

A Quantitative Medicine Framework for Optimizing Buprenorphine Dosing in Patients with Opioid Use Disorder: Defining Receptor Occupancy Target Trajectories to Promote Successful Transition from Fentanyl

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Background

Opioid Use Disorder is a chronic relapsing disorder characterized by compulsive use of opioids despite physical, social and psychological harms. Opioid overdose mortality presents a formidable public health challenge driven by contamination of the drug supply with highly potent synthetic opioids such as fentanyl [1].

Buprenorphine is a high-affinity, partial agonist of the μ -opioid receptor, and a commonly prescribed medication to treat individuals with OUD. While buprenorphine can successfully stabilize individuals with OUD, precipitated withdrawal during induction can lead to treatment discontinuation. Buprenorphine induction strategies to minimize risk of withdrawal have been proposed, but quantitative evidence to inform their design are limited. Two general dosing strategies for transitioning patients with OUD from fentanyl to buprenorphine include:

- **Macro-dosing:** characterized by abrupt cessation of nonprescribed opioids and initiation of high dose buprenorphine. This strategy may be preferred in high-risk emergency settings where immediate receptor blockade is required to prevent overdose, though it carries a high risk of precipitated withdrawal as buprenorphine displaces full agonists faster than physiological stimuli can adapt.
- **Micro-dosing:** characterized by continuation or tapering of nonprescribed opioids with gradual escalation of buprenorphine dosage to achieve therapeutic targets while minimizing risk for precipitated withdrawal.

This project aimed to propose a quantitative medicine framework (QMF) to: (i) identify buprenorphine receptor occupancy (RO) target-trajectories which could promote successful transition from fentanyl; and (ii) optimize buprenorphine induction regimens designed to achieve the buprenorphine RO target-trajectories in macro and micro dosing settings.

Methods

The QMF leveraged previously published buprenorphine and fentanyl population pharmacokinetic models [2]. A buprenorphine- μ receptor target-engagement model was developed with positron emission tomography (PET) data describing steady-state buprenorphine RO as a function of dose level and time following washout [3]. Buprenorphine RO target trajectories and induction regimens were optimized using a two-stage optimization process. First, the Non-dominated Sorting Genetic Algorithm (NSGA-II) [4] was used to characterize the Pareto front for buprenorphine- μ RO trajectories with respect to three objective functions:

Objective 1: Minimize the time to therapeutic receptor occupancy (T_{90})

$$f_1(D) = \min\{t \mid \phi_{bup}(t, D) \geq 0.90\} \quad (1)$$

where ϕ_{bup} is the buprenorphine RO and D is the dose required to achieve 90% RO.

Objective 2: Minimize the maximum stimulus deficit ($\max(\psi_t)$)

$$f_2(D) = \min_{t \in [0, T]} \{\max[0, \psi_{baseline} - \psi(t, D)]\} \quad (2)$$

where the stimulus deficit $\psi(t)$ is defined as:

$$\psi(t) = \alpha_{fen} \cdot \phi_{fen}(t) + \alpha_{bup} \cdot \phi_{bup}(t) \quad (3)$$

where α_{fen} , $\phi_{fen}(t)$, α_{bup} , and $\phi_{bup}(t)$ are the intrinsic efficacy (α) and RO (ϕ) of fentanyl and buprenorphine, respectively.

Objective 3. Minimize the velocity of opioid stimulus change ($\max_{t \in [0, T]} \frac{d\psi(t, D)}{dt}$)

$$f_3(D) = \max_{t \in [0, T]} \frac{d\psi(t, D)}{dt} \quad (4)$$

where the velocity of the opioid stimulus $\psi(t)$ is described by:

$$\frac{d\psi(t)}{dt} = \alpha_{fen} \cdot \frac{d\phi_{fen}(t)}{dt} + \alpha_{bup} \cdot \frac{d\phi_{bup}(t)}{dt} \quad (5)$$

For each dosing scenario, a Pareto-optimal RO trajectory was selected based on the clinical priority: macro-dosing favored target-trajectories with a short time to therapeutic RO (T_{90}), while micro-dosing favored target-trajectories with a low maximum velocity of the opioid stimulus change ($\max_{t \in [0, T]} \frac{d\psi(t, D)}{dt}$).

