Oxymorphone and Opioid Rotation

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ABSTRACT

To obtain the durable benefits of opioid analgesia, physicians must develop strategies to manage the negative attributes of opioid therapy. Side effects, opioid tolerance, and toxicity limit the use of opioids, yet specific guidelines have not emerged for appropriate doses. Furthermore, there are wide variations in interindividual responsiveness to opioid analgesia. Opioid rotation is an effective, emerging strategy to help manage the negative effects of opioids by limiting doses required to obtain pain relief with tolerable side effects. Tolerance to one particular type of opioid does not necessarily develop at the same rate as tolerance to another opioid (incomplete cross-tolerance). Side effects may vary and generally are reduced at lower doses. Oxymorphone is a highly potent molecule that offers linear dose proportionality, multiple preparations (IV, immediate release, extended release) and good analgesic effect. Strategies for rotating a patient from an opioid to oxymorphone require dose calculation based on equianalgesia, a conversion period and dose titration. In addition to converting a patient from other oral opioids to oxymorphone, special strategies are needed for particular preparations (extended release to extended release; extended release to immediate release to extended release; cross-titration; in-patient titration). Issues in opioid rotation involving oxymorphone are common to other opioid rotation plans: side effects, in particular nausea and constipation, as well as toxicity concerns. While pain patients present a unique challenge to physicians, opioid analgesia involving oxymorphone and opioid rotation strategies have been shown to be effective in pain management in some patients with tolerable side effects.

Key Words. Oxymorphone; Opioid Therapy; Opioid Rotation

Introduction

The use of opioids for analgesia has a complex history that continues to color opioid use today. Opioid analgesics, at one time, were considered more troublesome than useful. Their side effects and potentials for abuse prompted physicians to underutilize this analgesia tool with the result that much acute pain and pain from terminal diseases went untreated [1,2]. Today, the medical consensus is that opioid analgesia is a powerful and appropriate treatment for many patients confronting severe pain [3] and that its benefits reach beyond analgesia to encompass mood, functioning, and quality of life [4]. Although opioids were once considered ineffective in providing analgesia for neuropathic pain, recent clinical trials have shown that they can even be effective even in treating pain from neuropathy [5–7].

To obtain the desirable benefits of opioid analgesia, physicians need to develop strategies that help manage the negative attributes of opioid therapy. The negative attributes include side effects such as sedation, respiratory depression, impaired cognition, nausea, vomiting, loss of appetite, pruritus, urinary retention, impaired orthostatic tolerance, and constipation [8]. Long-term opioid therapy may also result in hyperalgesia [9], which can require escalating doses to maintain pain relief and could limit the clinical utility of opioid therapy in certain patients [10]. The mechanisms behind hyperalgesia are poorly understood [11] and patients with opioid-induced hyperalgesia may benefit from opioid rotation.
Both opioid-induced hyperalgesia and opioid tolerance result in the need for increasing doses of opioids to maintain equivalent analgesia, but it is not clear whether opioid-induced hyperalgesia and opioid tolerance are related, independent, or competing conditions.

Opioid tolerance is a better-known pharmacologic phenomenon that develops over time and requires the titration of opioid doses to maintain analgesic effect [13]; however, dose escalation carries the risks of toxicity and of more or exacerbated side effects. There are two types of tolerance, associative (learned) and nonassociative (adaptive), which appear to involve distinctly different neurotransmitters in the body. Associative (or conditioned) tolerance is situational and contextual, i.e., it depends on the animal forming associations with the environment [14]. For example, animals receiving morphine in a distinctive environment display greater morphine tolerance when tested in that environment than when tested in an unfamiliar environment. In such a situation, animals might display an opposite compensatory response that summates with the drug-induced effect, even leading to hyperalgesia if the drug is withheld in the presence of environmental cues [15]. The relative ability and clinical relevance of individual opioids to produce compensatory reactions are not known. By contrast, nonassociative tolerance takes place at the cellular level and involves a reduction in turnover rate or number of opioid receptors, their desensitization, or both [16,17]. Because tolerance results from a change in the opioid receptor transduction system (receptor-effector coupling) and downstream second-messenger biochemical pathways that are common to all opioids, tolerance to one opioid analgesic is accompanied by tolerance to all others that act at the same receptor (a phenomenon known as cross-tolerance). Functionally, tolerance or cross-tolerance is manifested as a rightward shift in the opioid’s dose-response curves (therapeutic and side effect). The magnitude of the rightward shift often differs for different drugs and for different endpoints. For opioids, tolerance typically develops more rapidly to the analgesic endpoint than it does, for example, to the endpoint of constipation. Thus, while increasing the dose of an opioid may overcome the analgesic tolerance and offer the patient sufficient pain relief, long-term high doses of opioids can be associated with worsening side effects, hormonal effects, and possible immunosuppressive effects, and may thereby increase the burden of care.

