Table S1. Drug groups and index drugs evaluated

		Index Drugs		
# in class	**Drug Group**	**Drug 1**	**Drug 2**	**Drug 3**
3	Antihistamine	Diphenhydramine		
9	Atypical antipsychotic	Clozapine	Quetiapine	Risperidone
6	Barbiturate	Pentobarbital		
9	*Benzodiazepines*	*Diazepam*	*{positive control}*	
2	Gamma-amino butyric acid (GABA) analogue	Gabapentin		
3	Imidazopyridine	Zolpidem		
3	Mono Amine Oxidase Inhibitors (MAOI)	Tranylcypromine		
2	Serotonin antagonist and reuptake inhibitor (SARI)	Trazodone		
4	Skeletal muscle relaxant	Baclofen	Carisoprodol	Cyclobenzaprine
5	Selective serotonin reuptake inhibitor (SSRI}	Paroxetine		
9	Tricyclic antidepressant	Amitriptyline	Imipramine	
10	Typical antipsychotic	Haloperidol	Thioridazine	
9	Ungrouped drugs	Meprobamate	Dextromethorphan	Mirtazapine
		Bupropion	Duloxetine	Venlafaxine
		Topiramate	Ramelteon	Suvorexant

Gray shading indicates drugs that were excluded from nonclinical evaluation as described in the article because of existing literature regarding respiratory impact, lack of adverse event reports and/or very low prescription use. No highlighting indicates drugs selected for nonclinical evaluation.

Selection of drugs for testing

For the purposes of evaluation, a wide net was cast for drugs that might be used in a psychiatric or neurological treatment regimen, that have a primary effect in the central nervous system (CNS), that might be used in place of a benzodiazepine and may have respiratory effects. Drug candidates were identified from a wide variety of sources including pharmaceutical classes utilized for benzodiazepine indications, specific pharmacological targets implicated in those indications (e.g., serotonergic, GABAergic, and histaminergic systems) and review of drugs with adverse events when co-administered with opioids. All drugs were being marketed in the US as of February 2017. After removal of duplicates, combination products and major anesthetics, there remained a total of 74 specific drugs, including the benzodiazepines. Where possible, the drugs were grouped by pharmaceutical class. These groupings were based on Established Pharmacological Classes, mechanism of action, known receptor binding, and structural similarity analyses. This approach resulted in 12 groups and 9 ungrouped drugs and a total of 27 drugs listed in Supplemental File 1. Following this initial grouping, representative (index) drugs were selected from each group for experimental investigation. Table 1 shows the selected index drugs. These index drugs were selected based on the known scientific information (number of peer-reviewed publications listed in Pubmed at the time of analysis), level of use (five-year outpatient prescription counts (QuintilesIMS, National Prescription Audit), number of adverse events (see sources below) and expert recommendations from FDA medical reviewers with subject matter expertise. For some drug classes, a single index drug was considered representative of the entire class, however in other classes, the experience and expertise of the FDA medical reviewers lead to inclusion of multiple drugs of interest or concern from the same class. Selection of an index drug was not predicated on and has no implication of the relative risk of the index drug compared to other drugs in the same group.

For each of the index drugs and for all the ungrouped drugs, more detailed information was collected from published nonclinical and clinical studies, product labeling, and drug usage data in February 2017. In addition, adverse event data were obtained from several sources: 1) Empirica Signal is a software program that aids in post-marketing safety surveillance by computing statistics on FDA Adverse Event Reporting System cases (Empirica Signal ver Feb 2017, Oracle, Austin, TX). Empirica Signal utilizes both Empirical Bayes Geometric Mean (EBGM) and the lower 90% confidence interval of this statistic, EB05, for safety signal detection. For this study, an EB05 score greater than 1.0 and EBGM greater than 2.0 was used to identify potential associations with respiratory depression in each the 74 drugs of interest. Additionally, combinations with the opioids morphine, fentanyl, sufentanil, tramadol, hydrocodone, hydromorphone, oxycodone, oxymorphone, and remifentanil were also evaluated. 2) the National Poison Data System (NPDS) is a database that contains all reports received by poison centers around the United States (Gummin et al, 2020). Report counts were obtained for fatal cases of at least one of the 74 drugs of interest in combination with one or more opioids from January 2000 – February 2017. For each drug of interest, individual report counts were divided by the total number of reports for all drugs in the dataset to obtain the percentage of reports. 3) the Toxicology Investigators Consortium (ToxIC) database is a voluntary registry containing reports of patients from medical toxicology practice sites around the country [Wax 2011]. Report counts were obtained for fatal cases of at least one of the 74 drugs of interest in combination with one or more opioids from 2010 – 2016. For each drug of interest, individual report counts were divided by the total number of reports for all drugs in the dataset to obtain the percentage of reports.

Information about the index drugs was evaluated to establish the strength of the integrated evidence for the effect on respiratory parameters including during co-administration with opioids. The drugs were placed into four groups, three of which were excluded from further consideration for prospective laboratory studies. An information summary that was the basis for these decisions for each of the selected drugs is located below.

Twelve of the identified index drugs were excluded from prospective laboratory studies because in the authors' opinion there was:

1. Sufficient existing evidence of respiratory effect: pentobarbital, gabapentin, amitriptyline and imipramine
2. Sufficient existing evidence of no respiratory effect: diphenhydramine, haloperidol, thioridazine, dextromethorphan and bupropion
3. Other miscellaneous reasons for exclusion: tranylcypromine (co-use unlikely due to serotonin syndrome, very low usage and no adverse event signal); meprobamate (very low usage and sufficient text in the FDA label); venlafaxine (very similar to another SNRI duloxetine)

Individual Drug Information Used for Decision Making

Background information on selected index drugs including opinion or rationale for including or excluding for testing in the rat model.

Antihistamine – Diphenhydramine

Nonclinical: In a nonclinical study in dogs and rats, IV Gamma-Aminobutyric Acid (GABA) caused an increased respiratory rate without modifying PO_2 or PCO_2. Treatment with diphenhydramine at 10 mg/kg (human equivalent dose (HED) 85 mg/kg rat, 5 mg/kg dog) did not alter the effect of GABA on respiratory parameters (Billingsley & Suria 1982).
Clinical: Diphenhydramine at a dose of 100 mg had no effect on respiratory depression in humans (Saarialho-Kere et al, 1989). Among 136 patients who attempted suicide with diphenhydramine, respiratory depression is listed as a 'less frequent' symptom (Koppel et al, 1987). No information was located on the effect of diphenhydramine in combination with an opioid.

Diphenhydramine

Label Text	"**Information for Patients:** Patients taking diphenhydramine hydrochloride should be advised that this drug may cause drowsiness and has an additive effect with alcohol. **Drug Interactions** Diphenhydramine hydrochloride has additive effects with alcohol and other CNS depressants (hypnotics, sedatives, tranquilizers, etc.)."
Clinical	50 mg IV (0.8 mg/kg)

Dose	
AE Data	FAERS: Diphenhydramine alone (EBGM: 3.6; EB05: 2.8) and in combination with opioids: EBGM: 2.3 – 8.1; EB05: 1.6 – 5.7 NPDS: Diphenhydramine represented 1.1% of our pulled cases.
Opinion	Massive OTC use; No Action Indicated (NAI), sufficient evidence of no effect on respiratory parameters.

Atypical antipsychotic – Clozapine No direct data on respiratory depression in nonclinical or clinical studies. No information located on effect in combination with an opioid.

Clozapine

Label Text	No relevant text identified
Clinical Dose	400 mg (6.7 mg/kg)
Prescription Count	9.1 million
AE Data	FAERS: Clozapine alone (EBGM: 2.1; EB05: 1.8) and in combination with opioids: EBGM: 3.9 – 4.8; EB05: 2.5 – 3.2 NPDS: Clozapine represented 0.1% of our pulled cases.
Opinion	Candidate for rat studies

Risperidone: No direct data on respiratory depression in nonclinical or clinical studies. No information located on effect in combination with an opioid.

Risperidone

Label Text	**7.2 Pharmacodynamic-related Interactions** **Centrally-Acting Drugs and Alcohol** Given the primary CNS effects of risperidone, caution should be used when RISPERDAL is taken in combination with other centrally-acting drugs and alcohol.
Clinical Dose	5 mg (0.08 mg/kg)
Prescription Count	62.8 million
AE Data	FAERS: Risperidone in combination with tramadol: EBGM: 2.8; EB05: 1.8 NPDS: Risperidone represented 0.8% of our pulled cases
Opinion	Candidate for rat studies

Quetiapine: No clear data on respiratory depression in nonclinical or clinical studies. No information located on effect in combination with an opioid. There is limited evidence of respiratory depression with both atypical antipsychotic drugs in overdose/abuse patients (Ciranni et al, 2009).

Quetiapine

Label Text	"7 DRUG INTERACTIONS: … Given the primary CNS effects of SEROQUEL, caution should be used when it is

	taken in combination with other centrally acting drugs."
Clinical Dose	50 mg TID (0.8 mg/kg each)
Prescription Count	93.0 million
AE Data	FAERS: Quetiapine alone: EBGM: 2.6; EB05: 2.2 NPDS: Quetiapine represented 1.0% of our pulled cases
Opinion	Candidate for rat studies

Barbiturate – Pentobarbital

Nonclinical: Evidence of respiratory depression in rats at 40 mg/kg (HED 5.7 mg/kg) (Field et al, 1993) and in humans (30 mg) (Gasser et al, 1975) is sufficient. Direct evaluations of the combination of pentobarbital with an opioid have not been identified.

Clinical: An indirect measure is that pentobarbital was used for sedation in children with fentanyl being the second line drug commonly used with pentobarbital if a stronger effect was needed (Egelhoff et al, 1997). Mild respiratory depression was noted in 0.79% of the 6006 patients in this series and was most commonly associated with enlarged adenoids or with a mild upper respiratory tract infection.

Pentobarbital

Label Text	"WARNINGS: . . . 5. Synergistic effects: The concomitant use of alcohol or other CNS depressants may produce additive CNS depressant effects. PRECAUTIONS: . . . 3. Alcohol should not be consumed while taking barbiturates. Concurrent use of the barbiturates with other CNS depressants (e.g., alcohol, narcotics, tranquilizers, and antihistamines) may result in additional CNS depressant effects. CLINICAL PHARMACOLOGY: . . . Barbiturates are respiratory depressants. The degree of respiratory depression is dependent upon dose. With hypnotic doses, respiratory depression produced by barbiturates is similar to that which occurs during physiologic sleep with slight decrease in blood pressure and heart rate."
Clinical Dose	150 mg IM (2.5 mg/kg)
Prescription Count	835 prescriptions, 13.9 million for phenobarbital (now off market), the rest of the marketed barbiturates have prescription counts in the hundreds to low thousands.
AE Data	FAERS: Pentobarbital alone: EBGM: 6.5; EB05: 3.1
Opinion	Existing clinical and nonclinical data sufficient for direct effects. NAI due to low usage.

Benzodiazepine – Diazepam

Nonclinical: In the rat, diazepam has no effect on PO_2 or on PCO_2 at a dose of 20 mg/kg sc (HED 2.9 mg/kg). Treatment with methadone at 5 mg/kg IP causes significant respiratory depression (+7 mm Hg PCO_2) and the combination of diazepam and methadone causes significantly greater respiratory depression than methadone alone (+15 mm Hg PCO_2). An effect on PO_2 was also observed but was of lesser magnitude (McCormick et al, 1984). Similar findings have been reported in rats treated with midazolam, buprenorphine and their combination (Gueye et al, 2002). A more complex picture is seen in a study evaluating several benzodiazepines alone or with buprenorphine. Oxazepam, nordiazepam and bromazepam, but not clonazepam significantly increased the AUC of $PaCO_2$. Buprenorphine alone also significantly increased the AUC of $PaCO_2$. The combination of buprenorphine with any one of the benzodiazepines did not significantly increase the AUC of $PaCO_2$ above the effect of buprenorphine alone (Pirnay et al, 2008). A different dimension of complexity is shown in a study where a low dose (1 nmol) of alprazolam potentiated the respiratory depression caused by dermorphin but antagonized the depression at a higher dose (3 nmol) (Paakkari et al, 1993).

Clinical: Ample evidence exists concerning the ability of diazepam to induce respiratory depression in humans. Two such studies will be mentioned. Children admitted to hospital for seizures were studied, of 111 cases treated with diazepam, respiratory depression was seen in 11 cases (9%) of whom eight required ventilation (Norris et al, 1999). In another study, diazepam and phenobarbital were compared in adult patients being treated for delirium tremens. Respiratory depression was observed in 4% of the patients treated with phenobarbital and in 1% of patients treated with diazepam (Michaelsen et al, 2010).

Diazepam

Label Text	"Black Box Text: **WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS** Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death (see Drug Interactions). • Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. • Limit dosages and durations to the minimum required. • Follow patients for signs and symptoms of respiratory depression and sedation. **WARNINGS** Concomitant use of benzodiazepines, including Valium, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for

	whom alternative treatment options are inadequate. Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe Valium concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. In patients already receiving an opioid analgesic, prescribe a lower initial dose of Valium than indicated in the absence of an opioid and titrate based on clinical response. If an opioid is initiated in a patient already taking Valium, prescribe a lower initial dose of the opioid and titrate based upon clinical response. Advise both patients and caregivers about the risks of respiratory depression and sedation when Valium is used with opioids. Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the opioid have been determined (see Drug Interactions). **Drug Interactions** Opioids The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at $GABA_A$ sites and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Limit dosage and duration of concomitant use of benzodiazepines and opioids and monitor patients closely for respiratory depression and sedation."
Clinical Dose	2 mg TID (0.33 mg/kg)
Prescription Count	73.0 million, 244.9 million for alprazolam
AE Data	FAERS: Diazepam alone (EBGM: 17.1; EB05: 15.5) and in combination with opioids: EBGM: 2.0 – 16.1; EB05: 1.4 – 11.1 NPDS: Diazepam represented 7.5% of our pulled cases ToxIC: Diazepam was present in 4 of 55 cases of multi-agent fatalities involving opioids
Opinion	*Positive control for rat studies*

GABA analog – Gabapentin

Nonclinical: A useful study in rabbits has measured the effect of gabapentin individually and in combination with morphine (Kozer et al, 2008). Animals

pretreated with gabapentin at 25 mg/kg (HED 8 mg/kg) and then injected with morphine at 5 mg/kg (HED 1.6 mg/kg) had a significantly larger increase in $PaCO_2$ as compared to rabbits pretreated with saline and then injected with morphine. The effect was significant only at 10 and 30 minutes after injection of morphine. The magnitude of the gabapentin effect was smaller (~5 mmHg $PaCO_2$) than the effect of the morphine (~15 mmHg $PaCO_2$) at the doses tested.
Clinical: Several studies have looked at the association between gabapentin as part of surgical anesthesia and post-operative respiratory depression. Two small studies (Bang et al, 2010; Durmus et al, 2007) found no association. However, a large study (8670 patients) found an increased risk of respiratory depression when gabapentin was used, OR 1.47 (95%CI: 1.22, 1.76) (Cavalcante et al, 2016).

Gabapentin

Label Text	"7.2 Opioids Hydrocodone Coadministration of NEURONTIN with hydrocodone decreases hydrocodone exposure [see Clinical Pharmacology (12.3)]. The potential for alteration in hydrocodone exposure and effect should be considered when NEURONTIN is started or discontinued in a patient taking hydrocodone. Morphine When gabapentin is administered with morphine, patients should be observed for signs of central nervous system (CNS) depression, such as somnolence, sedation and respiratory depression [see Clinical Pharmacology (12.3)]."
Clinical Dose	300 mg TID (5 mg/kg each)
Prescription Count	254.0 million
AE Data	FAERS: Gabapentin alone (EBGM: 4.0; EB05: 3.4) and in combination with opioids: EBGM: 2.2 – 8.5; EB05: 1.3 – 6.6 NPDS: Gabapentin represented 4.9% of our pulled cases ToxIC: Gabapentin was present in 6 of 55 cases of multi-agent fatalities involving opioids
Opinion	Nonclinical data sufficient

Imidazopyridine – Zolpidem
Nonclinical: No nonclinical research on the effects of zolpidem on respiratory parameters was identified.
Clinical: In a healthy volunteer study, no effect on mean inspiratory drive was seen a 5 or 10 mg doses while a statistically significant decrease was seen with 20 mg at 2 hours only. No change on pCO_2 parameters was observed (Cohn, 1993). In a study of COPD patients treated with 10 mg doses, no changes in respiratory parameters

was observed and pCO_2 and pO_2 on awakening were not altered (Girault et al, 1996).A few case reports of respiratory depression have been published related to suicide attempts (Hamad & Sharma, 2001).

Zolpidem

Label Text	"**5 WARNINGS AND PRECAUTIONS:** **5.1 CNS Depressant Effects and Next-Day Impairment** AMBIEN, like other sedative-hypnotic drugs, has central nervous system (CNS) depressant effects. Co-administration with other CNS depressants (e.g., benzodiazepines, opioids, tricyclic antidepressants, alcohol) increases the risk of CNS depression. **5.6 Respiratory Depression** Although studies with 10 mg zolpidem tartrate did not reveal respiratory depressant effects at hypnotic doses in healthy subjects or in patients with mild-to-moderate chronic obstructive pulmonary disease (COPD), a reduction in the Total Arousal Index, together with a reduction in lowest oxygen saturation and increase in the times of oxygen desaturation below 80% and 90%, was observed in patients with mild-to-moderate sleep apnea when treated with zolpidem compared to placebo. Since sedative-hypnotics have the capacity to depress respiratory drive, precautions should be taken if AMBIEN is prescribed to patients with compromised respiratory function. Post-marketing reports of respiratory insufficiency in patients receiving 10 mg of zolpidem tartrate, most of whom had pre-existing respiratory impairment, have been reported. The risk of respiratory depression should be considered prior to prescribing AMBIEN in patients with respiratory impairment including sleep apnea and myasthenia gravis."
Clinical Dose	5 or 10 mg (0.08 or 0.17 mg/kg)
Prescription Count	194.7 million
AE Data	FAERS: Zolpidem alone: EBGM: 5.2; EB05: 4.4 NPDS: Zolpidem represented 4.0% of our pulled cases ToxIC: Zolpidem was present in 2 of 55 cases of multi-agent fatalities involving opioids
Opinion	Candidate for rat study

MAOI – Tranylcypromine

Nonclinical: A single nonclinical study in decerebrate cats studied the ability of tranylcypromine (5 mg/kg, HED 1.65 mg/kg) to modulate morphine-induced (2 mg/kg, HED 0.66 mg/kg) respiratory depression. In this model the data showed that

the MAOI stimulated both resting respiration and the response to CO_2. The values in dual-treated cats were not distinguishable on an absolute basis from the response to morphine alone (Florez et al, 1972).
Clinical: No direct information was identified on the ability of this drug to directly affect respiration in humans. The most common serious interaction between MAOI and opiates is serotonin syndrome which has been well documented and will not be further discussed (Gillman 2005).

Tranylcypromine

Label Text	"**CONTRAINDICATIONS: PARNATE is contraindicated: . . .** **8. In combination with meperidine** Do not use meperidine concomitantly with MAO inhibitors or within 2 or 3 weeks following MAOI therapy. Serious reactions have been precipitated with concomitant use, including coma, severe hypertension or hypotension, severe respiratory depression, convulsions, malignant hyperpyrexia, excitation, peripheral vascular collapse, and death. It is thought that these reactions may be mediated by accumulation of 5-HT (serotonin) consequent to MAO inhibition. ADDITIONAL CONTRAINDICATIONS In general, the physician should bear in mind the possibility of a lowered margin of safety when PARNATE is administered in combination with potent drugs. PARNATE should not be used in combination with some central nervous system depressants such as narcotics and alcohol, or with hypotensive agents. A marked potentiating effect on these classes of drugs has been reported."
Clinical Dose	10 mg TID (0.17 mg/kg each)
Prescription Count	0.19 million
AE Data	FAERS: Tranylcypromine alone: EBGM: 0.9; EB05: 0.2
Opinion	Co-usage likely low due to serotonin syndrome issue. NAI due to low usage

SARI – Trazodone:
Nonclinical: No nonclinical data on the effect of trazodone on respiratory parameters were identified. In one study in mice, treatment with nefazodone at 50 mg/kg (HED 4.15 mg/kg) did not alter the LD_{50} of morphine (Pick et al, 1992).
Clinical: Treatment of healthy volunteers with trazodone (50 mg) caused a significant increase in VO_2 at six hours but not earlier (Casali et al, 1977). No human study data on the effect of nefazodone on respiratory parameters were located. In overdose reports, trazodone is not reported to cause fatalities. Some

fatalities have occurred with multiple drugs including trazodone but none of the other drugs in this report were opiates (Gamble & Peterson, 1986).

Trazodone

Label Text	no relevant text located
Clinical Dose	300 mg (5 mg/kg)
Prescription Count	145.8 million
AE Data	FAERS: Trazodone alone: EBGM: 3.8; EB05: 2.8 NPDS: Trazodone represented 4.2% of our pulled cases
Opinion	Candidate for rat studies

Skeletal muscle relaxants – Baclofen, Carisoprodol or Cyclobenzaprine

Nonclinical: For baclofen, there is nonclinical data from studies with guinea pigs at 10 mg/kg (HED 2.2 mg/kg) (Hey et al, 1995) and in cats at 4 mg/kg (HED 1.3 mg/kg) (Taveira da Silva et al, 1987) establishing that this drug causes direct respiratory depression. No nonclinical research on the effects of carisoprodol or cyclobenzaprine on respiratory parameters was identified.

Clinical: No clinical studies were located with direct measurement of respiratory parameters and baclofen treatment. Respiratory depression has been noted as an adverse event in baclofen overdose associated with ESRD wherein 2/5 patients required mechanical ventilation (Roberts et al, 2015). Therapeutically baclofen and morphine are used together as an intrathecal pump regimen for control of spasticity and neuropathic pain. Baclofen doses are initially reduced by half when morphine is added (Sadiq & Poopatana, 2007).

For carisoprodol and cyclobenzaprine, no direct nonclinical or clinical studies of respiratory effects were located. Carisoprodol is known to be abused in combination with opiates and sometimes in a triple combination adding benzodiazepines (Horsfall & Sprague, 2017).

Baclofen

Label Text	"ACTIONS . . . In studies with animals, baclofen has been shown to have general CNS depressant properties as indicated by the production of sedation with tolerance, somnolence, ataxia, and respiratory and cardiovascular depression."
Clinical Dose	5 mg TID (0.08 mg/kg each)
Prescription Count	38.7 million
AE Data	FAERS: Baclofen alone (EBGM: 12.1, EB05: 10.7) and in combination with opioids: EBGM: 2.2 – 14.7, EB05: 1.5 – 10.9 NPDS: Baclofen represented 0.9% of our pulled cases
Opinion	Nonclinical data sufficient

Carisoprodol

Label Text	5.2 Abuse, Dependence and Withdrawal Carisoprodol, the active ingredient in SOMA, has been subject to abuse, dependence, withdrawal, misuse, and criminal diversion. [see Drug Abuse and Dependence (9.1, 9.2, 9.3)]. Abuse of SOMA poses a risk of overdosage which may lead to death, CNS and respiratory depression, hypotension, seizures, and other disorders [see Overdosage (10)]. 9.2 Abuse Abuse of carisoprodol poses a risk of overdosage which may lead to death, CNS and respiratory depression, hypotension, seizures and other disorders [see Warnings and Precautions (5.2) and Overdosage (10)]."
Clinical Dose	250 mg TID (4.2 mg/kg)
Prescription Count	36.5 million
AE Data	FAERS: Carisoprodol alone (EBGM: 5.5, EB05: 4.0) and in combination with opioids: EBGM: 2.7 – 15.9, EB05: 1.7 – 10.1 NPDS: carisoprodol represented 3.9% of our pulled cases ToxIC: Carisoprodol was present in 4 of 55 cases of multi-agent fatalities involving opioids
Opinion	Candidate for rat studies

Cyclobenzaprine

Label Text	"WARNINGS . . . Cyclobenzaprine hydrochloride may enhance the effects of alcohol, barbiturates, and other CNS depressants."
Clinical Dose	5 mg TID (0.08 mg/kg each)
Prescription Count	140.9 million
AE Data	FAERS: Cyclobenzaprine alone (EBGM: 7.4, EB05: 5.5) and in combination with opioids: EBGM: 2.0 – 8.4, EB05: 1.3 – 5.5 NPDS: Cyclobenzaprine represented 3.9% of our pulled cases ToxIC: Cyclobenzaprine was present in 3 of 55 cases of multi-agent fatalities involving opioids
Opinion	Candidate for rat studies

Paroxetine

Nonclinical: No nonclinical studies were located evaluating the effect of paroxetine on respiration. For fluoxetine in an experiment in DBA/1 mice, measured by plethysmography, fluoxetine at 30 mg/kg IP (HED 2.5 mg/kg) caused a significant

reduction in Minute Ventilation and Respiratory Frequency, but not in Tidal Volume. This effect was seen in conscious mice but not in mice anesthetized with isofluorane (Zeng et al, 2015). A study in goats (45 kg) showed that fluoxetine dosed at 1 mg/kg (HED 0.95 mg/kg) caused an increase in $PaCO_2$ at rest (Henderson et al, 1999).
Clinical: No clinical studies were located evaluating the effect of paroxetine on respiration with or without opiates. For fluoxetine in a human study morphine titrated to 60 ng/ml in plasma caused the expected significant respiratory depression measured by End Tidal CO_2 (~5 mm Hg). The addition of fluoxetine at a dose of 30 mg did not alter the morphine-induced respiratory depression (Erjavec et al, 2000).

Paroxetine

Label Text	"Serotonin Syndrome: The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including PAXIL, alone but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort) and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue)."
Clinical Dose	40 mg (0.66 mg/kg)
Prescription Count	78.3 million
AE Data	FAERS: Paroxetine in combination with opioids: EBGM: 2.1 – 4.1; EB05: 1.5 – 2.5 NPDS: Paroxetine represented 1.4% of our pulled cases
Opinion	Nonclinical data for same class drug, fluoxetine, suggests a possible effect. Study in rat to provide interaction data.

Tricyclic antidepressants – Amitriptyline & Imipramine
Nonclinical: In nonclinical studies, imipramine (20 mg/kg) (HED 2.9 mg/kg rat; 10 mg/kg dog) markedly increased respiratory depression caused by morphine (7.5 mg/kg; HED 1 mg/kg rat; 3.85 mg/kg dog) or fentanyl (7.5 μg/ml) in anesthetized dogs or rats (Gavend et al, 1974). Continuous infusion of imipramine in the conscious rat leads to death by respiratory arrest (Zandberg & Sangster, 1982). In rabbits, fentanyl alone (11 μg/kg) caused a significant increase in $PaCO_2$. Imipramine alone at 4.35 mg/kg (HED 1.4 mg/kg) had a minimal effect on $PaCO_2$ (Bergman et al, 1991). Rabbits predosed with amitriptyline (7 mg/kg sc, HED 2.2 mg/kg) had a significantly higher increase in $PaCO_2$ after morphine injection as compared to saline pretreatment (Kozer et al, 2008). Specifically, the changes were +15 mm Hg for morphine alone and +20 mm Hg for morphine plus amitriptyline

over the baseline value.
Clinical: In a clinical study of 40 patients hospitalized for overdose by any tricyclic antidepressant (TCA) 16 patients required supportive ventilation. Amitriptyline and imipramine were taken by 29 of the 40 patients (Biggs et al, 1977).
There are two studies that evaluate the combined effect of amitriptyline and an opiate in healthy volunteers. In the first study buprenorphine (0.4 mg) and amitriptyline (25 mg) were found to cause significant respiratory depression as measured by minute ventilation and end tidal CO_2. The combination of both drugs significantly increased respiratory depression above that seen with buprenorphine alone (Saarialho-Kere et al, 1987). Strikingly similar findings were seen with the pair of the opiate pentazocine (30 mg) and amitriptyline (25 mg) (Saarialho-Kere et al, 1988).

Amitriptyline

Label Text	"WARNINGS . . . Amitriptyline hydrochloride may enhance the response to alcohol and the effects of barbiturates and other CNS depressants."
Clinical Dose	100 mg (1.67 mg/kg)
Prescription Count	70.4 million
AE Data	FAERS: Amitriptyline alone (EBGM: 8.2; EB05: 6.8) and in combination with opioids: EBGM: 2.2 – 12.5; EB05: 1.4 – 9.5 NPDS: Amitriptyline represented 5.4% of our pulled cases
Opinion	Nonclinical evidence of weak additional respiratory depression is clear and confirmed by clinical studies. Additional nonclinical studies not suggested.

Imipramine

Label Text	no relevant text located
Clinical Dose	50 mg BID (0.8 mg/kg each)
Prescription Count	5.7 million
AE Data	FAERS: Imipramine alone: EBGM: 3.7; EB05: 2.1 NPDS: Imipramine represented 0.2% of our pulled cases
Opinion	Nonclinical evidence of weak additional respiratory depression is clear and confirmed by clinical studies. Additional nonclinical studies not suggested.

