OPIOID SWITCHING IN PATIENTS WITH CHRONIC PAIN – PART 1

INTRODUCTION

The practice of switching a patient from one opioid analgesic to another in an effort to improve clinical outcomes has been termed “opioid switching” or “opioid rotation”.* It is a common practice, but one that involves many challenges and opportunities for error that can lead to significant adverse consequences, such as poor pain control, excessive side effects, and even death from respiratory depression if inadvertent overdosing occurs. As a result, it is important that pharmacists be prepared to make appropriate recommendations for opioid switching so that the goals of optimal analgesia and avoidance of intolerable side effects can be achieved. The following overview is intended to help pharmacists in this role. In Part 2 of this article, challenging situations in opioid switching will be discussed and examples of switching scenarios will be provided.

RATIONALE FOR SWITCHING

Patients receiving opioid analgesic therapy may require a switch to a different opioid for a variety of clinical reasons. Common reasons for switching include troublesome or unacceptable adverse events (e.g., sedation/somnolence, delirium) and inadequate pain relief despite appropriate dose titration. Problematic drug interactions, the need or preference for a different route of administration, and financial or drug availability considerations may also lead to the trial of a new opioid.

The theory behind opioid switching is based on the concepts of: (1) incomplete cross-tolerance to the analgesic and nonanalgesic effects among opioids, and (2) a high degree of individual variation in response to different opioids. Thus, the change from one opioid to another could potentially lead to a better balance of benefits to harms. *

OPIOID ROTATION: STEPWISE APPROACH

A stepwise approach to opioid switching is summarized in Box 1 and described in the following text. While this general approach (or a variation of it) is recommended most frequently in the literature, it is important to note that other novel approaches exist (see Box 2). Also notable is that there is a lack of methodologically sound studies evaluating opioid switching protocols, and well-founded recommendations for opioid switching are difficult to make. Nevertheless, available data suggest that 50–80% of patients with chronic pain who respond poorly to one opioid improve after being switched to another opioid.

Traditional stepwise approach to opioid switching

1. Select new opioid

Although selection of the new opioid is an important step in the switching process, a full discussion of all the factors that influence the choice of new opioid is beyond the scope of this review. Briefly, considerations should include the patient’s age, medical comorbidities, concomitant medications, and history of opioid exposure/response, as well as medication cost and convenience of administration. The Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain discusses specific safety issues to consider when selecting opioids, and the document is available online (see References, below, for URL).

2. Determine original opioid total daily dose

Before selecting an appropriate starting dose for the new opioid—one that is safe and reasonably effective—it is first necessary to determine the
total daily dose of the original opioid(s), including both scheduled and "as-needed" doses.

3. **Convert original opioid dose to morphine equivalents**

If the patient’s analgesic regimen consists of multiple opioids (e.g., one for scheduled long-acting doses and a different one for as-needed supplemental doses), the total daily dose of each should be converted to morphine equivalents using an equianalgesic dosing table (see Table 1). The value for each different opioid should then be added together to get the overall total daily dose in morphine equivalents.

If the patient’s analgesic regimen consists of a single opioid, converting the total daily dose to morphine equivalents is not necessary; however, some experts still advocate doing so since many of the studies upon which equianalgesic data are based used morphine as the comparator opioid.

4. **Calculate new opioid equianalgesic dose**

Once the overall total daily dose of the original opioid(s) has been determined, an equianalgesic dosing table (see Table 1) is used to calculate an approximate equianalgesic dose of the new opioid.

It is important to note that the calculated equianalgesic dose is **NOT** the starting dose of the new opioid, but rather an estimate from which the new opioid starting dose can be derived after considering a variety of factors (see Step 5).

Where the approximate equianalgesic dose in Table 1 is reported as a range, the more conservative value (i.e., the value that results in a lower calculated equianalgesic dose) should generally be used for calculations if there is concern about risk of adverse effects (e.g., in elderly patients and/or those with significant comorbidities). Some opioid analgesics not listed in Table 1 (e.g., buprenorphine, tramadol, tapentadol) will be discussed in Part 2 of this article.

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**Box 1 – Traditional stepwise approach to opioid switching**

1. Select new opioid
2. Determine original opioid total daily dose
3. Convert original opioid dose to morphine equivalents
4. Calculate new opioid equianalgesic dose
5. Calculate new opioid starting dose
6. Select new opioid supplemental/breakthrough dose
7. Monitor patient and titrate new opioid dose

* This step is only required when a patient’s analgesic regimen consists of multiple opioids.