### Opioid Rotation

Opioid therapy is part of a comprehensive treatment plan that should be considered only in light of pain that cannot be managed with nonopioid and nonmedication therapies. Patients should undergo a comprehensive examination and receive education about their drug therapy. A trial of opioid therapy should be given to assess the patient’s responsiveness in terms of degree of analgesia and side effects. The dose can then be titrated. Adjuvant therapies to help manage side effects may be appropriate for such patients.

Pain patients should be routinely and frequently evaluated for their degree of analgesia, functional daily activities, adverse events, and possible aberrant behavior. For patients who report pain relief, improvement in selected functional areas or psychosocial functioning, opioid therapy can be continued. Opioid therapy should be discontinued or rotation considered when patients have one or more of the following: insufficient analgesia, intolerable side effects, persistent non-compliance, rapid and intractable tolerance, or worsening function [18].

Opioid rotation is the change from one opioid to another in a patient whose treatment may be limited by toxicity levels produced by a particular opioid [19]. Owing to the vast variation in individual responsiveness to opioids [20], clinicians have observed that changing opioids can sometimes improve analgesia while simultaneously reducing side effects [21]. One of the main concerns in opioid rotation is transitioning from one drug to the next while maintaining equianalgesia without over- or under-dosing the patient. Many experts recommend establishing an equianalgesic dose and then reducing it, sometimes by as much as 50% at the outset of rotation, to account for incomplete cross-tolerance [22]. Although opioid dosing guidelines exist, a prospective study (N = 132) found that errors in opioid conversion and rotation were not uncommon [23].

A retrospective analysis of 37 rotations of long-acting opioids and 59 rotations of short-acting opioids to long-acting opioids found that rotations resulted in significantly improved analgesia in both groups (59% of patients rotated between long-acting opioids and in 73% of those rotated from short-acting to long-acting opioids), while rotations of long-acting opioids to other long-acting opioids also reduced side effects [24]. A small prospective study (N = 42) of patients in severe musculoskeletal, cancer, or neuropathic
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Pain were converted from high-dose morphine (120 to >240 mg/day) to transdermal buprenorphine and found a significant increase in patients reporting good to very good pain relief from 5% to 76% ($P < 0.001$) [25]. In terms of reducing side effects alone, one prospective study rotating cancer patients with morphine-induced delirium to fentanyl found significantly reduced symptoms with improved analgesia ($P < 0.001$) [26].

In fact, a review of the literature on opioid rotation concluded that for patients in severe chronic pain who receive inadequate pain relief or experience severe side effects or both, opioid rotation should be considered [27]. In a study of 132 consecutive cancer patients in palliative care, inadequate analgesia was the most common reason for opioid rotation (39%), followed by intolerable side effects (25%) or both (21%). These authors found that opioid rotation occurred in about 40% of advanced cancer patients. Most patients were rotated once, but almost a third required multiple rotations [28].

Studies have shown that there is great variation among patients in regard to opioid drugs—in terms of both analgesic response and adverse effects. In fact, two or three opioid drugs may have to be tried before effective analgesia with tolerable side effects is achieved [29]. The strategy of opioid rotation developed when it was found that tolerance to one opioid does not necessarily develop at the same rate or to the same extent as tolerance to another opioid [30]. Such incomplete cross-tolerance is thought to be due to different intrinsic activities of the opioid molecules and to interindividual pharmacogenetic factors, including genetic polymorphisms—variations in gene promoter, the coding region (exons), noncoding region (introns), or untranslated gene sequence where the least common allele occurs in >1% of the population—in the drug receptor-effector transduction mechanism or in the drug’s metabolism [31,32] as well as the degree of tolerance [33].

