Carbon dioxide responses at extreme conditions: opioid effects and tolerability

Schrier, R.M. van der

Chapter 3

Effect of Paroxetine or Quetiapine Combined With Oxycodone vs Oxycodone Alone on Ventilation During Hypercapnia

A Randomized Clinical Trial

Jeffry Florian, Rutger van der Schrier,
Victoria Gershuny, Michael C. Davis, Celine Wang,
Xiaomei Han, Keith Burkhart, Kristin Prentice,
Aanchal Shah, Rebecca Racz, Vikram Patel, Murali Matta,
Omnia A. Ismaiel, James Weaver, Rodney Boughner,
Kevin Ford, Rodney Rouse, Marc Stone, Carlos Sanabria,
Albert Dahan, David G. Strauss
JAMA 2022; 328(14):1405-1414

Introduction

Ventilation in humans is tightly controlled by feedback mechanisms involving carbon dioxide.[1,2] When chemical receptors in the brain and the carotid body sense increased carbon dioxide, ventilation increases to remove carbon dioxide from the body.[1,2] Opioids decrease this ventilatory response to hypercapnia (Figure 1),[2–5] which can lead to severe respiratory depression and death.[6] Some other drugs, such as benzodiazepines, have minimal effects on ventilation on their own at standard doses, but can exacerbate opioid induced respiratory depression.[7]

In 2016, the US Food and Drug Administration (FDA) required that drug labeling for benzodiazepines and opioids include boxed warnings about increased potential for respiratory depression with their simultaneous use.[7] Following this labeling change, the FDA took proactive steps to review whether other drugs that might be used in place of benzodiazepines (as prescribed or off-label) may exacerbate opioid induced respiratory depression and conducted in vivo rat studies with 14 drugs from diverse pharmacological classes.[8] The selective serotonin reuptake inhibitor (SSRI) paroxetine and the atypical antipsychotic quetiapine exacerbated oxycodone induced respiratory depression.[8] To further investigate these findings, this clinical trial involving healthy participants assessed whether paroxetine-oxycodone or quetiapine-oxycodone combinations decreased the ventilatory response to hypercapnia compared with oxycodone alone.

Methods

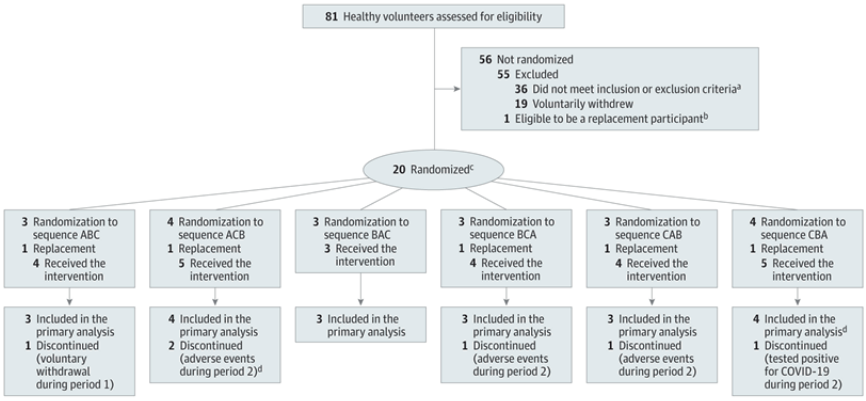
Study Setting and Dates

A randomized, double-blind, 3-way crossover trial involving healthy participants at a clinical pharmacology unit (Spaulding Clinical Research, West Bend, Wisconsin) from January to May 2021 evaluated the effects of paroxetine or quetiapine combined with oxycodone, compared with oxycodone alone, on the ventilatory response to hypercapnia (Figure 1). The Advarra Institutional Review Board approved this study (https://www.advarra.com). All participants provided written informed consent.

Participants and Randomization

Participants were recruited by standard approaches for healthy volunteer clinical pharmacology studies (ie, online advertising and emails or texts to individuals in the site's database). Self-identified race and ethnicity were collected in an open ended format by clinical staff as recommended by the FDA's guidance document Collection of Race and Ethnicity Data in Clinical Trials.[9] Key inclusion criteria were ages 18 to 50 years, nonsmoking, and negative test results for alcohol or illicit drugs. Participants were excluded if they had a history of sleep disorders, panic disorder, panic attacks, generalized anxiety disorder, hypoventilation syndrome, or sleep apnea; used opioid or psychotropic drug within 60 days of the study start; had a Mallampati

A Flow of participants in the study



B Study drug interventions

Treatment group	Study drugs[e]				
	Day 1	Day 2	Day 3	Day 4	Day 5
A	Placebo + oxycodone 10 mg	Placebo	Placebo	Placebo	Placebo + oxycodone 10 mg
B	Paroxetine 40 mg + oxycodone 10 mg	Paroxetine 40 mg	Paroxetine 40 mg	Paroxetine 40 mg	Paroxetine 40 mg + oxycodone 10 mg
C	Quetiapine 50 mg 2/d + oxycodone 10 mg	Quetiapine 100 mg 2/d	Quetiapine 150 mg 2/d	Quetiapine 200 mg 2/d	Quetiapine 200 mg + oxycodone 10 mg

C Illustration of the ventilatory response to hypercapnia at baseline[f]