Next, the Bound Optimization by Quadratic Approximation (BOBYQA) algorithm was used to identify the vector of buprenorphine doses which minimized the discrepancy between the model-predicted buprenorphine RO (ϕ_{bup}) and the target-trajectory under specified dosing frequencies (Q6H for macro and Q12H for micro dosing).

$$\mathbf{D} = \{d_1, d_2, d_3, \dots, d_{14}\} \in \mathbb{R}^n \quad (6)$$

where d_i represents the dose (mg) administered at the desired dosing interval.

$$f_1(\mathbf{D}) = \int_0^T [\Phi_{target}(t) - \phi_{bup}(t, \mathbf{D})]^2 dt \quad (7)$$

Conceptual Framework: The Clinical Pharmacology Challenge of Buprenorphine Induction

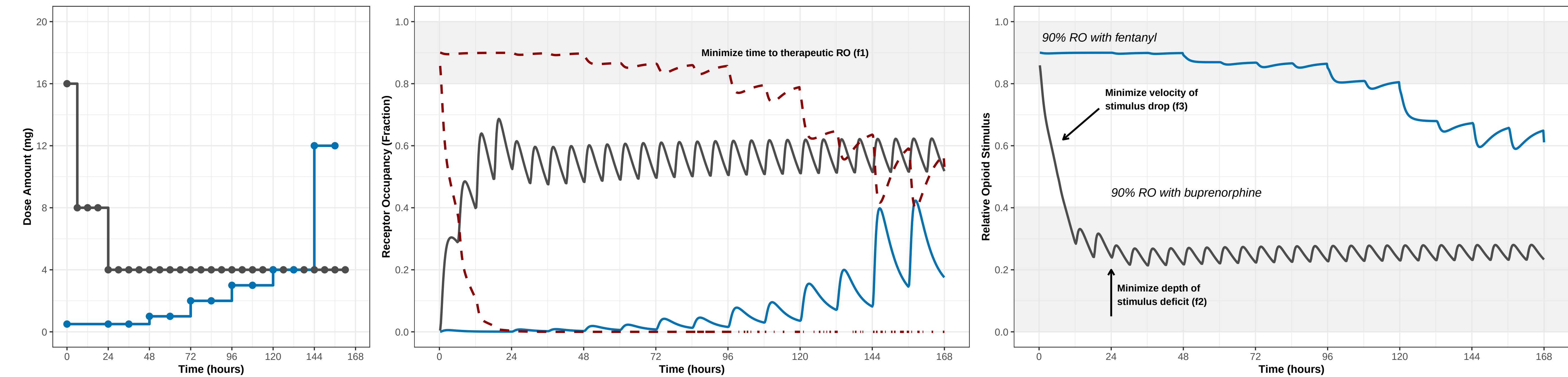
Clinical Pharmacology Challenge:

How should buprenorphine be dosed to safely transition patients with OUD from high-affinity full agonists (fentanyl, $\geq 90\%$ RO) to buprenorphine to minimize risk for overdose, precipitated withdrawal, and loss to followup?

Clinical Pharmacology Innovation:

This work proposes a QMF based on quantitative pharmacology models of buprenorphine and fentanyl, multi-objective optimization to identify buprenorphine RO target trajectories that balance competing clinical objectives, and dose optimizations designed to achieve buprenorphine RO along a temporal target trajectory.

