

**FAST FACTS AND CONCEPTS #358**  
**NON-ORAL ROUTES OF METHADONE FOR ANALGESIA IN PALLIATIVE CARE**  
**Katie Elsass PharmD, Sean Marks MD, Natalie Malone PharmD**

**Background:** Despite its complex pharmacology and its associated stigma from opioid addiction treatment, methadone remains a viable analgesic option for seriously ill adults and children (1-5). Oral methadone is the preferred route of administration and typically can be accomplished via methadone tablets, soluble tablets, or oral solutions of various concentrations. Still, select patients may be unable to tolerate oral methadone. This *Fast Fact* reviews non-oral formulations of methadone. See *Fast Facts* #75, 86, and 171 for additional methadone prescribing information.

**Non-oral Routes:** Of note: methadone has a large volume of distribution and lipophilic properties that causes the medication to accumulate in tissues with repeated doses when administered via any route. This contributes to its association with QTc prolongation and its notoriously long and variable half-life which can range from 8-59 hours. Clinical circumstances, access availability, and the care setting are important factors when selecting the most appropriate non-oral route of methadone administration.

- **Intravenous (IV):** IV methadone can be delivered by intermittent injections, continuous infusion through an indwelling catheter, or a patient-controlled analgesia pump. However, it has a higher incidence of QTc prolongation than oral methadone, likely due to its preservative, chlorobutanol (6). Additionally, conversion from other opioids to IV methadone is complex. Although published dose-conversion guidelines are available for IV methadone (see Table 1 for an example of a more conservative guideline), these guidelines vary and may not be reliable. Because of these risks, the prescription of IV methadone, especially for opioid-tolerant patients being rotated to IV methadone, should be restricted to pain management or palliative care experts with significant methadone management experience (7,8). Other important clinical pearls about IV methadone include:
  - IV onset of analgesia occurs in 10-20 minutes vs 30-60 minutes after oral administration.
  - For opioid-naïve patients, the starting dose of IV methadone is 1.25 to 2.5 mg every 8-12 hours.
  - Discontinue all other scheduled opioids when initiating IV methadone (7,8).
  - The oral to parenteral ratio is 2:1. Therefore 10 mg oral methadone = 5 mg IV methadone. Due to variations in bioavailability, there is no consensus to support one parenteral to oral ratio, although many experts recommend a ratio between 1:1 and 1:1.5.
  - The average wholesale price (AWP) of IV methadone is more expensive than oral tablets. For example, the AWP of IV methadone is \$420.09 for a 20-mL syringe (10 mg/mL) compared to \$32.15 for 100 tablets of 5 mg of methadone (9).
- **Rectal:** When administered rectally, methadone tablets or capsules are typically used, but compounded suppositories and enemas have also been described (10,11). Although associated with local discomfort, especially with repeated dosing, rectal administration has the advantage of preventing the need for infusions systems. Furthermore, rectal methadone is often absorbed within 30 minutes and has a simple and reliable oral to rectal dose ratio of 1:1. Cost, duration of action, and half-life are essentially equivalent with oral methadone (10,11).
- **Subcutaneous (SC):** In palliative care or hospice settings, IV methadone solution can be given SC in patients without an indwelling IV catheter. SC methadone, therefore, has similar risks and costs as IV methadone. Additional considerations include:
  - SC lines should be primed with the concentration of methadone that is being infused.
  - SC methadone has been associated with subcutaneous erythema and edema. However, if appropriate precautions are taken such as rotation of the infusion site every one or two days; diluting the intravenous solution to 5-10 mg/mL at a rate of 2-3 mL/hr; and/or a one-time co-administration of dexamethasone 1-2 mg or local hyaluronidase 150 units, these reactions are usually mild and manageable (12,13).
- **Enteric tubes:** Unlike many long acting opioids, methadone can be given as a solution or a crushed tablet via a nasogastric or gastrostomy tube without compromising effectiveness or duration of action.
- **Transmucosal:** A feasibility study suggested that concentrated oral solution (10 mg/mL) can be used for sublingual or buccal administration effectively (14). Larger studies are still needed and the dose may be limited by volume constraints (1-1.5 mL) (15,16).

- Other: The use of preservative-free parental methadone has been described for epidural administration in the post-operative setting (17,18). However, it may not offer substantial advantage over other routes considering its rapid systemic accumulation. There are also case reports of compounded topical methadone. Larger investigations are needed before either of these routes should be widely prescribed (19).

Daily PO Morphine Equivalent	Suggested PO Methadone Dose	Suggested IV Methadone Dose
< 60 mg	2.5 mg PO q8	1.25 mg IV q8
60 – 199 mg	10:1 ratio. Do not exceed 30 mg as initial total daily dose	20:1 ratio. Do not exceed 15 mg as initial total daily dose.
≥ 200 mg	20:1 ratio. But do not exceed 30 mg as initial total daily dose	40:1 ratio. Do not exceed 15 mg as initial daily dose

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**Author Affiliations:** Ohio Health, Columbus, OH; Medical College of Wisconsin, Milwaukee, WI  
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