Toward a systematic approach to opioid rotation

Howard S Smith\textsuperscript{1,†} John F Peppin\textsuperscript{2,3}

\textsuperscript{1}Department of Anesthesiology, Albany Medical College, Albany, NY, USA; \textsuperscript{2}Global Scientific Affairs, Mallinckrodt Pharmaceuticals, St Louis, MO, USA; \textsuperscript{3}Center for Bioethics, Pain Management and Medicine, St Louis, MO, USA

\textsuperscript{†}Author deceased May 18, 2013

Abstract: Patients requiring chronic opioid therapy may not respond to or tolerate the first opioid prescribed to them, necessitating rotation to another opioid. They may also require dose increases for a number of reasons, including worsening disease and increased pain. Dose escalation to restore analgesia using the primary opioid may lead to increased adverse events. In these patients, rotation to a different opioid at a lower-than-equivalent dose may be sufficient to maintain adequate tolerability and analgesia. In published trials and case series, opioid rotation is performed either using a predetermined substitute opioid with fixed conversion methods, or in a manner that appears to be no more systematic than trial and error. In clinical practice, opioid rotation must be performed with consideration of individual patient characteristics, comorbidities (eg, concurrent psychiatric, pulmonary, renal, or hepatic illness), and concurrent medications, using flexible dosing protocols that take into account incomplete opioid cross-tolerance. References cited in this review were identified via a search of PubMed covering all English language publications up to May 21, 2013 pertaining to opioid rotation, excluding narrative reviews, letters, and expert opinion. The search yielded a total of 129 articles, 92 of which were judged to provide relevant information and subsequently included in this review. Through a review of this literature and from the authors’ empiric experience, this review provides practical information on performing opioid rotation in clinical practice.

Keywords: chronic pain, opioid rotation, opioid analgesics

Introduction

Pain affects millions of individuals in the United States and in fact is more prevalent than either heart disease or cancer. In 2010, back pain was reported by an estimated 28% of adults in the United States, neck pain by 15%, and joint pain by 33%. Some level of functional impairment was reported by approximately 50% of patients with back or joint pain. By comparison, heart disease and cancer were prevalent in 12% and 6% of US adults, respectively.\textsuperscript{1}

Successful pain management rests on a full patient evaluation followed by implementation of a multidisciplinary and multimodal program of treatment that includes nonpharmacologic therapy (eg, diet, exercise, physical therapy, psychological therapy), nonopioid analgesics (eg, acetaminophen, nonsteroidal anti-inflammatory drugs), and adjuvants such as anticonvulsants and antidepressants.\textsuperscript{2} Opioid agents play an important role in the management of pain arising in a diverse set of clinical settings, including chronic pain of cancer origin,\textsuperscript{3} postoperative pain,\textsuperscript{4} and chronic pain of noncancer origin.\textsuperscript{5,6} However, their use must be selected on the basis of a careful balance of potential risks and benefits.\textsuperscript{7} Guidelines for the responsible use of opioids recommend...
careful patient assessment to establish a legitimate diagnosis of pain and to identify factors that may predispose a patient to misuse a prescribed opioid.7–9 Once treatment commences, vigilant monitoring in all opioid-treated patients is essential to ensure compliance with prescribed therapies and to allow for prompt response to misuse.7–9

In some patients, this balance may be optimized by careful dose adjustment or through implementation of other strategies, such as use of a bowel regimen to alleviate constipation or an antiemetic for nausea. Nonetheless, the selection of an appropriate opioid dose and treatment regimen that provides improved function and quality of life with acceptable tolerability is complicated by several factors that may not be amenable to these corrective measures. These factors include differences between opioids (eg, receptor binding, metabolism), efficacy and tolerability differences between patient subgroups (sex, ethnicity, age), interindividual variability of response, and the specific opioid used; patient factors of importance include comorbidities, concurrent medications, personal history (eg, substance abuse, psychiatric illness), and genetic makeup.10–12 Attempting to downplay these complexities does not improve patient care and, at worst, may contribute to some of the serious psychosocial costs associated with available analgesics. In some cases, the aggregate of factors limiting response to a given opioid will best be addressed by rotation to a substitute opioid that better aligns with the individual patient’s needs.

Guidelines for the safe and effective use of opioids have been proposed by several professional organizations (eg, American Pain Society, American Academy of Pain Medicine) and expert panels.7,8,13–15 However, the clinical practice of opioid rotation is predominantly guided by arbitrary routine, clinician preference, or formulary limitations. Expert opinion and consensus statements concur that there is generally a lack of high-quality evidence to support the practice of opioid rotation or to guide the selection of a new opioid when dose adjustments with the present opioid regimen cannot resolve increasing adverse effects or waning efficacy.13,14,16–18

The objectives of this review are to provide steps toward a systematic approach to opioid rotation with which clinicians can choose the new opioid based on a thoughtful assessment of the likely causes of the adverse effects or poor efficacy with the present therapy. This discussion is limited to opioids appropriate for long-term therapy for chronic pain.

