Rotating Opioids to Manage Chronic Pain

Opioid rotation is the switching of one opioid to another, with the goal of improving analgesia, minimizing adverse effects, and/or reducing the equivalent dose of chronic opioid therapy. A rotation is typically performed when a patient taking extended-release/long-acting (ER/LA) opioids continues to have an indication for opioid therapy, but the current opioid regimen is associated with a problem that can potentially be addressed by rotation.

Why Opioid Rotations Work

How an individual patient responds to a specific opioid depends on both the characteristics of the opioid and the characteristics of the patient:

Opioid Characteristics

- Metabolic pathways and metabolites
- Binding to receptors and subreceptors
- Interactions with other drugs
- Effects not mediated by opioid receptors, such as the effect of tramadol on serotonin and norepinephrine reuptake

Patient Characteristics

- Metabolic enzyme and pathway activity
- Expression of opioid receptors
- Other drugs used
- Medical and psychiatric comorbidities

Given these various characteristics, a patient may have a better analgesic response to one opioid than another; thus, if they switch opioids, they are often able to reduce the morphine milligram equivalents (MMEs) of their regimen while achieving equal or better pain relief. The switch may also result in fewer or less-severe adverse effects, both because of the MME reduction and because of variability in the patient's response to different opioids.

When to Consider Opioid Rotation

Opioid rotation may be helpful or necessary if a patient taking opioids is:

- Experiencing persistent adverse effects;
- Not having an adequate analgesic response;
- In need of a different route of administration than is available for the current opioid (e.g., oral to transdermal or vice versa);
- Experiencing opioid-induced hyperalgesia (paradoxical increased pain due to opioids);
- Taking high-dose therapy, thereby increasing their risk of adverse effects; or
- No longer able to pay for their current medication (or their insurance company has changed their formulary)

What to Consider When Selecting a New Opioid

A number of factors should be considered before choosing the new opioid in a rotation:

- The patient's age, medical conditions, and medication preferences
- The patient's prior experiences with different opioids
- Potential drug interactions based on concurrent medication use
- Known or suspected differences in opioid metabolism among patients, such as the fast vs. slow metabolism of codeine
- Patient predisposition to certain adverse effects (e.g., avoid methadone in patients with preexisting QT prolongation)

Of note, rotating patients on or off methadone requires special care because of the difficulties in calculating equianalgesic doses of methadone. These rotations are therefore typically performed by specialists.

What to Consider When Determining the Opioid Dose

Opioid equivalency charts and calculators are useful in determining the dose of the new opioid, but they:

- Are based on single-dose studies in non–opioid-tolerant, healthy volunteers
- Do not reflect individual patients' genetic makeups, comorbidities, or other drugs used
- Do not reflect the need for dose reductions for incomplete cross-tolerance
- Do not predict individual patient responses to a new opioid

Even when opioid equivalency charts are used and the opioid dose is adjusted based on individual characteristics, opioid rotation comes with a risk of too high of a dose (leading to sedation or overdose) or too low of a dose (leading to pain or withdrawal). Patient counseling is therefore of the utmost importance during an opioid rotation.

Incomplete cross-tolerance: Tolerance to one opioid's sedating or respiratory depressant effects do not extend completely to another, because different opioids exhibit variations in their affinity for various opioid receptor subtypes, and different patients may express different opioid receptor subtypes.

How to Counsel Patients During Opioid Rotation

Before initiating a rotation, inform the patient (and their family/friends) about:

Signs of too high a dose:

- Sedation, "nodding off" during conversation or activity
- Slurred or drawling speech
- Emotional lability
- Ataxia

If the patient experiences any of these signs, they should call immediately for instructions, should not be left alone, and should not take any additional opioid doses.

Sedation occurs before significant respiratory depression and overdose, so it is an important warning sign that the patient should have their dose held and ultimately reduced.

If the patient develops worsening sedation, the family should call 911 and consider administering naloxone if signs of overdose develop.

Signs of overdose:

- Difficult to arouse
- Slowed or stopped breathing
- Dusky lips and nailbeds
- Clammy skin
- Slow, erratic, or no heartbeat
- Pinpoint pupils

If a patient experiences any of these signs, the family should administer naloxone, provide rescue breathing if needed, and call 911.

Signs of withdrawal:

- Sleeplessness
- Restlessness
- Dilated pupils
- Diarrhea
- Goosebumps
- Muscle pain
- Stomach cramping
- Palpitations

Patients experiencing any of these signs should call for instructions.

Remember

Opioid withdrawal symptoms are typically not life-threatening, but overdose is. Be available to the patient for questions and concerns while rotating.

Evaluate the patient about 3 days after starting the new opioid and at intervals thereafter to check for signs of sedation and ensure acceptable pain relief.