Typical Antipsychotics – Haloperidol & Thioridazine
Nonclinical: A nonclinical study in mice showed that haloperidol at doses above 0.5 mg/kg (HED 0.04 mg/kg) caused a significant reduction in respiratory rate. In combination with morphine, haloperidol at 1.0 mg/kg (HED 0.08 mg/kg) but not at 0.25 mg/kg (HED 0.02 mg/kg)caused significant respiratory depression above the effect of morphine alone (McGilliard & Takemori, 1979). In rats given a continuous

infusion of thioridazine, PaO_2 decreased in concert with decreasing cardiac parameters but $PaCO_2$ was unaffected until terminal respiratory acidosis set in (Langemeijer et al 1985).
Clinical: In a study in healthy volunteers, nalbuphine caused respiratory depression but haloperidol at 0.5 mg/day had no effect on the nalbuphine-induced respiratory depression (Saarialho-Kere, 1988). A similar lack of effect of haloperidol was seen in COPD patients treated with 5 mg haloperidol IM (Tandon 1976).

Haloperidol

Label Text	"Drug Interactions Pharmacodynamic Interactions . . . As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates and alcohol."
Clinical Dose	5 mg IM (0.08 mg/kg)
Prescription Count	16.3 million
AE Data	FAERS: Haloperidol alone (EBGM: 4.1; EB05: 3.3) and in combination with opioids: EBGM: 2.6 – 7.7; EB05: 1.6 – 6.0 NPDS: Haloperidol represented 0.2% of our pulled cases
Opinion	Nonclinical data sufficient. Given the lack of clinical effect additional nonclinical studies are not suggested.

Thioridazine

Label Text	"WARNINGS . . . Central Nervous System Depressants As in the case of other phenothiazines, thioridazine is capable of potentiating central nervous system depressants (e.g., alcohol, anesthetics, barbiturates, narcotics, opiates, other psychoactive drugs, etc.) as well as atropine and phosphorus insecticides. Severe respiratory depression and respiratory arrest have been reported when a patient was given a phenothiazine and a concomitant high dose of a barbiturate"
Clinical Dose	50-100 mg TID (0.8 – 1.6 mg/kg each)
Prescription Count	0.97 million, promethazine 56.0 million
AE Data	FAERS: Thioridazine alone: EBGM: 3.01; EB05: 1.9
Opinion	Nonclinical data sufficient. Given the lack of clinical effect additional nonclinical studies are not suggested.

Other Drugs – Meprobamate (carbamate, $GABA_A$ agonist)
Nonclinical: No nonclinical research on the effects of meprobamate on respiratory parameters was identified.
Clinical: An analysis of meprobamate overdoses at the Massachusetts General Hospital from 1962 to 1975 was performed and included 50 admissions and 49

patients (Allen 1977). In the 15 cases that were attributed to meprobamate alone, five required assisted ventilation, and six reached grade 3 or 4 coma. One case included apneic episodes after ingestion of 18 grams of meprobamate.
A case report of a 52-year-old female who ingested 30-40 grams of meprobamate was found to be in respiratory failure upon admission (Lobo 1977). She subsequently regained consciousness approximately 54 hours after admission.
A prospective multi-center study in Oslo that included 1125 self-poisonings over the course of one year found that 15 cases of meprobamate overdosages led to grades 3 or 4 coma (5.3% of all grades 3 or 4 coma cases) (Jacobsen 1984). Additionally, out of 32 cases where meprobamate was the primary agent, five were complicated by respiratory depression.

Meprobamate

Label Text	"WARNINGS… Since the effects of meprobamate and alcohol or meprobamate and other CNS depressants or psychotropic drugs may be additive, appropriate caution should be exercised with patients who take more than one of these agents simultaneously.
Clinical Dose	1200-1600 mg daily in 3-4 divided doses (20 – 27 mg/kg each)
Prescription Count	0.26 million
AE Data	FAERS: Meprobamate alone (EBGM: 8.3; EB05: 5.0) and in combination with opioids: EBGM: 6.2 – 6.6; EB05: 4.1 – 5.6 NPDS: Meprobamate represented 0.1% of our pulled cases
Opinion	NAI due to low usage and existing label text.

Other Drugs – Dextromethorphan (Morphinan)
Nonclinical: A nonclinical study showed that male Wistar rats administered 10 mg/kg (HED 1.4 mg/kg) intraperitoneally with increasing doses of morphine (maximum 2.5 mg/kg) or fentanyl (maximum 0.16 mg/kg) experienced significantly higher pCO_2 values than when administered morphine (maximum 40 mg/kg) or fentanyl (maximum 2.5 mg/kg) alone (Hoffmann 2003). Other respiratory parameters measured, which included pO_2, and O_2, did not show a significant difference between the opioid alone and the opioid combined with dextromethorphan.
Clinical: In contrast, a placebo-controlled cross-over study conducted in 12 healthy volunteers showed that 60 mg of dextromethorphan did not potentiate the respiratory depressive effects of 60 mg of morphine as measured by the decrease in slope of the minute volume/CO_2 dose response curve (Jansinski 2000).

Dextromethorphan

Label Text	no relevant text located
Clinical	30 mg every 6-8 hours (0.5 mg/kg each)

Dose	
AE Data	FAERS: Dextromethorphan alone (EBGM: 2.4; EB05: 1.5) and in combination with opioids: EBGM: 3.2 – 20.4; EB05: 1.9 – 12.9 NPDS: Dextromethorphan represented 0.6% of our pulled cases
Opinion	NAI, massive OTC usage, clinical data suggests no issue.

Other Drugs – Mirtazapine (Noradrenergic and specific serotonergic antidepressant)

No literature data was found regarding mirtazapine and respiratory depression in animals or humans. Further, no data was found regarding the effects of mirtazapine combined with opioids.

Mirtazapine

Label Text	no relevant text located
Clinical Dose	15 mg daily (0.25 mg/kg)
Prescription Count	58.4 million
AE Data	FAERS: Mirtazapine alone (EBGM: 2.1; EB05: 1.5) and in combination with opioids: EBGM: 2.3 – 20.5; EB05: 1.6 – 13.3 NPDS: Mirtazapine represented 1.3% of our pulled cases
Opinion	Candidate for rat study

Other Drugs – Bupropion: Norepinephrine-dopamine reuptake inhibitor (NDRI)

No literature data was found regarding bupropion and respiratory depression in animals or humans. Further, no data was found regarding the effects of bupropion combined with opioids.

Bupropion

Label Text	no relevant text located
Clinical Dose	100 mg BID (immediate release); 150 mg daily (extended release) {1.7 mg/kg IR, 2.5 mg/kg ER}
Prescription Count	151.6 million
AE Data	FAERS: Bupropion alone (EBGM: 0.7; EB05: 0.5) and in combination with opioids: EBGM: 2.2 – 6.0; EB05: 1.4 – 3.7 NPDS: Bupropion represented 2% of our pulled cases
Opinion	NAI as the drug is not clinically sedating.

Duloxetine

No literature data was found regarding duloxetine and respiratory depression in

animals or humans. Further, no data was found regarding the effects of mirtazapine combined with opioids.

Duloxetine

Label Text	"WARNINGS… CNS Acting Drugs — Given the primary CNS effects of duloxetine delayed-release capsules, it should be used with caution when it is taken in combination with or substituted for other centrally acting drugs, including those with a similar mechanism of action" "Serotonin Syndrome: Serotonin syndrome has been reported with SSRIs and SNRIs, including with CYMBALTA, both when taken alone, but especially when co-administered with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's Wort)."
Clinical Dose	20 mg BID to 60 mg daily (0.3 to 1 mg/kg)
Prescription Count	105.5 million
AE Data	FAERS: Duloxetine in combination with opioids: EBGM: 2.0 – 8.4; EB05: 1.6 – 5.4 NPDS: Duloxetine represented 1.6% of our pulled cases
Opinion	Candidate for rat study

Other Drugs – Venlafaxine (SNRI)

No literature data was found regarding venlafaxine and respiratory depression in animals or humans. Further, no data was found regarding the effects of venlafaxine combined with opioids.

Venlafaxine

Label Text	"PRECAUTIONS… The risk of using venlafaxine in combination with other CNS-active drugs has not been systematically evaluated (except in the case of those CNS-active drugs noted above). Consequently, caution is advised if the concomitant administration of venlafaxine and such drugs is required" "The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including Effexor, alone but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort) and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Clinical Dose	75 mg daily in 2-3 divided doses (immediate release); 37.5 mg – 75 mg daily (extended release) (1.25 mg/kg/day)
Prescription Count	102.8 million
AE Data	FAERS: Venlafaxine alone: EBGM: 2.3; EB05: 1.9 NPDS: Venlafaxine represented 2.8% of our pulled cases
Opinion	NAI, group represented by duloxetine

Other Drugs – Topiramate (GABA agonist)

Nonclinical: No nonclinical research on the effects of topiramate on respiratory parameters was identified.

Clinical: A case report discussed a 37-year-old female patient who ingested an unknown amount of topiramate and required ventilation due to seizures and loss of consciousness (Lynch 2010). Prior to ventilation, the patient experienced metabolic acidosis with a pH of 7.26, pCO_2 of 41 mmHg, and a pO_2 of 320 mmHg. Initial serum topiramate levels were measured at 356.6 µg/mL (reference: 5-20 µg/mL).

Topiramate

Label Text	"DRUG INTERACTIONS… Concomitant administration of topiramate and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. Because of the potential of topiramate to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse reactions, topiramate should be used with extreme caution if used in combination with alcohol and other CNS depressants."
Clinical Dose	25-50 mg daily (0.4 – 0.8 mg/kg)
Prescription Count	62.6 million
AE Data	FAERS: Topiramate alone (EBGM: 1.1; EB05: 0.7) and in combination with tramadol: EBGM: 2.2; EB05: 1.4 NPDS: Topiramate represented 0.9% of our pulled cases
Opinion	Candidate for rat study

Other Drugs – Ramelteon (melatonin analog)

Nonclinical: No nonclinical research on the effects of ramelteon on respiratory parameters was identified.

Clinical: A placebo-controlled cross-over study funded by the manufacturer, Takeda, found that 16 mg of ramelteon does not induce respiratory depression during sleep in patients with mild to moderate sleep apnea (Kryger 2007). Respiratory endpoints included mean oxygen saturation (SpO_2) and Apnea Hypopnea Index (AHI) scores.

Additionally, another placebo-controlled cross-over study funded by Takeda found

that 8 mg of ramelteon does not induce respiratory depression during sleep in patients with moderate to severe chronic obstructive pulmonary disease (COPD) (Kryger 2009). Respiratory endpoints included mean oxygen saturation (SpO_2).

Ramelteon

Label Text	No relevant text
Clinical Dose	8 mg before bed (0.13 mg/kg)
Prescription Count	1.4 million
AE Data	No cases were present in ToxIC, FAERS, or NPDS.
Opinion	Clinical data sufficient for direct effect but no data on interaction with opiates, candidate for rat study

Other Drugs – Suvorexant (orexin agonist)

Nonclinical: No nonclinical research on the effects of suvorexant on respiratory parameters was identified.

Clinical: A placebo-controlled cross-over study funded by the manufacturer, Merck, found that 40 mg or 150 mg of suvorexant does not induce respiratory depression during sleep in healthy human subjects (Uemura 2015). Respiratory endpoints included mean oxygen saturation (SpO_2) and Apnea Hypopnea Index (AHI) scores.

Suvorexant

Label Text	"WARNINGS AND PRECAUTIONS…Co-administration with other CNS depressants (e.g., benzodiazepines, opioids, tricyclic antidepressants, alcohol) increases the risk of CNS depression. Patients should be advised not to consume alcohol in combination with BELSOMRA because of additive effects. Dosage adjustments of BELSOMRA and of concomitant CNS depressants may be necessary when administered together because of potentially additive effects. The use of BELSOMRA with other drugs to treat insomnia is not recommended."
Clinical Dose	10 mg before bed (0.17 mg/kg)
Prescription Count	0.8 million in 2 years, extrapolated to ~2.5 million over five years
AE Data	FAERS: Suvorexant alone: EBGM: 2.6; EB05: 1.4
Opinion	Add due to interaction concern from Psych

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Table S2: Dosing solutions or suspensions

SPD drug	Dose for combination treatment (mg/kg)	Drug concentration in dosing solution (mg/ml)	Solvent (%)							Dosage form
			Propylene glycol	Poly Ethylene Glycol 400 (PEG 400)	0.5% Methyl cellulose	100% Ethanol	Sterile water	NEOBEE® M-5 @	Dimethyl formamide (DMF)	
Carisoprodol	50	12.5			30	30	40			Solution
Clozapine	25	12.5	75	25						Solution
Cyclobenzaprine	30	15					100			Solution
Duloxetine	50	25	75	25						Solution
Mirtazapine	50	25	75	25						Solution
Paroxetine	50 or 5	25 or 2.5	50	50						Solution
Quetiapine	250 or 25	62.5 or 6.25	75	25						Solution
Ramelteon	30	3.75			25	25	50			Solution
Risperidone	10	5	75	25						Solution
Suvorexant	60	15						70	30	Solution
Topiramate	20	10	75	25						Solution
Trazodone	100	50	75	25						Suspension
Zolpidem	50	12.5	75	25						Solution

@ NEOBEE® M-5 is a caprylic/capric triglyceride. It is made using glycerol from vegetable oil sources and medium-chain fatty acids from coconut and palm kernel oils (Stepan Specialty Products, LLC, NJ, USA).

Bioanalytical Methods

Liquid chromatography tandem mass spectrometric assay methods were developed and validated to support the analysis of preclinical study samples. All the assays were developed with the aim of high sensitivity with reliable quantitation. While optimizing the lower limit of quantitation (LLOQ) of each analyte, various parameters like signal to noise, accuracy, and precision were evaluated. The upper limit of quantitation (ULOQ) was selected based on the concentration at which acceptable linearity range was observed (i.e., concentration vs linear detector response). All the methods were validated as per the current FDA bioanalytical method validation guidance. The details of individual methods are described below.

Analyte	Mass Spectrometer Conditions	Liquid Chromatographic Conditions	Sample Pretreatment
Clozapine **Linearity:** 0.5 to 1000 ng/mL	**Thermo TSQ** **Q1/Q3** Clozapine: 327/270.2 d_4Clozapine: 331/272.0 Source Temp: 350^0C	**Agilent 1290 Series** **Column:** ACQUITY UPLC HSS T32.1 x 50mm, 1.8 µm; Temp: 24^0C **Mobile Phase: A** 10 mM Ammonium formate with 0.1% formic acid **Mobile Phase: B** Acetonitrile **Gradient Flow:** 0.5 mL/min O min: 90% A; 0.4 min: 90% A; 1.6 min: 60% A; 1.8 min: 10% A; 2.0 min: 10% A 2.2 min: 90% A; 3.0 min: 90% A **Autosampler Temp**: 5^0C Injection Volume: 2 µL	**Protein Precipitation** 30 µl of plasma sample was quenched with 100 µl of acetonitrile containing internal standard (200 ng/mL of Clozepine-d4). The samples were vortexed for 5 min, followed by centrifugation at 4000 rpm for 5 min. Then add 30µL of 10mM ammonium formate in 0.1% formic acid (Mobile Phase A) to supernatant and shake for one minute
Cyclobenzaprine **Linearity:** 1.0 to 1000 ng/mL	**Sciex 6500+ Q trap** **Q1/Q3** Cyclobenzaprine: 276.4/216.1 d_3Cyclobenzaprine: 279.0/216.2 Source Temp: 500^0C	**Agilent 1290 Series** **Column:** ACQUITY UPLC® HSS-T3, 1.8 µm (2.1 x 500 mm); Temp: 24^0C **Mobile Phase: A** 10 mM Ammonium formate with 0.1% formic acid **Mobile Phase: B** Acetonitrile **Gradient Flow:** 0.6 mL/min O min: 90% A; 0.4 min: 90% A; 0.6 min: 60% A; 1.6 min: 60% A; 1.8 min: 90% A 2.0 min: 90% A; **Autosampler Temp**: 5^0C Injection Volume: 2 µL	**Protein Precipitation** 30 µl of plasma sample was quenched with 100 µl of acetonitrile containing internal standard (25 ng/mL of cyclobenzaprine-d3). The samples were vortexed for 5 min, followed by centrifugation at 4000 rpm for 5 min.

Duloxetine **Linearity:** 1.0 to 1000 ng/mL	**Thermo TSQ** **Q1/Q3** Duloxetine: 298.3/154 d_3Duloxetine: 301/157 Source Temp: 350^0C	**Agilent 1290 Series** **Column:** Zorbax SB C18; 2.1x50 mm; 3.5 µm; Temp: 24^0C **Mobile Phase: A** 2 mM amm acetate with 0.1% formic acid **Mobile Phase: B** Acetonitrile **Gradient Flow:** 0.5 mL/min O min: 90% A; 0.4 min: 90% A; 0.6 min: 25% A; 1.6 min: 25% A; 1.8 min: 90% A 2.0 min: 90% A; **Autosampler Temp**: 5^0C Injection Volume: 10 µL	**Protein Precipitation** 30 µl of plasma sample was quenched with 100 µl of acetonitrile containing internal standard (100 ng/mL). The samples were vortexed for 5 min, followed by centrifugation at 4000 rpm for 5 min.
Mirtazapine **Linearity:** 0.5 to 500 ng/mL	**Thermo TSQ** **Q1/Q3** Mirtazapine: 266.4/195.1 d_3Mirtazapine: 269.4/195.1 Source Temp: 350^0C	**Agilent 1290 Series** **Column:** Zorbax SB C18; 2.1x50 mm; 3.5 µm; Temp: 24^0C **Mobile Phase: A** 2 mM Ammonium formate with 0.1% formic acid **Mobile Phase: B** Acetonitrile **Gradient Flow:** 0.5 mL/min O min: 90% A; 0.4 min: 90% A; 1.6min: 40% A; 1.8 min: 90% A; 2.0 min: 90% A; **Autosampler Temp**: 5^0C Injection Volume: 2 µL	30 µl of plasma sample was quenched with 100 µl of acetonitrile containing internal standard (50 ng/mL). The samples were vortexed for 5 min, followed by centrifugation at 4000 rpm for 5 min. Then add 30µL of 10mM ammonium formate in 0.1% formic acid (Mobile Phase A) to supernatant and shake for one minute

Paroxetine **Linearity:** 1 to 1000 ng/mL	**Thermo TSQ** **Q1/Q3** Paroxetine: 330.3/192.1 d_6Paroxetine: 336/198 Source Temp: 350^0C	**Agilent 1290 Series** **Column:** Zorbax SB C18; 2.1x50 mm; 3.5 µm; Temp: 24^0C **Mobile Phase: A** 2 mM ammonium acetate with 0.1% formic acid **Mobile Phase: B** Acetonitrile **Gradient Flow:** 0.5 mL/min O min: 90% A; 0.4 min: 90% A; 0.6 min: 25% A; 1.6 min: 25% A; 1.8 min: 90% A 2.0 min: 90%A **Autosampler Temp**: 5^0C Injection Volume: 10 µL	**Protein Precipitation** 30 µl of plasma sample was quenched with 100 µl of acetonitrile containing internal standard (200 ng/mL). The samples were vortexed for 5 min, followed by centrifugation at 4000 rpm for 5 min.
Quetiapine L**inearity:** 4 to 2000 ng/mL	**Thermo TSQ** **Q1/Q3** Quetiapine: 384.5/253.1 d_8Quetiapine: 392.5/258.2 Source Temp: 350^0C	**Agilent 1290 Series** **Column:** ACQUITY UPLC HSS T32.1 x 50mm, 1.8 µm; Temp: 24^0C **Mobile Phase: A** 10 mM Ammonium formate with 0.1% formic acid **Mobile Phase: B** Acetonitrile **Gradient Flow:** 0.5 mL/min O min: 90% A; 0.4 min: 90% A; 1.6 min: 60% A; 1.8 min: 10% A; 2.0 min: 10% A 2.2 min: 90% A; 3.0 min: 90% A **Autosampler Temp**: 5^0C Injection Volume: 2 µL	**Protein Precipitation** 30 µl of plasma sample was quenched with 100 µl of acetonitrile containing internal standard (200 ng/mL). The samples were vortexed for 5 min, followed by centrifugation at 4000 rpm for 5 min. Then add 30µL of 10mM ammonium formate in 0.1% formic acid (Mobile Phase A) to supernatant and shake for one minute

Ramelteon **Linearity:** 4 to 2000 ng/mL	**Thermo TSQ** **Q1/Q3** Ramelteon: 260.2/204.1 d_3Ramelteon: 263.2/204.1 Source Temp: 350^{0}C	**Agilent 1290 Series** **Column:** ACQUITY UPLC HSS T32.1 x 50mm, 1.8 µm; Temp: 24^{0}C **Mobile Phase: A** 10 mM Ammonium formate with 0.1% formic acid **Mobile Phase: B** Acetonitrile **Gradient Flow:** 0.5 mL/min O min: 90% A; 0.4 min: 90% A; 1.6 min: 70% A; 1.8 min: 10% A; 2.0 min: 10% A 2.2 min: 90% A; 3.0 min: 90% A;4.0 min 90% **Autosampler Temp**: 5^{0}C Injection Volume: 1 µL	**Protein Precipitation** 30 µl of plasma sample was quenched with 100 µl of acetonitrile containing internal standard (200 ng/mL). The samples were vortexed for 5 min, followed by centrifugation at 4000 rpm for 5 min. Then add 30µL of 10mM ammonium formate in 0.1% formic acid (Mobile Phase A) to supernatant and shake for one minute
Risperidone **Linearity:** 0.5 to 500 ng/mL	**Thermo TSQ** **Q1/Q3** Risperidone: 411.2/191.1 d_4Risperidone: 415.2/195.2 Source Temp: 350^{0}C	**Agilent 1290 Series** **Column:** Zorbax SB C18; 2.1x50 mm; 3.5 µm; Temp: 24^{0}C **Mobile Phase: A** 2 mM Ammonium formate with 0.1% formic acid **Mobile Phase: B** Acetonitrile **Gradient Flow:** 0.5 mL/min O min: 90% A; 0.4 min: 90% A; 1.6 min: 40% A; 1.8 min: 90% A; 2.0 min: 90% A **Autosampler Temp**: 5^{0}C Injection Volume: 2 µL	**Protein Precipitation** 30 µl of plasma sample was quenched with 100 µl of acetonitrile containing internal standard (5 ng/mL). The samples were vortexed for 5 min, followed by centrifugation at 4000 rpm for 5 min. Then add 30µL of 10mM ammonium formate in 0.1% formic acid (Mobile Phase A) to supernatant and shake for one minute
Suvorexant **Linearity:** 1 to 1000 ng/mL	**Thermo TSQ** **Q1/Q3** Suvorexant: 451.1/186 d_5Estazolam: 300/272 Source Temp: 350^{0}C	**Agilent 1290 Series** **Column:** ACQUITY UPLC HSS T32.1 x 50mm, 1.8 µm; Temp: 24^{0}C **Mobile Phase: A** 10 mM Ammonium formate with 0.1% formic acid **Mobile Phase: B** Acetonitrile **Gradient Flow:** 0.5 mL/min O min: 90% A; 0.4 min: 90% A; 0.6 min: 70% A; 1.2 min: 70% A; 1.4 min: 10% A	**Protein Precipitation** 30 µl of plasma sample was quenched with 100 µl of acetonitrile containing internal standard (1000 ng/mL). The samples were vortexed for 5 min, followed by centrifugation at 4000 rpm for 5 min. Then add 30µL of 10mM ammonium formate in 0.1% formic acid (Mobile Phase A) to supernatant

		2.0 min: 10% A; 2.2 min: 90% A;2.5 min 90%;3.5 min 90% **Autosampler Temp**: 5^0C Injection Volume: 1µl	and shake for one minute
Topiramate **Linearity:** 20 to 5000 ng/mL	**Sciex 6500+ Q trap** **Q1/Q3** Topiramate: 338/77.9 d_{12}Topiramate: 350.0/78.1 Source Temp: 500^0C	**Agilent 1290 Series** **Column:** Zorbax SB C18, 2.1*50mm, 3.5µ; Temp: 24^0C **Mobile Phase: A** 10 mM Ammonium formate **Mobile Phase: B** Acetonitrile **Gradient Flow:** 0.5 mL/min O min: 90% A; 0.4 min: 90% A; 0.6 min: 70% A; 1.6 min: 70% A; 1.9 min: 20% A 2.2 min: 20% A; 2.3 min: 90% A;2.5 min 90% **Autosampler Temp**: 5^0C Injection Volume: 2µl	**Protein Precipitation** 30 µl of plasma sample was quenched with 100 µl of acetonitrile containing internal standard (1000 ng/mL). The samples were vortexed for 5 min, followed by centrifugation at 4000 rpm for 5 min. Then add 30µL of 10mM ammonium formate in 0.1% formic acid (Mobile Phase A) to supernatant and shake for one minute
Trazodone **Linearity:** 3 to 3000 ng/mL	**Thermo TSQ** **Q1/Q3** Trazadone: 372.2/176.2 d_6Trazadone: 378.4/182.2 Source Temp: 350^0C	**Agilent 1290 Series** **Column:** ACQUITY UPLC HSS T32.1 x 50mm, 1.8 µm; Temp: 24^0C **Mobile Phase: A** 10 mM Ammonium formate with 0.1% formic acid **Mobile Phase: B** Acetonitrile **Gradient Flow:** 0.5 mL/min O min: 90% A; 0.4 min: 90% A; 1.6 min: 70% A; 1.8 min: 70% A; 2.0 min: 10% A 2.2 min: 90% A; 3.0 min: 90% A **Autosampler Temp**: 5^0C Injection Volume: 2µl	**Protein Precipitation** 30 µl of plasma sample was quenched with 100 µl of acetonitrile containing internal standard (200 ng/mL). The samples were vortexed for 5 min, followed by centrifugation at 4000 rpm for 5 min. Then add 30µL of 10mM ammonium formate in 0.1% formic acid (Mobile Phase A) to supernatant and shake for one minute

Zolpidem **Linearity:** 1 to 1000 ng/mL	**Thermo TSQ** **Q1/Q3** Zolpedem: 308.2/176.2 d_6Zolpedem: 314/176.2 Source Temp: 350^0C	**Agilent 1290 Series** **Column:** ACQUITY UPLC HSS T32.1 x 50mm, 1.8 µm; Temp: 24^0C **Mobile Phase: A** HSS TX3 **Mobile Phase: B** Acetonitrile **Gradient Flow:** 0.6 mL/min O min: 90% A; 0.4 min: 90% A; 1.0 min: 60% A; 1.5 min: 60% A; 1.6 min: 90% A 2.0 min: 90% A; 2.5 min: 90% A **Autosampler Temp**: 5^0C Injection Volume: 1µl	**Protein Precipitation** 30 µl of plasma sample was quenched with 100 µl of acetonitrile containing internal standard (200 ng/mL). The samples were vortexed for 5 min, followed by centrifugation at 4000 rpm for 5 min. Then add 30µL of 10mM ammonium formate in 0.1% formic acid (Mobile Phase A) to supernatant and shake for one minute