Search methodology
References cited in this review were identified via a search of PubMed covering all English language publications up to May 21, 2013; the search included clinical trials, guidelines, meta-analyses, systematic reviews, and case reports but excluded narrative reviews, letters, and expert opinion. Using the search string “(opioid OR buprenorphine OR codeine OR fentanyl OR hydrocodone OR hydromorphone OR methadone OR meperidine OR morphine OR oxycodone OR oxymorphone) AND (switching OR rotation OR conversion) AND chronic”; the search yielded a total of 129 articles, 92 of which were judged to provide relevant information and were included in this review. Of these, 50 were clinical trials or case reports, and the remaining 42 pertained to the scientific rationale for various aspects of opioid rotation. Treatment guidelines and references identified via this strategy were reviewed for additional articles of interest.

Opioid rotation: published literature
Expert opinion, through a review of this literature, suggests that nearly all opioids may be effective for the relief of pain and that there is insufficient clinical evidence to support the selection of one opioid over another for the initiation of treatment or to systematically guide the selection of a new opioid when the need for opioid rotation arises.18–20 Such guidance is necessary because specific patient subgroups may be more or less susceptible to analgesic or specific side effects of a given opioid, whereas individuals within those subgroups also show variability of clinical response and ability to tolerate specific opioids.

Factors contributing to this variability include demographic differences that affect susceptibility to analgesic and adverse effects,10,21–22 the presence of comorbidities,23 and genetic factors that influence opioid metabolism24 and analgesic response.11 Of these, genetic factors are least clearly understood and are not routinely tested before initiating opioid therapy. To some extent, successful rotation is a process of trial and error. However, as discussed below, this process can be conducted more methodically to maximize the likelihood of a good clinical outcome with each trial.

Reasons for opioid rotation mentioned in the literature include the following: intolerable adverse events during dose titration, lack of analgesic efficacy despite optimal dose titration, occurrence of problematic drug–drug interactions (DDIs), change in clinical status (eg, risk for drug abuse), and practical issues (eg, cost, availability of drug).13 Clinical trials and case series examined for this article are summarized in Table 1.

We cited all of the clinical trials that described a rotation, and there was no selection process. All of the clinical trials evaluating opioid rotation identified in our search have inclusion and exclusion criteria for trial participants that may result in a rarefied study population. The goal of trial design was
Table 1 Characteristics of clinical trials/case series describing opioid rotation

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to reduce the potential impact of trial confounders through inclusion and exclusion criteria. Some of the populations presented in clinical trials are rotated either to a preselected opioid without regard to individual patient characteristics that might influence opioid choice or dose, or to a different opioid without any clearly stated criteria for choosing one agent over another.12,25–57

Examination of a 2010 study illustrates the shortcomings of clinical trial data for guiding opioid prescribing practices.40 In this open-label, prospective study, patients with chronic pain of cancer or noncancer origin (n = 326), which was not controlled by a long-acting opioid, were rotated to morphine immediate release (IR) 5 or 10 mg every 4 hours until adequate pain relief was achieved; they were then switched to a long-acting opioid different from baseline. The choice of the long-acting opioid used for rotation was left to the discretion of the investigator. In all, 70% of patients achieved adequate pain control after switching to morphine IR; after the subsequent rotation to a substitute long-acting opioid, the mean proportion of patients reporting breakthrough pain decreased from 73%–93% to 29%–49%, depending on the long-acting opioid. However, patients were excluded if they were on high doses of opioids, had a history of substance abuse, or had psychiatric, pulmonary, renal, and/or hepatic comorbidities.

Upon consideration, it becomes apparent that data from studies such as this, while of value, may be difficult to extrapolate to clinical practice. In a chronic pain practice most
physicians, either knowingly or unknowingly, will approach a patient’s treatment individually, using an “n of 1” approach. When prescribing opioids, this approach may start with an opioid that the physician is familiar and comfortable with and that has shown efficacy in the past; however, tailoring therapy will ultimately require consideration of the individual patient in ways that are not sufficiently addressed by clinical trials. Since clinical trials deal with distributions of a large number of patients whereas individual practitioners deal with individual patients, the “n of 1 trial” is a more empiric and common approach to treatment.

Case series have described a process wherein patients are prescribed sequential trials of up to five individual opioids in search of an agent that is effective and sufficiently well tolerated. However, the selection of agents and the sequence in which they are prescribed were not defined, leaving the reader without clear guidance. In addition, published case series typically do not provide specific information about patients’ health status, making it difficult to estimate how certain patient characteristics may have influenced the outcomes observed following rotation. In short, rotation methodology presented in published studies or case series appears to be fixed or random rather than patient-specific.

**Selecting an opioid for rotation: patient characteristics**

Chronic pain care must begin with a careful patient assessment that includes a complete history and physical examination to establish a clear pain diagnosis to support a rational multimodal treatment program that might include opioids. Before initiating treatment, clinicians should assess the risk of opioid abuse and the potential for idiosyncratic reactions to opioids by inquiring about previous therapeutic experience with opioids, previous use of sedating prescription or over-the-counter medications, and any previous substance abuse by the patient or family members.