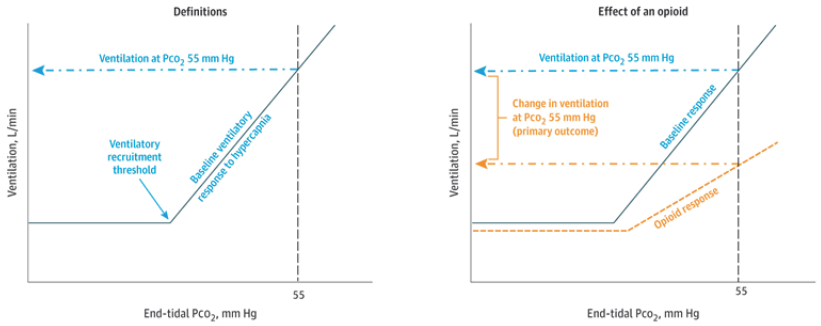


Figure 1: Flow of Participants in Study, Interventions and Overall Study Design:
a. Ten participants had a Mallampati score greater than 2, (predicts difficult tracheal intubation); 5, deemed unlikely to comply with protocol; 5, tested positive for alcohol or illicit drugs; 7, abnormal medical history, laboratory results, or physical examination findings
b. Participant was not needed as a replacement.
c. Five participants replaced the 6 who did not complete all treatment periods. The study design planned for 5 replacements.
d. One participant was included in the primary analysis for only day 1, after which the participant discontinued.
e. See the Methods section for timing of study drug administration. Participants received 4mg of ondansetron 30 minutes before each dose of oxycodone on days 1 and 5 only to prevent nausea and vomiting.
f. Ventilation increases at an approximately linear rate after carbon dioxide (PCO_2) is higher than the ventilatory recruitment threshold (VRT). The opioid causes small decreases in ventilation below the VRT, shifts the VRT to the right, and decreases the rate of rise in ventilation as PCO_2 increases further.

score (predicts difficult tracheal intubation) greater than 2; or could not tolerate the ventilatory assessment procedure during screening.

Participants were randomized to 1 of 6 treatment sequences (Figure 1) using a random number generator in R statistical software. Randomization was conducted in block sizes of 6 for the first 18 participants, and the remaining 2 participants were randomly assigned in 2 of the 6 treatment sequences. Replacement participants were assigned to the treatment sequence of the participant they replaced.

Study Procedures and Interventions

Participants checked in to the clinic the day before the study started, received study drugs on days 1 through 5 (oxycodone on days 1 and 5, and paroxetine or quetiapine [or matched placebos] on days 1 through 5), and checked out on day 6. (See Figure 1 for study drug dosing details.) This was repeated twice with 7 days ofwashout between periods. Study drugs were administered to align the time of maximum concentration for all drugs at the 5-hour time point (paroxetine at 0 hours, oxycodone at 3 hours, quetiapine at 3 and 14 hours). Each period included 16 ventilatory assessments (0 [predose], 4, 5, 6, 8, and 24 hours on days 1 and 5 and 0, 4, 5, and 6 hours on day 4) and 26 blood samples (0 [predose], 3, 4, 5, 6, 8, 9, 12, and 24 hours on days 1 and 5 and 0, 3, 4, 5, 6, 8, 9, and 12 hours on day 4). Plasma concentrations of paroxetine, quetiapine, oxycodone, and selected metabolites were measured by validated liquid chromatography and tandem mass spectrometry.

Participant safety was monitored with clinical laboratory tests, vital signs, electrocardiograms, and physical examinations. Continuous pulse oximetry and telemetry were performed on days when oxycodone was administered,and naloxone was available for participants with severe respiratory depression. Criteria for discontinuation of the study drugs included apnea defined as discontinuation of rhythmic breathing for more than 90 seconds, end-tidal carbon dioxide higher than 67.5 mmHg, or oxygen saturation less than 85% lasting more than 2 minutes.

Ventilatory Assessments

During each assessment, participants sat in an upright position with a fitted mask attached to a pneumotachometer and went through preparatory steps of relaxed breathing (5 minutes of room air then 3 minutes of 100% oxygen), hyperventilation to decrease end-tidal carbon dioxide (1-2 minutes 100% oxygen), followed by rebreathing.[10,11] Upon switching the circuit to the rebreathing bag (7% carbon dioxide, 93% oxygen),participants were instructed to take 3 deep breaths and then breathe normally. This causes approximate equilibration of carbon dioxide in mixed venous blood, arterial blood, brain, and lung with the rebreathing bag.[1,11] Subsequently, carbon dioxide increases at an approximately linear rate as exhaled carbon dioxide is rebreathed through the closed circuit, which increases ventilation above a certain carbon dioxide threshold (Figure 1).[1,12] The procedure continued until end-tidal carbon dioxide was approximately 55 mm Hg. Rebreathing data were reviewed by 2 independent assessors blinded to

study treatment and time of assessments to evaluate completeness of data for study outcomes.

Outcomes and Sample Size Calculation

The primary end point was the minute ventilation when endtidal carbon dioxide was 55 mmHg (Figure 1), which has been used in prior drug-induced respiratory depression studies.[4,5] The primary outcome comparisonswere performed between paroxetine or quetiapine combined with oxycodone vs placebo combined with oxycodone, assessed separately on days 1 and 5. Day 1 was included because quetiapine can cause more sedation after 1 dose than after 5 days of dosing,[13] and it was not known if a similar pattern would be observed with ventilation. Comparisons between paroxetine or quetiapine alone vs placebo on day 4 were secondary outcomes.