Table S3: Pharmacokinetic parameters of single dose, single drug administration

Drug	Dose (mg/kg)	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (h×ng/mL)
Oxycodone	6.25 (n=6)	0.5 ± 0.4	7.0 ± 2.2	11.7 ± 3.6
	60 (n=11)	0.9 ± 0.6	29.7 ± 12.6	89.0 ± 21.5
	150 (n=10)	0.9 ± 0.6	48.3 ± 14.7	145.4 ± 55.7
	300 (n=6)	0.8 ± 0.4	61.2 ± 40.2	201.3 ± 161.2
Diazepam	2 (n=6)	0.5 ± 0.3	22.6 ± 22.9	49.3 ± 64.3
	20 (n=6)	0.3 ± 0.1	286.5 ± 147.9	621.9 ± 388.9
	200 (n=6)	2.2 ± 0.4	1370.9 ± 505.3	6771.9 ± 2770.8
Clozapine	5 (n=6)	0.9 ± 0.6	19.5 ± 12.2	28.6 ± 17.6
	25 (n=6)	1.0 ± 0.8	65.3 ± 20.8	148.2 ± 65.5
	125 (n=6)	0.6 ± 0.2	653.9 ± 309.4	1637.5 ± 600.2
Cyclobenzaprine	3 (n=6)	*	*	*
	30 (n=6)	0.9 ± 0.2	6.4 ± 2.3	22.0 ± 7.3
	300 (n=6)	3.9 ± 3.9	86.1 ± 36.5	438.8 ± 156.9
Duloxetine	5 (n=6)	2.3 ± 1.0	10.6 ± 2.8	47.2 ± 16.5
	50 (n=6)	2.0 ± 0.9	465.1 ± 135.3	2514.8 ± 787.8
	250 (n=6)	4.3 ± 1.9	1235.1 ± 997.5	8195.1 ± 6549.5
Mirtazapine	5 (n=5)	1.0 ± 1.2	18.1 ± 7.6	46.9 ± 16.5
	50 (n=6)	1.8 ± 3.1	87.5 ± 59.4	317.4 ± 105.6
	250 (n=6)	0.4 ± 0.3	204.7 ± 42.9	611.6 ± 164.4
Paroxetine	5 (n=4)	4.5 ± 2.4	58.9 ± 29.3	315.5 ± 175.4
	50 (n=6)	5.3 ± 2.9	1090.0 ± 245.6	6854.1 ± 1956.7
	250 (n=4)	6.5 ± 3.0	1775.0 ± 160.4	11407.3 ± 1507.0
Quetiapine	25 (n=6)	1.0 ± 0.5	46.3 ± 44.3	107.3 ± 118.6
	250 (n=6)	5.6 ± 3.2	512.3 ± 222.4	2707.3 ± 1532.2
	1250 (n=6)	3.1 ± 3.2	1212.6 ± 1089.8	4917.4 ± 2131.7
Ramelteon	3 (n=6)	0.3 ± 0.1	68.9 ± 24.1	112.5 ± 33.6
	30 (n=6)	0.4 ± 0.1	768.2 ± 252.1	1527.7 ± 459.6
	300 (n=6)	2.7 ± 1.3	5904.0 ± 1680.8	31479.3 ± 10385.1
Risperidone	2 (n=6)	1.1 ± 0.7	48.4 ± 15.7	134.8 ± 33.6
	10 (n=6)	0.7 ± 0.6	108.5 ± 48.8	350.0 ± 105.6
	50 (n=6)	5.2 ± 3.7	508.8 ± 325.1	2063.4 ± 1133.7
Suvorexant	6 (n=6)	3.3 ± 1.5	122.2 ± 26.9	544.2 ± 117.1
	60 (n=6)	5.7 ± 0.8	2534.9 ± 2177.5	14308.8 ± 12618.7
	300 (n=5)	7.6 ± 0.9	4616.2 ± 3011.2	23711.3 ± 16209.9
Topiramate	20 (n=6)	1.5 ± 0.5	8830.3 ± 2146.7	39303.6 ± 8295.4
	200 (n=6)	1.3 ± 0.9	72835.1 ± 35373.7	321792.7 ± 119677.5
	1000 (n=5)	1.2 ± 0.4	164106.6 ± 67883.9	897417.2 ± 362698.2
Trazadone	20 (n=6)	0.8 ± 1.1	237.8 ± 127.4	582.2 ± 155.9
	100 (n=6)	0.9 ± 1.5	991.1 ± 650.6	2632.7 ± 498.7
	500 (n=6)	2.5 ± 3.5	3664.2 ± 3160.4	12224.9 ± 5251.2
Zolpidem	5 (n=6)	0.3 ± 0.1	115.9 ± 62.7	285.9 ± 92.4
	50 (n=6)	0.6 ± 0.7	1243.4 ± 889.5	2979.1 ± 993.5
	500 (n=6)	1.5 ± 3.2	12259.8 ± 7462.9	44488.9 ± 48913.3
Carisoprodol	5 (n=5)	0.3 ± 0.1	10.9 ± 7.6	15.4 ± 8.5
	50 (n=6)	0.7 ± 0.7	95.0 ± 65.7	203.8 ± 87.3
	250 (n=5)	0.5 ± 0.2	3178.5 ± 3134.2	5003.4± 3573.4

Table S4: Single Drug t_{max} and dose timing for combination experiments

Single Drug Study Drug and Dose	t_{max} (minutes)	Combination Drug Sequence and Intervals		
Oxycodone 150 mg/kg	60	**First Drug (time zero)**	**Interval (in minutes)**	**Second Drug**
Paroxetine 50 mg/kg	180	Paroxetine	180	Oxycodone
Paroxetine 5 mg/kg	240			
Risperidone 10 mg/kg	30	Oxycodone	30	Risperidone
Cyclobenzaprine 30 mg/kg	60	Cyclobenzaprine	30	Oxycodone
Mirtazapine 50 mg/kg	30	Mirtazapine	0	Oxycodone
Zolpidem 50 mg/kg	15	Oxycodone	30	Zolpidem
Duloxetine 50 mg/kg	180	Duloxetine	180	Oxycodone
Clozapine 25 mg/kg	30	Clozapine	0	Oxycodone
Quetiapine 250 mg/kg	60	Quetiapine	0	Oxycodone
Quetiapine 25 mg/kg	60			
Trazodone 100 mg/kg	15	Oxycodone	30	Trazodone
Topiramate 20 mg/kg	60	Topiramate	0	Oxycodone
Carisoprodol 50 mg/kg	15	Oxycodone	30	Carisoprodol
Ramelteon 30 mg/kg	30	Oxycodone	30	Ramelteon
Suvorexant 60 mg/kg	360	Suvorexant	180	Oxycodone

Table S5: Pharmacokinetic parameters of the drugs upon Coadministration

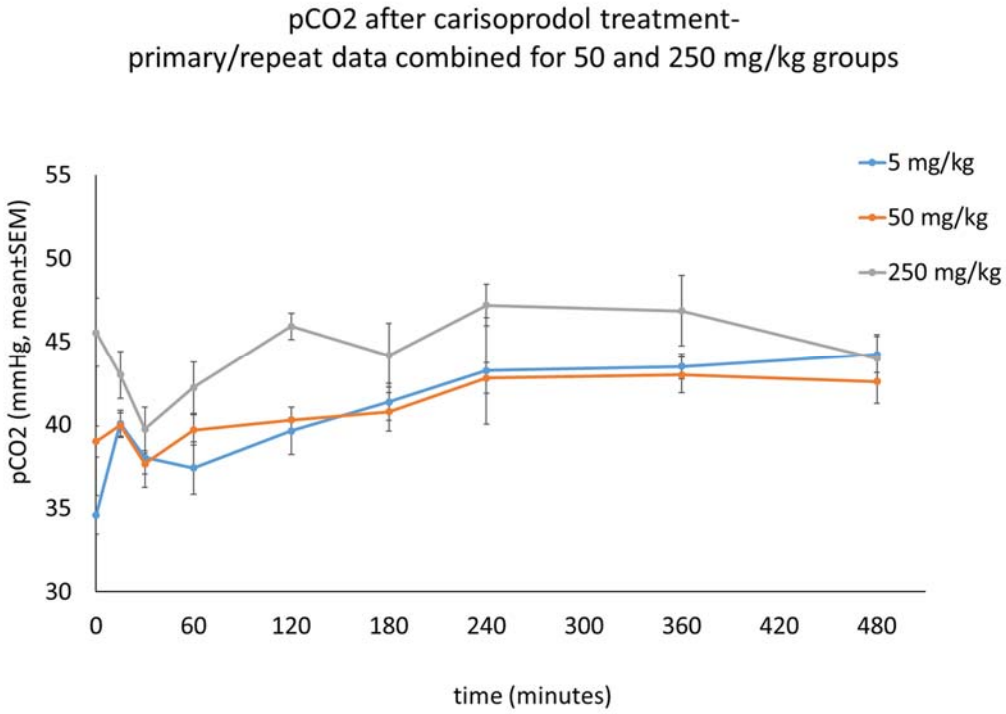
Drug		Dose (mg/kg)	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (h.ng/mL)
Diazepam	Oxycodone (Alone) n=17	150	1.1 ± 0.8	51.2 ± 28.3	95.1 ± 51.9
	Oxycodone (Combo) n=18	150	1.3 ± 0.9	102.3 ± 75.6	202.8 ± 135.6
	Diazepam (Alone) n=6	20	0.3 ± 0.1	286.5 ± 148.0	367.4 ± 190.2
	Diazepam (Combo) n=18	20	0.8 ± 0.9	134.4 ± 144.7	247.9 ± 239.0
Diazepam Repeat	Oxycodone (Alone) n=6	6.25	0.4 ± 0.1	6.7 ± 3.4	10.1 ± 5.1
	Oxycodone (Combo) n=6	6.25	0.5 ± 0.7	5.4 ± 3.6	7.3 ± 2.9
	Diazepam (Alone) n=6	20	0.3 ± 0.1	286.5 ± 148.0	367.4 ± 190.2
	Diazepam (Combo) n=6	20	1.2 ± 1.1	124.0 ± 67.3	226.5 ± 119.8
Clozapine	Oxycodone (Alone) n=6	150	0.9 ± 1.1	45.7 ± 13.9	72.1 ± 31.1
	Oxycodone (Combo) n=6	150	1.2 ± 0.4	36.5 ± 17.4	64.9 ± 31.9
	Clozapine (Alone) n=6	25	1.0 ± 0.8	65.3 ± 20.8	99.5 ± 37.7
	Clozapine (Combo) n=6	25	1.0 ± 0.0	9.6 ± 9.1	15.9 ± 14.8
Cyclobenzaprine	Oxycodone (Alone) n=12	150	1.6 ± 1.1	61.0 ± 40.8	98.2 ± 64.7
	Oxycodone (Combo) n=11	150	1.3 ± 1.0	103.6 ± 80.9	195.3 ± 160.9
	Cyclobenzaprine (Alone) n=6	30	0.9 ± 0.2	6.4 ± 2.4	14.1 ± 5.1
	Cyclobenzaprine (Combo) n=11	30	0.8 ± 0.0	9.3 ± 4.6	18.4 ± 9.0
Duloxetine	Oxycodone (Alone) n=6	150	0.5 ± 0.3	76.9 ± 30.5	105.0 ± 41.8
	Oxycodone (Combo) n=4	150	1.0 ± 1.2	181.5 ± 105.5	326.0 ± 172.8
	Duloxetine (Alone) n=6	50	2.0 ± 0.9	465.1 ± 135.3	1969.1 ± 720.1
	Duloxetine (Combo) n=4	50	3.3 ± 0.0	325.9 ± 52.7	1149.3 ± 222.5
Mirtazapine	Oxycodone (Alone) n=6	150	0.9 ± 0.2	52.5 ± 23.2	79.9 ± 21.4
	Oxycodone (Combo) n=6	150	0.8 ± 0.4	52.3 ± 43.4	96.2 ± 95.5
	Mirtazapine (Alone) n=6	50	1.8 ± 3.1	87.5 ± 59.4	156.4 ± 83.7
	Mirtazapine (Combo) n=6	50	1.3 ± 0.6	70.0 ± 38.1	134.9 ± 89.2
Paroxetine	Oxycodone (Alone) n=6	150	0.6 ± 0.3	33.1 ± 12.4	55.5 ± 14.5
	Oxycodone (Combo) n=6	150	0.6 ± 0.7	205.3 ± 182.7	253.5 ± 137.6
	Paroxetine (Alone) n-6	50	5.3 ± 2.9	1090.0 ± 245.6	4840.4 ± 1610.3
	Paroxetine (Combo) n=6	50	3.8 ± 1.1	554.5 ± 133.1	2276.7 ± 610.9
Paroxetine Repeat	Oxycodone (Alone) n=6	150	0.6 ± 0.3	50.3 ± 5.9	74.3 ± 13.6
	Oxycodone (Combo) n=6	150	0.8 ± 0.3	69.6 ± 32.6	117.3 ± 64.0
	Paroxetine (Alone) n=4	5	4.5 ± 2.4	58.9 ± 29.3	221.2 ± 124.3
	Paroxetine (Combo) n=6	5	3.3 ± 0.1	14.8 ± 16.0	55.6 ± 62.1
Quetiapine	Oxycodone (Alone) n=6	150	0.5 ± 0.2	27.6 ± 13.0	54.0 ± 25.6
	Oxycodone (Combo) n=5	150	1.3 ± 1.0	304.6 ± 165.2	421.3 ± 196.6
	Quetiapine (Alone) n=6	250	5.6 ± 3.2	512.3 ± 222.4	882.9 ± 607.3
	Quetiapine (Combo) n=5	250	1.3 ± 1.0	230.0 ± 125.0	334.4 ± 194.6
Quetiapine Repeat	Oxycodone (Alone) n=6	150	0.5 ± 0.1	29.7 ± 13.0	49.5 ± 23.3
	Oxycodone (Combo) n=6	150	1.2 ± 0.9	57.1 ± 39.8	89.8 ± 63.9
	Quetiapine (Alone) n=6	25	1.0 ± 0.5	46.3 ± 44.3	78.1 ± 80.7
	Quetiapine (Combo) n=6	25	1.0 ± 0.6	7.1 ± 4.7	6.5 ± 5.3
Ramelteon	Oxycodone (Alone) n=11	150	0.8 ± 0.6	66.8 ± 57.5	94.0 ± 62.1
	Oxycodone (Combo) n=12	150	1.5 ± 1.1	97.0 ± 70.2	177.6 ± 111.1
	Ramelteon (Alone) n=6	30	0.4 ± 0.1	768.2 ± 252.1	1029.2 ± 289.1
	Ramelteon (Combo) n=12	30	0.5 ± 0.8	434.5 ± 217.0	442.9 ± 226.2
Risperidone	Oxycodone (Alone) n=4	150	0.6 ± 0.3	61.8 ± 14.9	98.8 ± 14.6
	Oxycodone (Combo) n=6	150	1.3 ± 0.3	54.1 ± 33.6	121.5 ± 68.3

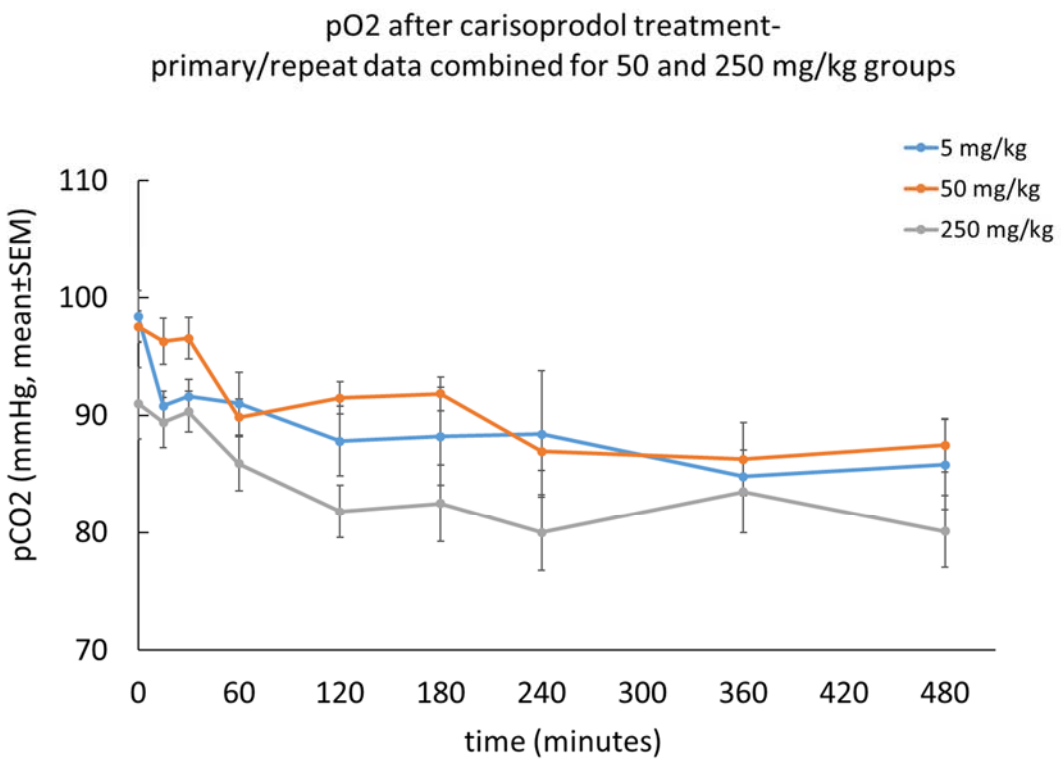
	Risperidone (Alone) n=6	10	0.7 ± 0.6	108.5 ± 48.8	216.4 ± 74.5
	Risperidone (Combo) n=6	10	0.8 ± 0.3	92.4 ± 47.8	167.3 ± 88.4
Suvorexant	Oxycodone (Alone) n=6	150	0.6 ± 0.2	128.0 ± 107.1	186.2 ± 137.7
	Oxycodone (Combo) n=6	150	1.5 ± 1.2	122.5 ± 53.8	230.9 ± 124.4
	Suvorexant (Alone) n=6	60	5.7 ± 0.8	2534.9 ± 2177.5	9848.3 ± 8683.8
	Suvorexant (Combo) n=6	60	3.4 ± 0.3	1016.9 ± 400.9	3379.5 ± 1339.4
Topiramate	Oxycodone (Alone) n=12	150	0.6 ± 0.5	58.5 ± 42.7	89.8 ± 71.9
	Oxycodone (Combo) n=12	150	1.4 ± 1.1	96.0 ± 128.2	151.1 ± 143.9
	Topiramate (Alone) n=6	20	1.5 ± 0.5	8830.3 ± 2146.7	19984.7 ± 4566.3
	Topiramate (Combo) n=12	20	1.8 ± 0.9	2435.1 ± 1729.3	5299.7 ± 3572.7
Trazadone	Oxycodone (Alone) n=12	150	1.2 ± 1.0	72.8 ± 80.4	102.2 ± 90.4
	Oxycodone (Combo) n=11	150	1.3 ± 0.8	73.3 ± 67.8	146.3 ± 154.0
	Trazadone (Alone) n=6	100	0.9 ± 1.5	991.1 ± 650.6	1423.6 ± 474.8
	Trazadone (Combo) n=11	100	0.5 ± 0.2	180.8 ± 175.9	317.2 ± 414.4
Zolpidem	Oxycodone (Alone) n=6	150	1.4 ± 1.2	162.4 ± 183.3	205.7 ± 228.3
	Oxycodone (Combo) n=5	150	1.4 ± 1.2	120.3 ± 150.0	181.9 ± 171.4
	Zolpidem (Alone) n=6	100	0.5 ± 0.7	1243.4 ± 889.5	1590.2 ± 1163.3
	Zolpidem (Combo) n=5	100	1.0 ± 0.6	548.0 ± 462.7	760.2 ± 549.3
Carisoprodol	Oxycodone (Alone) n=6	150	0.7 ± 0.3	44.6 ± 20.2	96.6 ± 52.0
	Oxycodone (Combo) n=6	150	0.8 ± 0.1	121.8 ± 128.2	169.7 ± 134.8
	Carisoprodol (Alone) n=6	50	0.7 ± 0.7	95.0 ± 65.7	148.2 ± 88.4
	Carisoprodol (Combo) n=6	50	0.8 ± 1.1	167.8 ± 234.8	127.8 ± 139.2

*Not reportable due to concentrations below the lower limit of quantitation of the analytical method

Figure S1: pCO2 & pO2 from individual SPD drug treatments and combination treatments with oxycodone

Carisoprodol

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50 mg/kg
250 mg/kg
pCO2 (mmHg, mean±SEM)
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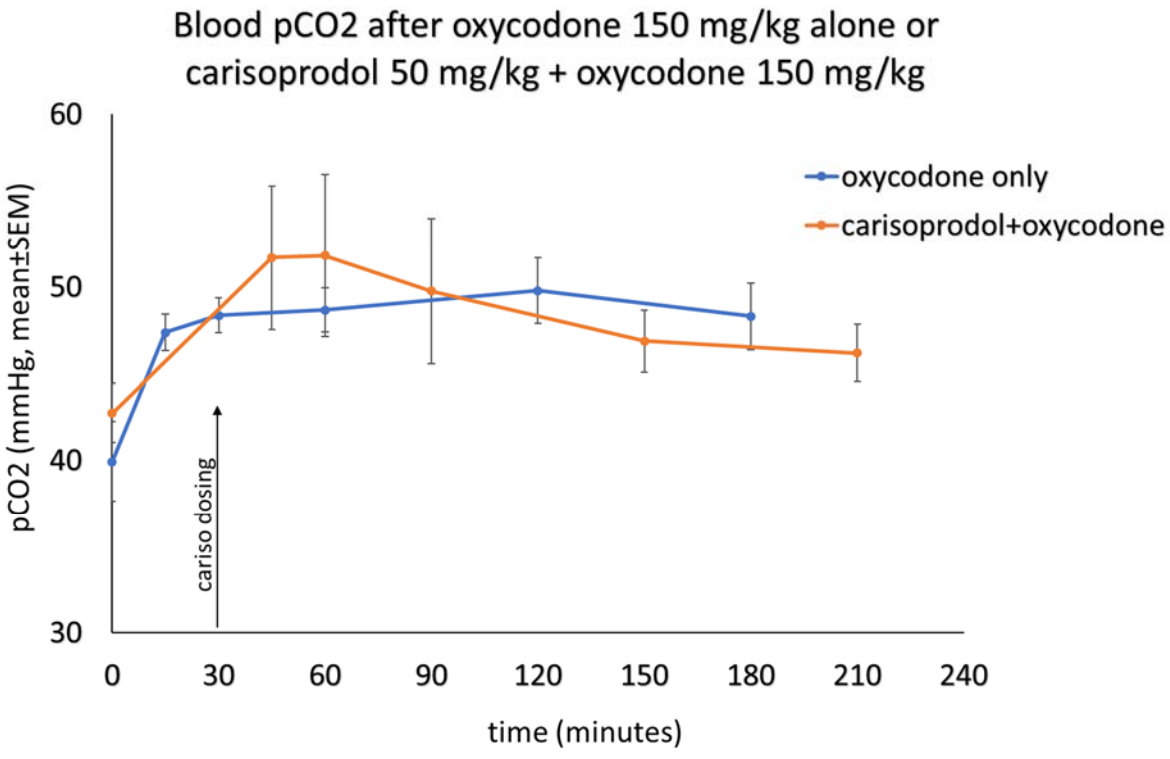
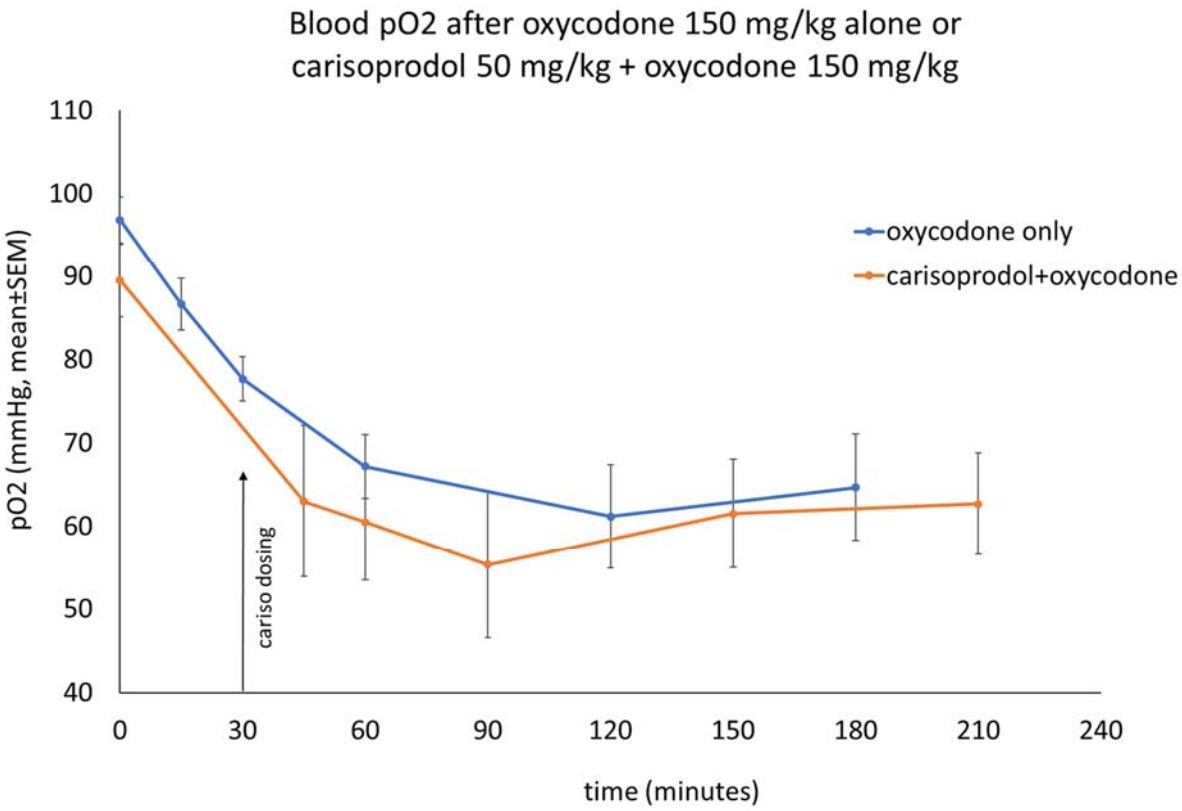
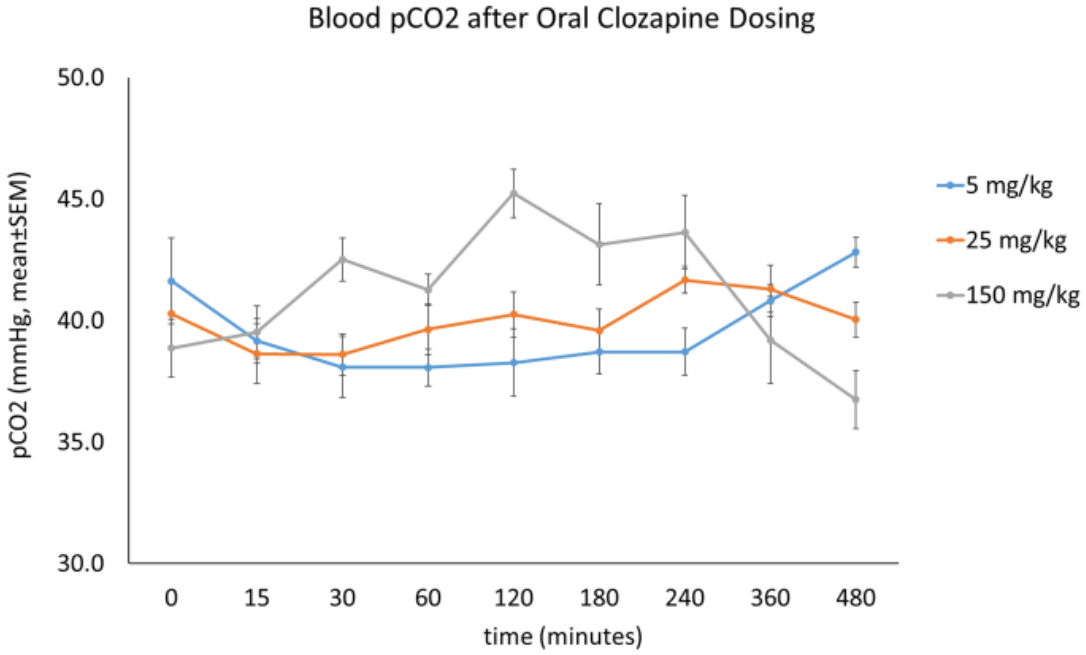
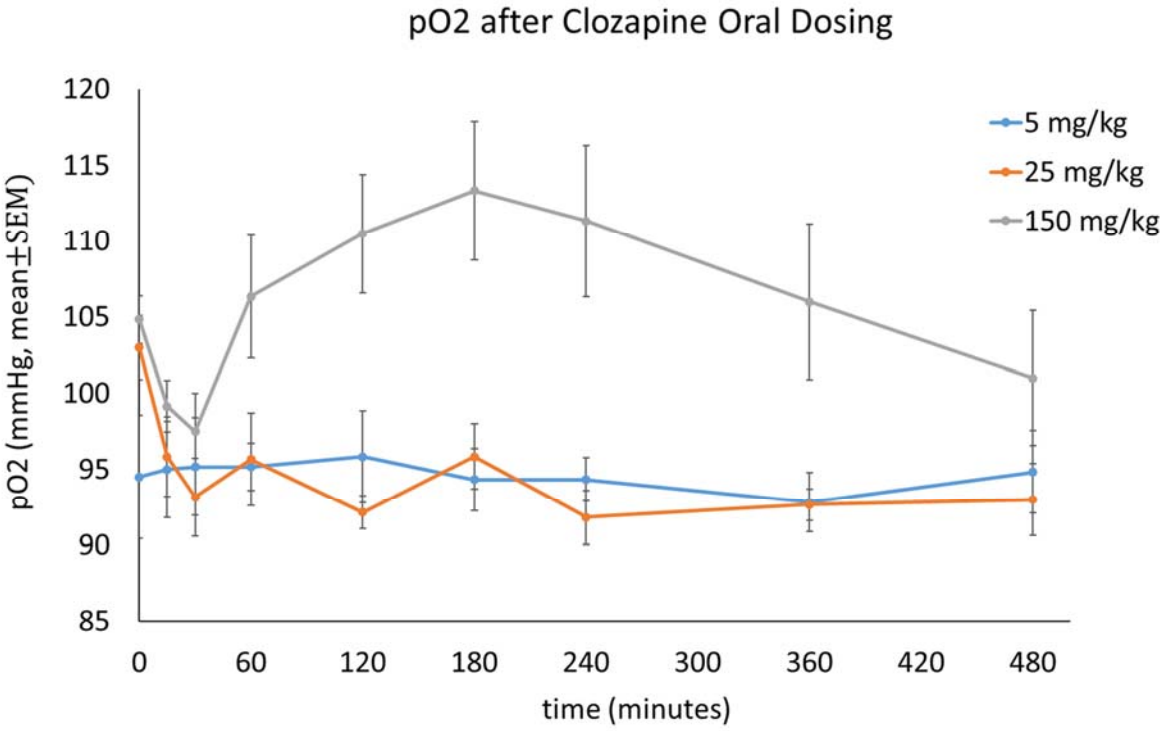
100
90
80
70
0
60
120
180
240
300
360
420
480
time (minutes)