Figure 1. Conceptual overview of the clinical pharmacology challenge of buprenorphine induction in patients with OUD and visual depiction of quantitative objectives proposed by the quantitative medicine framework. The panels illustrate: (1) sublingual buprenorphine dose amounts versus time for macro (Q6H, grey) and micro (Q12H, blue) dosing scenarios; (2) competitive μ -receptor engagement between buprenorphine (grey and blue) and fentanyl (red) (f_1 : time to therapeutic RO), and (3) relative opioid stimulus (f_2 : minimize max depth of stimulus deficit; f_3 : minimize max velocity of stimulus change).



Results: Buprenorphine Target-Engagement and Dose Optimizations to Achieve Receptor Occupancy Target Trajectories

Figure 2. Optimization of buprenorphine- μ receptor target engagement parameters to PET clinical data. A Michaelis-Menten binding model adequately described the relationship between buprenorphine dose levels, steady-state RO, and 72-hour washout. (Top) Comparison of steady-state RO predictions (blue line) and observed RO from PET imaging (red). Comparison of RO decay predictions (blue) and observations from PET imaging (red) following a single 16 mg dose of buprenorphine. The estimated *in vivo* buprenorphine- μ receptor dissociation constant ($K_D = 4.22$ nM) was approximately 20-fold higher than *in vitro* estimates ($K_D = 0.2157$ nM), reflecting lower *in vivo* binding affinity.