**Box 2 – Novel approach to opioid switching**

1. Reduce original opioid dose by ~10–30% while starting new opioid at initial recommended dose for opioid-naïve patients or at lowest available dose
2. Reduce total daily dose of original opioid by ~10–25% per week while increasing the new opioid total daily dose by ~10–20% per week, based on efficacy/safety (complete switch can generally take place in 3–4 weeks)
3. Provide sufficient immediate-release opioid during switch to prevent withdrawal and/or increased pain

* This approach is purported to be safer than traditional approaches that require the use of equianalgesic dosing tables and may be useful for patients in unmonitored settings.

**Box 3 – Recommendations for dosage individualization**

Apply a "safety factor" dose reduction to the calculated equianalgesic dose

- If the original opioid dose was high, reduce the calculated equianalgesic dose by 50% or more based on clinical judgment
- If the original opioid dose was moderate or low, reduce the calculated equianalgesic dose by 25–40% based on clinical judgment

* Recommendations do not apply to fentanyl and methadone; opioid switching involving these agents will be discussed further in Part 2 of this article.
† The safety factor dose reduction is necessary to account for unpredictable and incomplete cross-tolerance among opioids. Some experts have recommended that, after applying the safety factor dose reduction, a subsequent increase of 15–30% might be warranted based on level of pain or likelihood of withdrawal; however, the Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain does not recommend any such increases.
‡ No standard definition as to what constitutes a "high dose" exists; however, a reasonable definition proposed for high dose opioid therapy is >200 mg/day of oral morphine (or equivalent).
§ Characteristics that may warrant larger reductions include advanced age, significant comorbidities (e.g., cardiopulmonary, hepatic, or renal disease), and non-Caucasian heritage, particularly if more than one of these risk factors for toxicity is present. When switching to a different route of administration using the same opioid, reductions close to the lower end of the range are reasonable.
¶ Within the range of low to moderate doses, larger doses of the original opioid and presence of risk factors for toxicity likely warrant larger reductions in the starting dose of the new opioid. For example, a 25% reduction may be appropriate for a young and otherwise healthy patient originally receiving morphine 40 mg/day, whereas a 33–40% reduction might be more appropriate for an elderly patient originally receiving morphine 90 mg/day. When switching to a different route of administration using the same opioid, reductions close to the lower end of the range are reasonable.
|| No standard definition as to what constitutes a “moderate dose” or “low dose” exists; however, 60–90 mg/day of oral morphine (or equivalent) has been cited as the lowest threshold to be considered a moderate dose.
|| No standard definition as to what constitutes a “low dose” exists; however, a reasonable definition proposed for high dose opioid therapy is >200 mg/day of oral morphine (or equivalent).
¶ Within the range of low to moderate doses, larger doses of the original opioid and presence of risk factors for toxicity likely warrant larger reductions in the starting dose of the new opioid. For example, a 25% reduction may be appropriate for a young and otherwise healthy patient originally receiving morphine 40 mg/day, whereas a 33–40% reduction might be more appropriate for an elderly patient originally receiving morphine 90 mg/day. When switching to a different route of administration using the same opioid, reductions close to the lower end of the range are reasonable.

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† Some experts advise only including immediate-release opioid doses in the calculation of the original opioid total daily dose if the doses are used as regular daily supplements for pain that is generally uncontrolled, but not if they are used only for breakthrough pain that occurs in the setting of otherwise well-controlled pain.
‡ The term “equianalgesic” is somewhat of a misnomer, as truly equal doses of opioids cannot be defined.

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NEW DRUGS/DRUG NEWS Winter 2012/2013
Table 1 – Approximate equianalgesic doses of some opioid analgesics²,8,12–15

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Approximate equianalgesic dose (mg)¹</th>
<th>Oral</th>
<th>Parenteral</th>
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<tr>
<td>Morphone</td>
<td>30</td>
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<td>Hydromorphone</td>
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<td>Oxycodone</td>
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<td>Fentanyl</td>
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<td>0.1</td>
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<td>Methadone</td>
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<td>Not applicable¹</td>
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<tr>
<td>Codeine</td>
<td>200</td>
<td>130</td>
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<tr>
<td>Meperidine</td>
<td>300</td>
<td>75</td>
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</table>