A thorough patient history may also include very simple information indicating the presence or absence of genetic anomalies that might influence response and tolerability. For example, about 10% of the white population have impaired function of the cytochrome (CYP) P450 2D6 enzyme and consequently cannot efficiently metabolize codeine to its active metabolite, morphine. Patients with a history of inadequate response to codeine should be switched with great caution from codeine to a substitute opioid that is not metabolized by CYP2D6 (eg, morphine, fentanyl, oxymorphone) because these patients may not have developed opioid tolerance during previous treatment.

When assessing patients, it is important to remember that most patients with chronic pain have more than three specific and individual pain problems at their first visit, making careful assessment a significant challenge. Factors to be considered when selecting a substitute opioid include patient characteristics, comorbidities, concurrent medications, and adverse effects of the opioid being replaced, as summarized in Table 2.

**Demographic factors**

Successful pain management may require an understanding of demographic characteristics (eg, age, sex, race) that influence the effectiveness or tolerability of opioid therapy. Clinicians contemplating implementation of opioid rotation should consider the following: 1) potential reduction in clearance of morphine, oxycodone, fentanyl, and oxymorphone has been reported in elderly patients; 2) aging is associated with higher steady-state concentrations of water-soluble drugs and increased half-life of fat-soluble drugs; and 3) potential for higher steady-state concentration of drugs may necessitate dose adjustments (eg, lower doses; longer interval between doses) to maintain an appropriate balance between long-term analgesia and the risk for adverse events. As a result, older patients may experience similar analgesia at a lower opioid dose and have a greater risk for respiratory depression.

Women are more sensitive to the effects of κ agonists and are generally more likely than men to experience nausea and vomiting from opioids. Clearance of oxycodone and hydromorphone may be reduced in women, making dosage adjustments necessary. Patients of Chinese origin have increased clearance of morphine compared with white patients. Clearance of hydrocodone may be altered in Asian or black patients.

**Comorbidities**

**Cardiovascular comorbidities**

In patients with heart failure, particular care must be taken with methadone and caution should be used with morphine, oxycodone, and oxymorphone. Some patients who are placed on chronic methadone therapy for pain management may be at increased risk for development of a prolonged QT interval or may already have a congenital QT prolongation. This could influence rotation to methadone as an alternative. The Cardiac Expert Panel of the Center for Substance Abuse Treatment (CSAT) recommends the following: 1) informing patients of the arrhythmia risk associated with methadone; 2) asking about any history of structural heart disease, arrhythmia, and
Rational opioid rotation

Table 2 Selected patient factors influencing opioid efficacy and/or tolerability

<table>
<thead>
<tr>
<th>Opioids</th>
<th>Age</th>
<th>Sex</th>
<th>Ethnicity</th>
<th>Hepatic impairment$^{24}$</th>
<th>Renal impairment$^{24}$</th>
<th>Cardiovascular/respiratory disease</th>
<th>Risk of abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Clearance may be reduced in older patients</td>
<td>No effect</td>
<td>Chinese patients have higher clearance</td>
<td>Dose adjustments recommended</td>
<td>Dose adjustments recommended</td>
<td>Use with caution</td>
<td>Frequently abused</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Caution recommended in older patients</td>
<td>No effect</td>
<td>No effect</td>
<td>May be formulated in combination with acetaminophen; liver function testing advised in patients with hepatic impairment</td>
<td>May be formulated in combination with acetylsalicylic acid; renal function testing advised in patients with renal impairment</td>
<td>Use with caution</td>
<td>Frequently abused</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Concentrations nominally higher in older patients</td>
<td>Concentrations ≈ 25% higher in women than in men</td>
<td>No effect</td>
<td>Dose adjustments recommended</td>
<td>Dose adjustments recommended</td>
<td>More respiratory depression than morphine or tramadol</td>
<td>TRF available</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>No dose adjustment necessary</td>
<td>No effect</td>
<td>No effect</td>
<td>Not evaluated</td>
<td>No effect</td>
<td>Use with caution</td>
<td>Recommended for patients with confirmed or suspected misuse/with daily supervised dispensing</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>No effect</td>
<td>C$<em>{max}$ 25% higher in men; AUC$</em>{0–24}$ is the same in both sexes</td>
<td>No effect</td>
<td>Dose adjustments recommended</td>
<td>Dose adjustments recommended</td>
<td>Use with caution</td>
<td>Frequently abused</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>Steady-state concentrations ~40% higher in older patients</td>
<td>Concentrations the same in men and women after adjusting for body weight</td>
<td>No effect</td>
<td>Contraindicated in patients with moderate to severe hepatic impairment</td>
<td>Dose adjustments recommended</td>
<td>Use with caution</td>
<td>TRF available</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>Dose adjustments may be required for older patients</td>
<td>No effect</td>
<td>No effect</td>
<td>Not evaluated</td>
<td>Not evaluated</td>
<td>Dose adjustments recommended</td>
<td>Frequently abused</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>Dose adjustments recommended</td>
<td>No effect</td>
<td>No effect</td>
<td>Contraindicated in patients with severe hepatic impairment</td>
<td>Contraindicated in patients with severe renal impairment</td>
<td>Use with caution</td>
<td>TRF available</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Clearance may be reduced in older patients</td>
<td>No effect</td>
<td>No effect</td>
<td>Dose adjustment may not be necessary</td>
<td>Dose adjustment may not be necessary</td>
<td>Use with caution</td>
<td>Frequently abused</td>
</tr>
<tr>
<td>Methadone</td>
<td>Dose adjustments may be required for older patients</td>
<td>No effect</td>
<td>No effect</td>
<td>Dose adjustments recommended in patients with severe hepatic impairment</td>
<td>Dose adjustments recommended in patients with severe renal impairment</td>
<td>Avoid</td>
<td>Recommended for patients with confirmed or suspected misuse/with daily supervised dispensing</td>
</tr>
</tbody>
</table>