Additional secondary outcomes included the maximum plasma concentration and area under the curve (AUC) for plasma concentration vs time of oxycodone when combined with paroxetine or quetiapine compared with oxycodone with placebo. Multiple exploratory outcomes were assessed as specified in the protocol and statistical analysis plan, including pharmacokinetic parameters for paroxetine and quetiapine, additional respiratory measurements including during relaxed room-air breathing, sedation assessments, and pharmacokinetic-pharmacodynamic (concentration-response) modeling. Although reporting summary statistics for exploratory outcomes was prespecified, comparisons between study treatments for the exploratory outcomes were a post hoc assessment. In addition, study drug maximum plasma concentration and AUC were compared based on cytochrome-P450 2D6 (CYP2D6) metabolizer phenotype status as a post hoc assessment.

Sample size requirements were calculated based on 2 primary outcomes (day 1 and day 5) and adjusted for multiplicity (α = .025). The assessments with paroxetine or quetiapine were considered as separate experiments. A sample size of 20 participants was determined to have 90% power at a 1-sided significance level to detect a 4-L/min decrease in the primary end point (ventilation at 55 mmHg end-tidal carbon dioxide) assuming a standard deviation of 5 L/min, based on prior opioid ventilatory studies.[4,5] A 4-L/min decrease was the estimated approximate effect size from 10mg of oxycodone and would indicate that paroxetine or quetiapine was further decreasing hypercapnic ventilation by a similar amount.[4,5] The protocol allowed for enrollment of up to 5 replacement participants to account for discontinuations.

Statistical Analysis

All participants who completed paired rebreathing assessments with placebo plus oxycodone and at least 1 of the other 2 study treatments (paroxetine plus oxycodone or quetiapine plus oxycodone) for day 1 or day 5 were included in the primary analysis without imputation of missing data. Study treatments were compared using a linear mixed-effects model with baseline ventilation at an end-tidal carbon dioxide of 55 mmHg as a continuous variable; treatment, sequence,and period as categorical variables; and participant as a random effect. A similar analysis was performed on day 4 as a secondary outcome. For pharmacokinetic analyses, all

concentrations less than the lower limit of quantitation were considered 0. Maximum oxycodone concentration and AUC were log-transformed and the values between study treatments were compared using a linearmixed-effects model on days 1 and 5 with treatment as a categorical variable and participant as a random effect. Pharmacokinetic-pharmacodynamic modeling included drug concentration as a continuous variable and random effects by participant on the intercept and concentration variable. Demographics are reported with standard descriptive statistics.

A 1-sided P value was used to assess the primary outcomes because the study aim was to evaluate whether the study drugs decreased ventilation, and a value $< .025$ was considered significant based on Bonferroni correction for 2 primary outcomes. A 1-sided P value $< .025$ was also considered significant for the secondary ventilation outcome, and these outcomes are reported with 1-sided upper 97.5% CIs. For secondary and exploratory outcomes assessing pharmacokinetics, a difference in exposurewas concluded if the 2-sided 90% CI of the geometric mean ratio [GMR] excluded 1, which is standard in pharmacokinetic studies.[14] Post hoc comparisons are reported with 2-sided 95% CIs and a difference was reported if the CIs excluded 0. Secondary and exploratory CIs are not adjusted for multiplicity, and all analyses except for primary outcomes should be interpreted as exploratory because of the potential for type I error due to multiple comparisons. Statistical analyses were performed in R (version 4.1.2; The R Project for Statistical Computing).

Results

Study Participants

Twenty-five participants (20 originally randomized and 5 replacement participants; Figure 1) were enrolled (median age, 35 years [IQR, 30 to 40 years]; 11 female [44%]). Table 1 contains additional participant characteristics, including resting respiratory measurements and CYP3A4 and CYP2D6 metabolizer phenotypes. Nineteen participants completed the trial and 1 additional participant completed through day 1 of period 2 and had placebo plus oxycodone data available (Figure 1). Primary outcomes data were available for 20 participants on day 1 and 19 participants on day 5.

Primary Outcomes

The mean ventilation at 55 mm Hg end-tidal carbon dioxide with the paroxetine plus oxycodone combination on day 1 was 29.2 L/min (95% CI, 25.7 to 32.7); with quetiapine plus oxycodone, 33.0 L/min(95% CI, 30.0 to 36.0); with placebo plus oxycodone, 34.1 L/min (95% CI, 31.1 to 37.2). The day 5 values were 25.1 L/min (95% CI, 21.2 to 29.0) with paroxetine plus oxycodone; 34.7 L/min (95% CI, 30.9 to 38.5) with quetiapine plus oxycodone, and 35.3 L/min (95% CI, 31.4 to 39.2) with placebo plus oxycodone (Table 2).