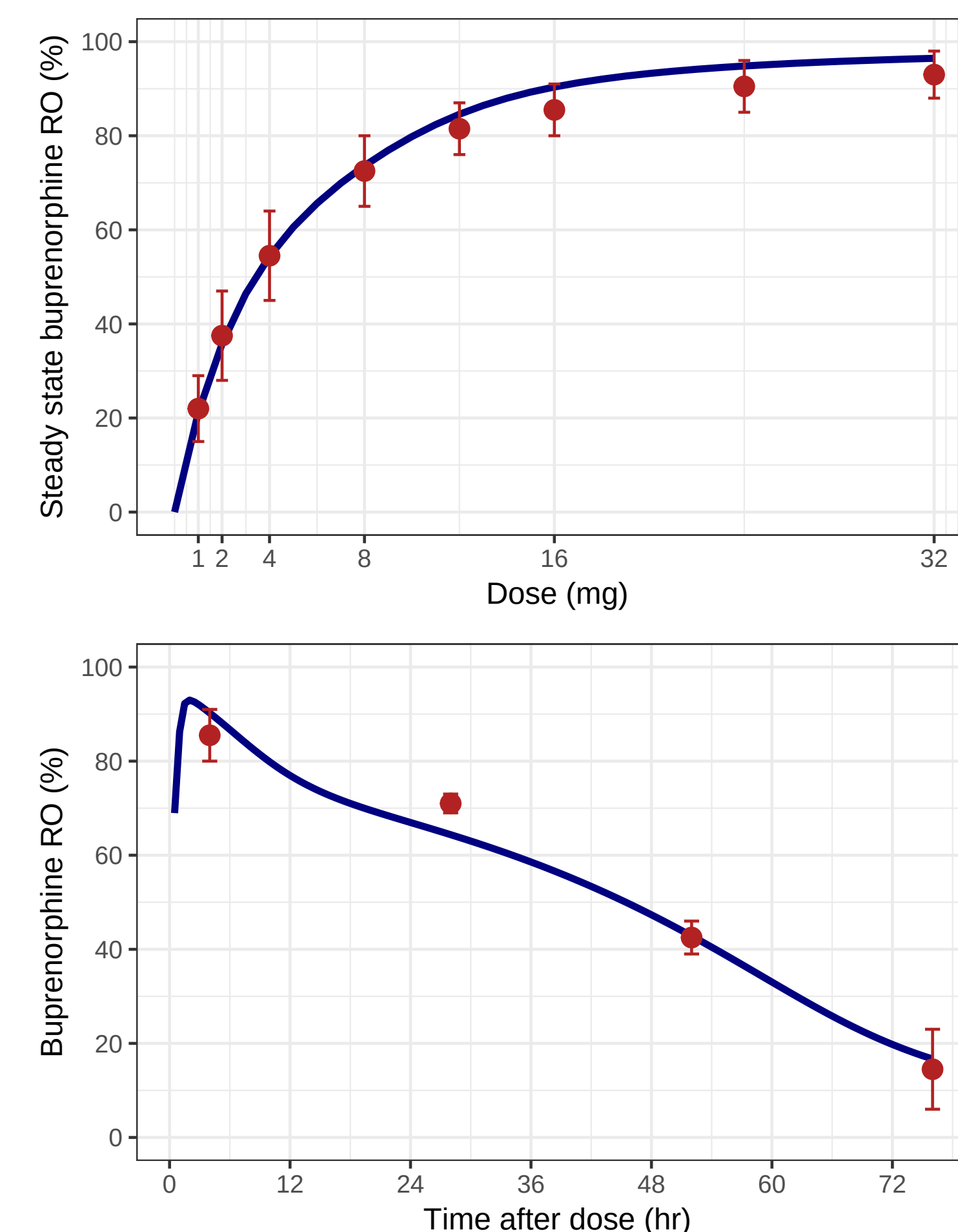


Table 1. Comparison of optimization objectives between reference and optimized induction regimens.

Objective	Dosing Strategy		Objectives Comparison		
	Reference	Optimized	Δ (-)	Δ (%)	Improved?
Macro (Q6H)					
Time to target (hr)	96.0	19.0	-77.0	-80.2	Yes
Stimulus deficit (-)	0.685	0.569	-0.116	-16.9	Yes
Stimulus velocity (1/hr)	-0.108	-0.135	-0.0274	-25.5	No
Micro (Q12H)					
Time to target (hr)	336	194	-142	-42.4	Yes
Stimulus deficit (-)	0.703	0.621	-0.0820	-11.7	Yes
Stimulus velocity (1/hr)	-0.0374	-0.126	-0.0882	-236	No

Figure 3. Optimization of a macro-dosing induction protocol with abrupt cessation of fentanyl. (Top) Sublingual dosing schedule for optimized (blue) and clinical reference (grey) macro dosing protocols. (Middle) Comparison of predicted buprenorphine RO (blue), fentanyl RO (red), and RO target trajectories. (Bottom) Predicted change in relative opioid stimulus versus time.