The pharmacologic effects of opioids are derived primarily from their interactions with three 7-transmembrane G protein-coupled opioid receptor types: mu, kappa, and delta. The most commonly used morphine-like (opioid) agonists have highest affinity for, and thus bind, predominantly to mu-opioid receptors. They also have the requisite intrinsic activity to initiate second-messenger signaling—a decrease in presynaptic $Ca^{2+}$ influx that decreases neurotransmitter release and an increase in postsynaptic $K^+$ efflux that hyperpolarizes the neuron—that together results in analgesia. At the other end of the opioid spectrum are the opioid antagonists. Opioid antagonists such as naloxone and naltrexone bind to the three opioid receptors but lack the intrinsic activity to activate them. However, their presence on the receptors blocks or displaces agonist binding and thereby blocks or reverses the effects of morphine-like agonists. Between these two extremes are mixed agonist-antagonist drugs that can demonstrate agonist activity at one opioid receptor type and antagonist activity at another opioid receptor type.

Morphine has always been the “gold standard” of opioid analgesic drugs. It and other morphine-like agonists share a similar pharmacodynamic profile, but they differ in terms of relative analgesic potency and oral-to-parenteral potency, pharmacokinetics (elimination half-life), and biotransformation to pharmacologically active metabolites. These characteristics may dominate when opioid administration is continued beyond a couple of days [34].

The recent availability of pharmacogenetic techniques has revealed a large number of polymorphisms in the mu-opioid receptor, which may partly account for the interindividual response variability to different opioids. In one study of 113 former heroin addicts in methadone maintenance and 39 individuals with no history of drug or alcohol abuse or dependence, five single-nucleotide polymorphisms (SNPs, mutations that involve a single DNA base substitution that occurs with frequency of ≥1% of a given population) were identified in the coding region of the mu-opioid receptor gene. The most prevalent was a nucleotide substitution at position 118 (A118G)m, which appeared in approximately 10% of the study population. Significant differences in allele distribution were also observed among ethnic groups studied. The A118G variant receptor binds $\beta$-endorphin, an endogenous opioid that activates the mu-opioid receptor, approximately three times more tightly than the most common allelic form of the receptor. The study results show that SNPs in the mu-opioid receptor gene can alter binding and signal transduction in the resulting receptor. It has been suggested that carriers of mutant alleles might display altered responses to narcotic analgesics [35–37].

Oxymorphone in Opioid Rotation

Oxymorphone (oxymorphone hydrochloride) is a semisynthetic mu-opioid agonist. It differs from
morphine by having a ketone-group substitution at the C-6 position of morphine and saturation of the C-tC double bond. This ketone-group substitution makes the molecule more lipid-soluble. Oxymorphone has greater potency than morphine. In clinical trials, this was shown to result in a higher therapeutic index along with less of the following: histamine release, hypotension, and myocardial depression [38]. Opana (Endo Pharmaceutical, Chadds Ford, PA), which is oxymorphone hydrochloride in an immediate-release (IR) formulation for oral administration, is indicated for the relief of moderate to severe acute pain where the use of an opioid is appropriate, and Opana ER (oxymorphone hydrochloride in an extended-release [ER] formulation for oral administration) is labeled for relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. Oxymorphone is a Schedule II controlled substance. Its side-effect profile is similar to that of morphine and other opioids. It is rapidly absorbed in the body and has a half-life of around 7 to 9 hours [39].

Oxymorphone in both IR and ER formulations is one of the newest additions to the opioid armamentarium and is recommended in the literature as an opioid to be considered in opioid rotation [40,41]. Oxymorphone was found to be safe and effective in patients with chronic low back pain (N = 213) in a randomized, prospective, placebo-controlled study, which found oxymorphone ER equianalgesic to oxycodone controlled release at half the milligram daily dose with comparable safety [42]. A number of clinical trials involving the use of oxymorphone for pain relief are ongoing [43].