Note: Adapted from Mayo Clin Proc, 84/7, Smith HS, Opioid metabolism, 613–624; Copyright © 2009, with permission from Elsevier.$^{24}$

Abbreviations: AUC$_{0–24}$ area under the concentration versus time curve from time 0 to 24 hours; C$_{max}$ maximum plasma concentration; TRF, tamper-resistant formulation.
Syncope; 3) obtaining a pretreatment electrocardiogram (ECG) for all patients to measure the QT interval and a follow-up ECG within 30 days and annually; 4) avoiding interactions between methadone and other drugs that possess QT interval–prolonging properties or slow the elimination of methadone; and 5) reducing or discontinuing methadone if the QT interval exceeds 500 milliseconds. Similar but less detailed precautions to avoid arrhythmias with methadone are recommended in the American Society of Interventional Pain Physicians (ASIPP) and American Pain Society (APS)/American Academy of Pain Medicine (AAPM) chronic noncancer pain guidelines.

Tramadol has been recommended ahead of nonsteroidal anti-inflammatory drugs for patients with significant cardiovascular risk and a similar case might be argued for tapentadol. Clinicians may also consider fentanyl, morphine, or oxycodone for these patients because none of these opioids is a significant cause of QT prolongation.

### Hepatic and renal impairment

Additional considerations for opioid rotation include the effects of hepatic and renal impairment on opioid dosing recommendations (Table 2). The US Food and Drug Administration (FDA) recommends assessment of hepatic function based on Child-Pugh ratings (mild, moderate, severe) and defines moderate and severe renal impairment as a creatinine clearance of 30–50 mL/minute and <30 mL/minute, respectively. Many opioid drugs undergo hepatic phase I metabolism mediated by the CYP mono-oxygenases (primarily CYP3A4 and CYP2D6), enzymes that produce both active and inactive metabolites that vary among commonly used opioid agents (Table 3).

Moreover, metabolism of opioids by CYP3A4 produces major metabolites of certain opioids that exhibit >30-fold higher (eg, hydrocodone produces norhydrocodone) and lower (eg, buprenorphine produces norbuprenorphine) affinity for the μ-opioid receptor. Thus, for patients with

### Table 3 Characteristics of commonly used opioids

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Receptor binding</th>
<th>Routes of administration</th>
<th>Metabolic pathway</th>
<th>Ceiling dose</th>
<th>Onset of effect</th>
<th>Duration of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>μ, κ (weak)</td>
<td>Oral tablet, oral liquid, intramuscular or subcutaneous, epidural or intrathecal, intravenous, rectal</td>
<td>Glucuronidation</td>
<td>None</td>
<td>NA</td>
<td>ER or IR</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>μ, κ</td>
<td>Oral</td>
<td>CYP2D6</td>
<td>Yes for combination products, no for pure hydrocodone</td>
<td>Rapid</td>
<td>ER or IR</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>μ, κ (strong)</td>
<td>Oral, rectal</td>
<td>CYP3A4, CYP2D6</td>
<td>Yes for combination product, no for pure oxycodone</td>
<td>Rapid</td>
<td>ER or IR</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>μ (antagonist), κ (agonist, weak partial)</td>
<td>Transdermal, transmucosal</td>
<td>CYP3A4, glucuronidation</td>
<td>Yes</td>
<td>Slow</td>
<td>Long</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>μ, κ (weak), δ (weak)</td>
<td>Oral, intramuscular or subcutaneous, intravenous, rectal</td>
<td>Glucuronidation</td>
<td>None</td>
<td>N/A</td>
<td>ER or IR</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>μ</td>
<td>Oral, intravenous, rectal</td>
<td>Glucuronidation</td>
<td>None</td>
<td>N/A</td>
<td>ER or IR</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>μ, κ, δ</td>
<td>Oral</td>
<td>Glucuronidation</td>
<td>6–12 mg/d</td>
<td>Rapid</td>
<td>Long</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>μ, 5-HT, NE</td>
<td>Oral</td>
<td>Glucuronidation CYP2C9 (minor) CYP2C19 (minor) CYP3A4</td>
<td>500 mg/d</td>
<td>Slow</td>
<td>ER or IR</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>μ, κ (weak)</td>
<td>Transdermal, transmucosal, intranasal, intravenous</td>
<td>CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2C9</td>
<td>None</td>
<td>Very rapid (transmucosal, intravenous)</td>
<td>Very short (transdermal, intravenous)</td>
</tr>
<tr>
<td>Methadone</td>
<td>μ, κ (weak), δ (strong), NMDA</td>
<td>Oral</td>
<td>CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP2C9</td>
<td>None</td>
<td>Very slow (transdermal)</td>
<td>Long</td>
</tr>
</tbody>
</table>

