# High Plasma Buprenorphine Concentrations Decrease Respiratory Effects of Intravenous Fentanyl

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## Introduction

- The number of U.S. drug overdose deaths exceeded 70,000 in 2017, partially driven by an increase in deaths involving potent synthetic opioids such as fentanyl
- Fentanyl overdose can cause respiratory depression, followed by decreased mental status, brain damage, and death
- Patients who enter medication-assisted treatment programs for opioid use disorder (OUD) have reduced risk of overdose and death but are still often exposed to fentanyl via illicit drug use

**Objective:** To examine the effects of sustained buprenorphine concentrations on respiratory depression induced by intravenous (IV) fentanyl injection

## Methods

- Participants: Opioid-tolerant participants (M/F, 18-55 years old) using opioids at daily doses ≥90 mg oral morphine equivalents

**Study Design**

- Open-label, placebo-controlled, 2-period crossover design
- Participants received placebo + fentanyl during Period 1 (Day 1) and buprenorphine + fentanyl during Period 2 (Day 3) (**Figure 1**)

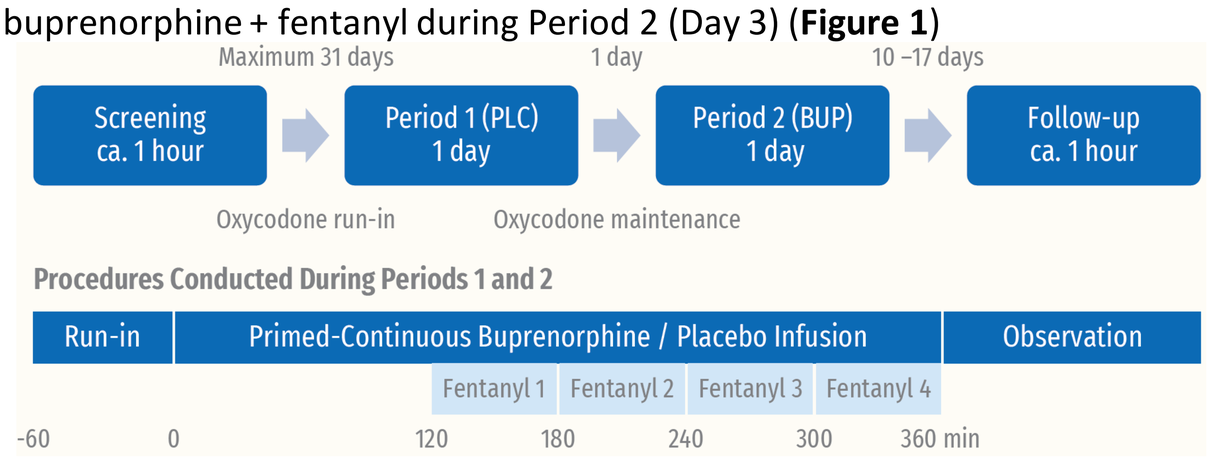



***Fig. 1** Study design, PLC placebo, BUP buprenorphine*

- Minute ventilation (MV) measured at isohypercapnia (baseline MV ~20 L/min)
- Primed-continuous infusion of PLC or BUP for 360 min
- Buprenorphine infusion targeted plasma concentrations of 1 (n=2), 2 (n=3) or 5 ng/mL (n=3)
- IV fentanyl bolus of 250, 350, 500 and 700 mcg/70 kg were administered at 2, 3, 4, and 5 h, respectively (cumulative dose 1800 mcg/70 kg over 4h)
- For these preliminary analyses, drug effects measured as decrease in MV, number/duration of apneic events (lasting >20 seconds), need for ventilatory stimulation and changes in oxygen saturation

## Results

- Eight opioid-tolerant participants were enrolled and received both placebo and buprenorphine infusions

**Placebo period**

- Abrupt declines in MV were generally evident following each fentanyl bolus
- 6 of 8 participants (75%) experienced 1 or more apneic events requiring verbal ventilatory stimulation
- IV fentanyl dose escalation was stopped early after the 2nd (n=2) or 3rd bolus (n=2) in 4 participants because of prolonged apnea or changes in oxygen saturation
- 5 participants had oxygen saturation values <90%

