

## FAST FACTS AND CONCEPTS #86 METHADONE: STARTING DOSING INFORMATION

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**Background** Methadone is an effective opioid analgesic for severe pain. Because of low cost (a month's supply may be US \$5-10) and apparent efficacy in complex pain syndromes, it is increasingly used as a first-line opioid. Retrospective analyses of consecutive patients initiated on methadone in an outpatient palliative care clinic confirm its effectiveness and safety (1). It is, in effect, a combination drug – part opioid and part NMDA receptor antagonist – although there is yet to be any evidence from controlled trials that it is a superior first-line analgesic to other opioids. Methods of dose conversion to methadone from other opioid analgesics that account for its dual action were discussed in *Fast Fact # 75*. This *Fast Fact* will describe strategies for beginning methadone when the patient has not been taking a strong opioid. **Note:** due to its complex pharmacology, clinicians are advised to seek consultation prior to initiating therapy (see *Fast Fact #171*).

**Pharmacology** Methadone is lipophilic, thus it takes time to develop tissue stores that maintain serum levels. There is enormous interindividual variation in how long this takes. After a single dose there is a short distribution phase (associated with acute pain relief) with a half-life of 2-3 hours and a slow elimination phase (half-life 15-60 hours). Dosing must account for the accumulation of drug over days. It is this accumulation that accounts for most therapeutic misadventures. Liver metabolites are inactive; therefore no dose reduction is required with renal failure. After steady-state is reached, about two-thirds of patients will get adequate pain relief with twice a day dosing. **Note:** a number of drugs will alter methadone metabolism, so there needs to be close follow-up to drug interactions.

There are several approaches to starting methadone for the treatment of pain. All take into account the long-half life of the drug that leads to drug accumulation over days.

### I. Conservative Approach

- a) Begin fixed dose methadone 5 or 10 mg orally bid or tid for 4-7 days.
- b) If incomplete pain relief, increase the dose by 50% and continue for 4-7 days.
- c) Continue increasing dose every 4-7 days until stable pain relief achieved.
- d) **Breakthrough pain:** use an alternative short acting oral opioid with short half-life (e.g. morphine 10 mg) every 1 h PRN for breakthrough pain and to provide pain relief during titration phase. This dose too may need to be titrated based on efficacy.

### II. Loading Dose Approach

- a) **Load:** Start methadone at fixed oral dose (e.g. 5 or 10 mg) q 4h **PRN only**.
- b) **Calculate Maintenance:** On day 8, calculate the total methadone dosage taken over the last 24 hour period and give that in scheduled, divided doses bid or tid. Give 10% of total daily methadone as PRN drug q1h for breakthrough pain. Instruct the patient to call you if they need to use more than 5 breakthrough doses per day. *Example:* if someone took a total of 45 mg methadone on day 7 they would be converted to 15 mg tid scheduled with 5 mg as the prn dose.

**Cardiac Safety** Due to methadone's potential to prolong the QTc interval, an independent expert panel developed five cardiac safety recommendations for clinicians (4):

1. Clinicians should inform patients for the potential risk for arrhythmia before initiating methadone
2. Clinicians should ask about any history of structural heart disease, arrhythmia or syncope
3. Clinicians should obtain a pretreatment ECG to measure the QTc interval as well as a follow up ECG within 30 days, annually, and/or if the dosage exceeds 100 mg/day or an unexplained syncopal event occurs
4. If the QTc > 500 ms, consider discontinuing methadone, reducing the dose, or eliminating cofactors which may raise the QTc unless prognosis is short (i.e. weeks to months).

If the QTc is between 450 ms to 500 ms, the clinician should discuss the risks and benefits with the patient

5. Clinicians should be aware of drug interactions with methadone which could slow its metabolism or prolong the QTc even more.

**References:**

1. Parsons, Henrique A., et al. "Methadone initiation and rotation in the outpatient setting for patients with cancer pain." *Cancer* 116.2 (2010): 520-528.
2. Bruera E, Sweeney C. Methadone use in cancer patients with pain: a review. *J Pall Med.* 2002; 5:127-138.
3. Bruera E, et al. Methadone versus morphine as a first-line strong opioid for cancer pain: a randomized, double-blind Study. *J Clin Oncol.* 2004; 22:185-92.
4. Krantz, Mori J., et al. "QTc interval screening in methadone treatment." *Annals of Internal Medicine* 150.6 (2009): 387-395.

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