

### *Morphine*

- Considered the gold standard in treating pain.
- Beliefs that other drugs act faster, last longer, or have a better balance between effect and adverse effect for a particular patient are not supported by evidence from clinical trials.
- Advantages include its long history of use and commercial availability in a variety of dosing forms.
- Oral bioavailability may vary widely among individuals. Patients not responding to usual doses may benefit from rectal administration.
- Generic controlled-release morphine, MS Contin, and Oramorph are the preferred agents. Kadian is significantly more expensive and does not provide significant advantages over other products.
- Steady state with around the clock dosing of long-acting formulations is typically reached in 1-2 days.
- **Requires dosage adjustment in renal dysfunction.** Morphine has an active metabolite, morphine-6-glucuronide (M6G), that is more potent than morphine and has decreased clearance in patients with severe renal dysfunction. Drug doses should be decreased substantially if creatinine clearance is less than 30 mL/min. In cases of less severe renal dysfunction, careful titration is needed. Smaller doses and longer dosing intervals may be necessary.

### *Transdermal Fentanyl*

- Transdermal fentanyl is an alternative for patients who are unable to take oral medications. This includes patients who have severe nausea or vomiting with oral morphine and/or methadone and prophylactic antiemetics, or patients with hypersensitivity to morphine and/or morphine derivatives.
- Transdermal fentanyl has a lag time of 6-12 hours to onset of action and after initiation.
- Steady state drug levels typically occur within 3-6 days following initial application or a dose change.

## APPENDIX B: DRUG MONOGRAPHS

- Because titration is slow, Transdermal fentanyl is not appropriate for unstable pain states.
- For opioid-naïve patients, begin with 25 mcg/hr and prescribe immediate release morphine for breakthrough pain if indicated. Wait at least 72 hours before assessing response. At that time, if needed, the fentanyl dose may be increased according to the amount of PRN immediate-release morphine needed using the ratio of 90 mg/24 hr of morphine to a 25 mcg/hr increase in fentanyl. Subsequent dose increases should occur no sooner than 6 days after the previous increase.
- Use caution when converting from other long-acting opioids to fentanyl because its relative potency to other opioids has not been definitively established.
- When the patch is removed, a subcutaneous drug depot remains and drug clearance may take up to 24 hours.
- Administration:
  - The patch should be applied to non-irritated and non-irradiated skin on a flat surface of the upper torso.
  - Hair at the application site should be clipped, not shaved.
  - If necessary, the area should be cleansed with water (do not use soaps, alcohol, oils, lotions) and allowed to dry completely before application.
  - Patients should be instructed to avoid applying heat to the application site – via heating pads, hot showers, prolonged direct sunlight, etc. —which can significantly increase drug absorption and toxicity.
  - Patches have been abused via ingestion of contents, application of multiple patches cutaneously, attempts to inject the solution, and volatilization and inhalation of fentanyl from the patch. Used patches should be folded with adhesive sides together and flushed down the toilet or disposed of carefully immediately after removal.
  - Do not cut patches in half. No studies have been conducted to address the pharmacokinetics of administration of non-intact systems.
- Discontinuation
  - Remove the patch and titrate the dose of the new analgesic to provide the appropriate level of pain control.
  - When the transdermal fentanyl patch is removed, a subcutaneous depot remains. Serum fentanyl concentrations decline gradually, falling by 50% in 17 hours (range 13-22 hours) (Prod Info Duragesic(R), 2001).

**Content of TDF Patch**

<b>SIZE (CM)</b>	<b>DOSE (MCG/HR)</b>	<b>FENTANYL CONTENT (MG)</b>
10	25	2.5
20	50	5.0
30	75	7.5
40	100	10.0

***Methadone***

- Over three decades of research has established the safety of methadone.
- Methadone can be used safely for pain when initial doses are small, conversion ratios are adjusted to the previous opioid dose, and dosage is slowly titrated to patient response.
- Methadone can be used for analgesia by any licensed practitioner with C-II prescribing authority.
- Advantages:
  - May have unique properties that make it beneficial in severe neuropathic and opioid-resistant pain states.
  - Excellent oral bioavailability.
  - An inherently long duration of action of at least 8 hours with repeat dosing.
  - Can be delivered down an NG tube.
  - Does not accumulate significantly with renal impairment.
  - May be used in patients with hypersensitivity to morphine and derivatives.
  - May cause less constipation than morphine.
  - Low rates of drug escalation and drug seeking.
  - Inexpensive.
- Pharmacokinetic and pharmacodynamic properties of methadone are complex and incompletely documented. However, the general principles of dosing are similar to other opioids.
- Recent experience suggests that toxicity such as sedation can be avoided with low starting doses and slow titration.

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- Methadone redistributes extensively into muscle and fat after administration. Drug accumulation occurs with repeat dosing, and close monitoring is required.
- Methadone typically takes 5-7 days to reach steady state at a particular dose.
- To minimize the risk of drug accumulation, begin with a PRN dosing regimen, allowing the patient to determine the interval needed between doses. Provide a short-acting agent such as immediate-release morphine for rescue doses. As the patient nears steady state, the amount of rescue doses needed will decrease.
- Duration of action typically ranges between 4 and 8 hours.
- Dose ratios for conversion among opioids have not been systematically studied and large interindividual variability exists. Equianalgesic dose ratios vary according to extent of prior opioid exposure. Methadone's potency increases with increasing prior exposure.
- The best dosing strategy has not been established and each should therefore be individualized. A conservative approach is recommended. Careful monitoring for delayed adverse effects, particularly sedation and cognition, should be performed frequently during conversion.
- Methadone is susceptible to several significant drug interactions. Phenytoin, carbamazepine, rifampin, barbiturates, and a few anti-retrovirals induce methadone metabolism necessitating methadone dose increases or doses larger than anticipated. The azole antifungals and the SSRI and tricyclic antidepressants may increase methadone levels and a dose reduction may be necessary.

### *Oxycodone*

- Reserve for patients who have a documented history of intolerance or failure with long-acting morphine and/or methadone and fentanyl.
- No clinical evidence exists to support claims that OxyContin provides superior analgesia or is better tolerated over other long-acting opioids.
- OxyContin may have a less favorable safety profile and cost:benefit ratio when compared to equianalgesic doses of other agents.
- Some patients report decreased analgesia during the last few hours of the dosing interval. These patients may benefit by decreasing the dosing interval. Prior to doing so, conduct a thorough evaluation of dosing, compliance and pain diary.