Oxymorphone offers some distinctive pharmacologic properties that set it apart from other opioids, including a longer half-life and a lack of interaction with the cytochrome P450 (CYP450) drug-metabolizing system [44]. CYP450 is a system of hemoproteins that act on exogenous and endogenous compounds as substrates in enzymatic reactions (phase I metabolism); this system plays a key role in drug metabolism for most drugs, including most opioids, and is a major source of adverse drug interaction as changes in CYP enzyme activity can affect the metabolism and clearance of other drugs. The key metabolic pathway is via the uridine diphosphate glucuronosyl transferase enzymes (glucuronidation) for a few opioids, such as hydromorphone, morphine, and oxymorphone [45,46].

If one drug inhibits the CYP-mediated metabolism of another drug, the second drug can accumulate in the body even to toxic levels. Thus, in cases of actual or potential drug interactions, dosage adjustments or selection of drugs, such as oxymorphone, which do not interact with CYP450, offer a distinct advantage.

Opioid rotation should be considered in patients who do not receive adequate pain relief, experience hard-to-tolerate side effects, or both, as there is evidence that switching opioids can improve analgesia with reduced side effects. However, acute and chronic pain patients typically have other and often complicated medical needs requiring polypharmacologic approaches. While oxymorphone should be considered a drug for opioid rotation in general, it is specifically advantageous for use in the patient who had previously taken an opioid metabolized in the CYP450 system, such as methadone [47].

### Conversion of Patients from Other Oral Opioids to Oxymorphone

When rotating a patient receiving another oral opioid to oxymorphone, determine the target dose by calculating the equivalent dosage using Table 1 (called the "calculated dose"), but note that this is not the dose to be administered initially. Begin by administering 50% to 70% of the calculated dose in two divided doses (assuming tolerance), every 12 hours. Gradually adjust the initial dose and titrate as needed by 10 mg every 12 hours every 3 to 7 days until adequate pain relief is achieved with acceptable side effects. For

| Table 1 Conversion from other oral opioids to oxymorphone [49] |
|---------------------------------|------------------|------------------|
| Opioid                          | Approximate Oral Dose (mg) | Oral Conversion Ratio |
| Oxymorphone                     | 10                | 1                |
| Hydrocodone                     | 20                | 0.5              |
| Oxycodone                       | 20                | 0.5              |
| Methadone*                      | 20                | 0.5              |
| Morphine                        | 30                | 0.333            |

* Care should be taken when converting to or from methadone due to its long half-life and patient variability.

This table provides only a suggested estimated equianalgesic dosing for various opioids. There is a wide variability among patients in terms of their responsiveness to opioids. This table is not intended to replace the prescriber's judgment.
breakthrough pain, administer IR oxymorphone (Opana) 10 mg every 4 to 6 hours as needed. Based on clinical trial data, the average length of time for successful conversion from one ER oral opioid to oral oxymorphone ER was 2.5 weeks with a range of 1 to 4 weeks [48]. Once a daily optimal analgesic dose is achieved, this total dose is divided into two equal doses of oxymorphone ER to be administered every 12 hours, along with an IR opioid of 5% to 15% of the daily equivalent dose of extended oxymorphone for rescue pain. All such patients should be very closely monitored throughout and following the transition. (Note that this article offers general guidelines and is not intended to replace the clinical judgment of the prescriber.)

If titration is required, increase the dose by 10 mg every 12 hours, as needed, every 3 to 7 days. When converting to or from methadone in any opioid rotation, take special care because of methadone’s long half-life and patient variability. For patients converting from the fentanyl transdermal system (FTS) to oral oxymorphone, begin by converting to an oral morphine-equivalent daily dose; for example, 25 mcg/h FTS converts to 60 mg/day of oral morphine. The next step is to convert the oral morphine dose to oral oxymorphone. For instance, 60 mg/day oral morphine converts to approximately 20 mg/day oral oxymorphone using the oral conversion ratio of 0.333. The suggested equianalgesic range for 25 mcg/h FTS to oral daily morphine is 60-134 mg/day. Due to this variability, care should be taken whenever converting from FTS to any oral daily opioid.

