Pain care across the country is very fragmented and uncoordinated. It has no attached value to it. And the increasing cost is unsustainable. The model of care should be this: coordinated care, measurement-based care, and value-based care. That’s what the bill is all about. It is better to work in coordination with specialty care, and if you have problems, there are solutions that are put in place,” he said.

**Perspective**

Although the law has generated some apprehension and opposition, it does not seem to be unreasonable and could be a step toward better and safer care for patients with chronic non-malignant pain, said Clifford Gevirtz, MD, MPH, medical director of Somnia Pain Management in New York, associate professor of anesthesiology at Louisiana State University, and editor of *Topics in Pain Management*.

“In my opinion, 120 mg of morphine is not a low dose, and once you cross that level in a chronic non-malignant pain patient—such as one who has low back pain—then having a specialist consult with the primary-care physician seems very reasonable to me,” Gevirtz said. “The law doesn’t say that the patient has to be transferred to the pain specialist—just a consult.”

Gevirtz referred to an article in the New York Times on January 5 reporting that the number of emergency-department visits resulting from abuse or misuse of prescription drugs has nearly doubled in just the last 5 years.²

“I think there has been a huge amount of poor opiate prescribing across the nation. The *New York Times* reported [January 5] that the number of ER visits due to prescription drug adverse reactions has increased 400% in the past decade,” Gevirtz said. “If pain experts object to this layer of review, then what do they suggest to reduce the number of ER visits? I think it is easy for experts to object to ‘unnecessary’ consultations; I would then challenge them to solve this difficult and rapidly growing problem.”

**The Opposition**

Opponents of the law have objected to the use of a stated dosage at which a consult is required. They also assert that the bill is not sufficient to improve safety because a patient could die from a dose lower than 120 mg morphine-equivalent with a drug such as methadone.

Amid discussion of this law, deaths related to methadone prescriptions for pain are the “elephant in the room” and not addressed at all by the bill at all, said Michael Schiesser, MD, an internist in Bellevue, Washington, who specializes in pain and issues with prescription opioid use and sleep medicine. He has been a vocal opponent of the language of the bill and who has been working with the APF to shift the focus on education for providers of care and patients.

However, language about methadone is in the draft rules written by the state’s medical professional boards.

“Methadone has important positive benefits for pain, low cost being one,” Schiesser said. “However, compared with other long-acting schedule II opioids, there are unique properties that make methadone very unforgiving to prescribe without running into drug interactions, unpredictable plasma levels, and lethal effects.”

In Washington, he said, methadone is responsible for 50% of opioid drug-related deaths (and 64% of drug-related Medicaid deaths).

“But nowhere near 50% of prescriptions are for methadone,” Schiesser said. “So from a public-safety standpoint, the dose-threshold concept is not only untested and unproven, but it generates a false confidence in the case of methadone.”

**Cahana: Not About One Drug**

“In the most recent iteration, there is language about methadone,” Cahana said. “Methadone is a very tricky drug, and like any tricky drug, if you don’t know how to use it, then you will get bad outcomes.

“Now, I think that putting it into the legislation or not putting it into the legislation is a moot point,” Cahana continued. “What I am concerned with is that a lot of the people against this bill seem to be tone deaf to what this bill is about. This bill is not just about opioids. This bill is about measurement-based care. It’s about the days being over when you can do stuff and
not measure how your patients are doing. I find it lamentable that some of the leadership in the pain universe are deaf to that game-changer. And they’re obsessing over what I see are epiphenomenal subjects [such as] methadone, or no methadone,” he said.

**Threshold in Law Oversimplifies a Complex Process**

Even with other drugs, the MED threshold is a problem for opponents of the new law.

“How one would calculate the 120 mg morphine equivalent is very complicated, especially since we’re coming out with new drugs that are in patches [for example]. It becomes more complicated when determining a daily dose on the provider’s end, to decide whether this patient falls above or below that mark,” said Elin Björling, PhD, a policy specialist and regional network manager for the APF. Her background is in public health and health research, including adolescent headache and migraines, chronic fatigue syndrome, and fibromyalgia. She also has a clinical-faculty appointment at the University of Washington-Tacoma School of Nursing.

“I think what this all comes down to, the problem that we have with the dosage level just saying that at this dose you need to refer, is that it moves us into this very simplistic thinking about opioids, which hasn’t been necessarily shown to improve the safety, by any stretch,” Björling said.

“This dosage level in the law creates an illusion that we are being safer. I can come up with many circumstances where this deters us from being safe in prescribing,” Björling said.

“We do have some providers possibly overprescribing. That’s not in question. We don’t want patients running around on high levels of opioids, and we don’t want prescribers mis-prescribing if a patient shouldn’t be on a high level,” Björling said. “We have that same concern that everybody else has. But clearly in our state, and in other states, there’s not enough education.”

“If they’re getting a hundred calls a week—and they won’t be reimbursed for these calls as far as I understand—they’re not going to be able to answer them all and still see their own patients.”