Compared with placebo plus oxycodone, paroxetine plus oxycodone significantly decreased

Table 1: Study Participant Demographics and Baseline Characteristics

Characteristics	No. (%) (N=25)
Sex	
Male	14 (56)
Female	11 (44)
Race, No. (%)[a]	
Asian	2 (8)
Black or African American	12 (48)
White	11 (44)
Hispanic or Latino ethnicity	5 (20)
Body weight, median (IQR), kg	68 (61-81)
BMI, median (IQR)	24.8 (22.0-26.1)
Resting respiratory measurements, median (IQR)	n = 24
Minute ventilation, L/min	7.8 (7.3-9.0)
Respiratory rate, breaths/min	15 (12-17)
Tidal volume, L	0.61 (0.54-0.68)
End-tidal carbon dioxide, mmHG	37.1 (35.6-39.0)
Oxygen saturation, %	97.1 (95.9-98.0)
CYP3A4 metabolizer phenotype	
Extensive metabolizers	25(100)
CYP2D6 metabolizers phenotype	
Extensive metabolizers	19 (76)
Intermidiate metabolizers	6 (24)

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; CYP, cytochrome P450.
[a]Self-identified race and ethnicity were reported by participants in an open-ended format.

ventilation on day 1 (mean difference [MD], -4.9 L/min [1-sided 97.5% CI, $-\infty$ to -0.6]; $P = .01$) and on day 5 (MD, -10.2 L/min [1-sided 97.5% CI, $-\infty$ to -6.3]; $P < .001$), while quetiapine plus oxycodone did not significantly decrease ventilation on day 1 (MD, -1.2 L/min [1-sided 97.5% CI, $-\infty$ to 2.8]; $P < .28$) or day 5 (MD, -0.6 L/min [1-sided 97.5% CI, $-\infty$ to 3.2]; $P < .37$).

Secondary Outcomes

Figure 2 show pharmacodynamic data across days 1, 4, and 5. On day 4, the oxycodone administered on day 1 had washed out, allowing for a comparison between effects of paroxetine and quetiapine alone and placebo. Mean ventilation at 55 mmHg end-tidal carbon dioxide on day 4 was 32.4 L/min (95%CI, 28.2 to 36.5) with paroxetine alone, 42.8 L/min (95% CI, 38.7 to 46.8) with quetiapine alone, and 41.7 L/min (95% CI, 37.7 to 45.6) with placebo (Table 2). Compared with placebo, paroxetine alone significantly decreased ventilation (MD, -9.3 L/min [1-sided 97.5% CI, $-\infty$ to -3.9]; $P < .001$), whereas quetiapine alone did not significantly decrease ventilation (MD, 1.1 L/min [1-sided 97.5% CI, $-\infty$ to 6.4]; $P = .67$). Paroxetine did not significantly increase oxycodone maximum plasma concentration (GMR, 1.06 [90% CI, 0.96 to 1.17]) or AUC (GMR, 1.03

(90% CI, 0.91 to 1.17) on day 1 but did significantly increase oxycodone maximum plasma concentration (GMR, 1.30 [90% CI, 1.19 to 1.43]) and AUC (GMR, 1.10 [90% CI, 1.02 to 1.19]) on day 5 (Table 2). Quetiapine did not significantly increase oxycodone AUC on day 1 (GMR, 1.06 [90% CI, 0.98 to 1.15]) but did significantly increase oxycodone maximum plasma concentrations on days 1 (GMR, 1.25 [90% CI, 1.14 to 1.37]) and 5 (GMR, 1.39 [90% CI, 1.22 to 1.57]) and AUC on day 5 (GMR, 1.27 [90% CI, 1.19 to 1.36]).

Exploratory Outcomes

Figure 3 displays the oxycodone-alone concentration response model and the day 5 primary end point observed data for the drug combinations. Multidrug concentration response analysis showed that increasing concentrations of paroxetine and oxycodone were each associated with decreased hypercapnic ventilation (paroxetine slope, -0.13 L/min per ng/mL [95% CI,-0.17 to -0.09]; oxycodone slope, -0.24 L/min per ng/mL [95% CI, -0.35 to -0.12]), whereas an increasing concentration of quetiapine or its metabolite norquetiapine was not associated with decreasedhypercapnic ventilation (quetiapine slope, 0.015 L/min per ng/mL [95% CI, 0.007 to 0.022]; norquetiapine slope, -0.015 L/min per ng/mL [95% CI, -0.038 to 0.001]; oxycodone slope, -0.25 L/min per ng/mL [95% CI, -0.34 to -0.16]).

Post Hoc Assessments

Compared with placebo plus oxycodone at the 5-hour time point on day 5, paroxetine plus oxycodone increased resting end-tidal carbon dioxide (41.4 vs 37.4 mmHg; MD, 4.0 mmHg [95% CI, 2.4 to 5.6 mm Hg]), decreased resting oxygen saturation (95.5% vs 96.6%; MD, -1.1% [95% CI, -2.1% to -0.1%], and decreased the slope of the hypercapnic ventilatory response curve (1.00 vs 1.44 L/min per mmHg; MD, -0.44 L/min per mmHg [95% CI, -0.85 to -0.03]); quetiapine plus oxycodone increased resting end-tidal carbon dioxide (40.4 vs 37.4 mmHg; MD, 3.0 mmHg [95% CI, 1.4 to 4.6]), decreased resting oxygen saturation (95.2% vs 96.6%; MD, -1.4% [95% CI, -2.4% to -0.4%]), and increased participant-reported sedation (40 vs 25mm; MD, 15mm [95% CI, 3 to 28]).