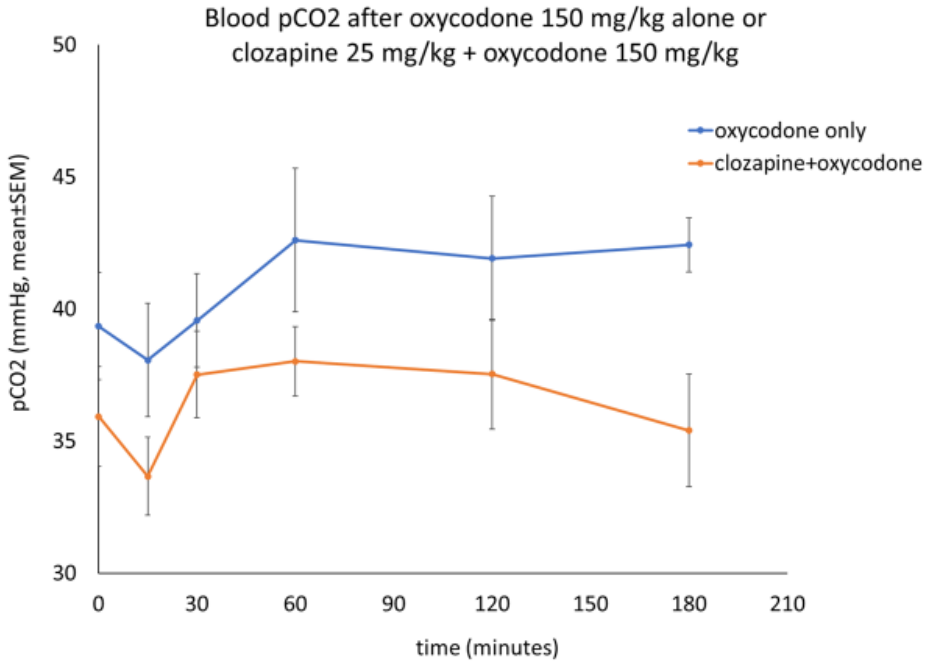

Blood pCO2 after oxycodone 150 mg/kg alone or
carisoprodol 50 mg/kg + oxycodone 150 mg/kg
oxycodone only
carisoprodol+oxycodone
pCO2 (mmHg, mean±SEM)
60
50
40
30
cariso dosing
0
30
60
90
120
150
180
210
240
time (minutes)

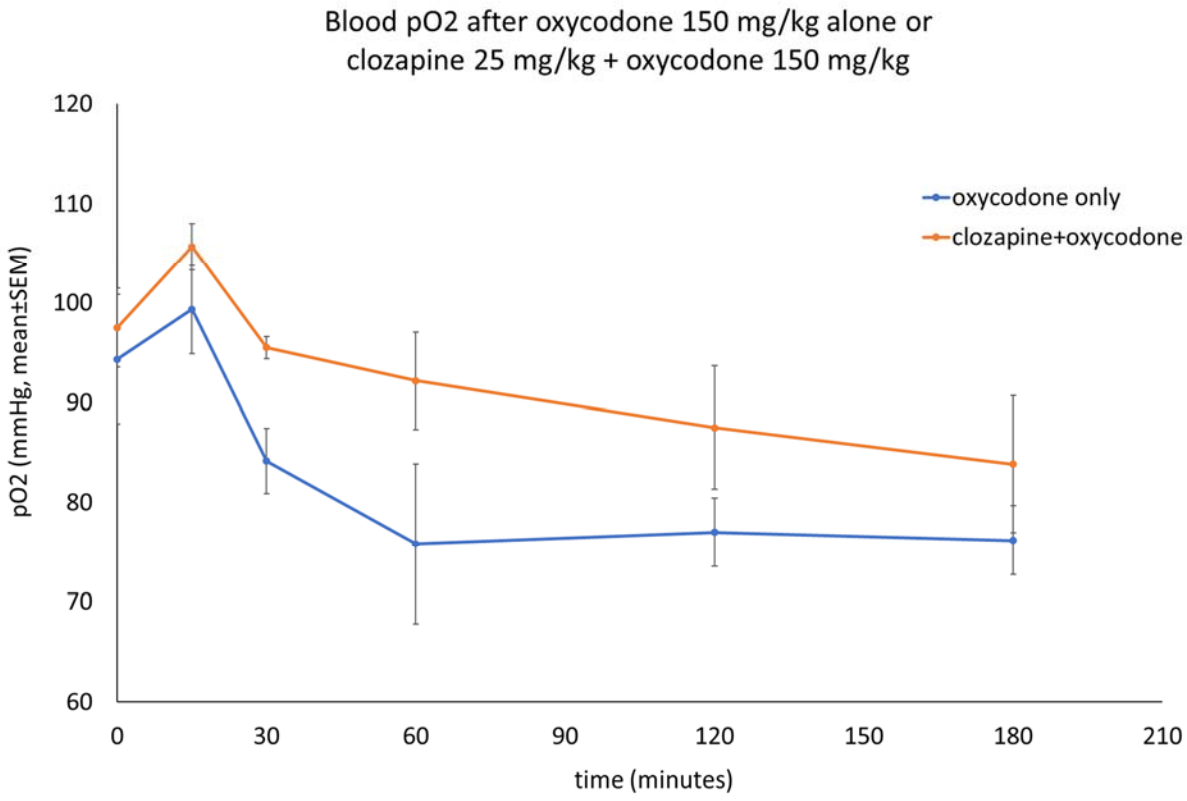

Blood pO2 after oxycodone 150 mg/kg alone or carisoprodol 50 mg/kg + oxycodone 150 mg/kg
pO2 (mmHg, mean±SEM)
110
100
90
80
70
60
50
40
0
30
60
90
120
150
180
210
240
time (minutes)
cariso dosing
oxycodone only
carisoprodol+oxycodone

Clozapine

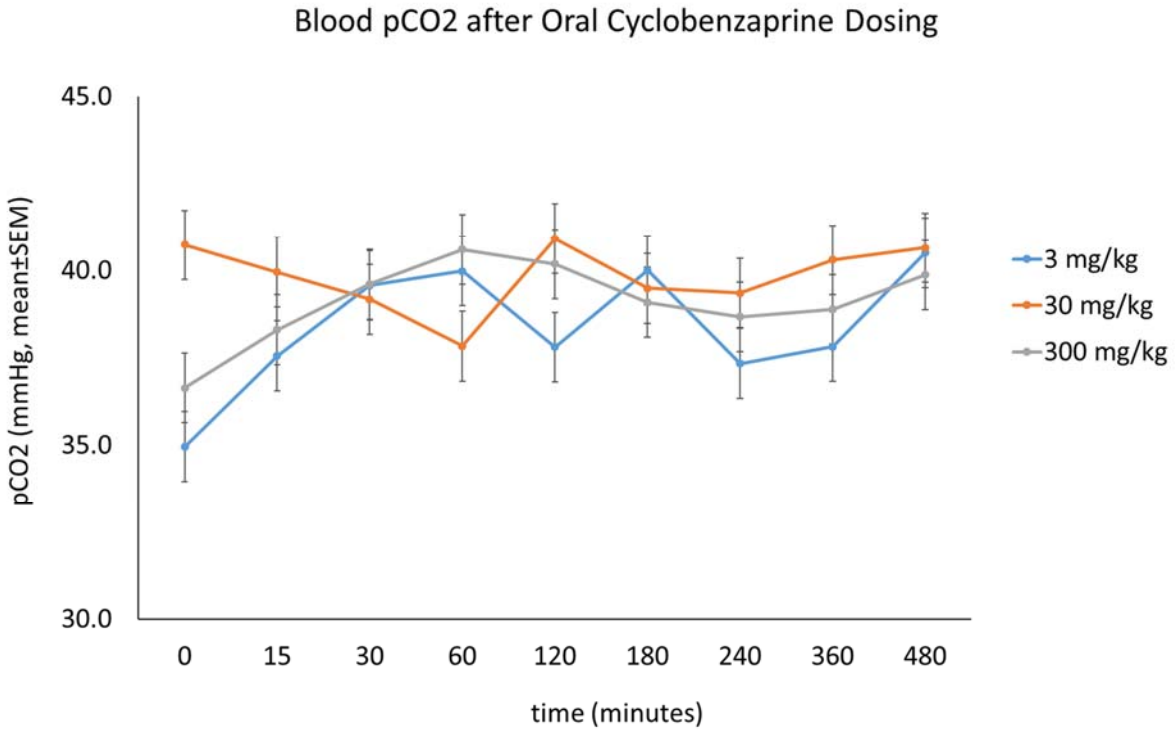

Blood pCO2 after Oral Clozapine Dosing
pCO2 (mmHg, mean±SEM)
50.0
45.0
40.0
35.0
30.0
0
15
30
60
120
180
240
360
480
time (minutes)
5 mg/kg
25 mg/kg
150 mg/kg

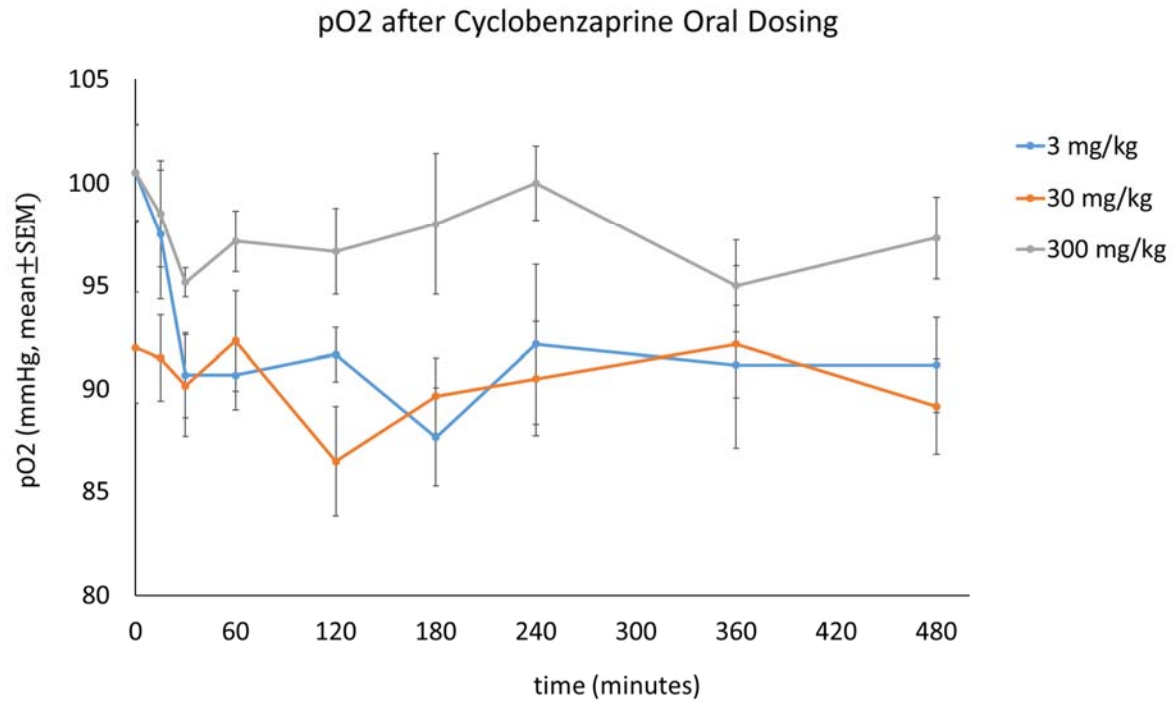

pO2 after Clozapine Oral Dosing
pO2 (mmHg, mean±SEM)
120
115
110
105
100
95
90
85
0
60
120
180
240
300
360
420
480
time (minutes)
5 mg/kg
25 mg/kg
150 mg/kg

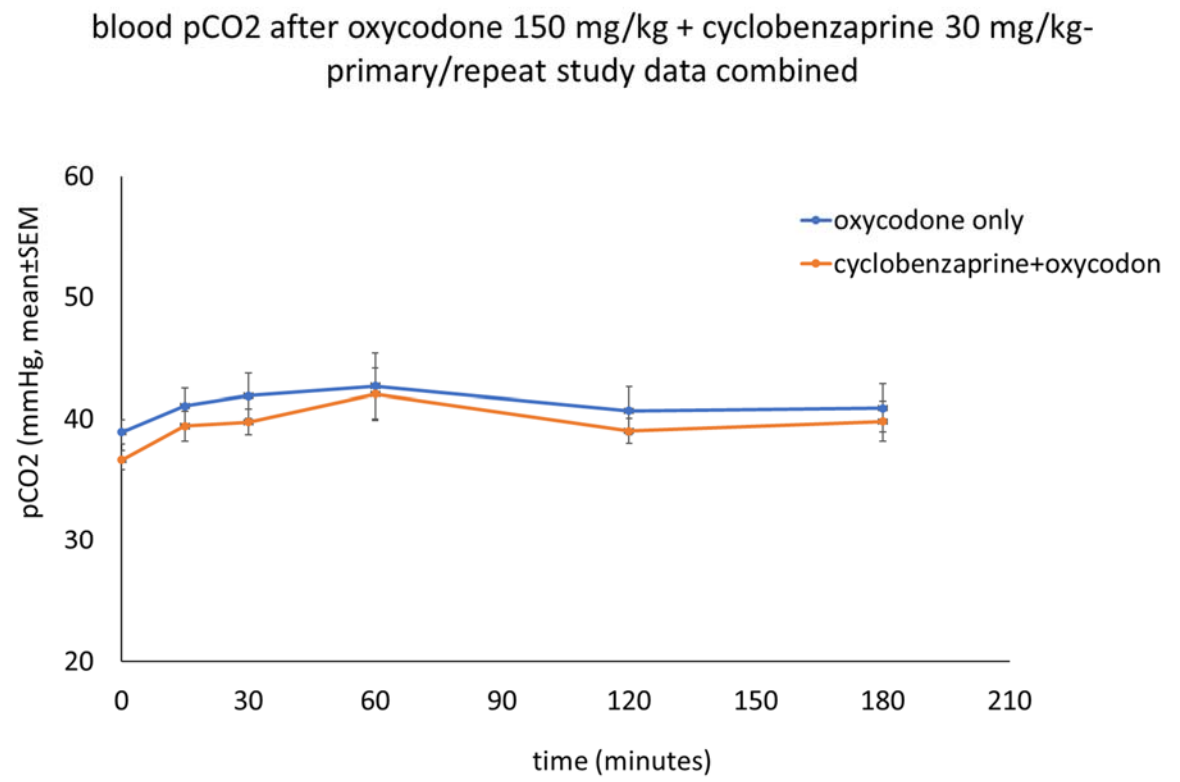

Blood pCO2 after oxycodone 150 mg/kg alone or
clozapine 25 mg/kg + oxycodone 150 mg/kg
pCO2 (mmHg, mean±SEM)
50
45
40
35
30
0
30
60
90
120
150
180
210
time (minutes)
oxycodone only
clozapine+oxycodone

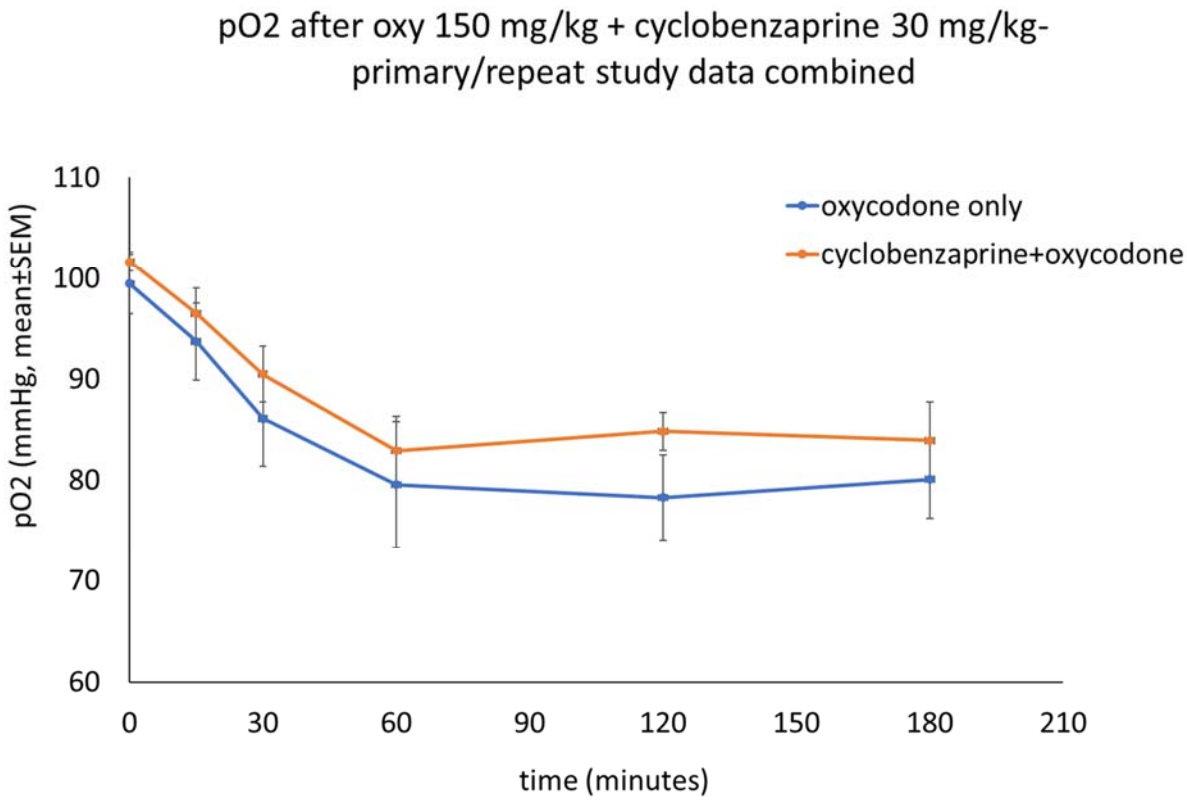


Cyclobenzaprine

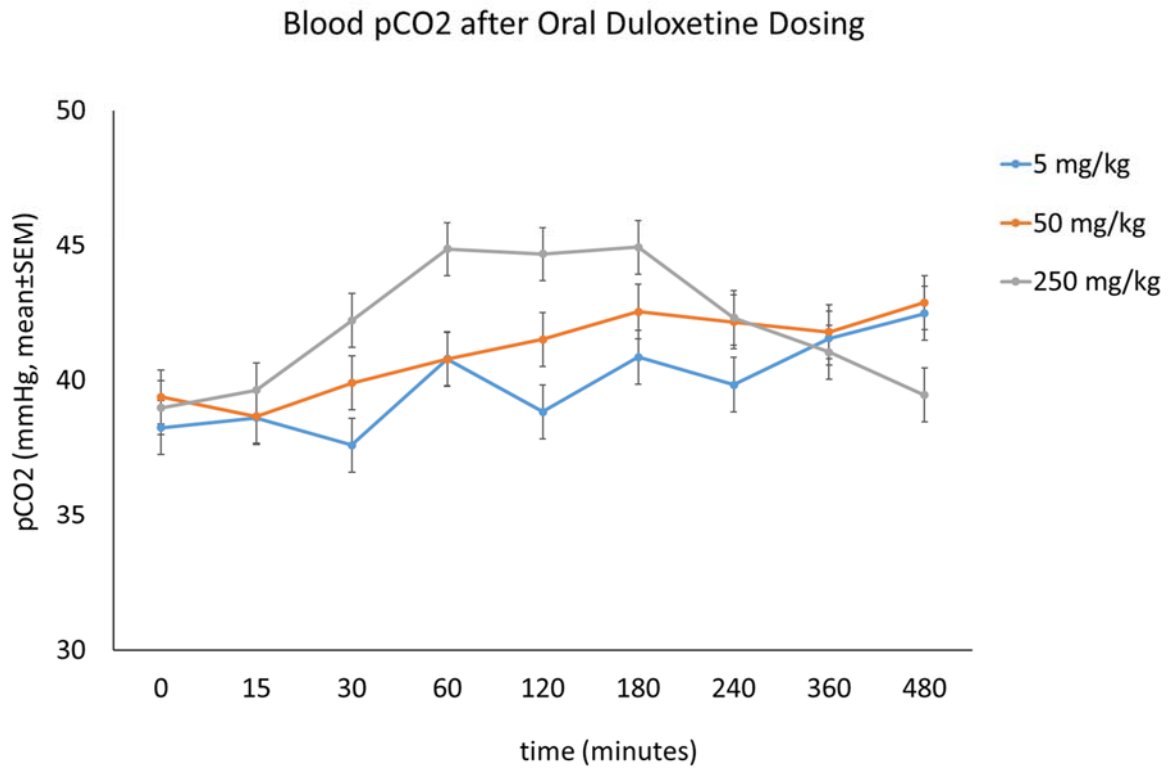

Blood pCO2 after Oral Cyclobenzaprine Dosing
45.0
40.0
35.0
30.0
pCO2 (mmHg, mean±SEM)
0
15
30
60
120
180
240
360
480
time (minutes)
3 mg/kg
30 mg/kg
300 mg/kg

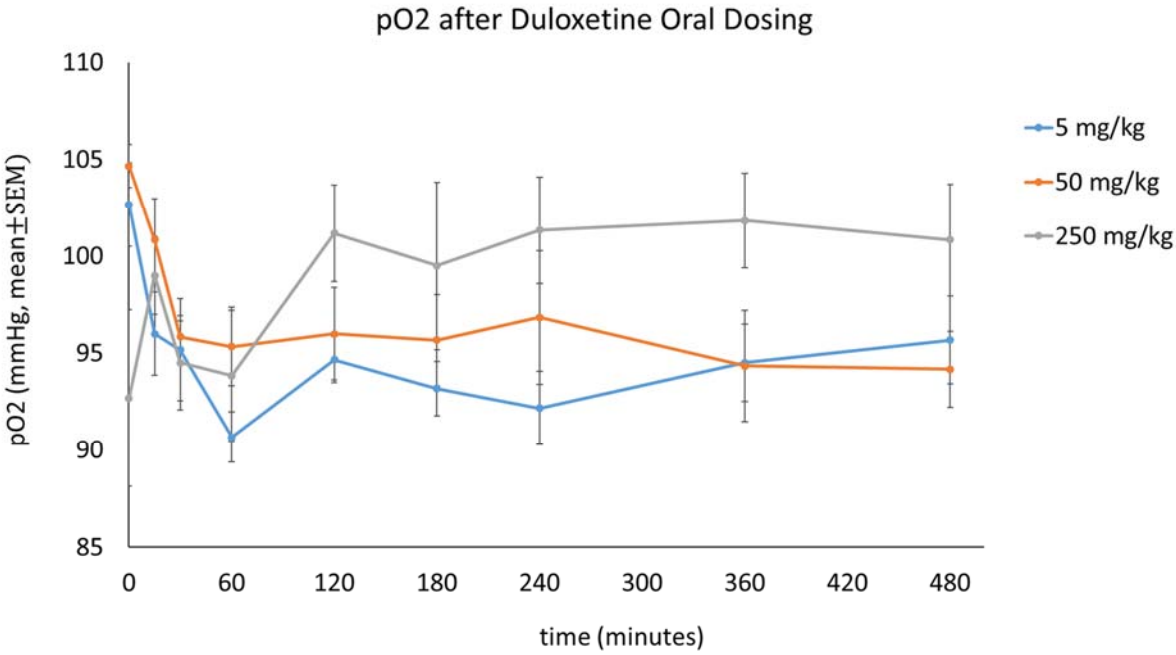

pO2 after Cyclobenzaprine Oral Dosing
105
100
95
90
85
80
pO2 (mmHg, mean±SEM)
0
60
120
180
240
300
360
420
480
time (minutes)
3 mg/kg
30 mg/kg
300 mg/kg

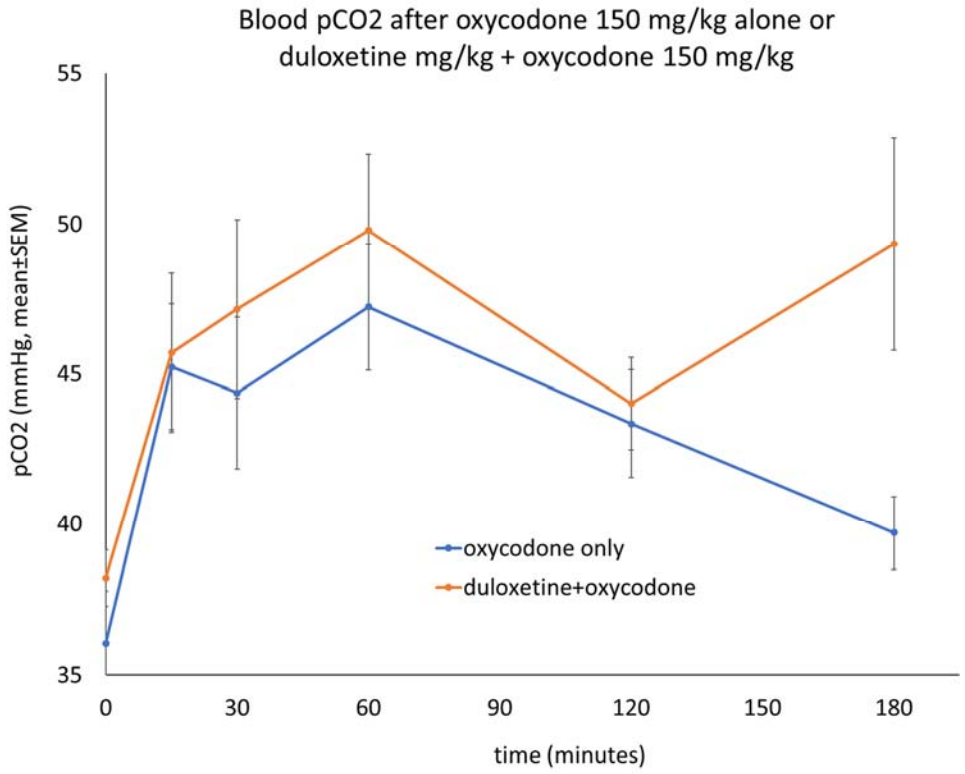

blood pCO2 after oxycodone 150 mg/kg + cyclobenzaprine 30 mg/kg- primary/repeat study data combined
pCO2 (mmHg, mean±SEM)
60
50
40
30
20
0
30
60
90
120
150
180
210
time (minutes)
oxycodone only
cyclobenzaprine+oxycodon

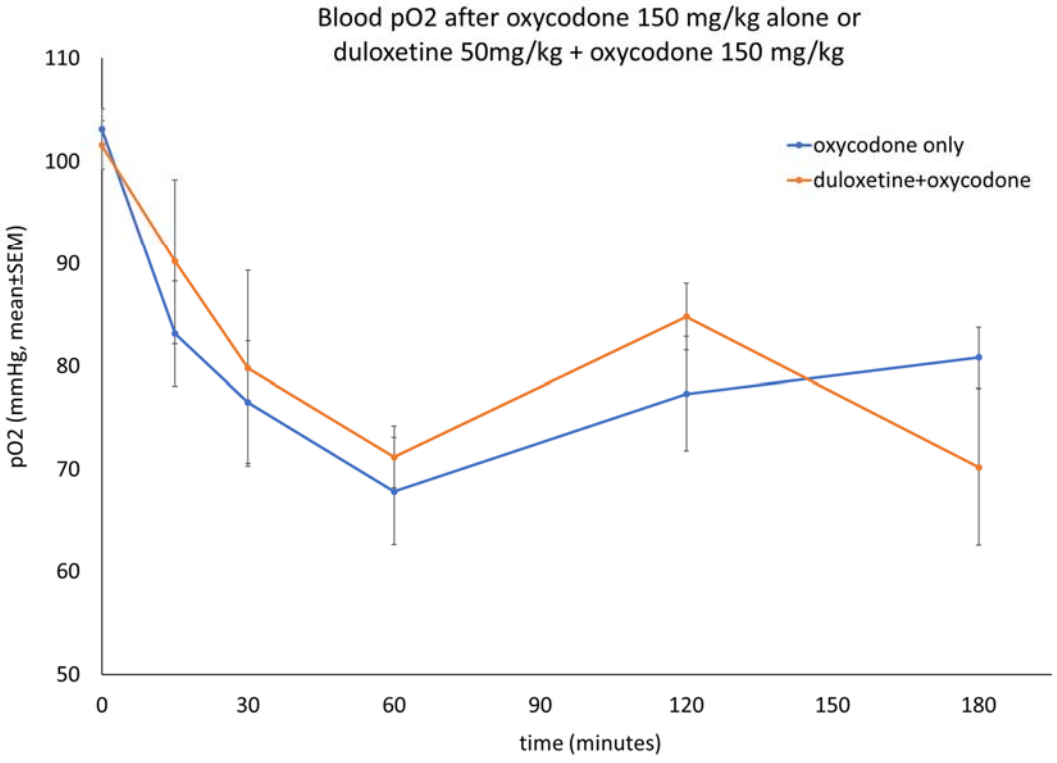

pO2 after oxy 150 mg/kg + cyclobenzaprine 30 mg/kg- primary/repeat study data combined
pO2 (mmHg, mean±SEM)
110
100
90
80
70
60
0
30
60
90
120
150
180
210
time (minutes)
oxycodone only
cyclobenzaprine+oxycodone