**“If it’s that important [to consult with a pain specialist], why did they write into the rule that you only have to make 3 attempts and then you’re done?”**

“One of the things they wrote in the rule was you have to show you attempted to contact a pain specialist on 3 occasions, and if you never make contact, then you can move forward above 120 mg. And that doesn’t make any sense to me. If it’s that important, why did they write into the rule that you only have to make 3 attempts and then you’re done? It just looks like red tape rather than trying to reduce risk.”

The new law is directed mostly at primary care, where approximately 60% of most pain care takes place.

“The truth is, it’s scaring providers, and we’re starting to hear from patients that they got a letter or e-mail from their doctor that they’re no longer seeing pain patients and they have to go to a pain specialist, but there’s a 3-month wait for an appointment,” Björling said.

**Law Is Meant to Increase Access**

Cahana dismissed fears that the new law will have a chilling effect and reduce access to pain care. On the contrary, he said, it will improve access.

“I can tell you that when we meet physicians in the community, it always starts with doom and gloom and existential fear. And it takes me about 5 minutes to explain what we’re all about, and everybody is elated,” he said.

He said the history of patients having difficulty has been because of the gray areas that have existed.

“I will give you a news flash: Doctors don’t want to see patients in pain because of the deregulation; because of all the craziness going on out there,” Cahana said.

He continued, “There is literature showing that medical school graduates [are not going] into primary care because of the experiences they have with pain patients. So to try to link the chilling effect is disingenuous.”

**References**


What the Law Says

The new law, ESHB 2876, An Act Relating to Pain Management, specifically exempts “hospice, palliative or other end-of-life care” and “acute pain caused by injury or surgical procedure,” but will provide new rules on chronic, noncancer pain management, including the following:

- Dosing criteria, including “a dosage amount which must not be exceeded” unless a prescriber consults with a “practitioner specializing in pain management.” The version of the bill obtained by Topics in Pain Management did not specify a dosage, but rules being written at the time of publication were using 120 mg/d morphine equivalent.
- Special circumstances under which dosage requirements can be exceeded without consulting with a practitioner specializing in pain management.
- Guidance on when electronic consultation with a specialist is sufficient.
- Guidance on tracking a patient’s clinical progress, including assessment tools.
- Guidance on tracking the use of opioids, especially in hospital emergency departments.

Such criteria, guidance, and details, the law reads, will come from “the agency medical directors’ group, the department of health, the University of Washington, and the largest professional associations for advanced registered nurse practitioners and certified registered nurse anesthetists in the state.”

Partial Veto

Washington Governor Christine Gregoire signed the bill but vetoed one section that called for state health care boards and commissions to adopt rules, including dosage standards, for the management of chronic noncancer pain, and submit those rules to the legislature before final adoption.

“Members of the Legislature may review agency rules, proposed or final, and their perspectives are valuable,” Gregoire wrote in her partial veto. “However, requiring proposed rules to be submitted to the Legislature would infringe upon the role of the executive branch and would blur the distinction between the Legislature and a state agency with regard to the rulemaking process.”

Excerpts From the Washington State Pain Management Legislation Draft Rules

The draft rules being written to accompany Washington’s new law on pain care stipulate the elements of a patient evaluation before prescribing opioids for chronic noncancer pain, including history of substance abuse, effect of the pain on physical and psychological functioning, etc.

The rules also call for a written treatment plan for all patients with periodic review at least every 6 months, or at least every 12 months for stable patients who are on a nonescalating 40 mg or less morphine equivalent dose.

Here are other excerpts from the rules drafted by professional boards:

Regarding Methadone and Other Long-Acting Opioids

Long-acting opioids, including methadone, should be prescribed only by a physician who is familiar with risks and use, and who is prepared to conduct the necessary careful monitoring. Special attention should be given to patients who are initiating such treatment. The physician prescribing long-acting opioids or methadone should have a one-time completion of at least 4 hours of continuing education relating to this topic.

Mandatory Consultation With Pain Specialists

2) Mandatory consultation at 120 milligrams morphine equivalent dose (MED). In the event a physician prescribes a dosage amount that meets or exceeds the consultation threshold of 120 milligrams MED per day, a consultation with a pain management specialist is required, unless the consultation is exempted under WAC 246-919-861 or 246-919-862.

(a) The mandatory consultation shall consist of at least one of the following:

i) An office visit with the patient and the pain management specialist;

ii) A telephone consultation between the pain management specialist and the physician;

(iii) An electronic consultation between the pain management specialist and the physician;

(iv) An audio-visual evaluation conducted by the pain management specialist remotely, where the patient is present with either the physician or a licensed health care practitioner designated by the physician or the pain management specialist.

(b) A physician shall document each mandatory consultation with the pain management specialist. Any written record of the consultation by the pain management specialist shall be maintained as a patient record by the specialist. If the specialist provides a written record of the consultation to the physician, the physician shall maintain it as part of the patient record.