Note that Table 1 represents data from the published prescribing information by the manufacturer of Opana ER. While useful in opioid conversion to oxymorphone, this information is at best a guideline and is not intended to override clinical judgment. Many factors are involved in a patient’s responsiveness to opioids and can result in doses that differ from this table.

Special consideration is required for elderly patients, patients with hepatic impairment, and those with moderate to severe renal dysfunction. These patients should be started at the lowest dose and titrated slowly while monitoring for side effects. Patients concurrently on a regimen of another central nervous system depressant should be started at one-third to one-half the recommended dose.

Oxymorphone ER should not be abruptly discontinued. Should the patient no longer require therapy with oxymorphone ER, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

When converting from oral opioids to ER oxymorphone (Opana ER), in general, it is safest to start by administering 50% to 70% of the calculated daily dose in two divided dose every 12 hours. Gradually adjust the initial dose of the ER oxymorphone until adequate pain relief and acceptable side effects are achieved. An IR (short-acting) oxymorphone should be provided for breakthrough pain at a dose of 5% to 15% of the total daily equivalent dose of ER oxymorphone. Owing to the wide variability in patient response to opioid drugs, Table 1 should be taken only as a guide.

Three Special Conversion Strategies from Other Oral Opioids to Oxymorphone

It is important to avoid “oligoanalgesia” (inadequate analgesia) when rotating patients on modest to high doses of an oral opioid in order to reduce the likelihood of precipitating withdrawal-like symptoms. For these patients, there are three specific strategies employed in conversion to oxymorphone from other oral opioids that warrant specific discussion. These strategies involve conversion from ER to ER formulation; from ER to IR to an ER formulation; and cross-titration. These strategies are explained in greater detail below.

**ER to ER**

Using Table 1 as a guide, calculate the daily dose of oxymorphone ER, including dosing for breakthrough pain. Assuming incomplete cross-tolerance, administer 50% to 70% of this calculated daily dose in two equally divided doses every 12 hours. Titrate each 12-hour dose, as needed, by 5 to 10 mg every 3 to 7 days.

As an example, consider a patient was receiving a daily dose of 60 mg of morphine.

1. Calculate the equivalent dose: 60 mg of morphine × 0.333 equals approximately 20 mg of oxymorphone.
2. Multiply the calculated daily dose (20 mg) by 50% (10 mg) and divide by two for the 12-hour dose (5 mg); administer 5 mg of ER oxymorphone (Opana ER) every 12 hours.
3. Titrate, as needed, by 5 mg every 12 hours every 3 to 7 days.
In general, it is safest to start by administering half of the calculated daily dose of oxymorphone ER in two divided doses, every 12 hours, and provide appropriate amounts of medication for breakthrough pain.

**ER to IR to ER**

When converting from a higher daily pill count to a lower count, for example, TID oxycodone ER to BID oxymorphone ER, be aware that pill-taking behavior has the potential to affect conversion success rates. This scheme would work, for example, for conversion as TID oxycodone ER to BID oxymorphone ER. Calculate the appropriate dose of oxymorphone IR using Table 1, and administer this amount as six equal doses every 4 hours. Titrate by 5 mg IR every 4 hours every 3 to 5 days for 10 to 14 days. Do not exceed 20 mg of oxymorphone IR per 4 hours.

As an example, for a patient receiving 190 mg of oxycodone (60 mg TID ER plus IR):

1. Use Table 1 for calculation (190 mg of oxycodone × 0.5 = 90 mg of oxymorphone).
2. Figure the dose to administer by taking 50% to 70% of the calculated daily dose, for example, 70% of 90 mg of oxymorphone ER equals approximately 60 mg of oxymorphone ER every 12 hours.
3. Convert the daily oxymorphone ER to oxymorphone IR every 4 hours. For example, 60 mg in six doses equals 10 mg. Administer 10 mg every 4 hours.
4. Titrate, as needed, by 5 mg every 4 hours every 3 to 5 days for a total of 14 days.
5. Convert the final stable dose of oxymorphone IR every 4 hours to oxymorphone ER every 12 hours. Let us assume this patient wound up requiring an average of 13 mg every 4 hours of oxymorphone IR. That is an approximate daily dose of 80 mg oxymorphone IR (13 × 6).
6. Convert the total daily dose of oxymorphone IR (previous step) to oxymorphone ER. For example, 80 mg of oxymorphone IR converts to 40 mg of oxymorphone ER every 12 hours.