Duloxetine

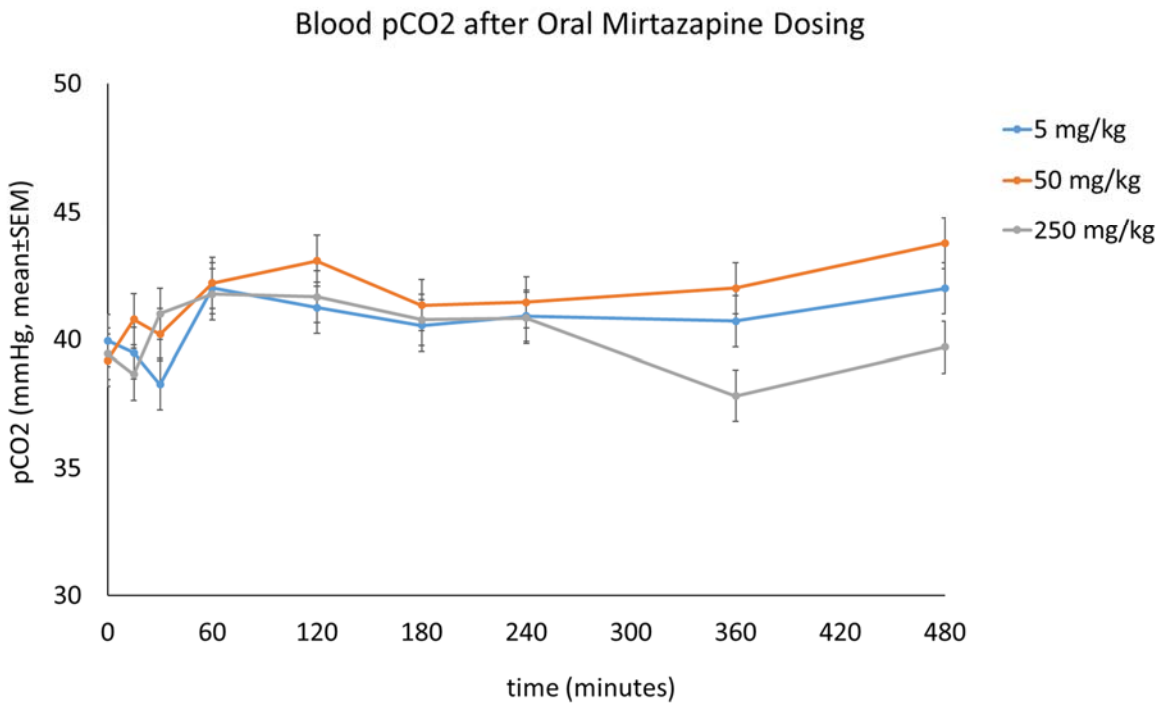

Blood pCO2 after Oral Duloxetine Dosing
pCO2 (mmHg, mean±SEM)
50
45
40
35
30
0
15
30
60
120
180
240
360
480
time (minutes)
5 mg/kg
50 mg/kg
250 mg/kg

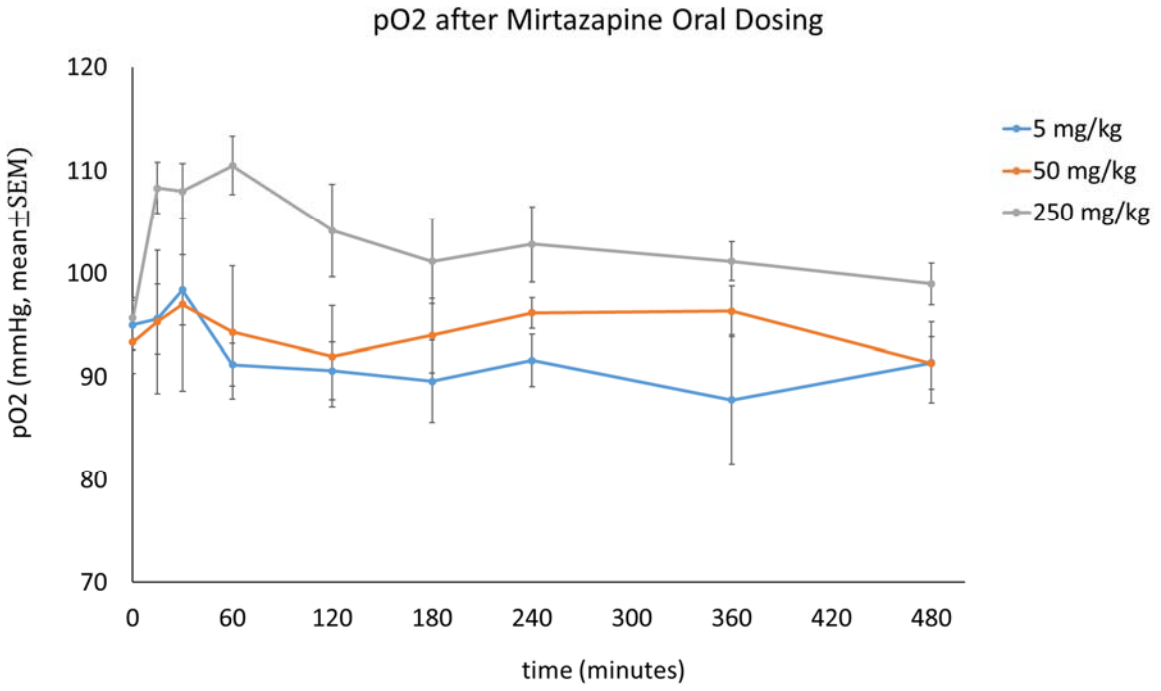

pO2 after Duloxetine Oral Dosing
pO2 (mmHg, mean±SEM)
110
105
100
95
90
85
0
60
120
180
240
300
360
420
480
time (minutes)
5 mg/kg
50 mg/kg
250 mg/kg

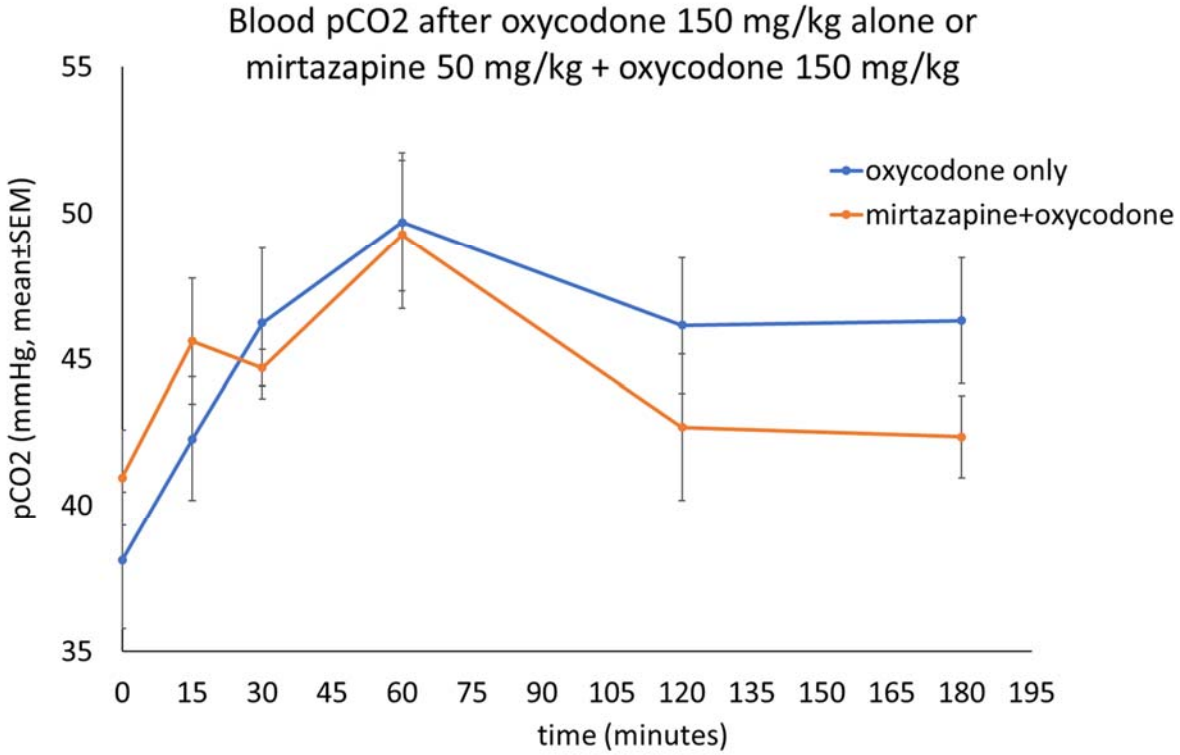

Blood pCO2 after oxycodone 150 mg/kg alone or duloxetine mg/kg + oxycodone 150 mg/kg
pCO2 (mmHg, mean±SEM)
55
50
45
40
35
0
30
60
90
120
150
180
time (minutes)
oxycodone only
duloxetine+oxycodone

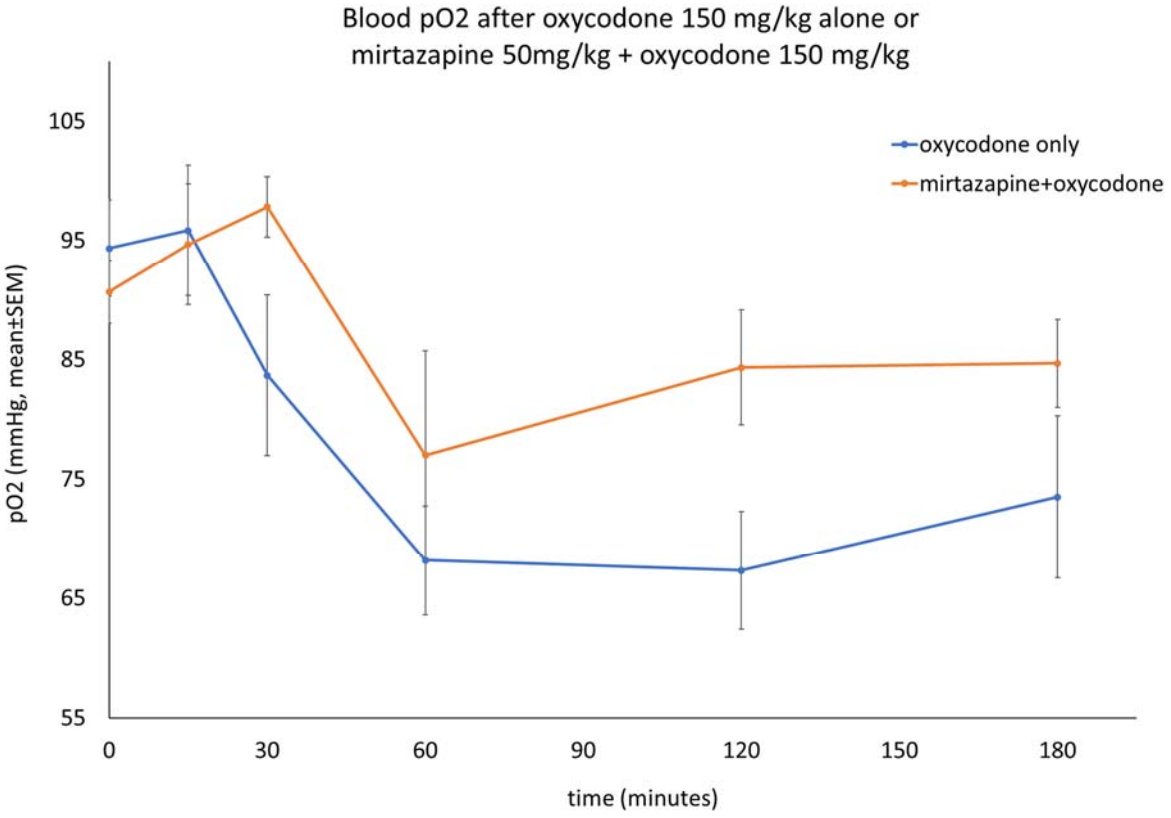

Blood pO2 after oxycodone 150 mg/kg alone or duloxetine 50mg/kg + oxycodone 150 mg/kg
pO2 (mmHg, mean±SEM)
110
100
90
80
70
60
50
0
30
60
90
120
150
180
time (minutes)
oxycodone only
duloxetine+oxycodone

Mirtazapine

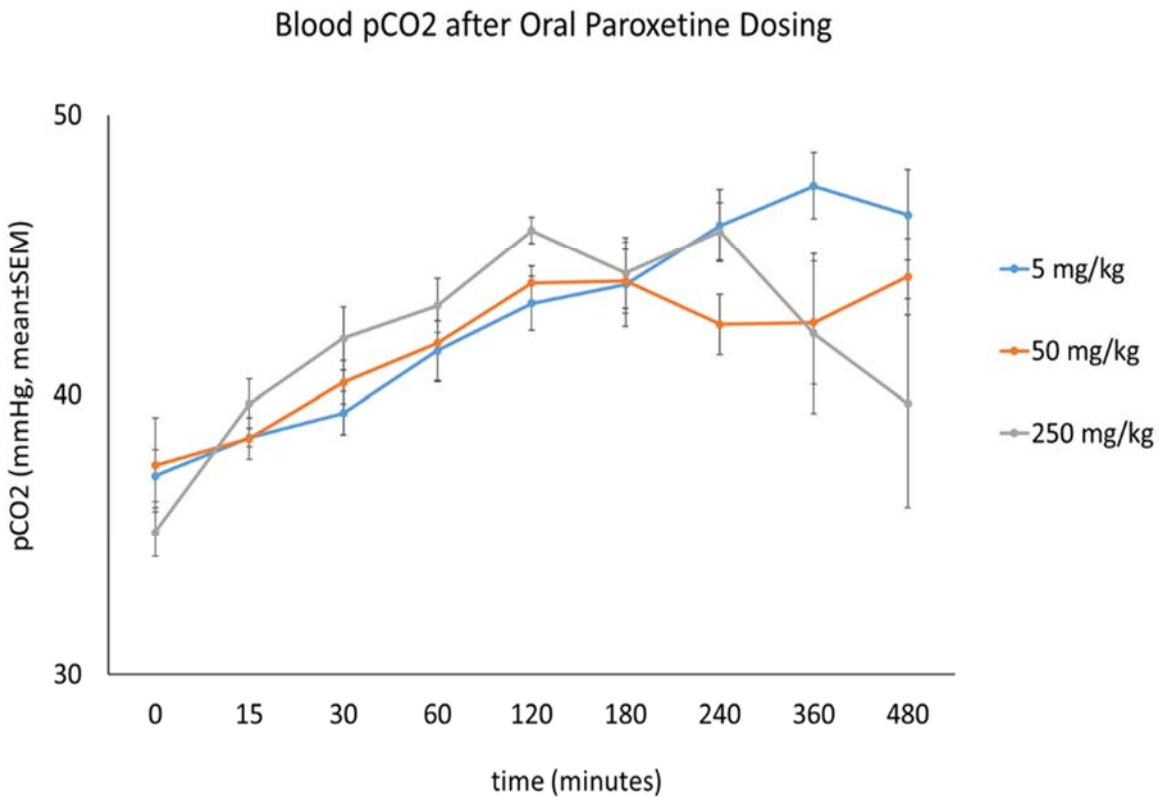


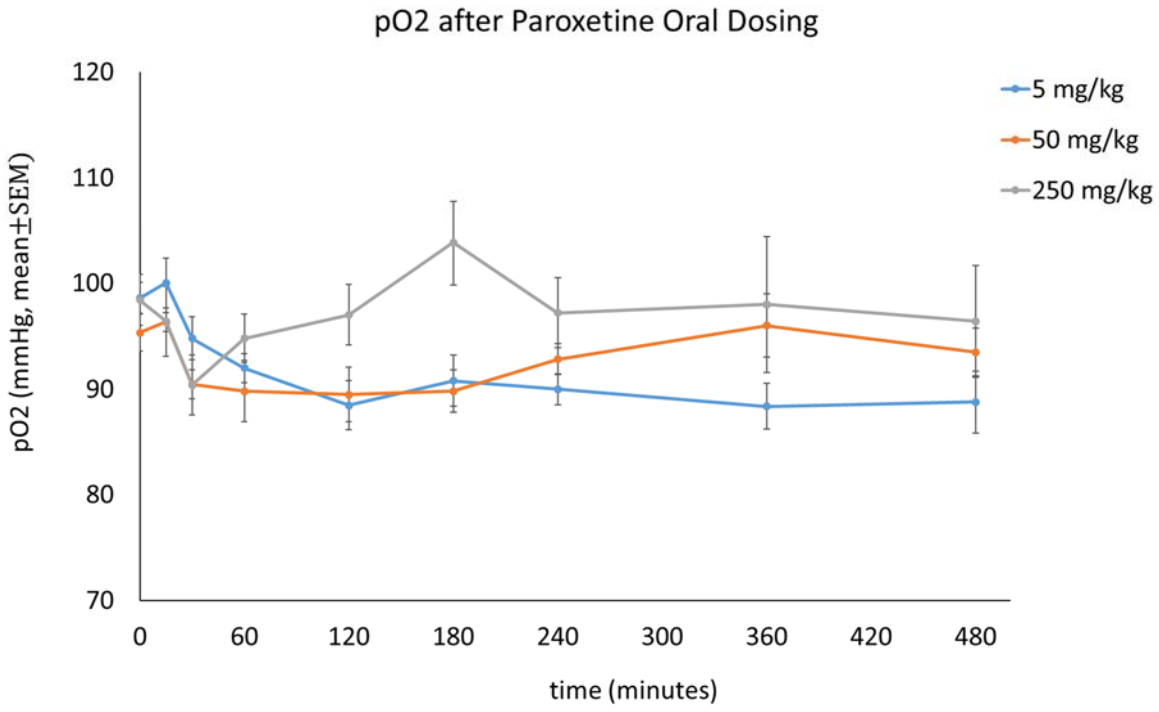


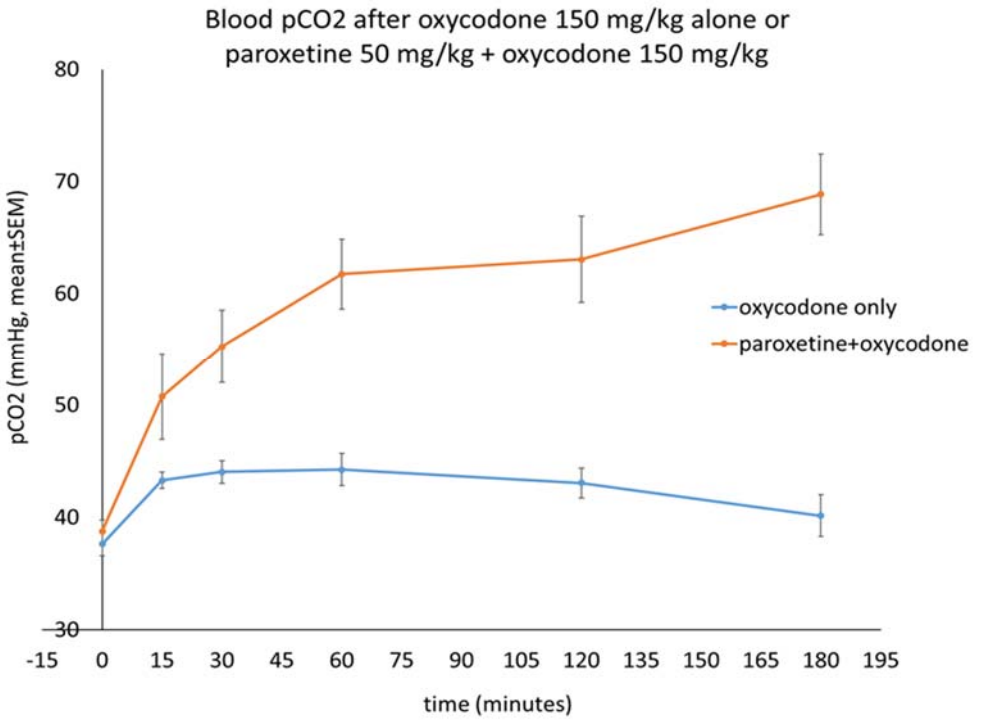

Blood pCO2 after oxycodone 150 mg/kg alone or
mirtazapine 50 mg/kg + oxycodone 150 mg/kg
oxycodone only
mirtazapine+oxycodone
pCO2 (mmHg, mean±SEM)
55
50
45
40
35
0 15 30 45 60 75 90 105 120 135 150 165 180 195
time (minutes)

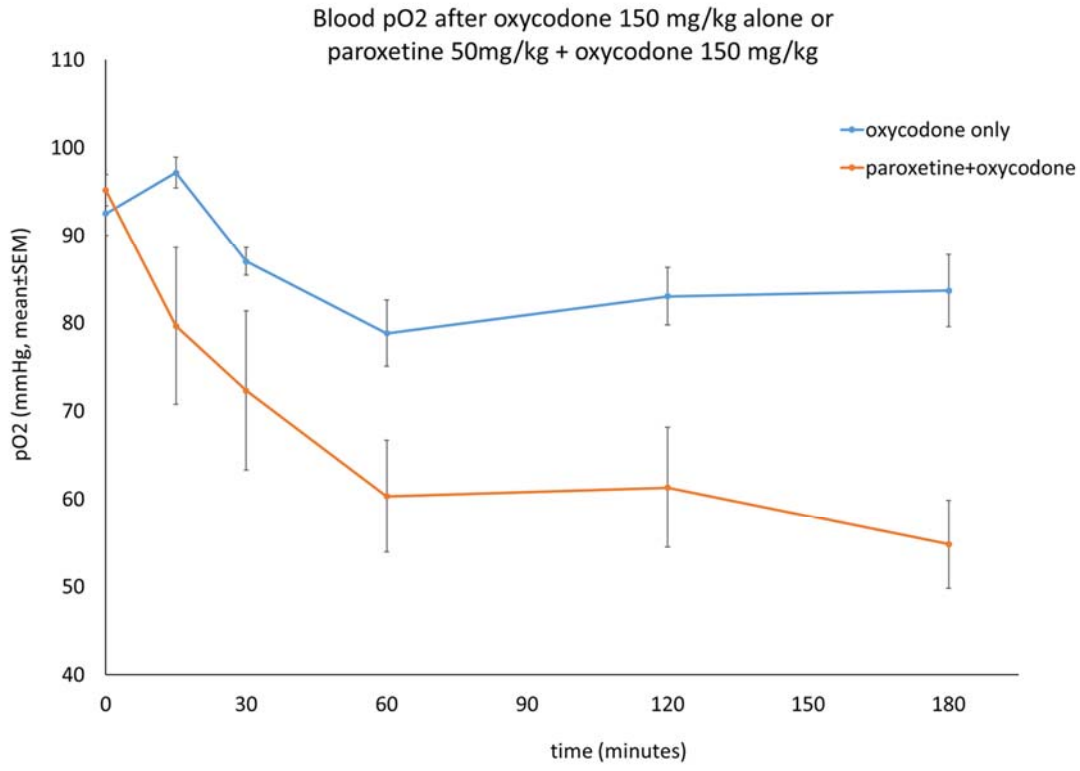

Blood pO2 after oxycodone 150 mg/kg alone or
mirtazapine 50mg/kg + oxycodone 150 mg/kg
oxycodone only
mirtazapine+oxycodone
pO2 (mmHg, mean±SEM)
105
95
85
75
65
55
0 30 60 90 120 150 180
time (minutes)

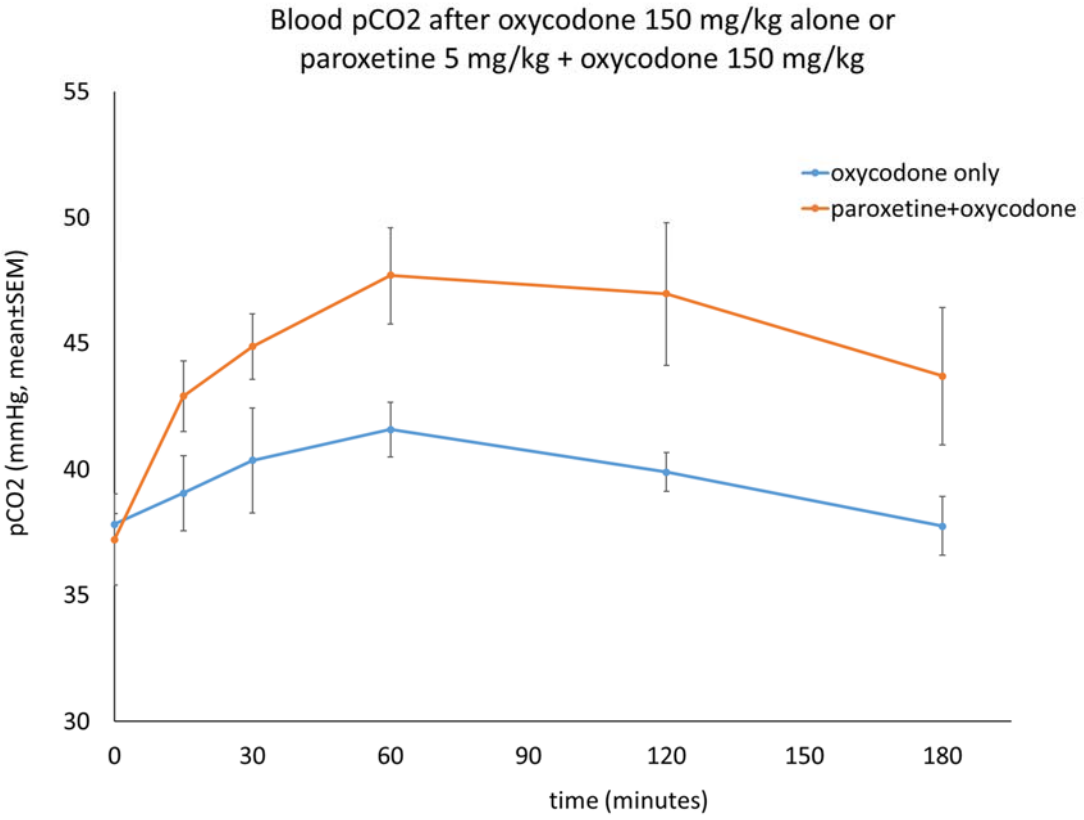
Paroxetine

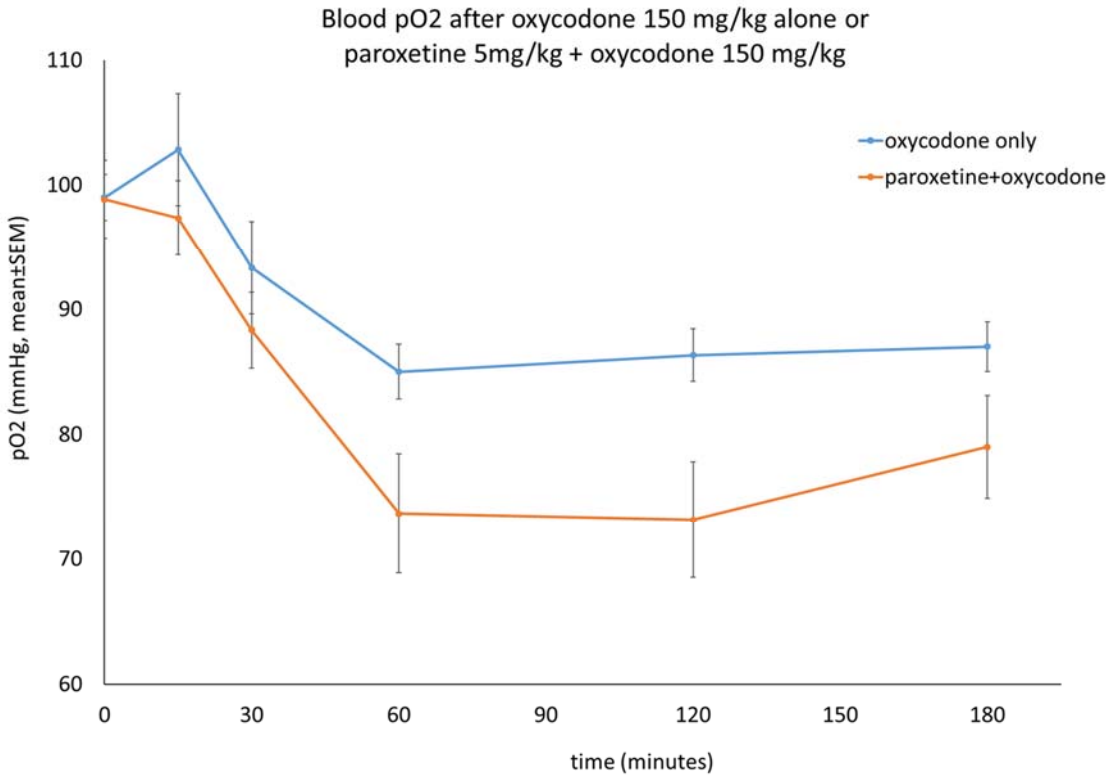

Blood pCO2 after Oral Paroxetine Dosing
pCO2 (mmHg, mean±SEM)
50
40
30
0
15
30
60
120
180
240
360
480
time (minutes)
5 mg/kg
50 mg/kg
250 mg/kg


pO2 after Paroxetine Oral Dosing
pO2 (mmHg, mean±SEM)
120
110
100
90
80
70
0
60
120
180
240
300
360
420
480
time (minutes)
5 mg/kg
50 mg/kg
250 mg/kg

