# Proposing a More Optimal Methadone Induction Strategy

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**Introduction:** Methadone is a long acting opioid with NMDA receptor antagonist properties which has been commonly used for both chronic pain and as a drug detoxification for opioid abuse. Methadone induction is a clinical challenge due to its long and variable half-life [1-4] thus requiring many days to achieve steady state. While only 1% of opioid users take methadone, it accounts for over 20% of opioid-related deaths [5]. While the present recommendations are to titrate slowly, we argue that if a given patient's methadone pharmacokinetics can be estimated, one can more rapidly achieve steady state with an optimal induction dosing strategy.

**Methods:** The appendix outline the induction strategy and involves: 1) estimation of the terminal elimination rate constant, β after a test dose and blood sampling and 2) creating an induction dose by using, in part, the accumulation index [6].

Using Matlab (R2017b), we compared the performance of the induction strategy to standard induction. Patient were simulated with T ½ α between 1.5 and 4.2 hours and T ½ β between 8.5 and 65 hours. The value were randomly selected using a truncated Normal distribution. A test dose was simulated and sampled at the 24 hour and 48 hour interval. The samples were given measurement errors with coefficient of variation of 3% [7]. β was estimated and limited to achieve a T ½ β between 8.5 and 65 hours.

Four different induction sequence were simulated on the same patient at a time: daily dosing, q8h dosing, daily dosing with optimal induction, q8h dosing with optimal induction. The total simulation time was 30 days, sampled every 15 minutes.

The following parameters were measured: time to converge to within 10% of the steady state trough (settling time), maximum blood concentration and time at which it occurred. Analysis was performed with Wilcoxon signed-rank test.

**Results:** 100,000 patients were simulated. Median settling time for the optimal daily and q8h dosing were both 16 hours, which contrasts with the settling time for the standard dosing regimen: 144 hours for daily dosing and 128 hours for q8h ($p < 1E\text{-}16$). Settling time is achieved in 48 hours for 91% and 93.9% of daily and q8h dosing respectively. Figure 1 shows the distribution of settling times for all four regimens. Incidence of overshoot greater than 20% is 0.69% for the daily dosing regimen and 1.5% for q8h dosing. These would occur between the 28$^{th}$ and 32$^{nd}$ hour and 11$^{th}$ and 28$^{th}$ hour respectively

**Conclusion:** The optimal induction strategy for methadone provides a rapid induction with a predictable peak effect. This can potentially decrease the harm caused by either delayed steady state or patient self-medication leading to overdose. Its performance in clinical practice has yet to be determined.

References


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Appendix: Optimal Methadone induction strategy
There are two phases to the induction:

1) After giving a small test dose the patient blood level of R-methadone is measured over the next few days to estimate the terminal elimination rate constant, β (in 1/hour) . At a minimum two blood levels should be measured with enough time between them to have an appreciable change in blood concentration. If two samples are taken, β can be estimated as follows:

$$\beta = \frac{\ln(C(t_1)) - \ln(C(t_2))}{t_2 - t_1}$$

With $C(t_1)$ being the blood concentration of the drug at time $t_1$. For β values at or beyond the margins of a typical population, additional blood samples may be required.

2) The Induction sequence makes use of the accumulation index [6] for periodic drug dosing with a period T (in hours):

$$R_{ac}(\beta, T) = \frac{1}{1 - e^{-\beta T}}$$

For 8 hour dosing (q8h), one multiplies the first dose of the drug by $R_{ac}$ (β,8) and then proceeds with the desired maintenance dose. For daily dosing, while one can multiply the first dose by $R_{ac}$(β,24). Alternatively, to minimize overshoot from model mischaracterization, one can start the first 24 hours by providing three doses every 8 hours as follows:

   a) The initial dose is the maintenance dose multiplied by $e^{-\beta(24-8)} * R_{ac}(\beta, 24)$
   b) The next two doses are multiplied by $e^{-\beta(24-8)} * R_{ac}(\beta, 24)/R_{ac}(\beta, 8)$
   c) All doses thereafter will be the desired maintenance dose

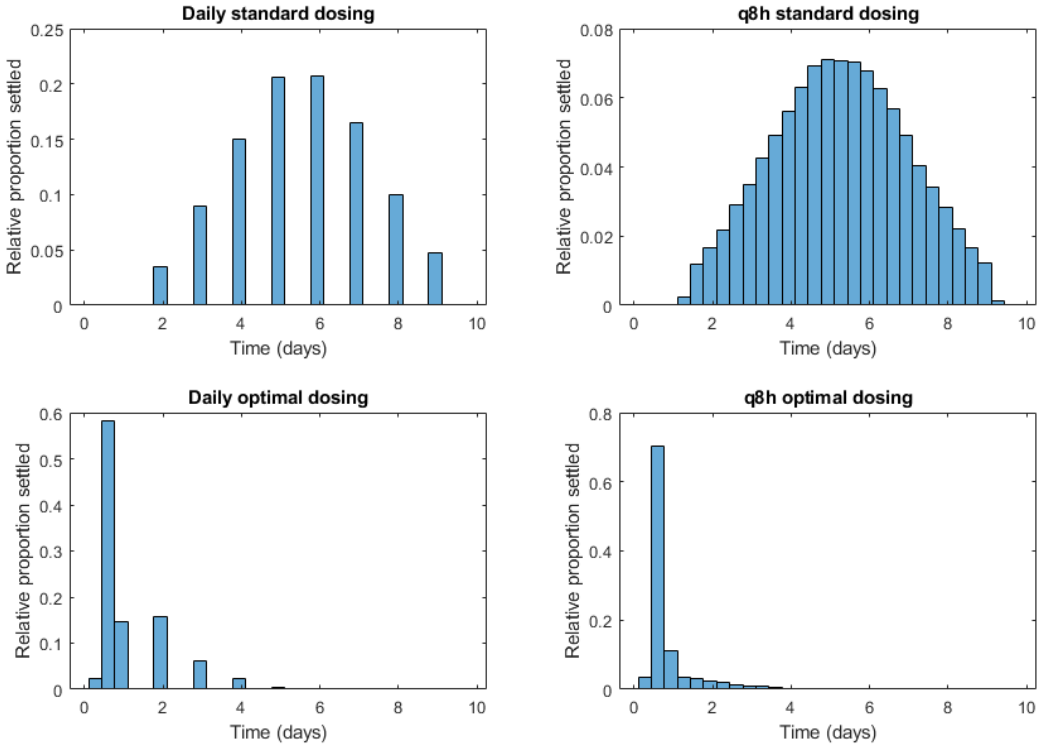


Figure 1: relative histogram of settling time for standard daily dosing, standard q8h dosing, daily dosing with optimal induction, q8h dosing with optimal induction