* Equianalgesic doses reported in the literature vary widely.¹⁴
† Doses listed refer to analgesic potency; they should not be used for purposes of estimating psychoactive effects or ability to relieve withdrawal symptoms.⁷
‡ Some evidence indicates directional differences in potency for dose conversions to and from morphine, with morphine being more potent when switching from hydromorphone or oxycodone than when switching to hydromorphone or oxycodone.⁷
§ Some sources suggest that oral hydromorphone may be more potent in the setting of cancer pain (e.g., oral hydromorphone 4 mg = oral morphine 30 mg).²,¹⁶
¶ Parenteral dosage format not available in Canada.
†† Switching from some oral and parenteral opioids to transdermal fentanyl is discussed in detail in the transdermal fentanyl product monographs; see monographs for details. Opioid switching involving fentanyl will be discussed further in Part 2 of this article.
§§ Reported equianalgesic doses vary widely depending upon factors such as the dose and duration of previous opioid therapy; higher previous opioid doses and longer durations of therapy generally require more conservative doses of methadone upon switching. Opioid switching involving methadone will be discussed further in Part 2 of this article.
¶¶ Not recommended for chronic pain management due to risk of accumulation of neurotoxic metabolite.¹⁰

5. Calculate new opioid starting dose

As noted above, the calculated equianalgesic dose should generally not be used as the starting dose for a new opioid in order to prevent unintentional overdose.¹ Individualization of the new opioid starting dose is necessary; recommendations outlined in Box 3 summarize a proposed approach for doing so. It is worth pointing out that dosage individualization is recommended by some experts even when switching routes for the same opioid.¹ In contrast, switches from short-acting to long-acting oral formulations of the same drug (and from one long-acting formulation to another of the same drug) can normally take place using the same total daily dosage according to product monographs for some commonly used agents (e.g., morphine, hydromorphone, oxycodone).¹⁰

The goal is to start the new opioid at a dose that will provide meaningful pain relief (or at least no worsening of pain), but will not cause toxicity or physiological withdrawal symptoms.²,¹⁰ In clinical practice, determining the optimal starting dose of the new opioid is challenging, and recommendations for dosage individualization put a higher priority on risk reduction than on ensuring sufficient analgesia.¹ As such, the use of adequate short-acting supplemental doses, in addition to close monitoring and dose titration, is essential (see Steps 6 and 7).

Once the new opioid starting dose is selected, it is normally administered on a scheduled basis according to the manufacturer’s recommended dosing interval.

6. Select new opioid supplemental/breakthrough dose

In most instances, a short-acting ("immediate-release") opioid should be made available to treat pain not adequately controlled by the regularly scheduled starting dose of the new opioid.¹³ Ideally, patients should use the same opioid for both short- and long-acting doses.¹³ For the majority of opioids¹⁰, a short-acting dose that is 5–15% of the total daily dose may be recommended at an appropriate interval**.¹ One such dose should be offered at least until effective titration of the regularly scheduled dose is achieved.²

7. Monitor patient and titrate new opioid dose

Close patient monitoring and judicious dose titration of the new opioid (both long- and short-acting doses) will help ensure that the new treatment regimen is efficacious and well tolerated.² Follow-up in the first 7–14 days after a switch is particularly important,¹³ and frequent/intense monitoring is often appropriate for patients receiving total daily doses >200 mg of morphine (or equivalent).³ To assist with fine-tuning of the new opioid regimen, patients should keep a diary that details the amount of short-acting medication they use each day, their average daily pain intensity, and the amount of pain relief provided by breakthrough doses.¹³ Adverse effects should also be documented.

Patients and caregivers should be instructed to hold doses and seek medical attention in the event of confusion, excessive sedation, or respiratory depression (the latter warranting emergency assistance).¹²
References