When considering this approach, it should be noted that oxymorphone IR (Opana) is rapidly absorbed with a median t\text{\textsubscript{max}} (time to reach C\text{\textsubscript{max}}) of 0.5 hours for single doses and steady state of oxymorphone IR. Its terminal elimination half-life (t\textsubscript{1/2}) is approximately 7.25 to 9.43 hours. Finally, the maximum daily dose of oxymorphone IR is 20 mg every 4 to 6 hours.

**Cross Titration**

Using Table 1 as a conversion chart, calculate the equipotent dose of oxymorphone ER, including breakthrough medication; assuming incomplete cross-tolerate, take 50% to 70% of that calculated dose to use as the starting amount of oxymorphone ER. In the initial phase, the patient will receive 60% of the original opioid daily dose, divided into two equal 12-h doses, and 30% of the calculated amount of oxymorphone ER, also divided into two equal 12-h doses, for a period of 3 to 7 days. Then decrease the dose of the original opioid by a third, i.e., take about 30% of the original dose of the original opioid, while simultaneously increasing the oxymorphone to about 60% of the starting amount. Opioids should be administered in two equal 12-h doses for a period of 3 to 7 days. Titrate, as needed, by 5 mg to 10 mg every 12 hours during the cross-titration period. Finally, discontinue the original opioid and administer the full calculated dose of oxymorphone ER in two equal 12-h doses.

As an example, consider a patient who is receiving a daily dose of 120 mg of oxycodone ER (60 mg BID):

1. Calculate the appropriate dose based on Table 1 (120 mg × 0.5). This results in a calculated dose of approximately 60 mg. This is the calculated dose. It is not the dose that is administered at first.
2. Determine the initial dose of oxymorphone by taking 50% to 70% of that calculated dose. Seventy percent of 60 mg is approximately 40 mg of oxymorphone ER per day, that is, 20 mg every 12 hours.
3. The patient must undergo a transitional phase during which he or she receives both the original opioid and oxymorphone. At first, the patient receives mostly the original opioid. Calculate 60% of the original opioid dose (in this case 60% of 120 mg is approximately 80 mg) and figure 30% of the oxymorphone dose determined in step 2 (30% of 40 mg is approximately 10 mg). The patient should receive 80 mg of the original opioid together with 10 mg of oxymorphone, administered in equivalent 12-hour doses. This means the patient would receive 40 mg of oxycodone and 5 mg oxymorphone ER every 12 hours. Administer this for 3 to 7 days.
4. The transitional phase must then shift so that the patient receives mostly oxymorphone ER while still taking some of the original opioid. In this example, oxycodone would decrease from 40 mg to 20 mg every 12 hours, while oxymor-
phone ER would simultaneously increase from 5 mg to 10 mg every 12 hours. Continue this for 3 to 7 days.

5. Discontinue oxycodone while increasing oxymorphone from 10 mg to 20 mg every 12 hours for 3 to 7 days.

6. Titrate, as needed, by 5 mg every 12 hours for 3 to 7 days.

**In-Patient Titration**

In-patient rapid opioid conversion might be facilitated by converting from oral opioids to oxymorphone I.V. and then to oxymorphone ER. Calculate the appropriate dose of oxymorphone ER, including breakthrough medication, from Table 1. Next, calculate 50% to 70% of that daily dose and convert this dose to an I. V. dose by multiplying by 10%. Administer that amount in a controlled setting for 3 to 5 days. Titrate, as needed, by 0.5 mg to 1.0 mg every 2 to 4 hours during the conversion period.

**Issues During Opioid Rotation**

Opioid-related adverse events are one reason for conversion failure. Headache, somnolence, and gastrointestinal toxicities, especially constipation, nausea, and vomiting, are associated with opioids and can be treatment limiting. Multimodal strategies, both pharmacologic and nonpharmacologic, are commonly used to manage toxicities, but they have variable success rates. Novel approaches to the management of opioid side effects, such as constipation, have the potential to improve clinical management of patients who are candidates for opioid treatment.

