



PCSS-Methadone Guidance

Topic: Opioid Treatment Program Methadone Induction Dosing.

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Guideline Coverage

CSAM Guidelines for California Physicians (p.32-34)

<http://www.csam-asam.org/files/GuidelineforPhysiciansWorkinginCA2008.pdf>

CSAT TIP 43 (p.65-70)

<http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat5.section.82907>

Guidelines from Canada, Australia, and Europe also have guidance on safe induction doses.

Europe: Verster A, Buning E. Methadone Guidelines. Vol Directorate General V: Euro-Metwork; 2000.

http://www.aidslex.org/site_documents/DR-0116E.pdf

Australia: Opioid Treatment Program: Clinical Guidelines for methadone and buprenorphine treatment: NSW Public Health Department; 2006.

http://www.health.nsw.gov.au/policies/gl/2006/GL2006_019.html

Canada: Best Practices: Methadone Maintenance Treatment: Health Canada Publications; 2002.

www.hc-sc.gc.ca/hc-ps/pubs/adp-apd/methadone-bp-mp/index-eng.php

OTP Federal Regulations coverage: 42 CFR Part 8.12.

<http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&sid=f50060b97c6e00e1af7c1cd5265fbfb2&rgn=div8&view=text&node=42:1.0.1.1.9.2.1.2&idno=42>

Clinical Questions

1. How should an initial methadone dose be determined?
2. How rapidly can the initial dose be safely raised?
3. How should need for a higher dose be determined in the first week of treatment (before tissue stores have accumulated)?

Background: Mortality related to methadone in patients who are in treatment is highest during the first few days of care.¹⁻³ In fact, mortality in treatment during this time exceeded mortality related to heroin use in one study.⁴ For this reason, safety overrides any other concern during this phase of care. Although most patients eventually stabilize at maintenance doses between 60-120mg,⁵ these doses aren't given on the first day, or even during the first week of outpatient treatment.

Effectiveness of methadone to control opioid dependence is partly based on its long duration of action. This benefit relies on tissue stores that may take three to seven days to develop. This initial phase of treatment before steady state blood levels have been achieved can be frustrating for patients who find that during the induction phase of treatment the beneficial effect of a daily methadone dose may only last for several hours. Clinicians often

feel a sense of urgency to raise the dose to control these symptoms, when the patient may actually need 'more time, not more dose' as tissue pools continue to build.

Methadone metabolism varies: Even known observed tolerance to other opioids may not help to determine initial methadone dose because of large differences in methadone metabolism between individuals. Equi-analgesic conversion tables are based on analgesia achieved after a single dose of medication and are not useful in this setting.⁶ Metabolism of methadone may be slower at first,⁷ and half-life can vary between 2 to 50 hours.⁸ One study showed a 17-fold variation in blood level for a given dose, making a genetic link to blood level based on inherited liver enzyme activity.⁹

Initial opioid tolerance can only be estimated: There is no direct way to measure degree of opioid tolerance on intake day, so clinicians can only estimate high or low opioid tolerance based on history and examination. In the case of heroin, purity can vary substantially based on locale or source. It's not unusual for patients to estimate their daily use as high as three or four grams of heroin daily. Use of concentrated forms of oxycodone or other pharmaceutical opioids may also suggest a high tolerance. Exclusive use of lower potency opioids - such as codeine, hydrocodone or opium – suggests lower tolerance. The presence of withdrawal documents dependence and implies some tolerance, but the severity of withdrawal does not indicate the degree of tolerance.

Opioids of abuse are usually not like methadone: Most abused opioids have rapid onset and short duration. In contrast methadone's peak effect is felt several hours after ingestion, when patients may be more used to a waning effect. Patients may be confused by this, at first thinking that 'nothing is happening'. Later they may feel like 'it's just building and building' and fear overdose. For patients who have never taken methadone, education about methadone's timeline of onset, duration and about the buildup of tissue stores is part of treatment. Patients can be cautioned that they will not achieve full symptom control until they reach steady state, or their 'tank fills up' with methadone. The very same dose given a second day will have greater effect, because it builds upon the tissue stores that were saved from the first day.