Adverse Events

No serious adverse events occurred. Twenty-two participants (88%) experienced 1 or more adverse events. The most common adverse eventswere nausea (64%), dizziness (52%), headache (48%), somnolence (32%), and fatigue (32%).

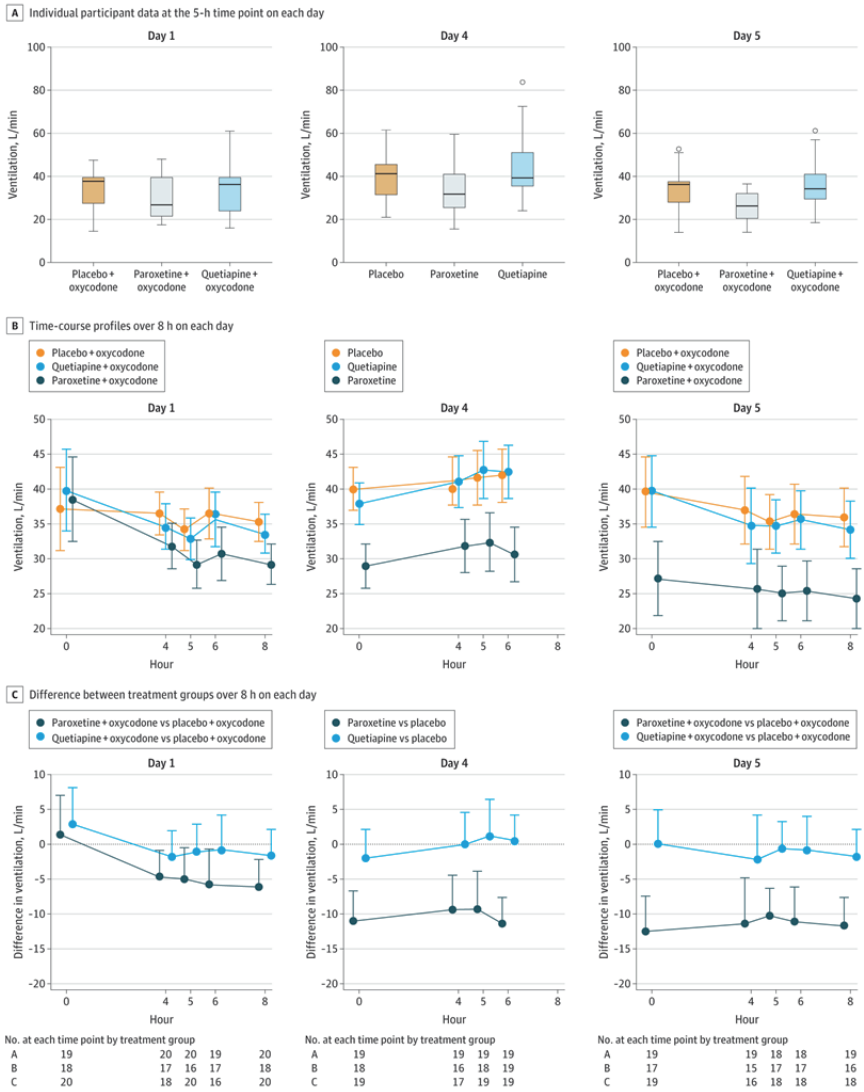


Figure 2: Minute Ventilation at End-Tidal Carbon Dioxide of 55 mmHg
A: Bars indicate medians; box borders, IQRs; and circles, outside the range. Whiskers extending from box borders to the last observation within 1.5 × the IQR.
B: For dosing administration, see the Figure 1. Data points indicate model-estimated means and whiskers 2-sided 95%CIs.
C: The primary outcome comparisons at 5 hours are on days 1 and 5; secondary outcomes, day 4, the secondary outcome comparison. Data points indicate the model-estimated mean difference; whiskers, the upper 1-sided 97.5%CIs.

Table 2: Primary and Secondary Outcomes

	No. of participants	Mean (2-sided 95% CI)		Mean difference (1-sided 97.5% CI)	P value[a]
Primary Outcomes					
Ventilation at 55 mmHG end-tidal PCO2, L/min		Paroxetine + oxycodone	Placebo + oxycodone		
Day 1	20	29.2 (25.7 to 32.7)	34.1 (31.1 to 37.2)	-4.9 ($-\infty$ to -0.6)	0.01
Day 5	19	25.1 (21.2 to 29.0)	35.3 (31.4 to 39.2)	-10.2 ($-\infty$ to -6.3)	< 0.001
		Quetiapine + oxycodone	Placebo + oxycodone		
Day 1	20	33.0 (30.0 to 36.0)	34.1 (31.1 to 37.2)	-1.2 ($-\infty$ to 2.8)	0.28
Day 5	19	34.7 (30.9 to 38.5)	35.3 (31.4 to 39.2)	-0.6 ($-\infty$ to 3.2)	0.37
Secondary outcomes					
Ventilation at 55 mmHg end-tidal PCO2, L/min		Paroxetine	Placebo		
Day 4	19	32.4 (28.2 to 36.5)	41.7 (37.7 to 45.6)	-9.3 ($-\infty$ to -3.9)	< 0.001
		Quetiapine	Placebo		
Day 4	19	42.8 (38.7 to 46.8)	41.7 (37.7 to 45.6)	1.1 ($-\infty$ to 6.4)	0.67
		GM (CV%)		GMR (2-sided 90% CI)	Pvalue[b]
Oxycodone maximum plasma concentration, ng/mL		Paroxetine + oxycodone	Oxycodone + placebo		
Day 1	19	19.1 (25)	18.0 (30)	1.06 (0.96 to 1.17)	0.33
Day 5	19	23.4 (26)	18.0 (26)	1.30 (1.19 to 1.43)	< 0.001
		Quetiapine + oxycodone	Oxycodone		
Day 1	20	22.9 (28)	18.3 (30)	1.25 (1.14 to 1.37)	0.64
Day 5	19	24.9 (26)	18.0 (26)	1.39 (1.22 to 1.57)	< 0.001
Oxycodone AUC, ng/mL x h		Paroxetine + oxycodone	Oxycodone		
Day 1	20	107 (29)	104 (20)	1.03 (0.91 to 1.17)	0.64
Day 5	19	112 (30)	102 (24)	1.10 (1.02 to 1.19)	0.05
		Quetiapine + oxycodone	Oxycodone		
Day 1	20	113 (25)	107 (25)	1.06 (0.98 to 1.15)	0.24
Day 5	19	129 (23)	102 (24)	1.27 (1.19 to 1.36)	< 0.001