**Abbreviations:** 5-HT, serotonin; CYP, cytochrome P450; d, day; ER, extended release; IR, immediate release; N/A, not applicable; NE, norepinephrine; NMDA, N-methyl-D-aspartate.
Rational opioid rotation

Sedation or analgesia should be the primary goals of any opioid rotation. Clinicians should consider the following recommendations.

1. **Dose adjustments**: If the patient is taking a different opioid, dose adjustments may be necessary. It is important to consider the potency and potency of the new opioid, as well as the patient's current pain level.

2. **Drug interactions**: When switching to a different opioid, consideration should be given to potential drug interactions. For example, if the patient is taking a benzodiazepine, a switch to an opioid with a different mechanism of action (e.g., fentanyl) may be necessary.

3. **Side effects**: The patient should be monitored for side effects of the new opioid. For example, if the patient is experiencing nausea, antiemetic medication may be necessary.

4. **Monitoring**: Regular monitoring of the patient's response to the new opioid is essential. This includes monitoring for pain control, side effects, and adherence to the treatment plan.

Strategies for addressing misuse or addiction may include structured opioid therapy with heightened monitoring, more frequent dispensing of small quantities of opioid, and witnessed administration. A structured trial of methadone or buprenorphine may be indicated if structured therapy with other opioids is associated with continued misuse.

Methadone has demonstrated efficacy in patients with chronic pain; its use for opioid maintenance in substance use disorders is falling out of favor. Methadone, with its complicated metabolism and potential cardiotoxic effects, has an increased propensity for overdose death. This makes methadone a less preferred first choice for patients requiring opioid rotation as part of long-term opioid therapy. Moreover, patients may believe that methadone is reserved for addicts and may resist taking it for fear of the stigma associated with its use.

However, in a responsible and reliable patient who is known to the practitioner, and in the hands of a clinician who is knowledgeable and experienced with the drug, methadone can be an option. In a retrospective observational study, there was no excess mortality observed in nearly 30,000 Veterans Administration (VA) patients treated with methadone compared with nearly 80,000 VA patients treated with long-acting morphine. However, because this study was not randomized, the populations treated with methadone and with morphine may not have been equivalent, and because these patients were treated within the VA system, the training of prescribers and quality of monitoring may not have been representative of the standard of care received by patients in the general population.

As an alternative to methadone, buprenorphine has shown analgesic efficacy, either singly or in formulations combining buprenorphine with naltrexone (to discourage intravenous abuse). The use of buprenorphine appears not to be accompanied by the stigma associated with methadone and may therefore be more acceptable to patients. Although there are data suggesting that buprenorphine may be less attractive for abuse compared with methadone and that buprenorphine/naltrexone is less attractive for abuse compared with buprenorphine alone, there is also more recent evidence showing that buprenorphine/naltrexone is being diverted in record numbers. This suggests that any assumption that buprenorphine or buprenorphine/naltrexone is less likely than methadone to be abused remains to be proven; it also suggests that abuse liability is a product of multiple factors (e.g., availability, cost, street reputation) that includes factors that cannot be easily measured in controlled experiments.
Selecting an opioid for rotation: opioid characteristics
Receptor binding profile
Opioid receptors are widely distributed throughout the central nervous system and include μ-receptors, located mainly in the brainstem and medial thalamus; δ-receptors in limbic areas, brainstem, and spinal cord; and κ-receptors, found predominantly in the brain. Each of these opioid receptors modulates pain through a similar molecular mechanism that involves a G protein–coupled signal transduction pathway that causes a block in calcium channel conductance and the release of pain mediators (eg, glutamate, substance P, calcitonin gene-related peptide). At usual doses, some opioid agents exhibit selectivity for μ-receptors; the relative effects of differences among μ-receptors may result in different mechanisms of response. However, other opioid agents exhibit mixed μ/κ-agonist (eg, morphine), μ/κ/δ-agonist (eg, hydromorphone, levorphanol, methadone), or mixed agonist/antagonist activity (eg, buprenorphine) (Table 3). If a patient does not respond to or tolerate an opioid, clinicians may consider rotation to a substitute opioid with a different binding profile.