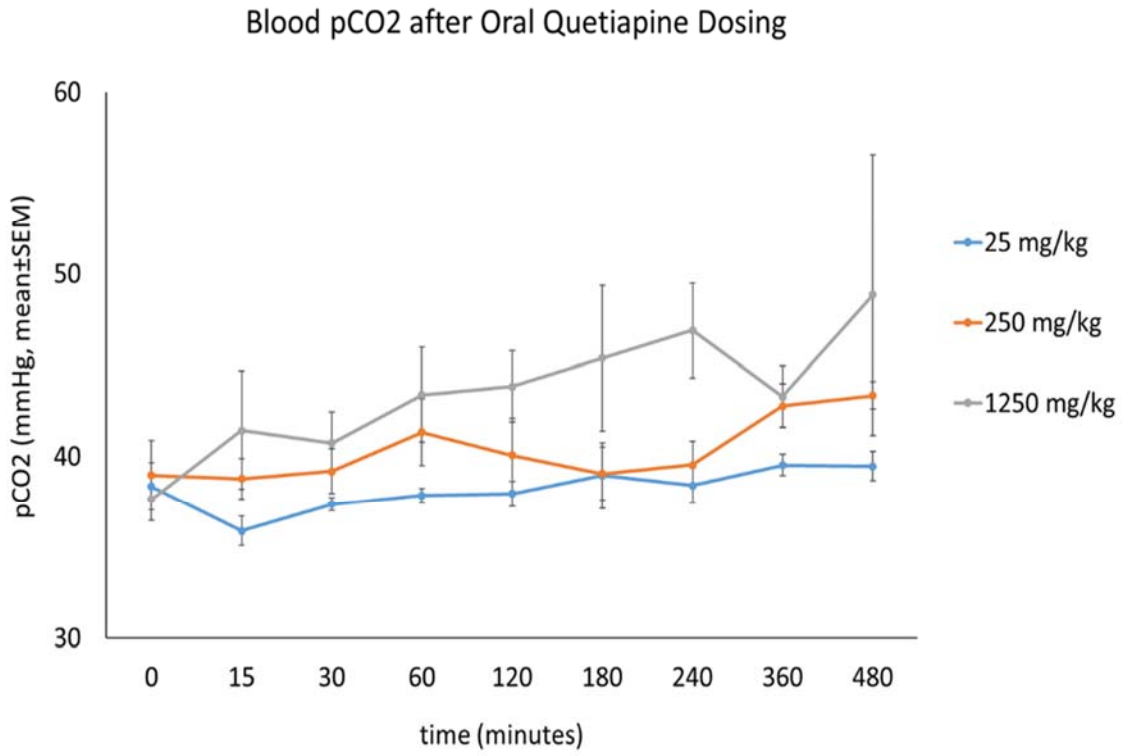

Blood pCO2 after oxycodone 150 mg/kg alone or paroxetine 50 mg/kg + oxycodone 150 mg/kg
pCO2 (mmHg, mean±SEM)
80
70
60
50
40
30
-15
0
15
30
45
60
75
90
105
120
135
150
165
180
195
time (minutes)
oxycodone only
paroxetine+oxycodone

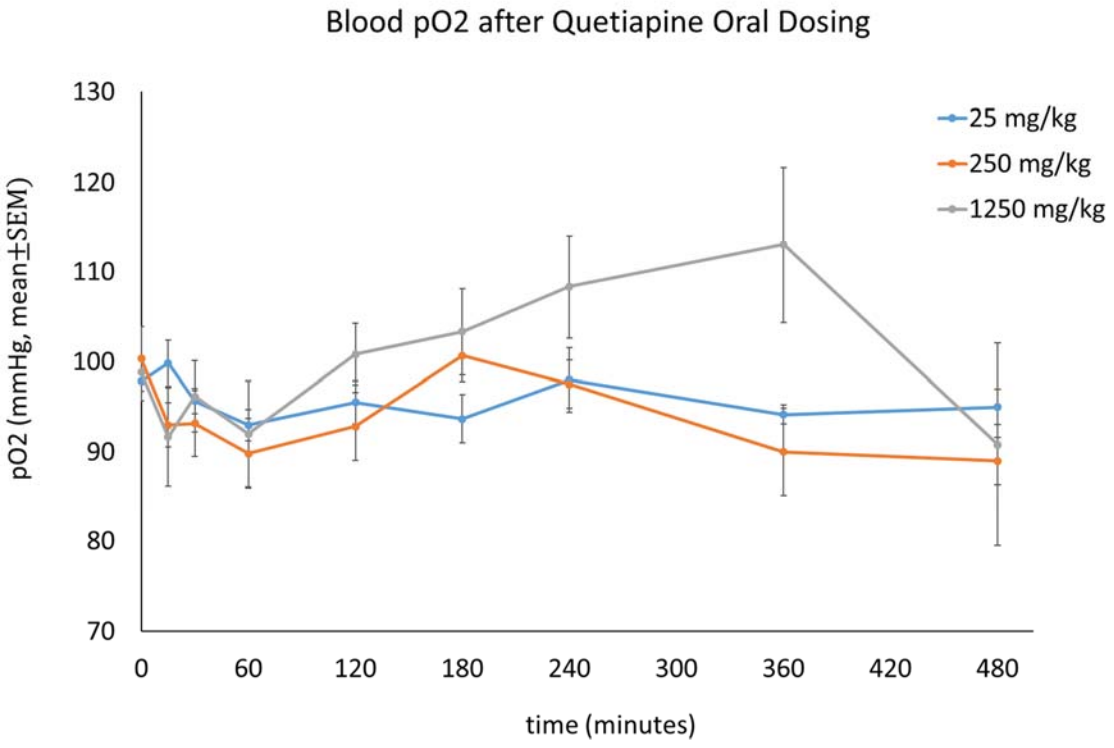

Blood pO2 after oxycodone 150 mg/kg alone or paroxetine 50mg/kg + oxycodone 150 mg/kg
pO2 (mmHg, mean±SEM)
110
100
90
80
70
60
50
40
0
30
60
90
120
150
180
time (minutes)
oxycodone only
paroxetine+oxycodone

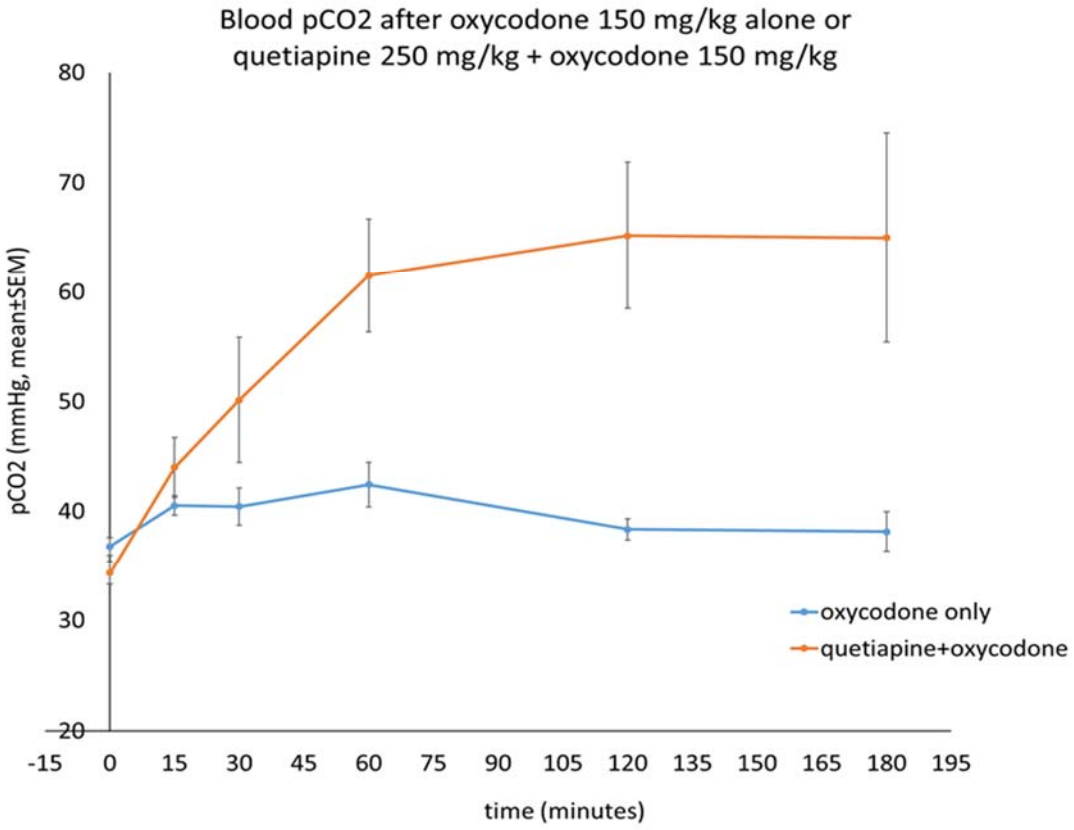

Blood pCO2 after oxycodone 150 mg/kg alone or paroxetine 5 mg/kg + oxycodone 150 mg/kg
55
50
45
40
35
30
pCO2 (mmHg, mean±SEM)
0
30
60
90
120
150
180
time (minutes)
oxycodone only
paroxetine+oxycodone

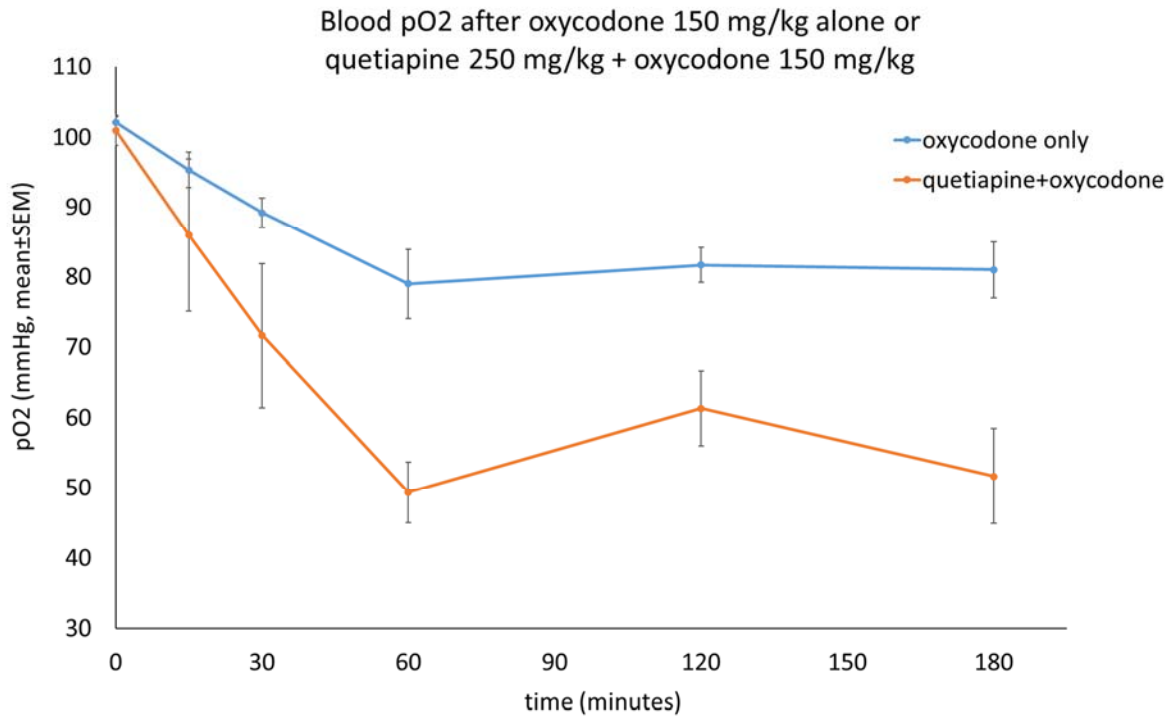

Blood pO2 after oxycodone 150 mg/kg alone or paroxetine 5mg/kg + oxycodone 150 mg/kg
110
100
90
80
70
60
pO2 (mmHg, mean±SEM)
0
30
60
90
120
150
180
time (minutes)
oxycodone only
paroxetine+oxycodone

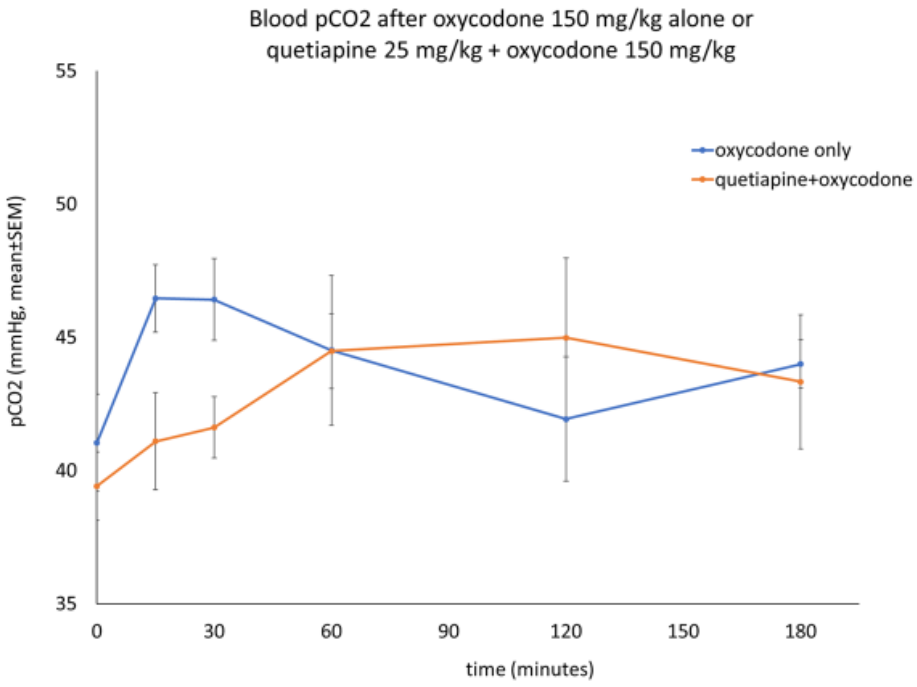
Quetiapine

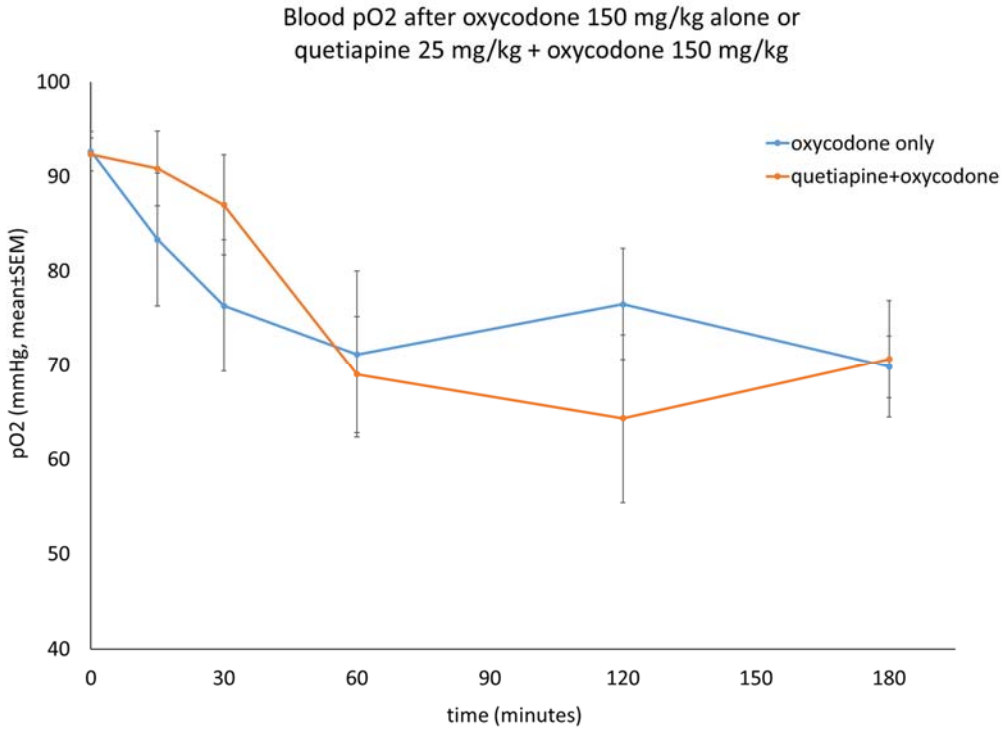

Blood pCO2 after Oral Quetiapine Dosing
pCO2 (mmHg, mean±SEM)
60
50
40
30
0
15
30
60
120
180
240
360
480
time (minutes)
25 mg/kg
250 mg/kg
1250 mg/kg


Blood pO2 after Quetiapine Oral Dosing
pO2 (mmHg, mean±SEM)
130
120
110
100
90
80
70
0
60
120
180
240
300
360
420
480
time (minutes)
25 mg/kg
250 mg/kg
1250 mg/kg

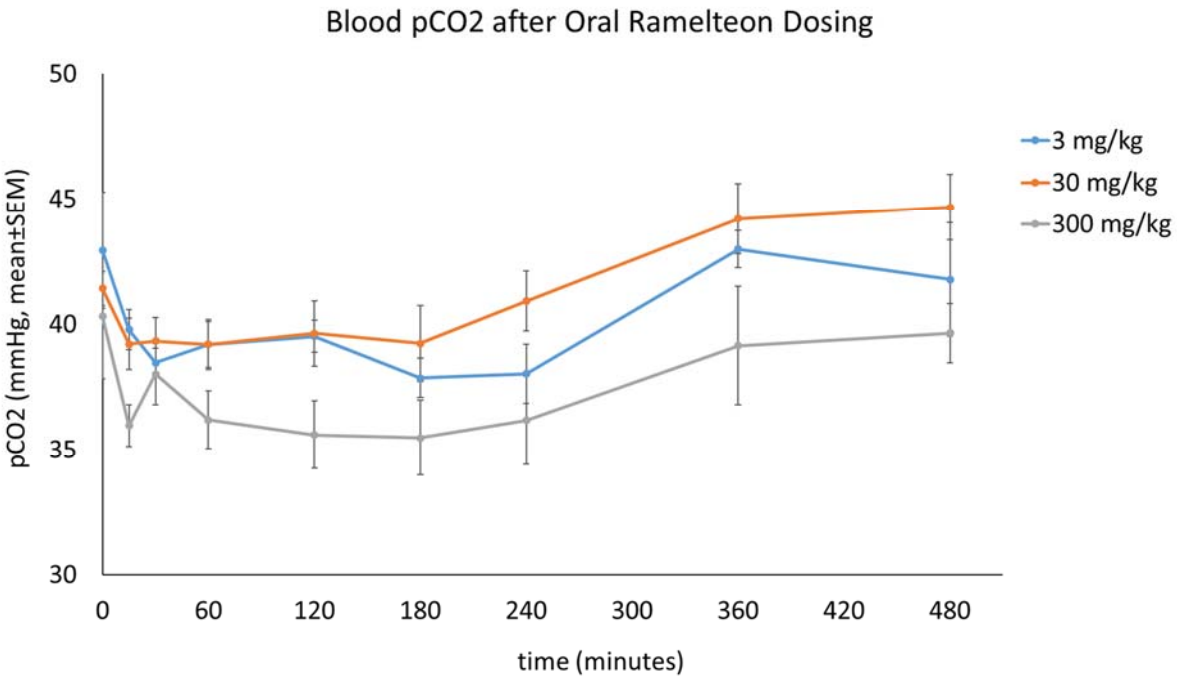

Blood pCO2 after oxycodone 150 mg/kg alone or quetiapine 250 mg/kg + oxycodone 150 mg/kg
pCO2 (mmHg, mean±SEM)
80
70
60
50
40
30
20
-15
0
15
30
45
60
75
90
105
120
135
150
165
180
195
time (minutes)
oxycodone only
quetiapine+oxycodone

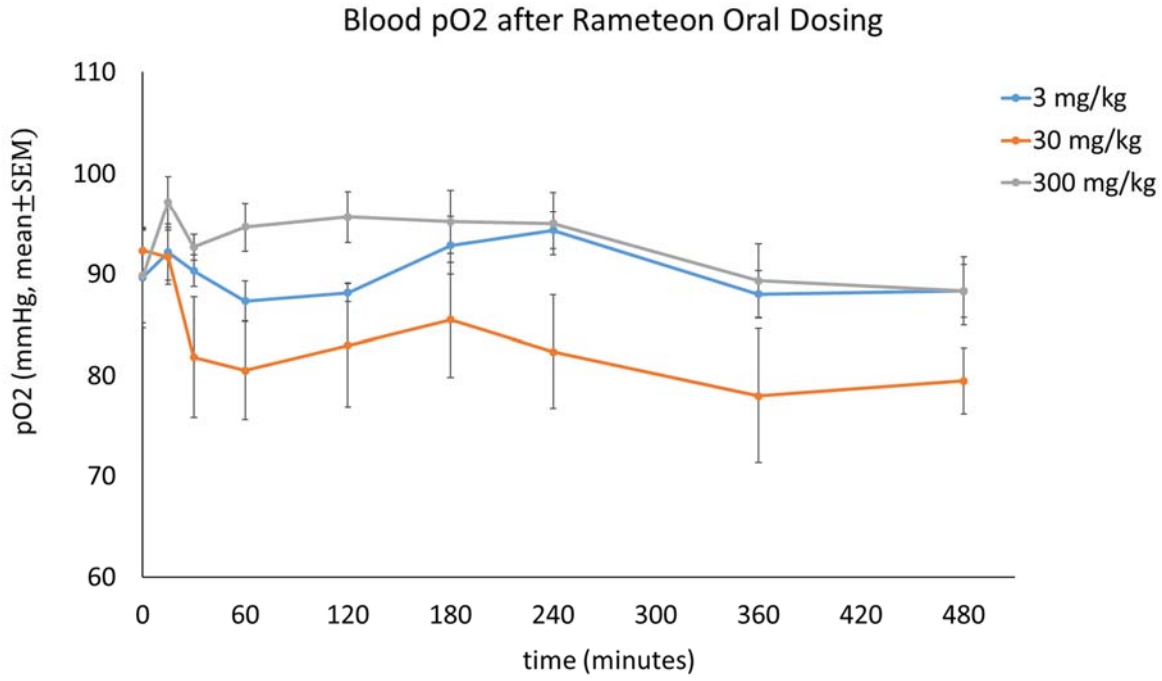

Blood pO2 after oxycodone 150 mg/kg alone or quetiapine 250 mg/kg + oxycodone 150 mg/kg
pO2 (mmHg, mean±SEM)
110
100
90
80
70
60
50
40
30
0
30
60
90
120
150
180
time (minutes)
oxycodone only
quetiapine+oxycodone

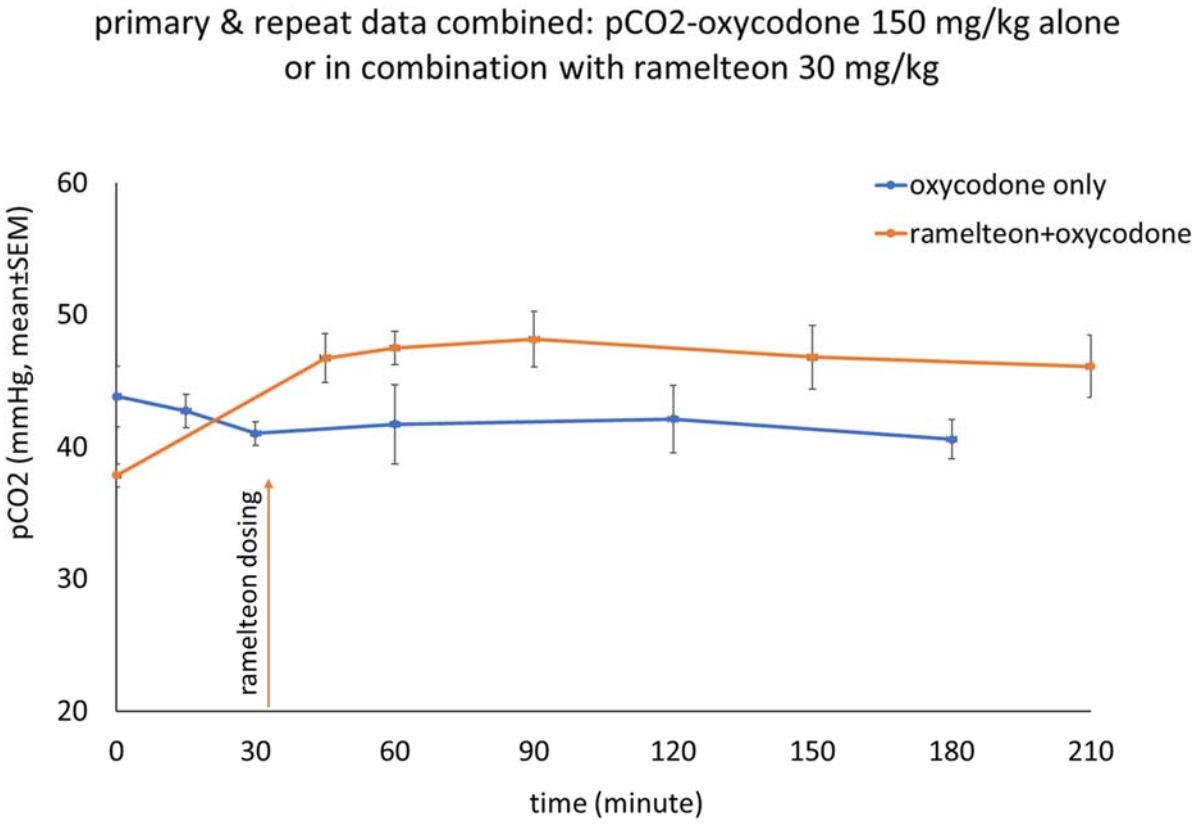

Blood pCO2 after oxycodone 150 mg/kg alone or quetiapine 25 mg/kg + oxycodone 150 mg/kg
55
50
45
40
35
pCO2 (mmHg, mean±SEM)
0
30
60
90
120
150
180
time (minutes)
oxycodone only
quetiapine+oxycodone

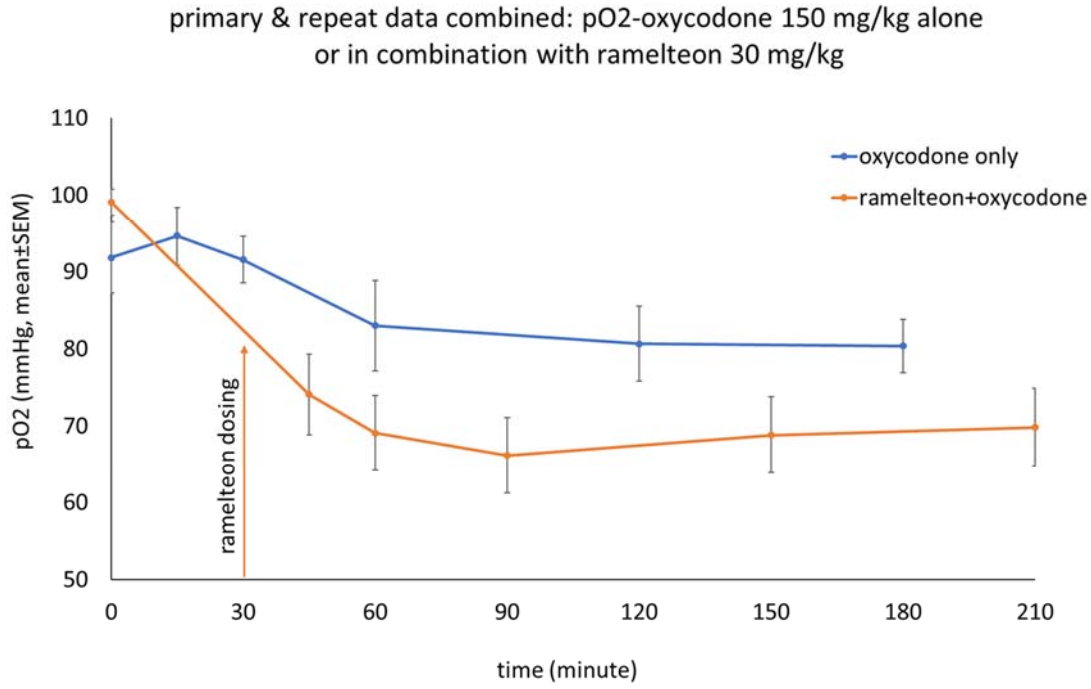

Blood pO2 after oxycodone 150 mg/kg alone or quetiapine 25 mg/kg + oxycodone 150 mg/kg
100
90
80
70
60
50
40
pO2 (mmHg, mean±SEM)
0
30
60
90
120
150
180
time (minutes)
oxycodone only
quetiapine+oxycodone