## NEW PRODUCTS/PRODUCT UPDATES

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<th>TRADE NAME</th>
<th>GENERIC NAME</th>
<th>SOURCE</th>
<th>CLASSIFICATION</th>
<th>SUPPLIED/COMMENTS</th>
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<tr>
<td>Apprilon</td>
<td>Doxycycline</td>
<td>Galderma Canada Inc.</td>
<td>Anti-rosacea agent</td>
<td>40 mg modified-release capsules; blister packages of 28</td>
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<td>Arzerra</td>
<td>Ofatumumab</td>
<td>GlaxoSmithKline Inc.</td>
<td>Antineoplastic agent (for chronic lymphocytic leukemia)</td>
<td>20 mg/mL solution for injection (intravenous); packages of 3 x 5 mL (100 mg) and 1 x 50 mL (1000 mg) single-use vials</td>
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<td>Cipralex Meltz</td>
<td>Escitalopram</td>
<td>Lundbeck Canada Inc.</td>
<td>Antidepressant, anxiolytic, antiobsessional</td>
<td>10 mg and 20 mg orally disintegrating tablets; blister packages of 30 and 60</td>
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<td>Divigel</td>
<td>Estradiol</td>
<td>Ferring Inc.</td>
<td>Estrogens</td>
<td>0.1% w/w transdermal gel in single-dose packets of 0.25 g, 0.5 g, and 1.0 g; packages of 30</td>
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<td>Edarbi</td>
<td>Azilsartan medoxomil</td>
<td>Takeda Canada Inc.</td>
<td>Angiotensin II AT, receptor blocker</td>
<td>40 mg and 80 mg tablets; bottles of 30 and 90; blister packages of 28</td>
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<td>Eliquis</td>
<td>Apixaban</td>
<td>Bristol Myers Squibb Canada</td>
<td>Anticoagulant</td>
<td>New Indication: Prevention of stroke and systemic embolism in patients with atrial fibrillation</td>
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<td>New Strength: 5 mg tablets; bottles of 180 and 500; blister packages of 10 and 60</td>
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<td>Herceptin</td>
<td>Trastuzumab</td>
<td>Hoffmann-La Roche Limited</td>
<td>Antineoplastic</td>
<td>Indication Extension: Early stage breast cancer indication now specifies use: (1) following adjuvant chemotherapy consisting of doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel; or (2) in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin</td>
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<td>Humira</td>
<td>Adalimumab</td>
<td>AbbVie Corporation</td>
<td>Biological response modifier</td>
<td>New Indication: For use in combination with methotrexate in moderately to severely active polyarticular juvenile idiopathic arthritis (4–17 years) in patients who have had an inadequate response to ≥1 DMARD; can be used as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is not appropriate</td>
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<td>Inspra</td>
<td>Eplerenone</td>
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<td>Intelence</td>
<td>Etravirine</td>
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<td>New Strength: 25 mg tablets; bottles of 120 (expected availability: May 2013)</td>
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<td>Janumet</td>
<td>Sitagliptin/ metformin</td>
<td>Merck Canada Inc.</td>
<td>Oral antihyperglycemic agent, DPP-4 inhibitor, incretin enhancer</td>
<td>New indication: For use in combination with pioglitazone</td>
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<td>Kalydeco</td>
<td>Ivacaftor</td>
<td>Vertex Pharmaceuticals (Canada) Incorporated</td>
<td>Cystic fibrosis transmembrane conductance regulator</td>
<td>150 mg tablets; bottles of 60; blister packages of 56</td>
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Continued on page VI
## NEW PRODUCTS/PRODUCT UPDATES

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<td>Latuda</td>
<td>Lurasidone hydrochloride</td>
<td>Sunovion Pharmaceuticals Canada Inc.</td>
<td>Antipsychotic</td>
<td>40 mg, 80 mg, and 120 mg tablets; bottles of 30, 90, and 500; blister packages of 100 (hospital unit dose)</td>
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<td>Pradaxa</td>
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<td>Boehringer Ingelheim Canada Ltd.</td>
<td>Anticoagulant</td>
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<td>Prolia</td>
<td>Denosumab</td>
<td>Amgen Canada Inc.</td>
<td>RANKL inhibitor, bone metabolism regulator</td>
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<td>Tamiflu</td>
<td>Oseltamivir</td>
<td>Hoffmann-La Roche Limited</td>
<td>Antiviral agent</td>
<td>New Strength: 6 mg/mL (supplied as powder for suspension [oral]); packages of 1 bottle (390 mg/65 mL after reconstitution)</td>
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<td>Targin</td>
<td>Oxycodone hydrochloride/ naloxone hydrochloride</td>
<td>Purdue Pharma</td>
<td>Opioid analgesic; opioid antagonist</td>
<td>New Strength: 5 mg/2.5 mg tablets; bottles of 60</td>
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<td>Treanda</td>
<td>Bendamustine hydrochloride</td>
<td>Lundbeck Canada Inc.</td>
<td>Antineoplastic (for B-cell non-Hodgkin lymphoma and chronic lymphocytic leukemia)</td>
<td>25 mg and 100 mg powder for solution (intravenous); packages of 1 single-use vial</td>
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<td>Collagenase Clostridium histolyticum</td>
<td>Actelion Pharmaceuticals Canada Inc.</td>
<td>Collagenase Clostridium histolyticum (for Dupuytren's contracture)</td>
<td>0.9 mg powder for solution (intralesional); packages of 1 single-use vial (plus diluent)</td>
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