Abbreviations: AUC, area under the curve; CV, coefficient of variation; GM, geometric mean; GMR, geometric mean ratio; PCO2, end-tidal partial pressure of carbon dioxide.

[a] *A 1-sided P value <.025 was considered significant for the primary and secondary ventilation outcomes.*

[b] *A difference in exposure was concluded if the 2-sided 90% CI of the geometric mean ratio excluded 1 (2-sided P < .1).*

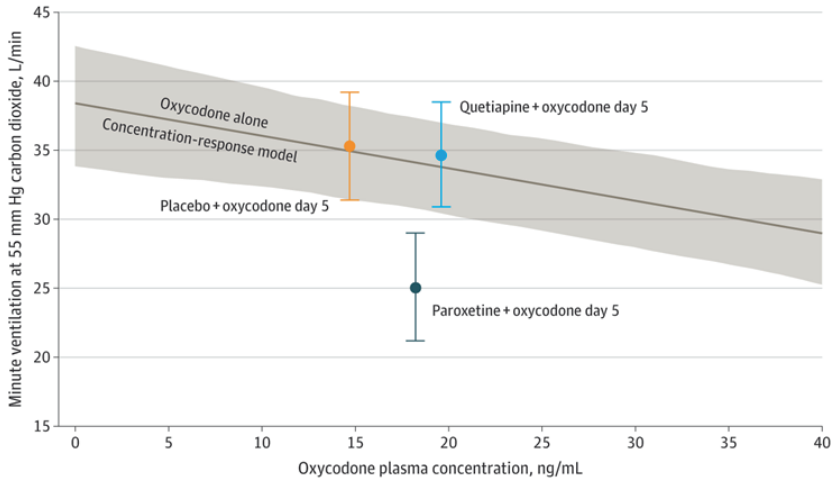


Figure 3: The oxycodone concentration–response model is based on a linear mixed-effect model with all data from oxycodone alone. The downward sloping black line indicates the prediction; the shaded region, 95% CI (mean slope, -0.29 L/min per ng/mL [95% CI, $-0.47 to -0.11$); mean intercept, 39.8 L/min [95% CI, 34.0 to 45.7]). Data points represent the observed data from the 5-hour time point on day 5 (primary end point) for mean ventilation at 55 mmHg carbon dioxide (values in Table 2) and geometric mean oxycodone plasma concentration with placebo plus oxycodone was 14.7 ng/mL (coefficient of variation [CV], 31%); oxycodone concentration with paroxetine, 18.2 ng/mL (CV, 21%); and oxycodone concentration with quetiapine, 19.6 ng/mL (CV, 21%).

Discussion

In this randomized, double-blind, crossover clinical trial involving healthy participants, paroxetine (40mg daily for 5 days) combined with oxycodone (10mg on days 1 and 5) compared with oxycodone alone decreased ventilation when end-tidal carbon dioxide was 55 mmHg. In contrast, quetiapine (increasing daily doses from 100mg to 400mg) combined with oxycodone did not decrease ventilation when end-tidal carbon dioxide was 55 mmHg.

The finding that paroxetine combined with oxycodone, compared with oxycodone alone, decreased the ventilatory response to hypercapnia is concerning because this is the primary feedback mechanism for the body to rescue itself from opioid-induced respiratory depression.[2,6] The secondary outcomes supported that paroxetine decreased the ventilatory response to hypercapnia through a direct pharmacodynamic effect rather than by a pharmacokinetic interaction because paroxetine had a similar effect on its own compared with placebo on day 4. Furthermore, exploratory concentration response modeling supported that the increase in oxycodone

concentration with paroxetine did not explain the observed effect of paroxetine on the primary outcome (Figure 3). This study included exploratory outcomes of resting respiratory measures while participants breathed room air for 5 minutes prior to the rebreathing procedure. When performing post hoc comparisons at the primary end point time on day 5, neither drug combination significantly decreased resting minute ventilation; however, both drug combinations significantly increased resting end-tidal carbon dioxide (by $\approx 3-4$ mm Hg) and decreased resting oxygen saturation (by $\approx 1.1\%-1.4\%$).