Ramelteon

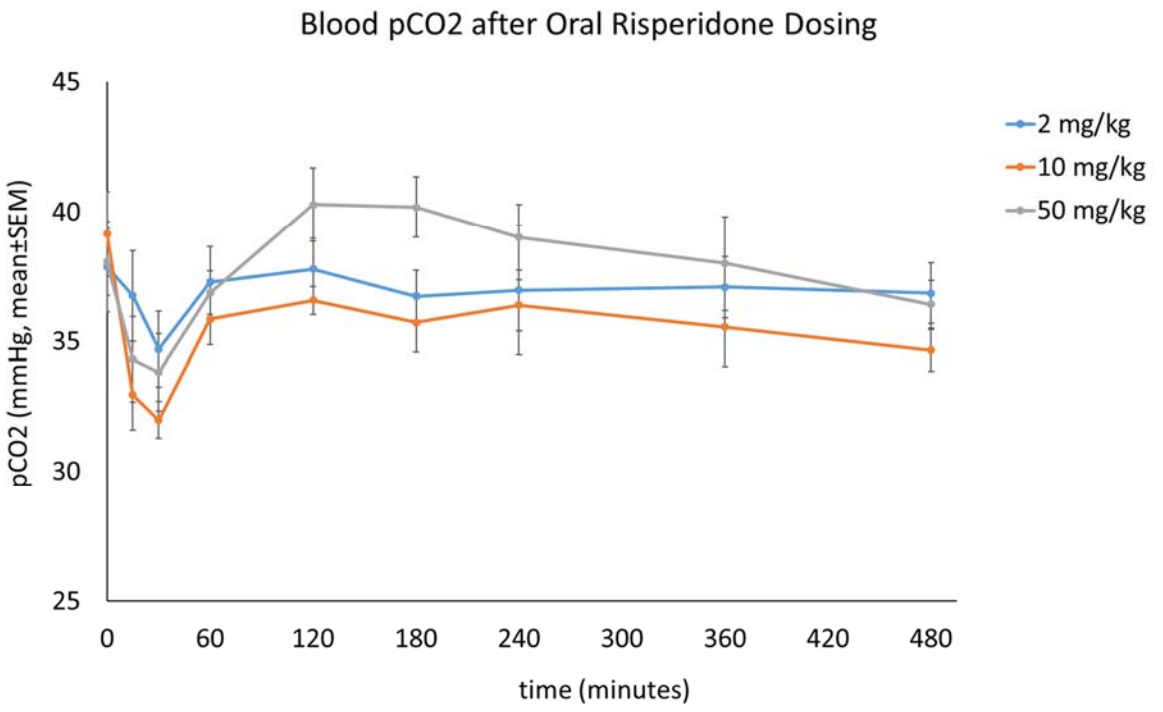

Blood pCO2 after Oral Ramelteon Dosing
pCO2 (mmHg, mean±SEM)
50
45
40
35
30
0
60
120
180
240
300
360
420
480
time (minutes)
3 mg/kg
30 mg/kg
300 mg/kg

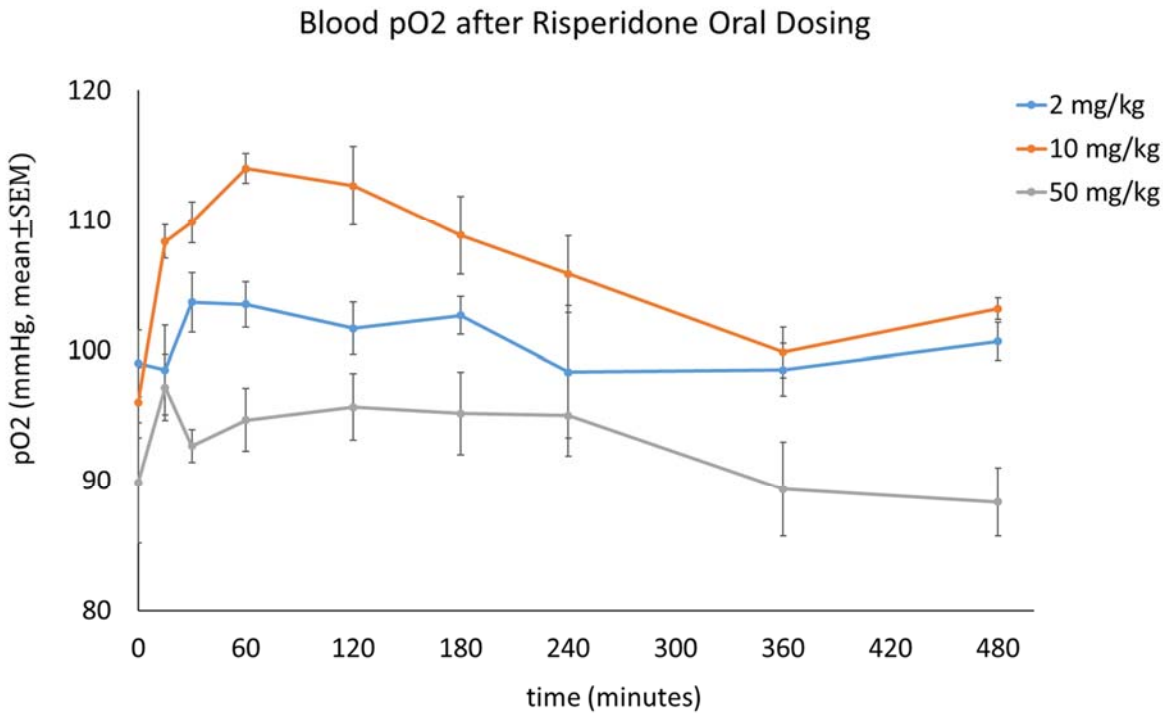

Blood pO2 after Rameteon Oral Dosing
pO2 (mmHg, mean±SEM)
110
100
90
80
70
60
0
60
120
180
240
300
360
420
480
time (minutes)
3 mg/kg
30 mg/kg
300 mg/kg

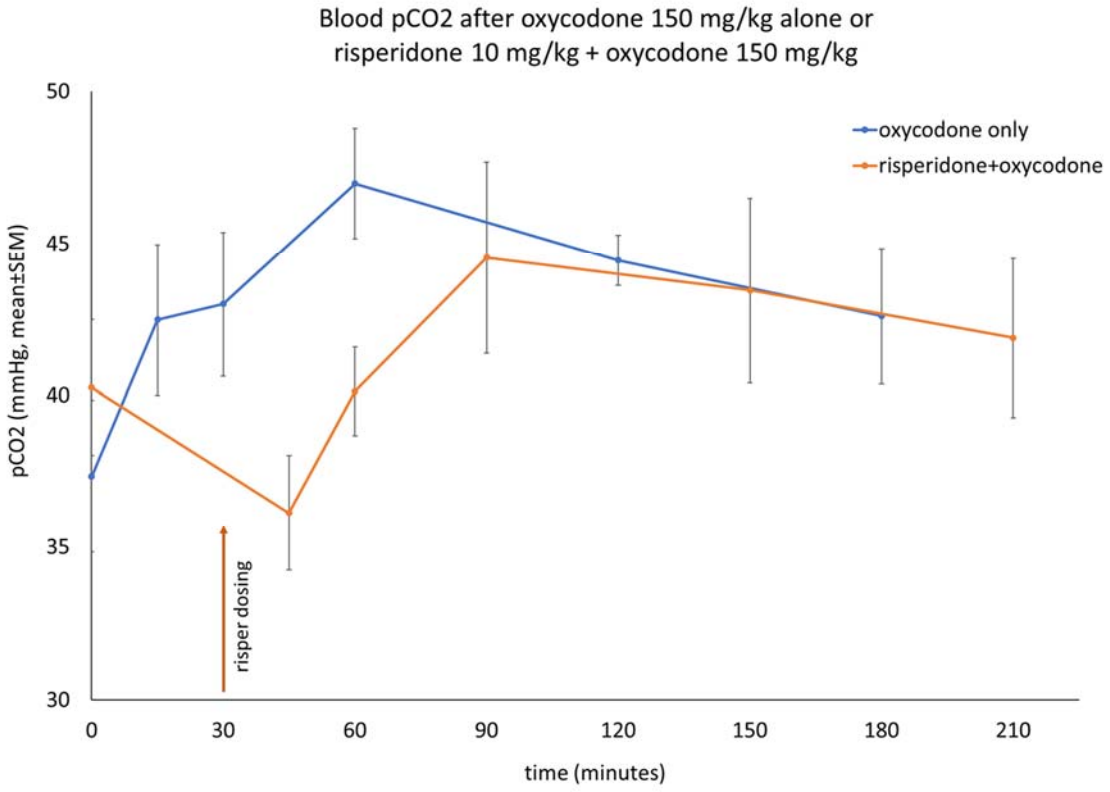

primary & repeat data combined: pCO2-oxycodone 150 mg/kg alone
or in combination with ramelteon 30 mg/kg
oxycodone only
ramelteon+oxycodone
pCO2 (mmHg, mean±SEM)
60
50
40
30
20
ramelteon dosing
0
30
60
90
120
150
180
210
time (minute)

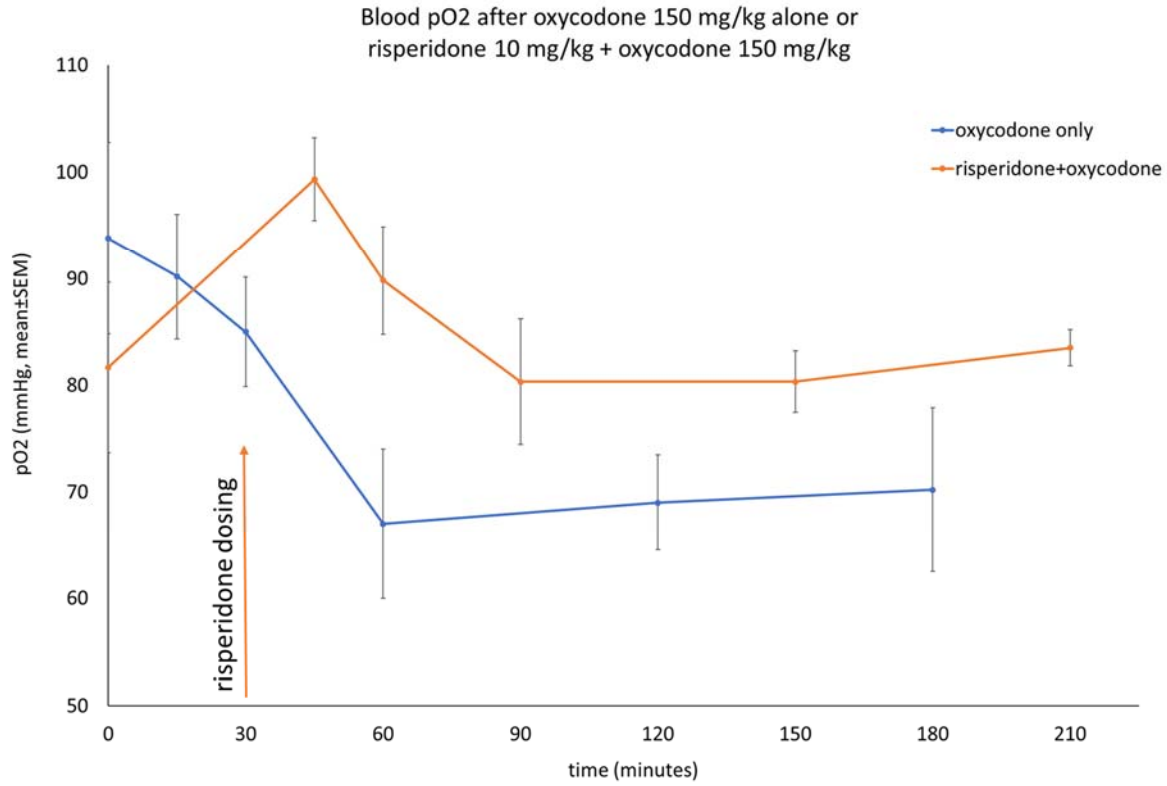

primary & repeat data combined: pO2-oxycodone 150 mg/kg alone
or in combination with ramelteon 30 mg/kg
oxycodone only
ramelteon+oxycodone
pO2 (mmHg, mean±SEM)
110
100
90
80
70
60
50
ramelteon dosing
0
30
60
90
120
150
180
210
time (minute)

Risperidone

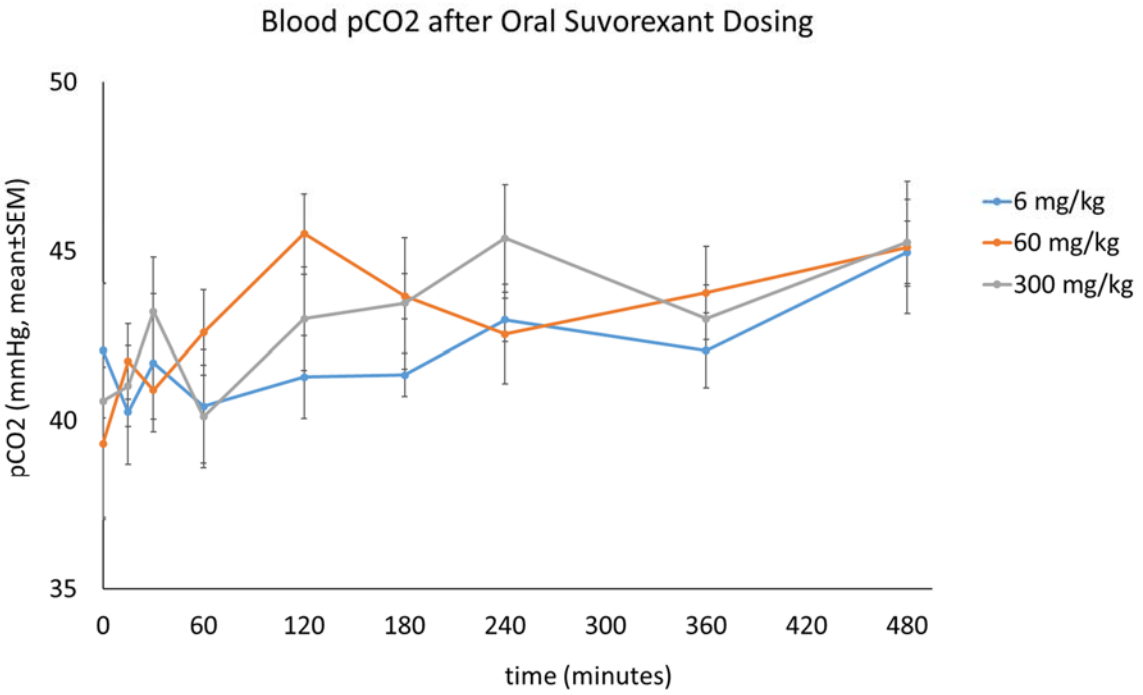


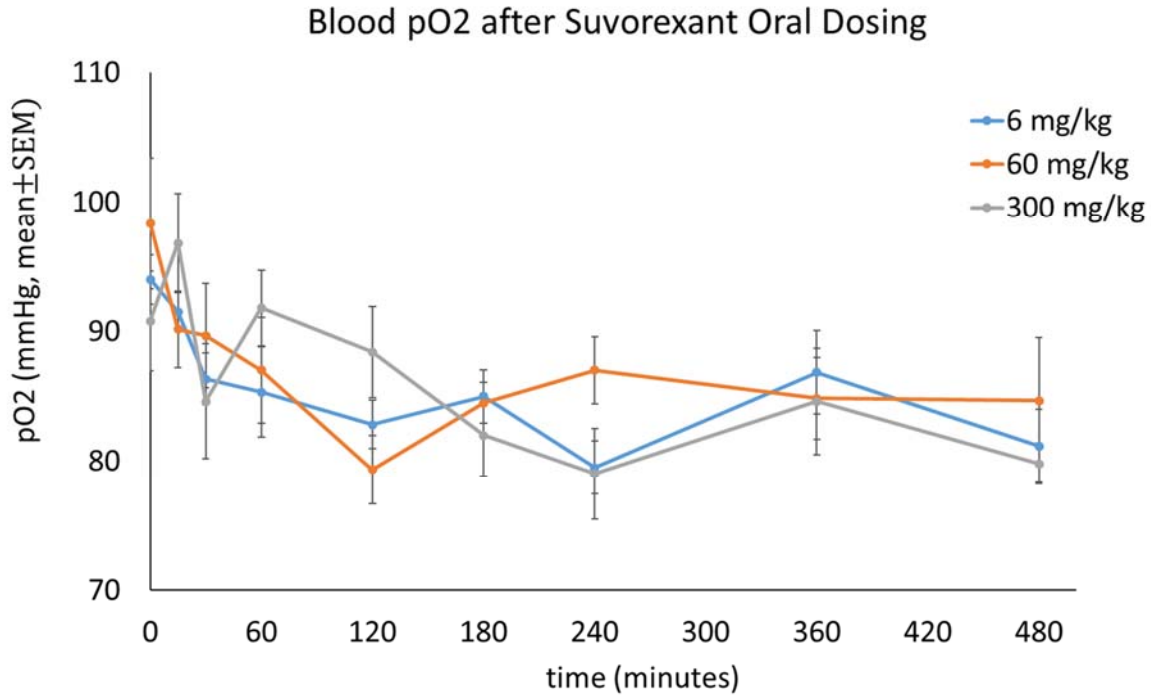


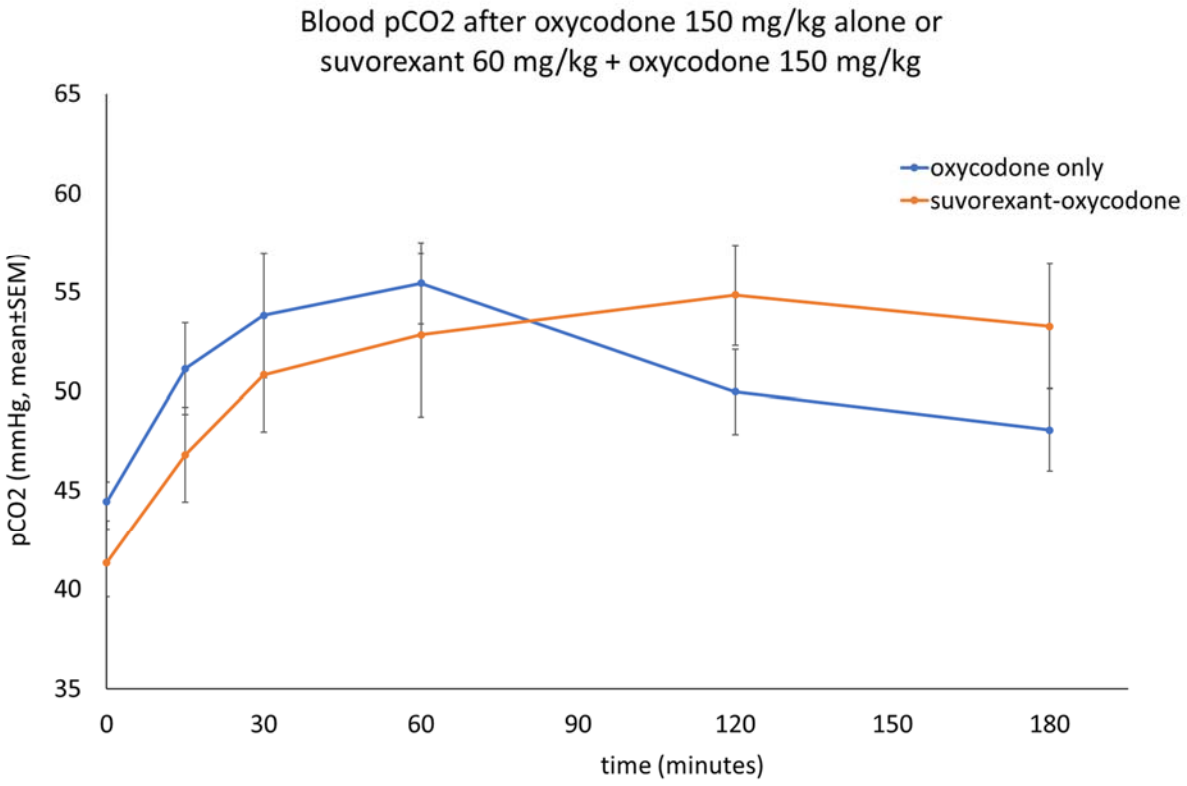

Blood pCO2 after oxycodone 150 mg/kg alone or
risperidone 10 mg/kg + oxycodone 150 mg/kg
oxycodone only
risperidone+oxycodone
pCO2 (mmHg, mean±SEM)
50
45
40
35
30
risper dosing
0
30
60
90
120
150
180
210
time (minutes)

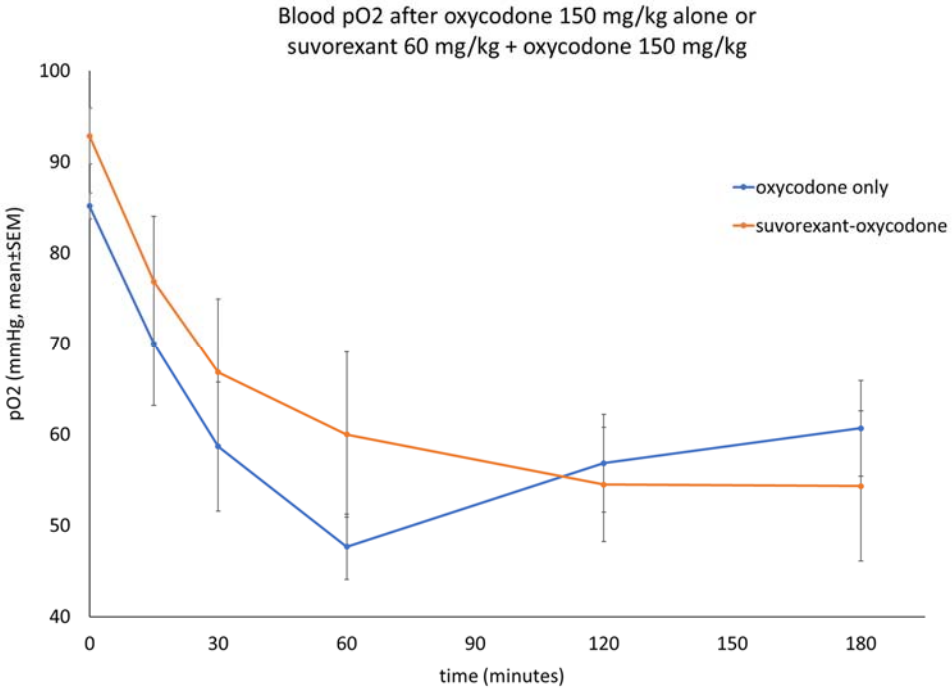

Blood pO2 after oxycodone 150 mg/kg alone or
risperidone 10 mg/kg + oxycodone 150 mg/kg
oxycodone only
risperidone+oxycodone
pO2 (mmHg, mean±SEM)
110
100
90
80
70
60
50
risperidone dosing
0
30
60
90
120
150
180
210
time (minutes)

Suvorexant

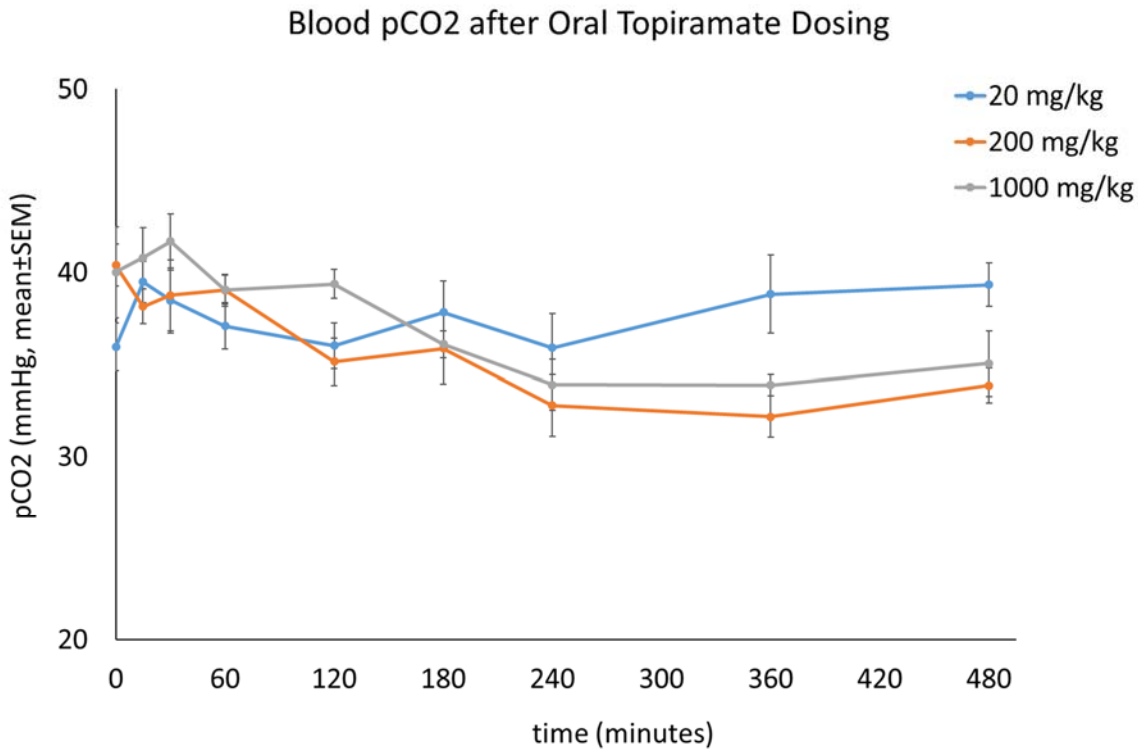

Blood pCO2 after Oral Suvorexant Dosing
pCO2 (mmHg, mean±SEM)
50
45
40
35
0
60
120
180
240
300
360
420
480
time (minutes)
6 mg/kg
60 mg/kg
300 mg/kg

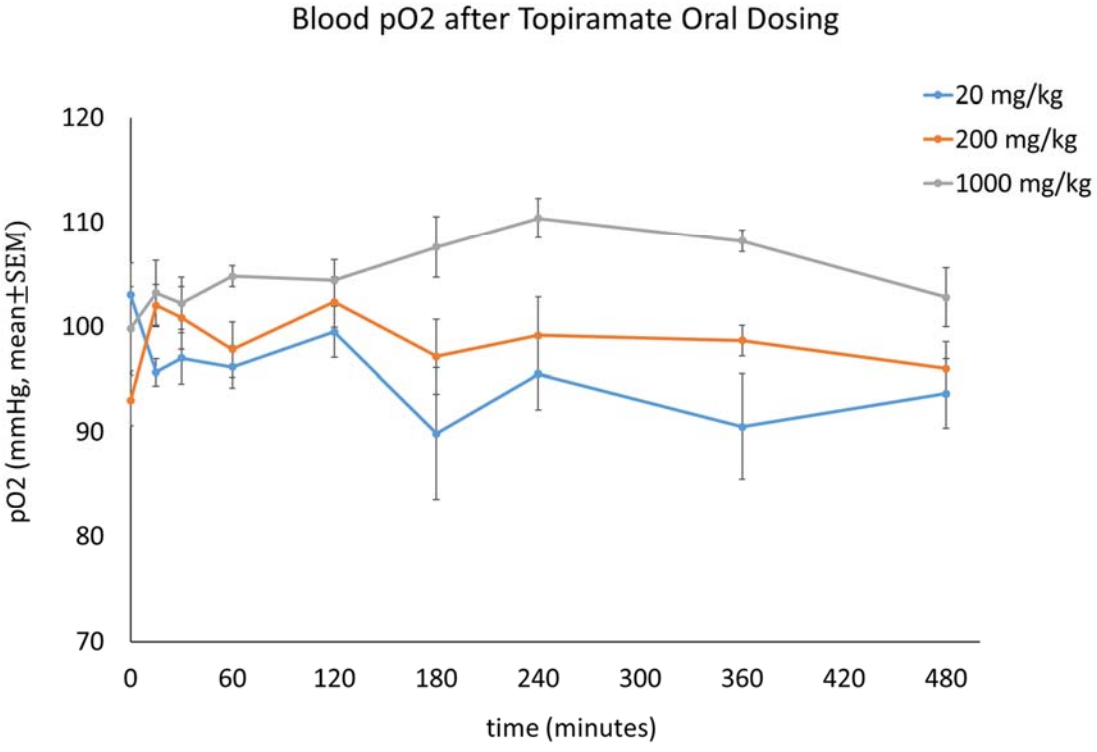

Blood pO2 after Suvorexant Oral Dosing
pO2 (mmHg, mean±SEM)
110
100
90
80
70
0
60
120
180
240
300
360
420
480
time (minutes)
6 mg/kg
60 mg/kg
300 mg/kg