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To earn CME credit, you must read the CME article and complete the quiz and evaluation assessment survey on the enclosed form, answering at least 70% of the quiz questions correctly. Select the best answer and use a blue or black pen to completely fill in the corresponding box on the enclosed answer form. Please indicate any name and address changes directly on the answer form. If your name and address do not appear on the answer form, please print that information in the blank space at the top left of the page. Make a photocopy of the completed answer form for your own files and mail the original answer form in the enclosed postage-paid business reply envelope. Your answer form must be received by Lippincott CME Institute by February 29, 2012. Only two entries will be considered for credit.

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1. All of the following statements regarding the binding of oxymorphone to opiate receptors are true except
   A. Oxymorphone binds to delta receptors.
   B. Oxymorphone does not bind to mu receptors.
   C. Oxymorphone does not avidly bind to kappa receptors.
   D. There is no information on whether oxymorphone binds to sigma receptors.

2. There are significant gaps in our knowledge of the pharmacology of oxymorphone. These gaps include all of the following statements except
   A. There are no studies of rectal administration.
   B. There are no published studies on the relationship between sex, age, and metabolism.
   C. There is no information on the bioavailability after subcutaneous administration.
   D. The American Academy of Pediatrics has not yet rated the safety of oxymorphone in breast-feeding.

3. Oxymorphone ER does not induce or inhibit CYP activity in healthy adults during steady-state administration.
   A. True
   B. False

4. Oxymorphone ER is more expensive than methadone, morphine ER, and oxycodone ER.
   A. True
   B. False

5. All of the following statements are true except
   A. Cimetidine can potentiate opioids, presumably by altering hepatic blood flow and/or extraction ratio.
   B. Monoamine oxidase inhibitors delay metabolism and increase the number of adverse effects.
   C. Phenothiazines, including promethazine and chlorpromazine, potentiate opioids.
   D. Barbiturates and phenytoin do not induce hepatic metabolism.

6. A patient taking methadone requests a new breakthrough medication because he found oxycodone IR too sedating. Oxymorphone is a viable option because it
   A. is cheaper than other drugs
   B. is faster acting than the fentanyl lollipop
   C. has few drug interactions
   D. is safe to use in patients with end-stage liver disease

7. Patients with end-stage renal disease are appropriate candidates for opiate maintenance with oxymorphone ER.
   A. True
   B. False

8. A patient with liver failure is awaiting liver transplantation and has significant abdominal pain. Oxymorphone is an appropriate choice of therapy.
   A. True
   B. False

9. A patient on intrathecal oxymorphone develops bilateral lower extremity edema. After ruling out congestive heart failure and poor blood pressure control, the issue of deep venous thrombosis versus idiopathic edema due to intrathecal opiates remains. All of the following statements are true except
   A. A venogram could eliminate deep venous thrombosis as a cause.
   B. Several intrathecal opiates cause this problem.
   C. If it is opiate-mediated, then it will resolve without other therapy if the intrathecal opiate is discontinued.
   D. The edema can be reduced by vein stripping.

10. You are consulted by the US Drug Enforcement Agency regarding the “excessive narcotic prescribing” of another physician. You note that the physician routinely writes prescriptions for oxymorphone IR orally every 2 hours around the clock on more than 95% of his scripts. In preparing your report, you note this fact
   A. but cannot render an adverse decision on this basis alone
   B. but interpret it as individual patient variation with no medical significance
   C. but think it is probably a clerical error on the part of the filling pharmacist
   D. as clear evidence of excessive prescribing
Continued from page 10.

**Special Circumstances Required to Exceed 120 mg Without a Consultation**

A physician is not required to consult with a pain management specialist when he or she has documented adherence to all standards of practice as defined in this chapter and when any one or more of the following conditions apply:

1. The patient is following a tapering schedule;
2. The patient requires treatment for acute pain which may or may not include hospitalization, requiring a temporary escalation in opioid dosage, with expected return to or below their baseline dosage level;
3. The physician documents reasonable attempts to obtain a consultation with a pain management specialist and the circumstances justifying prescribing above 120 milligrams MED per day without first obtaining a consultation; or
4. The physician documents that the patient’s pain and function is stable and the patient is on a nonescalating dosage of opioids.

**Physicians Exempt From Consultation Requirement**

The physician is exempt from the consultation requirement in WAC 246-919-860 if one or more of the following qualifications are met:

1. The physician is a pain management specialist under WAC 246-919-863;
2. The physician has successfully completed, within the last two years, a minimum of twelve continuing education hours on chronic pain management approved by the profession’s continuing education accrediting organization, with at least two of these hours dedicated to long acting opioids, to include methadone; or
3. The physician is a pain management practitioner working in a multidisciplinary chronic pain treatment center, or a multidisciplinary academic research facility; or
4. The physician has a minimum three years of clinical experience in a chronic pain management setting, and at least thirty percent of his or her current practice is the direct provision of pain management care.