Tapentadol and tramadol target the opioid receptors to a lesser extent than pure opioids, exerting some of their analgesic effects through serotonin-norepinephrine reuptake inhibition. Patients experiencing pain with a neuropathic component or who have difficulty tolerating a pure opioid agonist may experience adequate analgesia with improved tolerability with one of these agents. However, mixed targeting of opioid and serotoninergic receptors (ie, 5-hydroxytryptamine receptors) and adrenergic receptors (ie, norepinephrine receptors) may increase the risk for serotonin syndrome in a patient taking other serotonergic medications.

Several opioids function as mixed opioid agonist-antagonists (oxycodone-naloxone, buprenorphine), with the antagonist component blunting adverse events or offering less reinforcement of the positive subjective effects associated with abuse. Although there is no physiologic ceiling dose for most opioids (eg, morphine, hydromorphone, oxymorphone, fentanyl, methadone), there is some evidence that opioid efficacy for mixed agonists-antagonists may be blunted above a certain dose.

Route of administration
The availability of different formulations provides alternate routes of administration (eg, transdermal or transmucosal and oral) and may facilitate opioid rotation. For example, in patients with chronic pain of cancer origin, morphine is the most often considered opioid for pain relief. However, a patient may have problems that may complicate oral administration (eg, dysphagia, aspiration, oral cancers). In this setting, clinicians may consider rotation to a transdermal patch (Table 1) that can be administered despite swallowing difficulties. A transdermal patch may also be appropriate, in a monitored setting, for a patient who has a reduction in cognition and chronic pain. If the patient experiences sweating or skin irritation that causes a problem with a transdermal patch, subcutaneous, intramuscular, intravenous, transmucosal, or rectal administration can be used if the patient is at the end of life.

Metabolic pathway and DDIs
Opioid agents undergo phase II metabolism through the formation of active and inactive glucuronide conjugates, mediated primarily by the membrane-bound enzyme uridine 5’-diphospho-glucuronosyltransferase-2B7. When a patient requires opioid rotation, clinicians may consider the following: 1) severe renal impairment may increase the plasma concentration of active metabolites of morphine (eg, morphine-6-glucuronide) and the potentially neuroexcitatory 3-glucuronide metabolite of morphine; 2) consider rotation to other opioids (eg, fentanyl, hydromorphone) that are little affected by renal impairment; and 3) consider the need for opioid dose adjustments in elderly patients to accommodate declining renal function and prevent the occurrences of adverse events.

Patients seeking treatment for relief of chronic pain often present with comorbidities and may require coadministration of opioids with other systemically-acting drugs, resulting in unwanted DDIs. In these patients, clinicians may consider the following: 1) opioids metabolized by CYP450 enzymes (eg, CYP2D6, CYP3A4) are associated with the potential for numerous DDIs (eg, reduced or enhanced opioid effects) (Table 4); 2) the prevalence of opioid-related DDIs was greater in women (approximately 31% versus 22%) but similar across all age groups (range, 18–34 to ≥65 years); and 3) the majority of DDIs (approximately 68%–71%) were associated with coadministration of drugs that inhibited CYP2D6 rather than drugs that inhibited CYP3A4 (approximately 28%–29%). Thus, patients using hydrocodone should be monitored for potentially increased or decreased opioid effects when coadministered inducers or inhibitors, respectively, of CYP3A4. Alternatively, if effective management of medically complicated patients requires coadministration of drugs that inhibit CYP2D6, clinicians...
may consider opioids that are not substrates for this enzyme (eg, fentanyl, oxymorphone).

In addition to CYP450-mediated DDIs, clinicians considering rotation to certain opioids (eg, fentanyl, tapentadol) should instruct patients regarding the following: 1) additive effects of central nervous system depressants (eg, fentanyl in combination with alcohol, sedatives);2) constipating effects of tricyclic antidepressants;3) increased risk for seizures with tramadol or tapentadol in combination with a monoamine oxidase inhibitor antidepressant; 4) increased risk for serotonin syndrome with tapentadol or tramadol in combination with serotonin reuptake inhibitors; and 5) risks of central nervous system depressant effects associated with the addition of benzodiazepines.62,80,93,105,106

Adverse events
Discussion of the many adverse events and side effects from the use of opioids is beyond the scope of this article. However, a few will be discussed to give examples of why opioid rotation may be helpful when these issues present themselves.

Constipation
Clinical results indicate that inadequately controlled constipation occurs in approximately 10%–60% of patients undergoing opioid treatment for chronic pain of cancer and noncancer origin.107,108 For patients on an opioid who complain of constipation, the following guidance may be useful: 1) prescribing a bowel regimen is a necessity with every opioid; however, an effective bowel regimen may or may not overcome the relative propensity of the specific opioid to cause constipation;107 2) if constipation continues to limit quality of life, opioid antagonists (eg, methylnaltrexone, lubiprostone) and upcoming combination products, such as prolonged-release oxycodone plus prolonged-release naloxone (a μ-receptor opioid with limited systemic bioavailability), may improve bowel function;109 3) transdermal fentanyl has been associated with a significantly lower rate of constipation compared with oral morphine,111,112 making it a potential option for opioid-experienced patients with a history of constipation during opioid therapy; and 4) tapentadol IR exhibits weaker μ-receptor activity compared with pure opioid agonists and may be associated with a lower incidence of constipation than oxycodone.56,94,110

Nausea and vomiting
Inadequately controlled nausea and vomiting is frequently reported in patients receiving opioids for pain management.107 For example, tapentadol has displayed effective analgesia with a decreased risk for nausea and vomiting compared with oxycodone.113,114 Clinicians may therefore consider rotation to tapentadol in patients who complain of nausea and vomiting after initiation/rotation to other opioids.