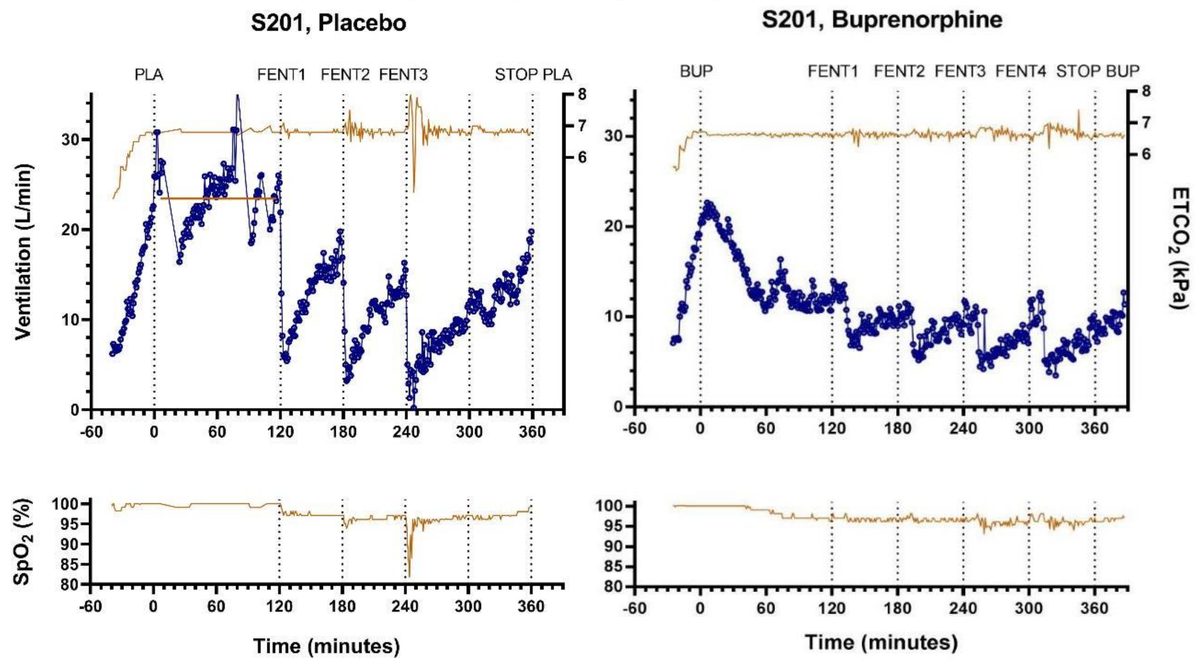
**Buprenorphine period**

- Each participant completed all 4 fentanyl boluses
- Only 1 participant experienced an apneic episode after the 3rd and 4th boluses
- Verbal ventilatory stimulation was not required
- Oxygen saturation did not drop below 90%

**Buprenorphine dose response**

- 1 ng/mL – declines in MV were evident after fentanyl boluses; the 1 participant with apneic events during buprenorphine infusion was in this group
- 5 ng/mL – marked changes in MV did not occur after the fentanyl infusions and repeated apneic events did not occur
- Buprenorphine infusion itself had a visible effect on MV, but no apneic events were observed prior to fentanyl dosing

**A. Low-Dose Buprenorphine (0.1 mg/70kg/hr)**




**B. High-Dose Buprenorphine (0.5 mg/70kg/hr)**

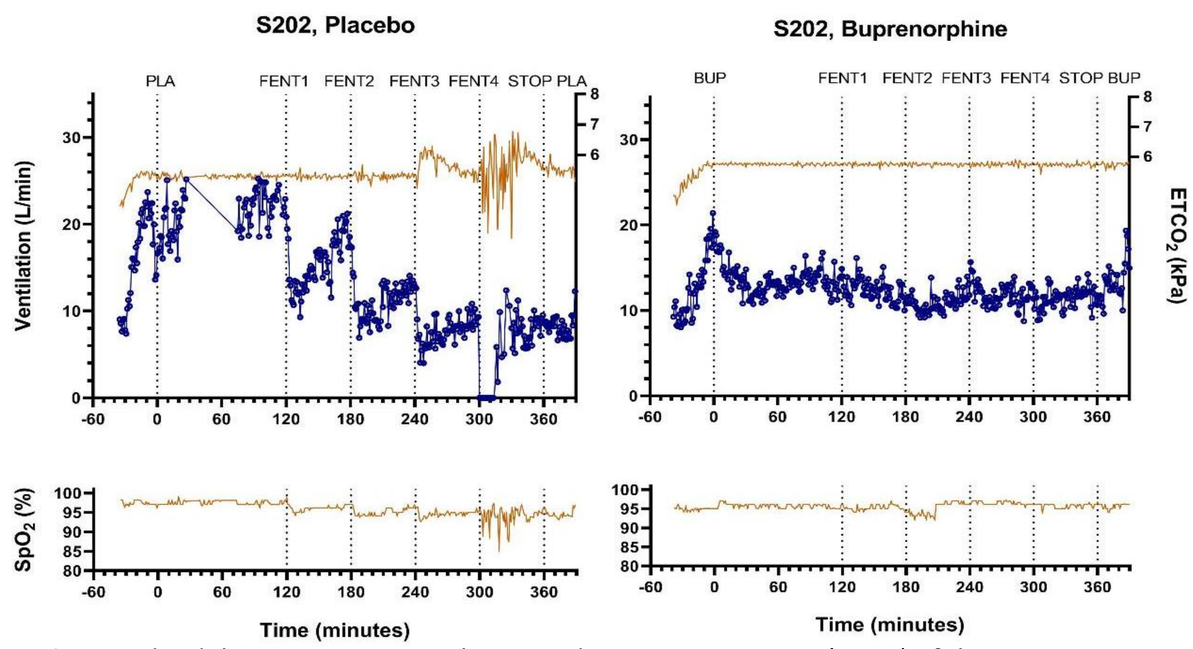



***Fig. 2** End-Tidal CO2, Minute Ventilation and Oxygen Saturation (SpO2) of the First Participant Who Received Low-Dose (A) and High-Dose (B) Buprenorphine With Fentanyl Boluses*

## Conclusions

- These data suggest buprenorphine is a competitive inhibitor of fentanyl boluses up to 700 mcg/70 kg (cumulative dose 1800 mcg/70 kg over 4h)
- Buprenorphine reduces fentanyl-induced respiratory depression, most notably at higher doses and higher concentrations
- Although this is a small patient sample, the potential protective effect consistent across this group of patients warrants additional investigation

**Disclosure** This study was supported by Indivior UK ltd.

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