Blood pCO2 after oxycodone 150 mg/kg alone or
suvorexant 60 mg/kg + oxycodone 150 mg/kg
pCO2 (mmHg, mean±SEM)
65
60
55
50
45
40
35
0
30
60
90
120
150
180
time (minutes)
oxycodone only
suvorexant-oxycodone

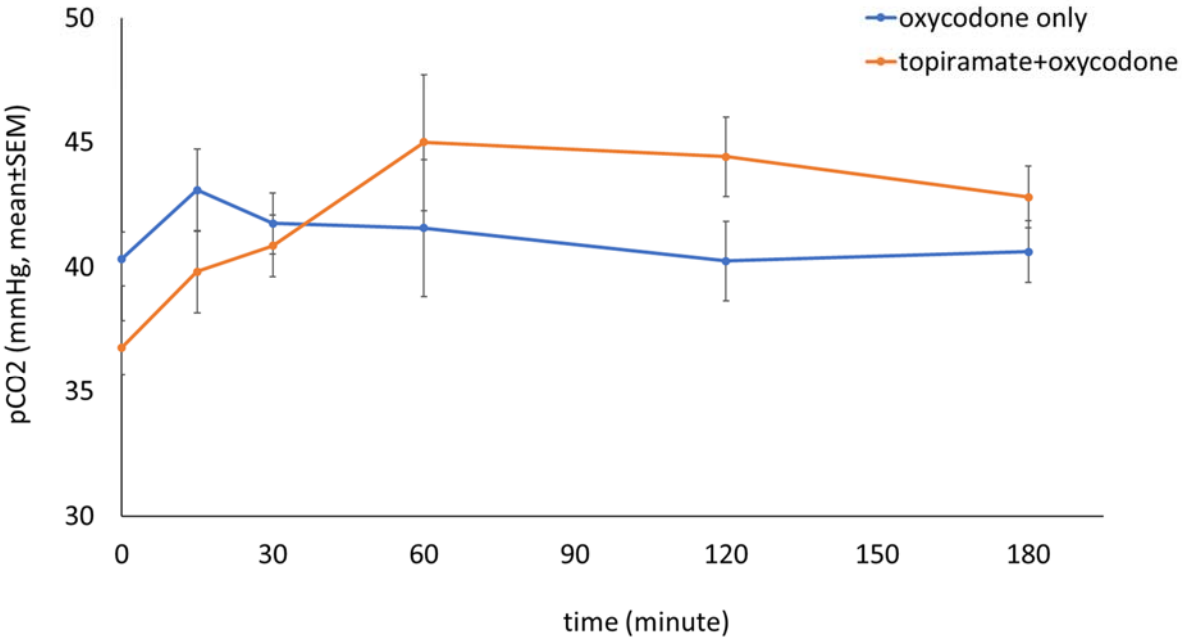

Blood pO2 after oxycodone 150 mg/kg alone or
suvorexant 60 mg/kg + oxycodone 150 mg/kg
pO2 (mmHg, mean±SEM)
100
90
80
70
60
50
40
0
30
60
90
120
150
180
time (minutes)
oxycodone only
suvorexant-oxycodone

Topiramate

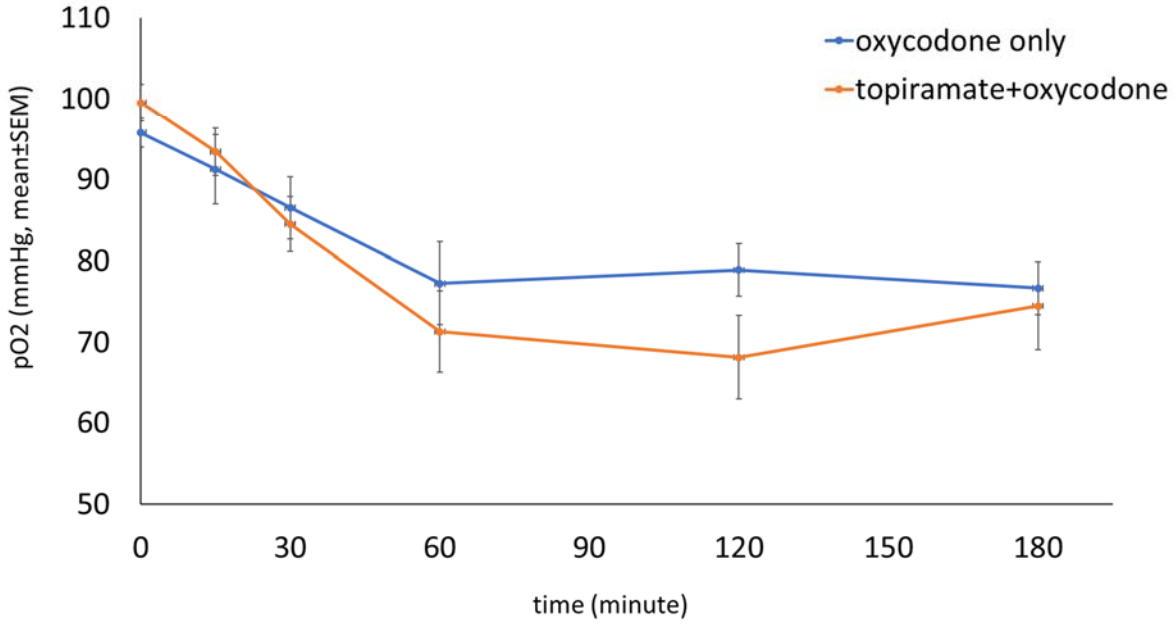

Blood pCO2 after Oral Topiramate Dosing
20 mg/kg
200 mg/kg
1000 mg/kg
pCO2 (mmHg, mean±SEM)
50
40
30
20
0
60
120
180
240
300
360
420
480
time (minutes)


Blood pO2 after Topiramate Oral Dosing
20 mg/kg
200 mg/kg
1000 mg/kg
pO2 (mmHg, mean±SEM)
120
110
100
90
80
70
0
60
120
180
240
300
360
420
480
time (minutes)

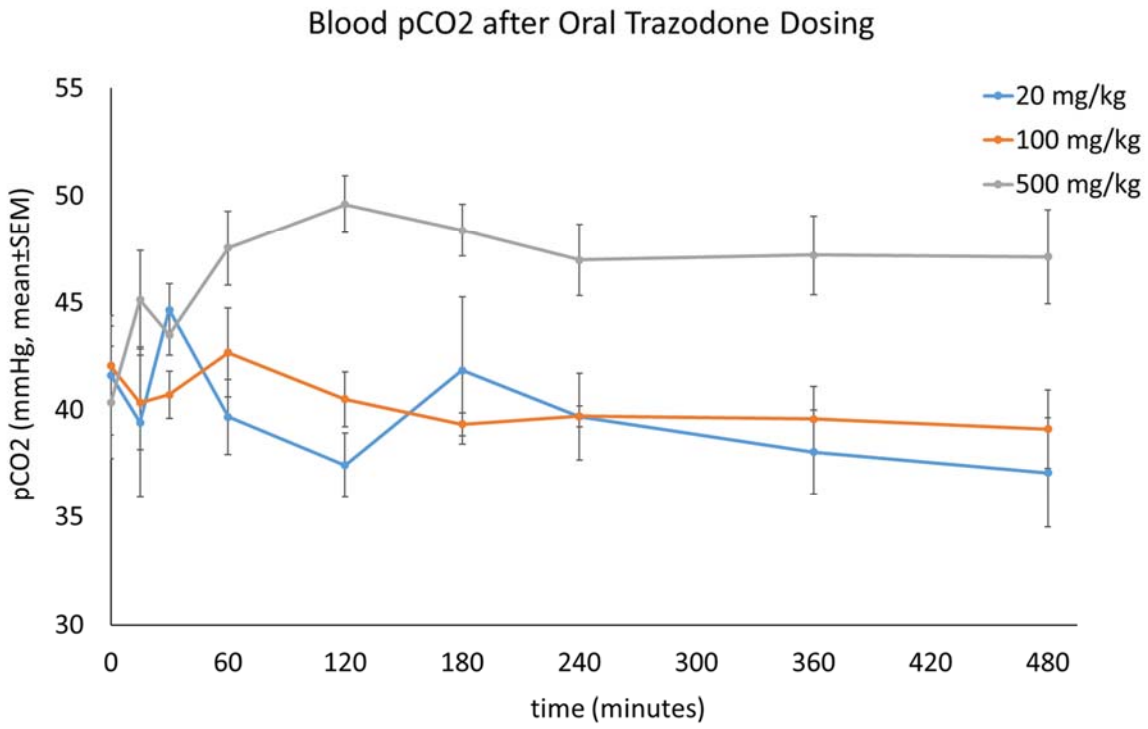
primary & repeat data combined: pCO2- oxycodone 150 mg/kg alone or topiramate 20 mg/kg + oxycodone 150 mg/kg

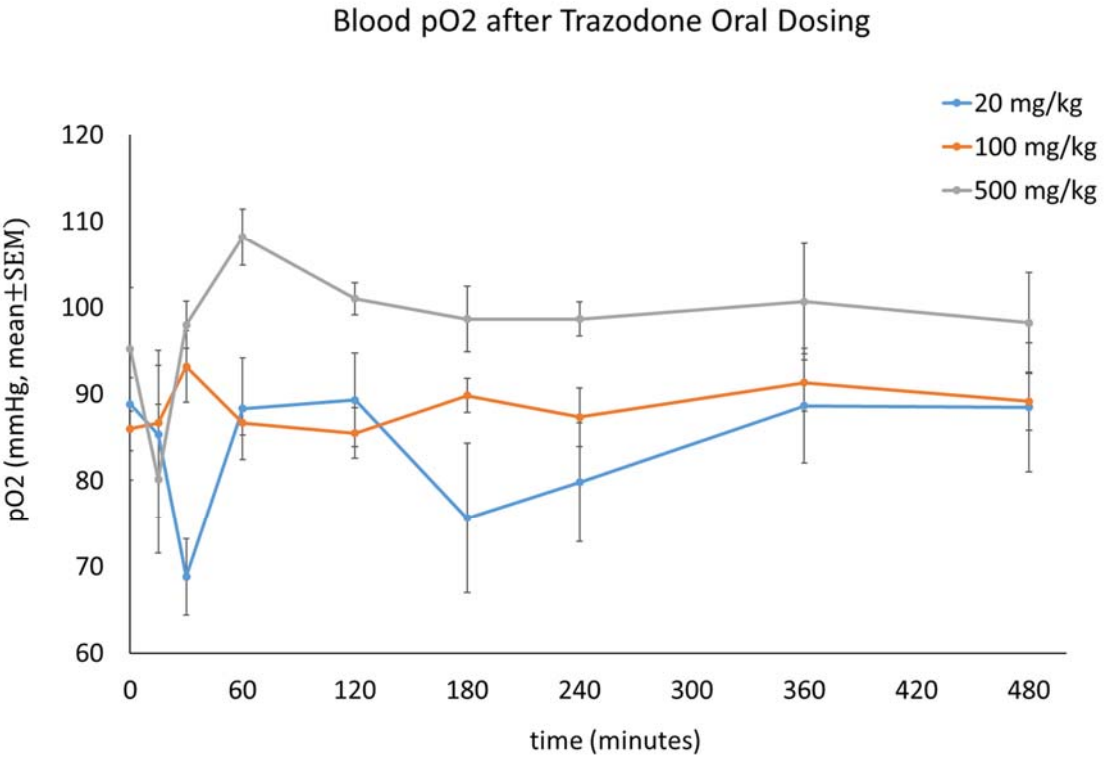


primary & repeat data combined: pO2- oxycodone 150 mg/kg alone or topiramate 20 mg/kg + oxycodone 150 mg/kg

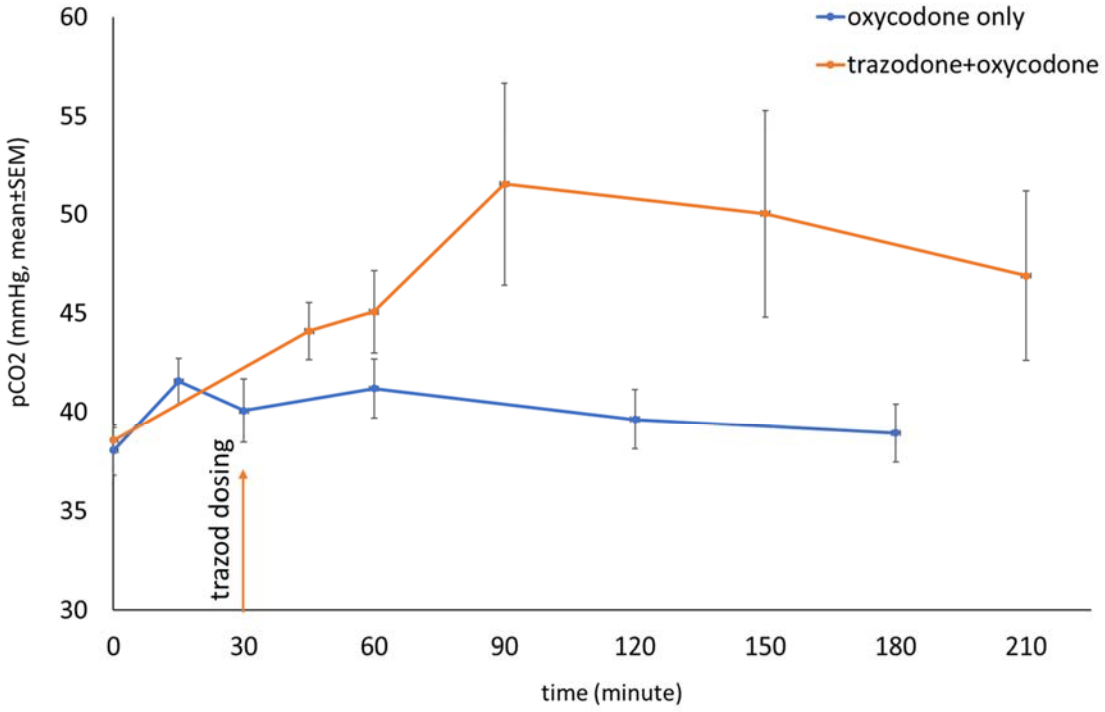


Trazodone

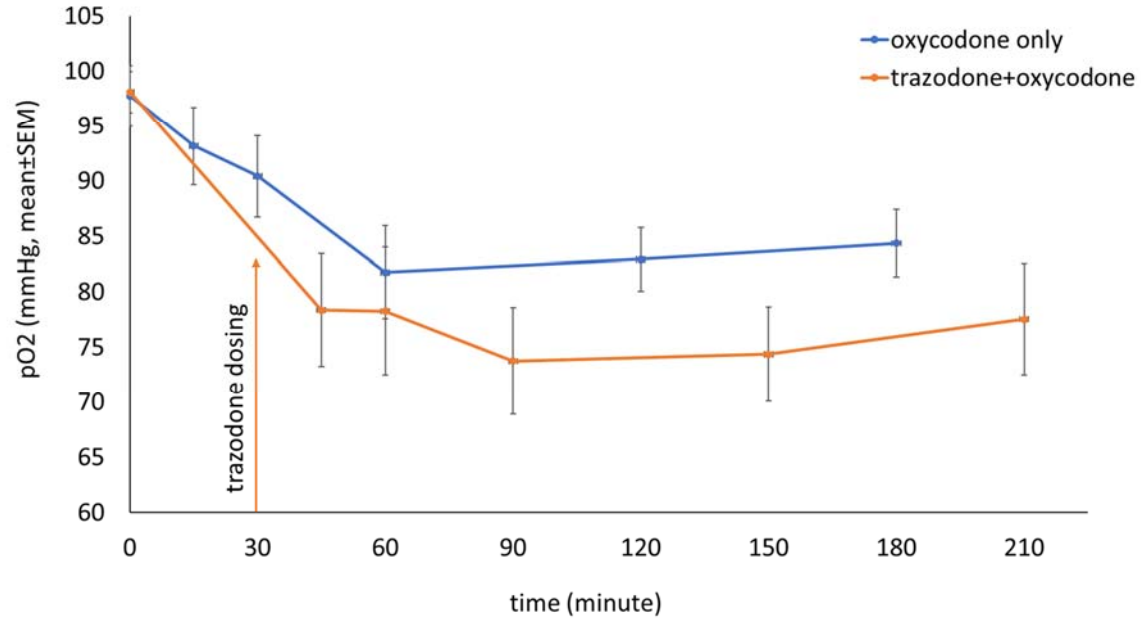

Blood pCO2 after Oral Trazodone Dosing
20 mg/kg
100 mg/kg
500 mg/kg
pCO2 (mmHg, mean±SEM)
55
50
45
40
35
30
0
60
120
180
240
300
360
420
480
time (minutes)


Blood pO2 after Trazodone Oral Dosing
20 mg/kg
100 mg/kg
500 mg/kg
pO2 (mmHg, mean±SEM)
120
110
100
90
80
70
60
0
60
120
180
240
300
360
420
480
time (minutes)

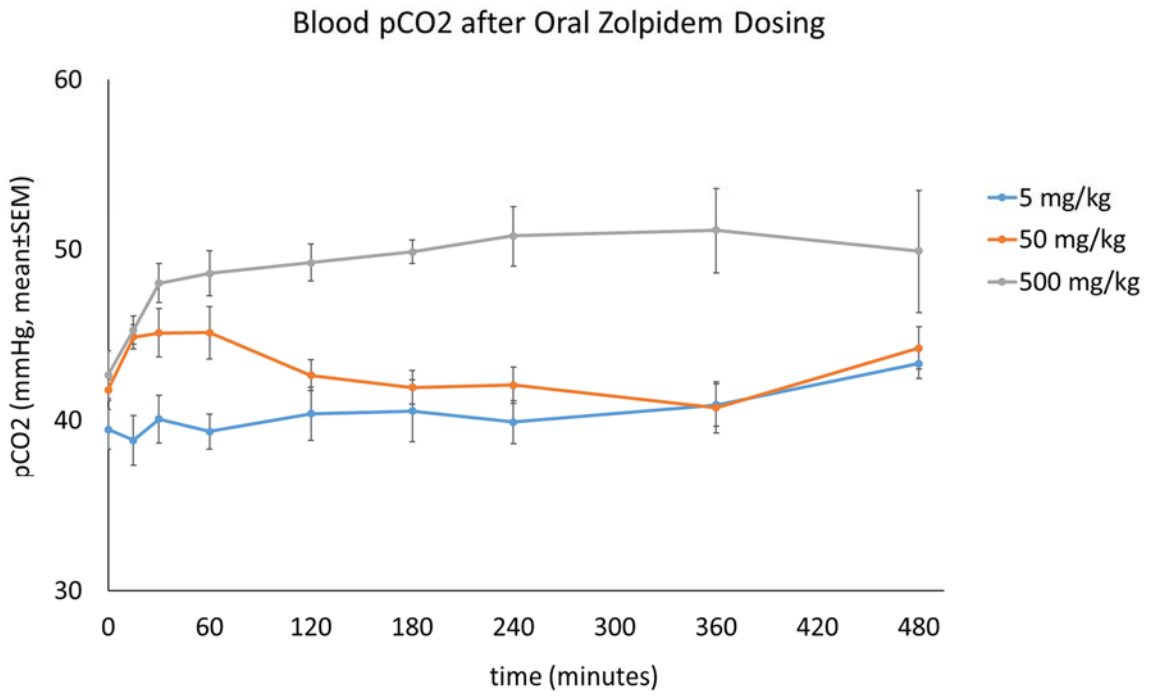
primary & repeat data combined: pCO2- oxycodone 150 mg/kg alone or trazodone 100 mg/kg+oxycodone 150 mg/kg

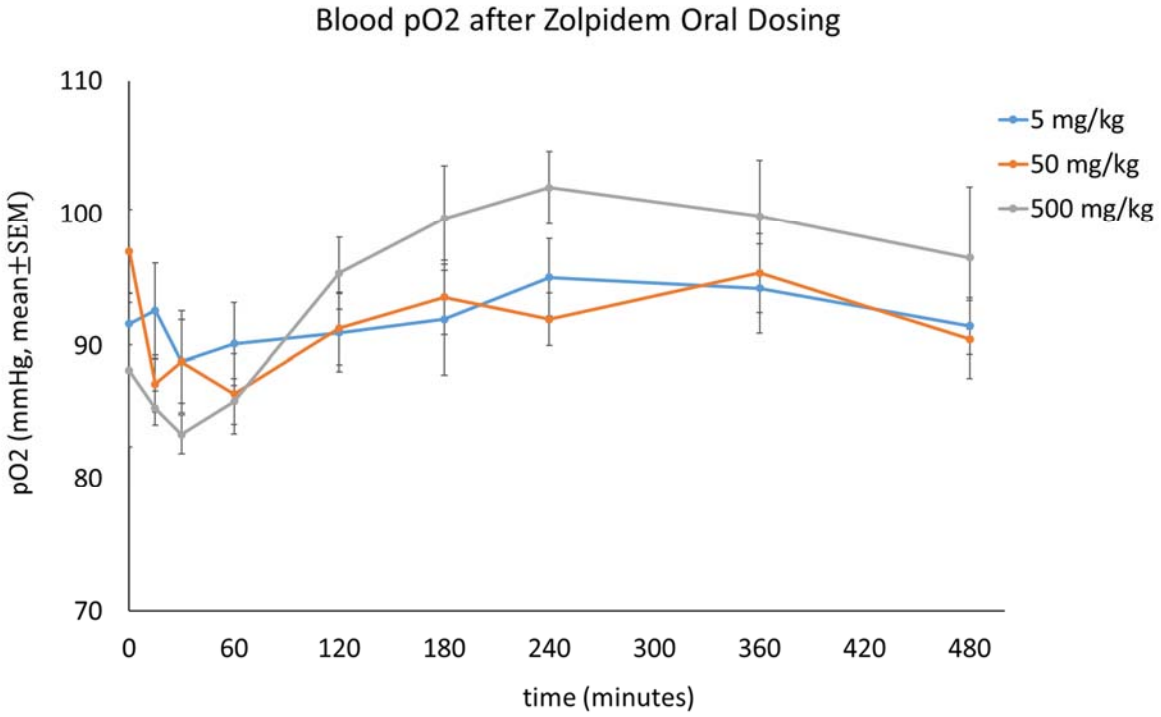


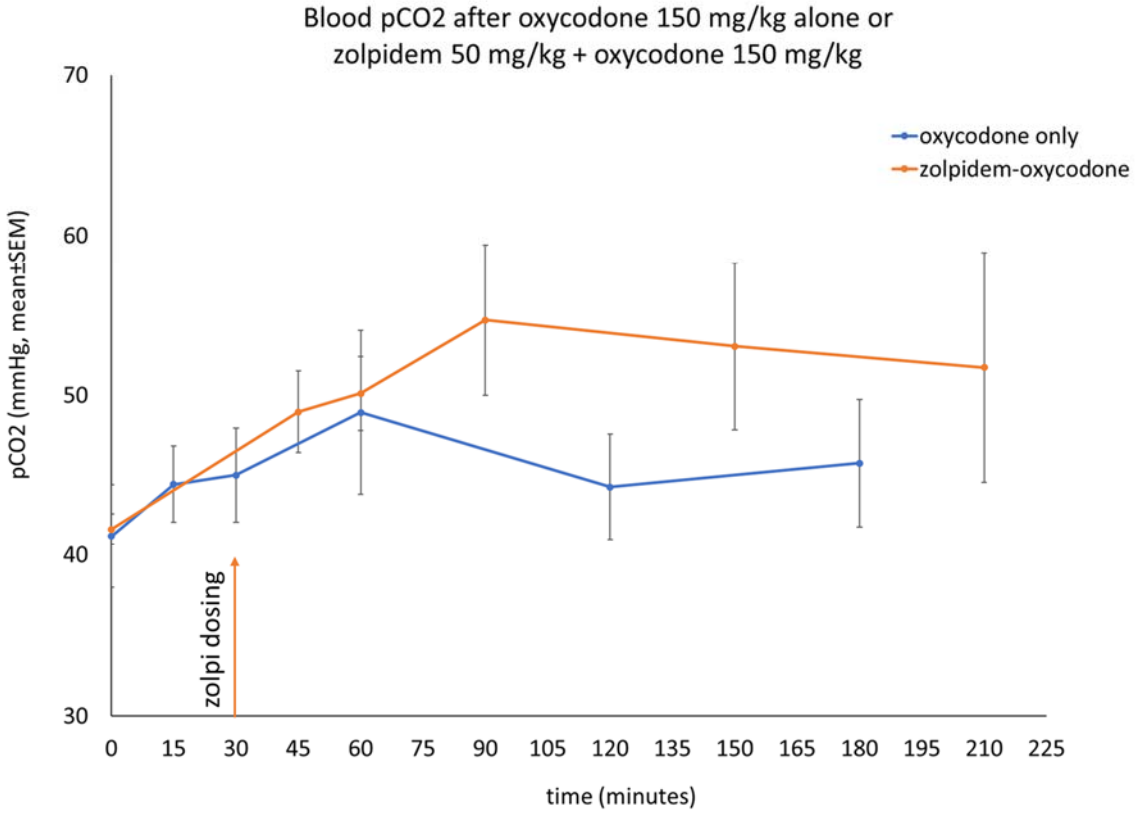
primary & repeat data combined: pO2- oxycodone 150 mg/kg alone or trazodone 100 mg/kg+oxycodone 150 mg/kg

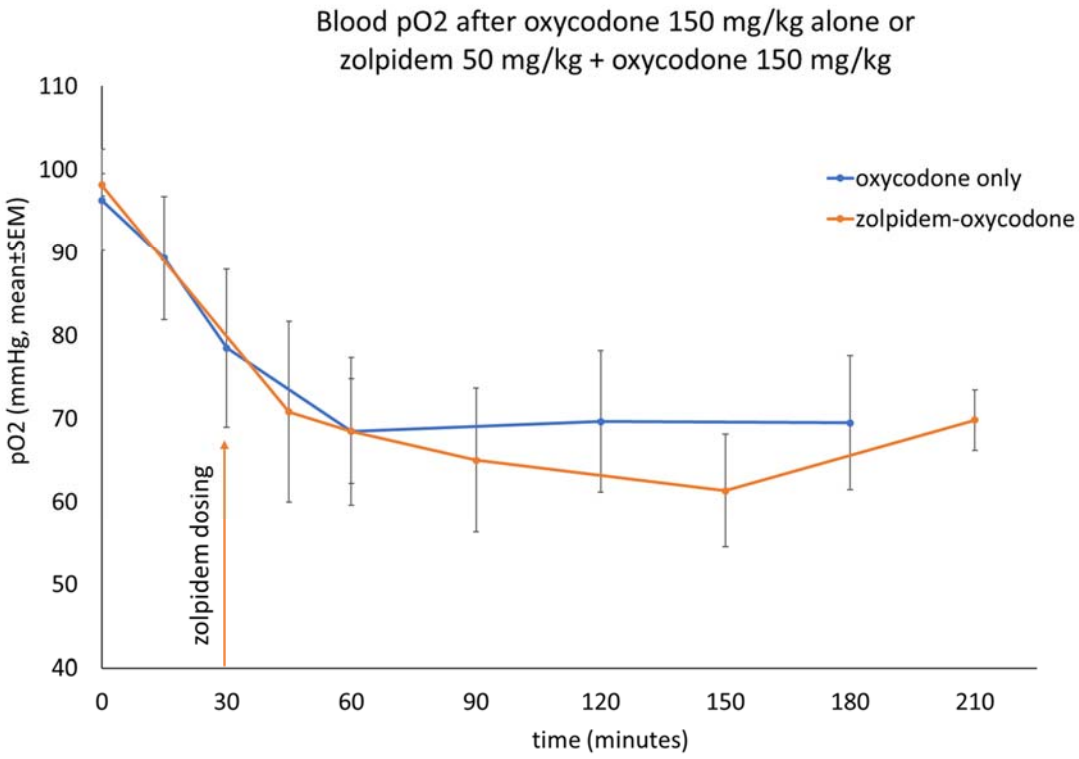


Zolpidem


Blood pCO2 after Oral Zolpidem Dosing
pCO2 (mmHg, mean±SEM)
60
50
40
30
0
60
120
180
240
300
360
420
480
time (minutes)
5 mg/kg
50 mg/kg
500 mg/kg


Blood pO2 after Zolpidem Oral Dosing
pO2 (mmHg, mean±SEM)
110
100
90
80
70
0
60
120
180
240
300
360
420
480
time (minutes)
5 mg/kg
50 mg/kg
500 mg/kg


Blood pCO2 after oxycodone 150 mg/kg alone or
zolpidem 50 mg/kg + oxycodone 150 mg/kg
oxycodone only
zolpidem-oxycodone
pCO2 (mmHg, mean±SEM)
70
60
50
40
30
zolpi dosing
0
15
30
45
60
75
90
105
120
135
150
165
180
195
210
225
time (minutes)


Blood pO2 after oxycodone 150 mg/kg alone or
zolpidem 50 mg/kg + oxycodone 150 mg/kg
oxycodone only
zolpidem-oxycodone
pO2 (mmHg, mean±SEM)
110
100
90
80
70
60
50
40
zolpidem dosing
0
30
60
90
120
150
180
210
time (minutes)