Equianalgesic dose conversion
There are two general approaches to opioid conversion for clinicians conducting opioid rotation. Some clinicians may prefer to calculate dose conversions themselves using package inserts and/or with reference to the published literature.115 Second, clinicians can use an online dose calculator. These include the Johns Hopkins Opioid Conversion Program calculator, sponsored by the Sidney Kimmel

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Table 4 Potential for DDIs associated with disruption of key cytochrome P450 enzymes

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Induction of CYP3A4</th>
<th>Inhibition of CYP3A4</th>
<th>Inhibition of CYP2D6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>No likely clinical consequences</td>
<td>No likely clinical consequences</td>
<td>N/A</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Potential increase in opioid effects; patient monitoring recommended</td>
<td>Potential decrease in opioid effects; patient monitoring recommended</td>
<td>N/A</td>
</tr>
<tr>
<td>Oxycodeone</td>
<td>Decrease in opioid effects; avoid combination when possible</td>
<td>Increase in opioid effects (black box warning); avoid combination</td>
<td>Potential decrease in opioid effects</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Decrease in opioid effects</td>
<td>Increase in opioid effects</td>
<td>N/A</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Decrease in opioid effects; avoid combination when possible</td>
<td>Increase in opioid effects (black box warning); avoid combination</td>
<td>N/A</td>
</tr>
<tr>
<td>Methadone</td>
<td>Decrease in opioid effects; avoid combination</td>
<td>Increase in opioid effects; avoid combination when possible</td>
<td>Increase in opioid effects; avoid combination</td>
</tr>
</tbody>
</table>

Notes: ‘Drugs metabolized primarily by UGT2B7 (Phase II) and not likely to be associated with significant DDIs caused by alterations to CYP3A4 and CYP2D6. For more information on Buprenorphine see McCance-Katz et al.14 Copyright © 2011. Adapted from The American Journal of Managed Care. Overholser BR, Foster DR. Opioid pharmacokinetic drug-drug interactions. Am J Manag Care. 2011;17(suppl 11):S276–S287.147

Abbreviations: CYP, cytochrome P450; DDIs, drug–drug interactions; N/A, not applicable.
Comprehensive Cancer Center at Johns Hopkins; the GlobalRPH calculator, sponsored by Novartis Pharmaceuticals Corporation (Basel, Switzerland); and the Practical Pain Management Opioid calculator, sponsored by Vertical Health Media, LLC (Montclair, NJ, USA). The authors recommend use of the Practical Pain Management Opioid calculator as being the most inclusive of available opioids but advise that any table or calculator be used with caution because recommended equianalgesic doses as shown in dose conversion tables may vary (eg, conversion ratios of oral to parenteral morphine range from 3.1 to 2:1 to 6:1). Further, it is the experience of the authors that this conversion table reflects how they apply dose conversion in their own practices. In addition, conversion tables do not fully consider the contributions that individual patient characteristics, comorbidities, and concurrent medications may have on opioid dose. In the opinion of the authors and other authorities on pain management, these tables and converters are not based on good science and research, being derived mainly from expert opinion or single-dose studies in patients with acute pain of noncancer origin.

To account for potential variability of response, clinicians may convert patients from one opioid to another using a two-step guideline developed by an expert panel and presented by Fine and Portenoy. For step one, the clinician calculates the equianalgesic dose using an online dosage calculator as suggested (eg, Practical Pain Management Opioid calculator). However, no system of dose conversion is perfect, and the difference between package inserts (which may not be based upon the most current or extensive evidence) and other conversion tables may be significant. The initial dose administered, however, should be 25%–50% lower than the calculated equianalgesic dose. The reduction should be closer to 50% of the calculated dose if the patient is receiving a high dose of the opioid being discontinued or if they are elderly, medically frail, or not white. The reduction should be closer to 25% in patients without these attributes or if they are switching to a different route of administration of the same opioid. Fine and Portenoy recommend that patients switched to methadone should receive an initial methadone dose 75%–90% lower than the original opioid because higher-than-anticipated potency has been observed in the clinical setting. The safe use of methadone can be challenging for reasons outlined in Tables 2 and 4.

For step two, clinicians should assess and reassess the patient as appropriate for individual circumstances; this should be done after initiating the substitute opioid to gauge the extent of analgesia on the new opioid, adverse events, and other medical and psychosocial factors that might guide dose adjustments. After this assessment, the dose should be increased 15%–30% if additional analgesia is required or to minimize the risk of withdrawal or other adverse events. Rescue medication, if provided during titration, should be administered at 5%–15% of the total daily dose of the substitute opioid.

