



MCSTAP TIP SHEET FOR INITIATING LONG ACTING OPIOIDS

Author team: James Baker, MD, MPH; Amy Fitzpatrick, MD; Jason Worcester, MD

Introduction: For patients experiencing chronic moderate to severe pain that has responded to opioid analgesics, use of a long acting (LA) opioid for continuous relief with a short acting (SA) opioid breakthrough (aka: rescue) dose for intermittent exacerbations is currently considered an appropriate best clinical practice. This combination of LA and SA opioid formulations is thought to avoid the sawtooth pain relief effect that results from waxing and waning analgesic serum levels associated with the absorption and metabolism of repeated doses of only SA agents. LA/SA combinations of these medications are often used for palliative care in terminally ill patients and, in selected circumstances, are also appropriate to treat persistent, unremitting chronic pain.

Background: When initially introduced decades ago for treatment of chronic non-malignant pain, LA opioids were considered safe when used as directed. However, they were aggressively marketed and often prescribed indiscriminately. Soon some patients learned that if some long acting (LA) / extended release (ER) formulations (e.g., OxyContin) were crushed and ingested (injected or inhaled), this exposed individuals to much higher medication levels which in turn often led to a marked increase in opioid dependence and/or addiction. Many of these medications have been reformulated to reduce the likelihood of misuse. Despite this, it is important to recall that all current misuse deterrent measures can be defeated by committed users. For this reason, all prescribing clinicians must universally and vigilantly monitor for safety risk given the significantly higher risk of dependence and addiction associated with these medications.

Long Acting Opioid Options:

1. Common prescribed medications: Extensive clinical experience, usually more cost effective

Medication	Usual Dosing Interval
Morphine extended release (MSContin, Kadian)	12 – 24 hrs.
Fentanyl transdermal patch (Duragesic)	72 hrs.
Methadone (Dolophine)	8 – 12 hrs.
Oxycodone extended release (OxyContin)	12 hrs.

2. Less commonly used agents (ceiling effect, less clinical experience, high to very high cost)

Medication	Usual Dosing Interval
Buprenorphine transdermal patch (Butrans)	7 days
Tapentadol extended release (Nucynta)	12 hrs.
Tramadol extended release (Ultram ER)	12 hrs.
Hydrocodone extended release (Zohydro)	12 hrs.

Long Acting Dose Conversion Method:

Step One: Convert all current opioid agents to **Morphine Equivalent Daily Dose (MEDD)** per day using an opioid conversion table or calculator. We recommend using [the Oregon Pain Guidance Opioid Medication Calculator](#).

For example, Patient A is prescribed the following medications simultaneously:

- Oral hydrocodone (CR=1:4): 20 mg daily equates to 80 MEDD
- Oxycodone conversion ratio (CR=2:3): 60 mg daily equates to 90 MEDD
- Morphine (CR=1:1); 100 mg daily equates to 100 MEDD

Step Two: Calculate the Total MME daily dose of all prescribed opioids by adding converted MME for each opioid taken per day (24 hrs.). For example, Patient B is prescribed:

- Oral hydromorphone (CR=1:4): 15 mg daily equates to 60 MEDD
- Oral oxycodone (CR=2:3): 20 mg daily equates to 30 MEDD

Add Hydromorphone 60 MEDD & oxycodone 30 MEDD to calculate the Total MEDD (90 MEDD)

Step Three: Divide total MEDD by # of doses/day to calculate MME per dose, so in above example:

Since the patient requires 90 MEDD; divide 90 MEDD by 2 for twice daily dosing which equates to 45 MEDD per dose.

Step Four: Perform the following sub-steps to calculate the dose and frequency of the new opioid to replace.

- A. Select the new opioid medication to be started to replace the two previously prescribed medications
- B. Calculate the MEDD required to replace the existing opioid medications using a conversion table or better the [calculator](#) noted above.

See the following examples to convert 90 MEDD:

- Convert 90 MEDD Morphine (CR=1:1) to 90 Total MEDD, then divided by 2 doses daily equates to Morphine ER 45 mg BID
- Convert 60 MEDD Oxycodone (CR=2:3) to 90 Total MEDD, divide by 3 doses daily, then convert back to Oxycodone using the conversion ratio (CR=2:3) in reverse equates to Oxycodone ER 20 mg TID

Dose Reduction for Incomplete Cross Reactivity: Patients may be less tolerant to different opioids, and many clinicians will reduce initial long acting agent calculated conversion dose by 25-50% with short acting rescue dose available and then titrate up to effect. This is not necessary when merely calculating the dose for a long acting formulation dose of the same opioid. An additional approach to decreasing the dose is to remember that while the patient may have a strong fixed opinion of what the correct dose is for their currently prescribed opioid, they typically have no idea the of the effectiveness of the new opioid that they will be started on. Using this fact, the savvy clinician will take advantage of the placebo effect and set expectation that not only is this a different molecule but that the Clinician is quite optimistic that this new medication will be highly, if not more, effective for their pain. Remind the patient that this is a trial to see how it works and advise the patient to clearly communicate if they detect any issues or have questions during the conversion.

Methadone: Although methadone is not available in an extended release formulation, it is generally considered a "long acting opioid" because of its long half-life of 30-100 hours. Because of the long and somewhat unpredictable half-life of methadone, in the outpatient setting, where close medical supervision is limited at best, it is critical to **start low and go very slow** (< 5 - 10 mg per dose increase) when titrating the dose to desired clinical effect. It is also important to understand that the duration of analgesic effect is typically only 8-12 hours.

Challenges to using methadone effectively for chronic pain management include its: high protein binding, lipid solubility, multiple drug-drug interactions (can cause change in the patient's effective serum levels), as well as possible disease-related impact on the potency and duration of action due to hepatic cytochrome P450 metabolism. For example, hepatocellular impairment from any cause may inhibit cytochrome P450 activity and lead to increased circulating levels of methadone, while acute systemic hypoxia related to respiratory or cardiac insufficiency may up-regulate CYP3A4 activity. Examples of strong CYP3A4 inhibitors are clarithromycin, ketoconazole, and loperamide among many others (inhibitors DECREASE methadone metabolism and INCREASE methadone concentration). Examples of strong CYP3A4 inducers are phenobarbital, phenytoin, rifampicin, and many others (inducers INCREASE methadone metabolism and DECREASE methadone concentration). More detailed information regarding methadone metabolism and drug-drug interaction can be accessed through these open-access articles:

[Actual and Potential Drug Interactions Associated with Methadone](#)

Methadone—metabolism, pharmacokinetics and interactions

Methadone is also known to cause Torsades de pointes typically in the setting, via the mechanism of dose-related development of a prolonged QTc (≥ 500 milliseconds). When prescribing methadone for chronic pain management is considered, we highly recommend that initiation and use only proceed in conjunction with clinicians with at least modest experience in its use.