Pay especially close attention to patients who:

- Are pregnant or elderly
- Are taking other sedatives, such as benzodiazepines or alcohol
- Have renal or hepatic impairment
- Have cognitive impairment
- Have chronic obstructive pulmonary disease, sleep apnea, or another sleep disorder

How to Conduct an Opioid Rotation

The specific details of any opioid rotation depend on the specific patient scenario. Below we outline the 7 steps typically involved in a rotation, along with a clinical example and sample calculations.*

Steps	Example
Step 1 **Determine the current total daily dose of each opioid taken by the patient.**	A patient taking ER oxycodone 10 mg every 8 hours and immediate-release (IR) oxycodone 2.5 mg five times daily is transitioning to ER hydromorphone. ER oxycodone 10 mg every 8 hours = 30 mg daily IR oxycodone 2.5 mg five times daily = 12.5 mg daily
Step 2 **Convert the total daily dose of each current opioid to morphine milligram equivalents (MMEs), and determine the current total MMEs daily.**	**Conversion factor for oxycodone:** **1 mg = 1.5 MME** ER oxycodone: $30\text{ mg} \times \frac{1.5\text{ MME}}{1\text{ mg}} = 45\text{ MME}$ + IR oxycodone: $12.5\text{ mg} \times \frac{1.5\text{ MME}}{1\text{ mg}} = 18.75\text{ MME}$ **Current total daily opioid dose: 63.75 MME**
Step 3 **Calculate the equivalent daily dose of the new opioid.**	**Conversion factor for hydromorphone:** **1 mg = 4 MME** $63.75\text{ MME} \times \frac{1\text{ mg}}{4\text{ MME}} = 15.9\text{ mg}$ **Equivalent daily hydromorphone dose: 15.9 mg**
Step 4 **Reduce the equivalent daily dose of the new opioid by 25% to 50%.**	Reduce by 25%: $15.9\text{ mg} - (0.25 \times 15.9) = 12\text{ mg}$ Reduce by 50%: $15.9\text{ mg} - (0.5 \times 15.9) = 8\text{ mg}$ **Reduced target daily dose of hydromorphone:** **8 to 12 mg**
Step 5 **Prescribe the reduced target daily dose of the new opioid in appropriately divided doses.**	ER hydromorphone is dosed once daily and is available in 8-, 12-, 16-, and 32-mg tablets. For ease of dosing in this case, prescribe **ER hydromorphone 8 mg once daily.** In addition, prescribe **IR hydromorphone 2 mg as needed, up to twice daily,** during the transition period. Instruct the patient to hold the next dose if sedated and call for adjustment.

Step 6

In 3 to 7 days:

- **Assess the amount of the IR opioid required to manage breakthrough pain.**
- **Add the daily IR opioid requirement to the ER/LA opioid.**
- **The goal is to discontinue the IR opioid once a suitable dose of the ER/LA opioid has been found; non-opioid medications are preferred for breakthrough pain.**

Four days into the rotation, the patient reports that she is taking ER hydromorphone 8 mg once daily and has experienced breakthrough pain requiring two doses each day of the 2-mg IR hydromorphone (4 mg daily).

Total hydromorphone dose:

8 mg + 4 mg = 12 mg

Increase the dose of the ER hydromorphone to 12 mg daily and either discontinue the IR hydromorphone or provide as-needed doses as appropriate.

Step 7

Throughout the rotation process and thereafter, monitor for sedation, adverse effects, and unrelieved pain — and adjust the dosing accordingly.

* These calculations can be performed using online calculators, such as https://globalrph.com/medcalcs/opioid-pain-management-converter-advanced/

Alternative Methods

The practice of opioid rotation continues to evolve. The above method provides a useful framework for performing an opioid rotation, but other methods are available. For example, if a patient is taking high doses of opioids or is at high risk of adverse effects, the clinician may choose a lower dose of the new ER/LA opioid and have the patient rely more heavily on IR opioids in the beginning. Another method involves gradually weaning the patient off the original opioid while at the same time gradually ramping up the dose of the new opioid, thus giving the patient more time to adjust to the new opioid, although insurance coverage restrictions often limit the ability to apply this method. The correct method to use depends on the specific patient scenario; there is no one right approach.

References:

1. Treillet E et al. Practical management of opioid rotation and equianalgesia. J Pain Res 2018; 11:2587.

2. Fine PG et al. Establishing "best practices" for opioid rotation: conclusions of an expert panel. J Pain Symptom Manage 2009 Sep; 38:418.

3. Webster LR and Fine PG. Review and critique of opioid rotation practices and associated risks of toxicity. Pain Med 2012 Apr; 13:562.

Last reviewed Apr 2022. The information included here is provided for educational purposes only. It is not intended as a sole source on the subject matter or as a substitute for the professional judgment of qualified health care professionals. Users are advised, whenever possible, to confirm the information through additional sources.

NEJM
Knowledge+

Copyright © 2022 Massachusetts Medical Society. All rights reserved.