This two-step method may greatly increase the safety of opioid rotation. However, clinicians still need to understand the potential contribution of basic clinical factors when selecting a substitute opioid for rotation and deciding how much to reduce the equianalgesic dose when making the switch. Clinicians who are unclear of the appropriate conversion method for a particular patient should consult a pain specialist, oncologist, or other reliable mentor.

Whenever an opioid is prescribed, an exit strategy should always be considered and discussed with the patient. Opioid tapering may be undertaken owing to inadequate response or if the patient is suspected of using his opioid inappropriately. As noted in Canadian guidelines, tapering of an opioid may be accompanied by a reduction in pain and improvements in mood owing, perhaps, to the reduction or elimination of hyperalgesia and withdrawal symptoms; the alleviation of adverse effects, such as sedation or dysphoria; or the psychological interventions that may be implemented in conjunction with the decision to taper. US guidelines state that an opioid may be tapered using a schedule ranging from a 10% dose reduction each week to a 25%–50% dose reduction every few days. If possible, patients who abuse their opioid or otherwise have difficulty tapering on their own should be referred to a facility allowing for a structured, supervised approach.

**Future directions**

Genetic research may one day simplify the selection of initial and substitute opioids for individual patients. Recent studies have identified functional single-nucleotide polymorphisms (SNPs) in genes encoding receptors (eg, OPRM1 that encodes the μ-1 opioid receptor), transporter proteins (eg, ABCB1 [MDR1] that encodes p-glycoprotein), CYP (eg, CYP2D6) Phase II (eg, UGT2B7) enzymes involved in opioid metabolism, and other genetic changes. Recent studies suggest an association between the presence of these SNPs and altered responsiveness to opioids; although the identification of SNPs presents intriguing possibilities for guiding opioid treatment, a recent genotyping analysis in more than 2,000 patients with cancer who were undergoing opioid treatment of moderate to severe pain found no association between the presence of SNPs (eg, OPRM1, ABCB1, COMT) and opioid dose in patients.
administered morphine, oxycodone, or fentanyl alone. Moreover, screening for the presence of SNPs of interest may not be available outside major medical centers and is not currently economically feasible in individual clinical practices.

Further, the role of glial cells in the generation of pain and opioid function has become a recent focus. The effects of glial activation and potential targets to reduce this activation are an exciting new area of pain research.

**Summary**

Our review of the literature has identified many factors that can be considered when planning an opioid rotation, in the hope of selecting an opioid less likely to perpetuate the tolerability problems observed with the first opioid. We have compiled these factors into an algorithm to guide the selection of the new opioid for rotation (Figure 1). The authors caution that there are no data to support our proposition that

**Figure 1** Algorithm for initial patient assessment and initiation and rotation of opioid therapy.

Abbreviation: CYP, cytochrome P450.
a patient may be more likely to find the new opioid tolerable and effective when it has been selected using a systematic approach to rotation, and it should be noted that nonclinical factors, such as formulary restrictions, may greatly complicate efforts to take such an approach.

Clinically, however, factors such as patient demographics, opioid receptor affinity, and opioid metabolism and so on, should be considered when the new opioid is selected instead of relying on a set protocol or the clinician’s standard routine. Moreover, it is important to note that many adverse events associated with opioids are dose related. Consequently, if one rotates a patient from one opioid to another, following the advice to reduce the starting dose of the new opioid by 25%-50% of the calculated equianalgesic dose of the first opioid, this reduction in dose may result in improved tolerability while incomplete cross-tolerance may result in equivalent efficacy. There is a need for clinical trials to test the value of selecting the opioid for rotation on a systematic basis versus random or arbitrary selection.

Dedication
This manuscript is dedicated to Dr Howard S Smith, who passed away suddenly before its publication. The profession has lost a gifted clinician and teacher, whose originality, dedication, and kindness were appreciated by his colleagues, students, and patients. His passing is a great loss to the profession of pain and palliative medicine as well as to his friends and acquaintances personally.

Author contributions
The authors contributed to the literature search design; the analysis and interpretation of the literature reviewed in this manuscript, and to the preparation, review, and final approval to submit the manuscript; independent of the funding organization (Endo Pharmaceuticals Inc., Malvern, PA, USA).

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Disclosure
Drs Smith and Peppin have served as advisors and consultants for Endo Pharmaceuticals Inc., and Dr Smith has presented research at scientific meetings with reimbursement of associated expenses from Endo Pharmaceuticals Inc.; Dr Peppin is an employee of Mallinckrodt Pharmaceuticals (St Louis, MO, USA). Editorial support for this review was provided by Complete Healthcare Communications, Inc. (Chadds Ford, PA, USA), with funding from Endo Pharmaceuticals Inc. (Malvern, PA, USA). However, neither Drs Smith nor Peppin, who had complete control over the content of this paper, received any remuneration for developing and writing this review.

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