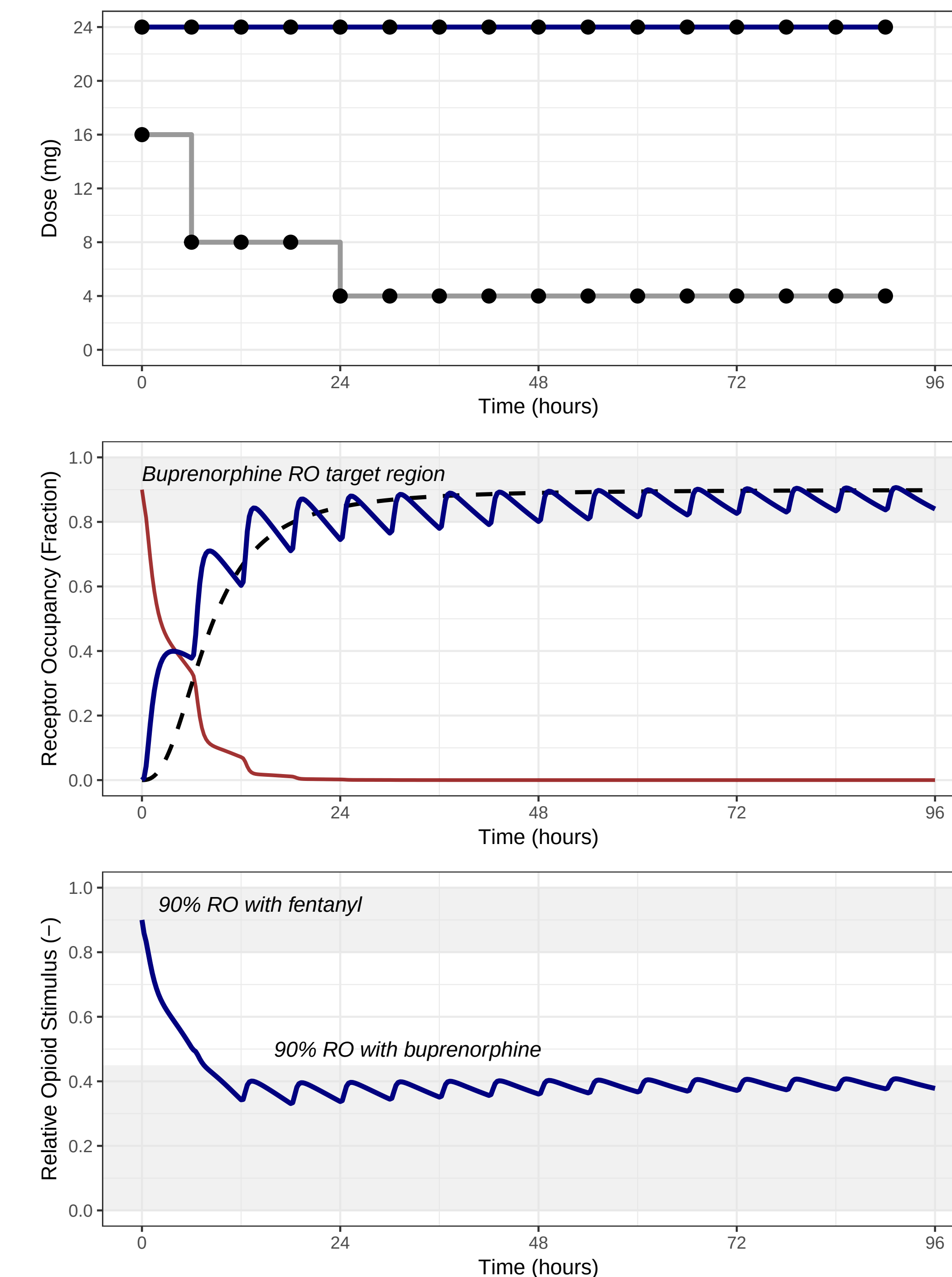
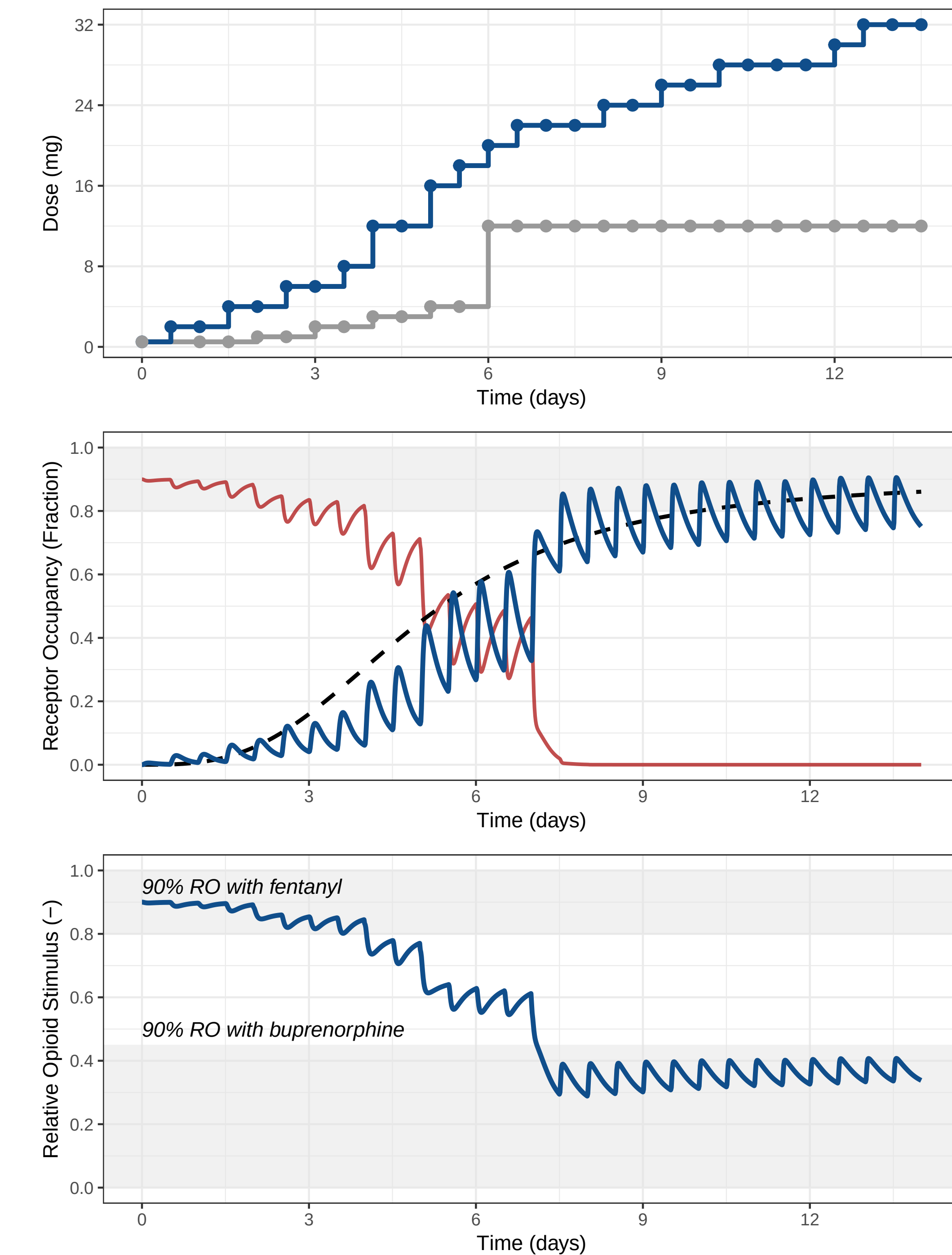