In the nonclinical study that motivated this clinical trial,[8] quetiapine caused a substantially larger increase in oxycodone maximum plasma concentration than what was observed in this clinical trial, likely explaining the different respiratory effects observed with the quetiapine-oxycodone combination in the nonclinical study vs this clinical trial. This was likely due to interspecies differences in pharmacokinetics and that substantially higher doses of each drug were administered. The nonclinical study findings with paroxetine were similar to those observed in this trial. Review of older literature identified additional nonclinical studies supporting a relationship between certain systemically administered drugs that affect serotonin and ventilatory depression.[15–20] Inhibition of serotonin synthesis increased baseline ventilation and the ventilatory response to carbon dioxide, which was reversed by administering a serotonin precursor.[18–20] Furthermore, morphine induced respiratory depression was enhanced by drugs that increase serotonin, including monoamineoxidase inhibitors and the SSRI fluoxetine.[18,19] Other studies identified a relationship between paroxetine or fluoxetine alone and decreased ventilation.[21–24] Additional studies have shown that specific types of serotonin neurons increase their firing rate in response to hypercapnia and that activation of specific serotonin receptor subtypes stimulates ventilation.[25] However, paroxetine does not bind to serotonin receptors at clinically relevant concentrations but rather is highly selective for inhibiting the serotonin transporter, leading to its SSRI properties.[26] Regarding clinical data, a retrospective analysis of patients referred to a sleep clinic found that SSRIs, compared with a norepinephrine-dopamine reuptake inhibitor, were associated with impaired breathing and worse nocturnal oxygen saturation.[27] Several previous studies involving patients with panic disorder used inhalation of carbon dioxide as a trigger for anxiety and panic symptoms. In addition to finding that multiple SSRIs[28–31] and certain tricyclic antidepressants[28,29] decreased hypercapnia-induced anxiety, a subset of studies using the carbon dioxide rebreathing method found that chronic treatment with SSRIs or certain tricyclic antidepressants decreased the ventilatory response to hypercapnia in this population.[32,33] In overdose, paroxetine and other SSRIs are not known to cause severe respiratory depression or death on their own,[34] suggesting that ventilatory depressant effects may plateau after exceeding a certain exposure, which is consistent with the findings from the nonclinical study with paroxetine alone.[8]

Sound data regarding concomitant medications can be difficult to obtain on patients who overdose while taking opioids because information often relies on death certificates, which vary by death investigation practice (eg, performing comprehensive postmortem drug testing) and

reporting practice (eg, focusing ona single lethal drug or listing multiple drugs).[35] Retrospective analyses of administrative health care data that grouped all antidepressants together identified prior antidepressant prescription as a predictor of opioid overdose or serious opioid-induced respiratory depression, and antidepressant use was included in a developed risk index.[36,37] However,these studies[36,37] did not evaluate the causal link between antidepressants and overdose and were limited by potential treatment and outcome misclassification. An additional recent retrospective analysis with similar limitations and the potential for unmeasured confounding variables found that use of SSRIs that inhibit oxycodone metabolism (paroxetine or fluoxetine; inhibit CYP2D6) at the time of oxycodone initiation was associated with a small but significantly higher risk of opioid overdose compared with the use of other SSRIs.[38] The results from this clinical trial confirmed that paroxetine caused a relatively small increase in oxycodone concentration; however, quetiapine, which inhibits CYP3A4, also increased oxycodone plasma concentration without affecting the primary outcome.

This clinical trial is a part of the FDA's proactive work to address the opioid crisis and help reduce opioid overdoses and deaths and more specifically to determine whether drugs that might be used in place of benzodiazepines may also exacerbate opioid-induced respiratory depression.8 The findings may have important clinical implications for patients taking paroxetine, or potentially other SSRIs, who concomitantly use opioids, but further research is needed to determine this. SSRIs take approximately 3 weeks to reach maximal therapeutic effect, which correlates with the time required for presynaptic inhibitory serotonergic receptors to desensitize.[39,40] Some prior nonclinical studies suggest different effects of SSRIs on respiration over a similar time frame.[21] Further clarifying the potential time-dependent risks of SSRIs when combined with opioids will be important because treating co-occurring mental health conditions is a critical part of addressing the opioid crisis.

Limitations

This study has several limitations. First, it is not known if the findings with paroxetine will extend to other SSRIs; however, as reviewed in this article, the effects may be due to paroxetine's primary mechanism of action common among SSRIs. Second, the study was conducted in a controlled setting with procedures to increase end-tidal carbon dioxide. Although this differs from what patients would experience, the method allows testing drug combinations at doses that do not lead to severe respiratory depression when breathing room air while still assessing ventilatory effects as carbon dioxide increases, which reflects the physiology of severe respiratory depression seen with opioid overdoses.[2,6] Third, the study involved healthy participants with 5 days of dosing; thus, it is not known if the paroxetine effect on ventilation would persist with longer term treatment. However, clinical studies discussed earlier that involved patients referred to a sleep clinic and with panic disorder suggest that SSRIs affect ventilation after longer term treatment.[27,33]

Conclusions

In this preliminary study that involved healthy participants,paroxetine combined with oxycodone, compared with oxycodone alone, significantly decreased the ventilatory response to hypercapnia on days 1 and 5, whereas quetiapine combined with oxycodone did not cause such an effect. Additional investigation is needed to characterize the effects after longer-term treatment and to determine the clinical relevance of these findings.

