Integrated Quantitative Systems Pharmacology and Pharmacometric Model to Evaluate Effective Buprenorphine Induction Treatment Strategies in the Era of Synthetic Opioids

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Introduction

- Buprenorphine (BUP) treatment induction has been associated with an increased risk of precipitated withdrawal (PW) in chronic fentanyl users diagnosed with opioid use disorder (OUD).
- Because PW can discourage initiation or continuation of BUP treatment in patients with OUD, we developed an integrated quantitative systems pharmacology (QSP) and non-linear mixed effects model (Figure 1) to understand the factors responsible for the increased incidence of PW in chronic fentanyl users and evaluate BUP induction strategies that minimize PW.

Methods

- A QSP model was developed for BUP and fentanyl, integrating information on opioid pharmacokinetics (PK), mu-opioid receptor (MOR) binding kinetics, MOR tolerance mechanisms, and MOR agonist activity (Figure 2).
- Prior population PK models for intravenous (IV) fentanyl and buprenorphine (IV, sublingual, and subcutaneous extended-release: BUP-XR) were incorporated to predict drug plasma exposure.
- The fentanyl PK model was adapted to include an adipose tissue compartment to investigate the impact of delayed release of lipophilic fentanyl on PW in chronic fentanyl users (Figure 3).
- The QSP model was calibrated using published data on respiratory depression measured after IV administration of fentanyl and BUP, either alone or in combination.
- The relationship between opioid agonist activity (predicted by the QSP model) and withdrawal symptoms measured in patients with the Clinical Opiate Withdrawal Scale (COWS) was estimated by non-linear mixed effects modeling, using data from a clinical study of buprenorphine induction in patients with fentanyl-positive urine tests (NCT04995029).
- Fentanyl doses were assumed to follow a normal distribution with mean 2.2 mg based on a 2021 DEA report. Patients were assumed to take fentanyl IV q3 hours with a 6-hour washout before BUP.

Results

- The integrated model successfully described changes in COWS scores in patients with and without PW following initiation of BUP treatment, as well as the incidence of PW (Figure 4)
- The model suggests the occurrence of PW is related to an abrupt decrease in MOR agonist activity when BUP is initially administered.

A successful BUP induction strategy should account for several factors[4]

- ❖ Residual agonist activity at the time of induction
- ❖ Prior opioid characteristics (lipophilicity, affinity, intrinsic activity)
- ❖ Patient's level of tolerance