Figure 4. Optimization of micro-dosing induction protocol with fentanyl taper. (Top) Sublingual dosing schedule for optimized (blue) and clinical reference (grey) micro dosing protocols. (Middle) Comparison of predicted buprenorphine RO (blue), fentanyl RO (red), and RO target trajectories. (Bottom) Predicted change in relative opioid stimulus versus time.



Conclusions

A QMF was developed to inform the transition from fentanyl to buprenorphine by balancing competing clinical objectives and identifying RO target trajectories for macro- and micro-dosing strategies. Optimized trajectories suggested substantial dose increases (relative to conventional clinical practice) were needed to achieve the specified RO target. Given the degree of deviation from current practice, further work is needed to understand and evaluate QMF optimized dosage protocols. However, this work establishes a quantitative framework for evaluating alternative buprenorphine induction strategies.

References & MetrumRG Publications and Posters

[1] Strang, J., Volkow, N., Degenhardt, L. Opioid Use Disorder. Nat Rev Dis Primers. (2020). [2] Björnsson, M., Acharya, C., Strandgärden, K., Tiberg, E. Population Pharmacokinetic Analysis Supports Initiation Treatment and Bridging from Sublingual Buprenorphine to Subcutaneous Administration of a Buprenorphine Depot (CAM2038) in the Treatment of Opioid Use Disorder. Clin Pharmacokinet. (2023). [3] Greenwald, M., Comer, S., Fiellin, D. Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy. Drug Alcohol Depend. (2014). [4] Deb, K., Pratap, A., Agarwal, S., Meyarivan, T. A fast and elitist multiobjective genetic algorithm: NSGA-II. IEEE Trans Evol Comput. (2002).