Tolerance to early doses can be observed at peak: Oral methadone has a slow onset of action. Effect of a single dose usually peaks around 2-4 hours after ingestion.^{10, 11} If the patient is comfortable at peak, it means the dose is very nearly correct, even if the patient is in withdrawal later because of low tissue stores. If the patient is drowsy or intoxicated 2-4 hours after taking his or her dose, it means the dose should be lowered, because this effect will increase daily until steady state is achieved. If the patient is in visible withdrawal at peak, the dose may be increased. Some clinics are set up to allow a supplemental 5-10mg dose after examining the patient. Others raise the next day's dose.

The 2-4 hour waiting time to evaluation at peak can be difficult to schedule in the clinic, or for patients who have other obligations. Sometimes patients return for a brief visit at peak, other clinics designate a person to interview the patient by phone about how he or she feels or felt yesterday at peak, etc. Information about whether the patient needs an increase or a decrease in dose is impossible to determine without having information regarding signs and symptoms at peak (2-4 hours), unless 5-7 days elapse at a given dose, to allow steady state to be achieved. Because of the lack of tissue stores after a single dose, evaluating the patient at 24 hours after the first dose is not useful in making dose adjustments early in treatment. Because oral onset is slow, evaluating the patient immediately after ingestion provides little useful information regarding dosing needs.

Adequate dose affects outcome: The reason to exert an effort to evaluate the patient at peak of action in spite of inconvenience is that effectiveness of methadone is tied to dose adequacy.¹² Retention in treatment and decrease in illicit opioid use both improve with increasing doses.^{13, 14} Average methadone doses in the US are 60-120mg a day,⁵ and some studies suggest that the minimum therapeutic dose for heroin addiction treatment is 50 - 60mg.^{14, 15} In an outpatient setting it may take several weeks to safely raise the dose to this range.

First dose is usually given during withdrawal: Giving opiates to a patient who is already sedated or under the influence of opiates is potentially more dangerous than giving opiates to someone in visible and measurable opiate

withdrawal. Opiate withdrawal syndrome is not a guide to how much the patient will eventually need, however it is a suggestion that the patient is 'safe to dose' with the initial dose.

There are regulatory constraints on dose: The federal regulations that govern practice in opioid treatment programs limit the maximum initial dose of methadone to 30mg, and the maximum dose on the first day to 40mg. Any deviation from this limit should be carefully justified and documented in the patient record.

Recommendations:

Level of evidence: **Low - observational studies, guidelines and regulations**

Initial daily dose choice:

- For highly tolerant person in withdrawal: 30mg (an additional 10 mg dose can be given on day 1 if physician documents in the medical record that 30 mg was insufficient to suppress opioid withdrawal within 2 to 4 hours after the initial dose)
- For low tolerant person in withdrawal: 10-15mg
- For persons not in severe withdrawal, regardless of estimated tolerance level, the dose is often kept low on the first day, in the 10-15mg range.

Early dose adjustments (first week or 10 days):

- If comfortable at peak, maintain dose for 5-7 days and re-evaluate
- If in withdrawal at peak, increase dose 5-10 mg, and evaluate at peak daily, or maintain new dose 5-7 days and re-evaluate.
- If sedated or intoxicated at peak, reduce next day dose 5-10mg and evaluate daily at peak for continued or increased intoxication.

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PCSS Guidances use the following levels of evidence*:

High = Further research is very unlikely to change our confidence in the estimate of effect.

Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low = Any estimate of effect is very uncertain.

Type of evidence:

Randomised trial = **high**

Observational study = **low**

Any other evidence = **very low**

* Grading quality of evidence and strength of recommendations

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