Figure 1. Mechanistic Model for Buprenorphine Induction

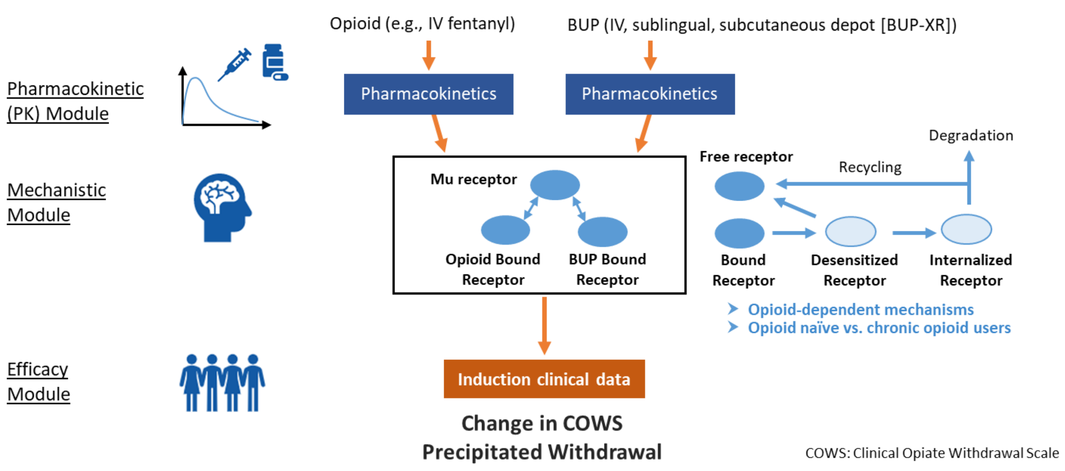


Figure 2. Mechanistic Model Development

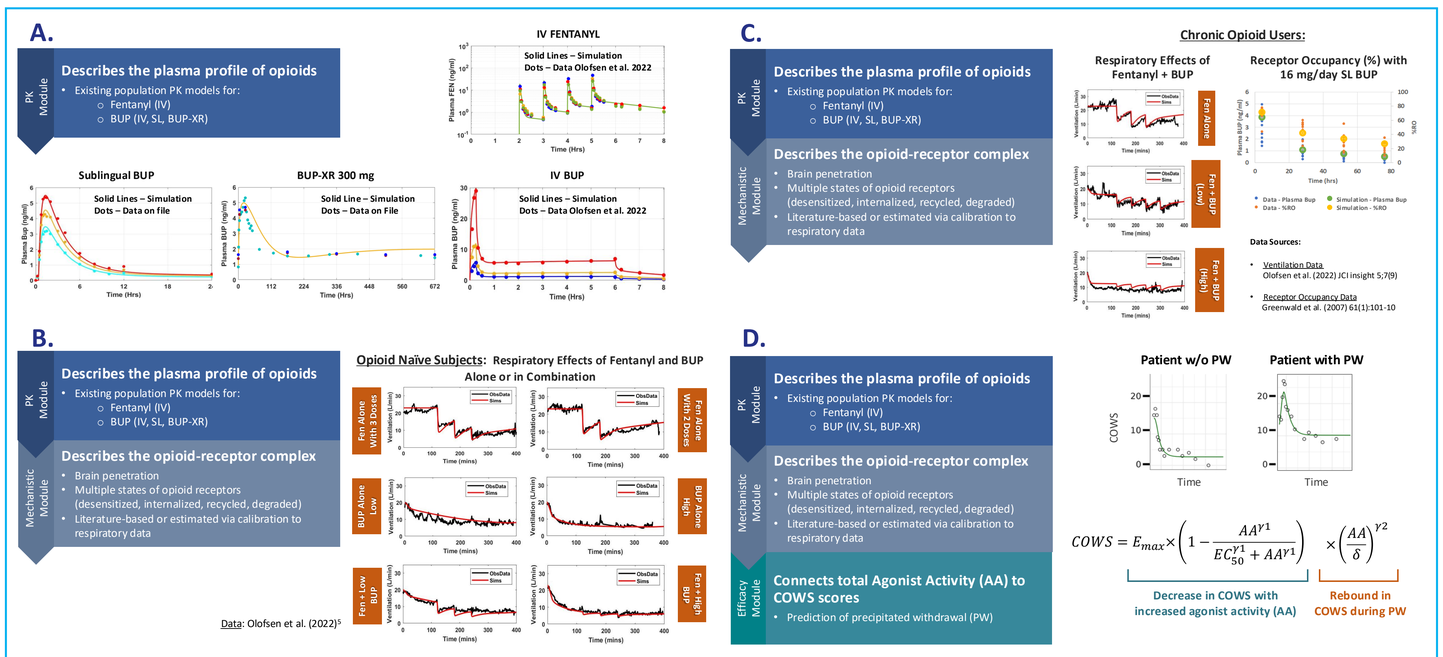
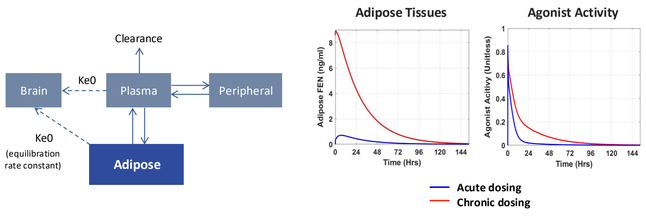


Figure 3. Adjusted Fentanyl PK Model to Account for Re-Distribution from Fat and Slower Elimination After Chronic Dosing

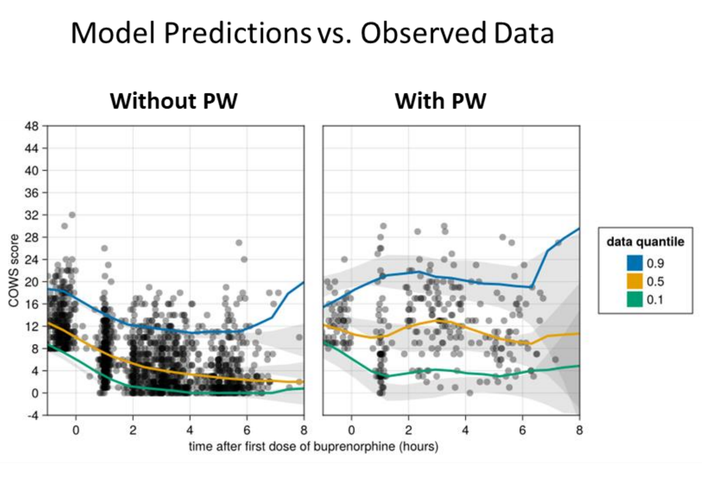
- Adjusted model with an adipose compartment to match the reported plasma half-life of 1 day after chronic fentanyl exposure[6,7]



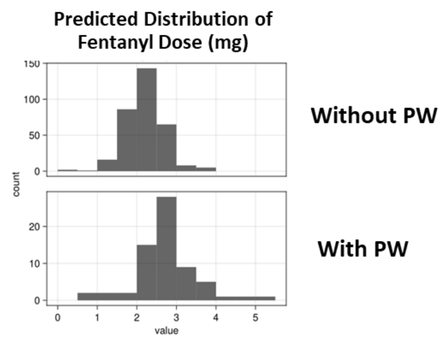
Clinical Data Used for Efficacy Module

- **Patient data**
  - Randomized open-label study (NCT04995029) comparing rapid induction (1 dose of 4 mg SL BUP) and standard induction (≥ 7 days SL BUP) to 300 mg BUP-XR (SUBLOCADE®)
    - Only patients with a COWS score ≥ 8 were eligible for induction
  - Data in 392 fentanyl positive patients with PK and COWS measures available
- **Precipitated withdrawal**
  - Calculated as an increase of ≥ 6[1] on COWS scores with last score ≥ 8

Figure 4. Modeling Results: COWS and Precipitated Withdrawal (PW)



Fraction of Patients with PW (COWS increase ≥ 6 and last score ≥ 8)	
Observed	Predicted (95% CI)
18.1%	17.7% (13.9% - 21.4%)



Conclusions: An integrated model characterizing the effects of fentanyl and BUP on MORs, and COWS scores was developed. This model enables the design and evaluation of improved BUP induction protocols to reduce the risk of PW in chronic fentanyl users while providing adequate MOR agonist activity to motivate patient continuation in maintenance treatment.

Limitations: Fentanyl dose unknown (assumption on distribution). No measures of recent polysubstance use/exposure (e.g. xylazine).

Next Steps: Analyze patients negative for fentanyl (Urine Drug Screening) assuming morphine intake. Validation needed with independent sets of clinical data assessing alternative BUP induction regimens (e.g., micro/macrodosing)

References

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Disclosures

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