**Managing Opioid-Induced Nausea and Vomiting**

During any of the above-described opioid conversion strategies, patients may experience opioid-induced symptoms of nausea and vomiting, which can be medically managed in some patients [50,51]. Various antiemetics can be used as monotherapy or combination therapy. A transdermal scopolamine patch 1.5 mg behind the ear every 3 days for 12 days (total of four patches) is a useful monotherapy. A combination therapy approach might include 12.5 mg diphenhydramine plus 4 mg ondansetron PO every 12 hours.

**Constipation Management (Opioid Bowel Dysfunction [OBD])**

OBD is a common side effect of opioid therapy that creates sometimes debilitating symptoms which decrease the patient’s quality of life and can compromise effective long-term opioid therapy [52,53]. During opioid conversion, all patients should either be started on or should continue their preconversion bowel regimens. Commonly, laxatives and/or stool softeners are used to minimize constipation from opioids.

Novel approaches to the management of constipation have shown promise for improving clinical management of patients who are receiving opioid treatment [54]. The approval of methylnatrexone bromide marks the first United States Food and Drug Administration (FDA) approval of a new class of agents called peripherally acting mu-opioid receptor (PAM-OR) antagonists. As the name suggests, these agents specifically block the “peripheral” action of opioids on the gut without interfering with pain relief mediated in the central nervous system (they do not readily cross the blood-brain barrier). Methylnatrexone bromide is indicated to help restore bowel function in patients with late-stage advanced illness who are receiving opioids on a continuous basis to help alleviate their pain.

Alvimopan, another PAM-OR antagonist, is the first and only FDA-approved agent indicated to accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis [55,56]. This agent is currently being studied for OBD and shows promise in terms of being effective without compromising analgesia [57]. PAM-OR antagonists, such as methylnatrexone bromide and possibly alvimopan can provide an effective and well-tolerated tool for managing OBD.

Finally, NKTR-118 is an investigational oral drug that combines a novel small molecule PEGylation technology platform with naloxol, a derivative of the opioid-antagonist drug, naloxone. In preclinical studies, NKTR-118 did not cross the blood-brain barrier, an important potential advance for this therapy which could allow it to act selectively in a similar fashion to PAM-OR antagonists [58].

**Oxymorphone and Opioid Toxicities**

Adverse events associated with opioid treatment in greater than or equal to 2% of patients during the titration and treatment period reported by Hale et al. in their study on the efficacy and safety of oxymorphone ER for relief of moderate to severe chronic low back pain in opioid-experienced patients included nausea, constipation, headache, somnolence, vomiting, pruritus, and dizziness (Table 2). The adverse event rates are lower once patients are stabilized [59].
Table 2  Adverse events associated with opioid treatment in ≥2% of patients treated with oxymorphone ER for relief of moderate to severe low back pain

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<td>Placebo % (N = 72)</td>
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* All patients were administered a bowel regimen.

ER = extended release.

Conclusion

The pain patient represents one of modern medicine's most complex challenges. Physicians who care for such patients may be confounded by a multitude of variables: individual genetic variations, advancing disease, comorbid conditions, drug interactions, and psychosocial issues can come into play for pain management strategies. Fortunately, as our knowledge of opioids increases, so does our effective deployment of this type of analgesic therapy. Opioid rotation has proven effective in some patients to maintain analgesia with tolerable side effects. The new formulation of oral oxymorphone (Opana and Opana ER) is a potent, fast-acting opioid analgesic that has been successfully used in opioid rotation, showing acute tolerance to the side effects with a prolonged durable analgesic effect.

Disclosures

Dr. Pergolizzi is a speaker and a consultant for Edno Pharmaceuticals, GlaxoSmithKline, and Adolor. Dr. Pergolizzi has acted as an investigator for GlaxoSmithKline.

Dr. Raffa is a past or current speaker, consultant, and/or basic science investigator for Adolor, Ateon, Asta Medica, Discovery Research Consultants, Grunethal, Johnson & Johnson, IAPID, Novartis, Onconova, and Pain Therapeutics.

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