References

1. J Duffin. “Measuring the respiratory chemoreflexes in humans”. In: *Respiratory physiology & neurobiology* 177.2 (2011), pp. 71–79.
2. Kyle TS Pattinson. “Opioids and the control of respiration”. In: *British journal of anaesthesia* 100.6 (2008), pp. 747–758.
3. LA Ladd et al. “Ventilatory responses of healthy subjects to intravenous combinations of morphine and oxycodone under imposed hypercapnic and hypoxaemic conditions”. In: *British journal of clinical pharmacology* 59.5 (2005), pp. 524–535.
4. R Van der Schrier et al. “An experimental study comparing the respiratory effects of tapentadol and oxycodone in healthy volunteers”. In: *BJA: British Journal of Anaesthesia* 119.6 (2017), pp. 1169–1177.
5. Rutger van der Schrier et al. “Influence of ethanol on oxycodone-induced respiratory depression: a dose-escalating study in young and elderly individuals”. In: *Anesthesiology* 126.3 (2017), pp. 534–542.
6. Jeffrey B Gross. “When you breathe IN you inspire, when you DON’T breathe, you… expire: new insights regarding opioid-induced ventilatory depression”. In: *The Journal of the American Society of Anesthesiologists* 99.4 (2003), pp. 767–770.
7. L Woodcock J to Wen and L Alexander-Scott. *Re: Docket No. FDA-2016-P-0689*. 2016. URL: `https://www.regulations.gov/document/fda-2016-P-0689-0003`.
8. Lin Xu et al. “Effects of sedative psychotropic drugs combined with oxycodone on respiratory depression in the rat”. In: *Clinical and Translational Science* 14.6 (2021), pp. 2208–2219.
9. *Collection of Race and Ethnicity Data in Clinical Trials Guidance for Industry and Food and Drug Administration Staff*. 2016. URL: `https://www.fda.gov/media/75453/download`.
10. DJC Read. “A clinical method for assessing the ventilatory response to carbon dioxide”. In: *Australasian annals of medicine* 16.1 (1967), pp. 20–32.
11. Anthony S Rebuck. “Measurement of ventilatory response to CO2 by rebreathing”. In: *Chest* 70.1 (1976), pp. 118–121.
12. James Duffin. “Role of acid-base balance in the chemoreflex control of breathing”. In: *Journal of applied physiology* 99.6 (2005), pp. 2255–2265.
13. Catherine Datto et al. “Self-reported sedation profile of immediate-release quetiapine fumarate compared with extended-release quetiapine fumarate during dose initiation: a randomized, double-blind, crossover study in healthy adult subjects”. In: *Clinical therapeutics* 31.3 (2009), pp. 492–502.

14. US Food and Drug Administration. *Bioavailability studies submitted in NDAs or INDs—general considerations*. 2019. URL: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bioavailability-studies-submitted-ndas-or-inds-general-considerations.
15. Armand L Bianchi, Monique Denavit-Saubié, and Jean Champagnat. "Central control of breathing in mammals: neuronal circuitry, membrane properties, and neurotransmitters". In: *Physiological reviews* 75.1 (1995), pp. 1–45.
16. RA Mueller et al. "The neuropharmacology of respiratory control." In: *Pharmacological Reviews* 34.3 (1982), pp. 255–285.
17. JA Armtjo and J Florez. "The influence of increased brain 5-hydroxytryptamine upon the respiratory activity of cats". In: *Neuropharmacology* 13.10-11 (1974), pp. 977–986.
18. J Flórez, G Delgado, and JA Armijo. "Adrenergic and serotonergic mechanisms in morphine-induced respiratory depression". In: *Psychopharmacologia* 24 (1972), pp. 258–274.
19. MJ Meldrum and GE Isom. "Role of monoaminergic systems in morphine-induced respiratory depression". In: *Neuropharmacology* 20.2 (1981), pp. 169–175.
20. Robert A Mueller, Dag Lundberg, and George R Breese. "Evidence that respiratory depression by serotonin agonists may be exerted in the central nervous system". In: *Pharmacology Biochemistry and Behavior* 13.2 (1980), pp. 247–255.
21. Kristina Annerbrink et al. "Acute and chronic treatment with serotonin reuptake inhibitors exert opposite effects on respiration in rats: possible implications for panic disorder". In: *Journal of Psychopharmacology* 24.12 (2010), pp. 1793–1801.
22. Daniel R Henderson, Darlene M Konkle, and Gordon S Mitchell. "Effects of serotonin reuptake inhibition on ventilatory control in goats". In: *Respiration physiology* 115.1 (1999), pp. 1–10.
23. Janna Leigh Morrison et al. "Effect of maternal fluoxetine administration on uterine blood flow, fetal blood gas status, and growth". In: *Pediatric research* 51.4 (2002), pp. 433–442.
24. Marie Olsson et al. "Paroxetine influences respiration in rats: implications for the treatment of panic disorder". In: *European neuropsychopharmacology* 14.1 (2004), pp. 29–37.
25. Andrea E Corcoran et al. "Medullary serotonin neurons and central CO2 chemoreception". In: *Respiratory physiology & neurobiology* 168.1-2 (2009), pp. 49–58.
26. Michel Bourin, Pierre Chue, and Yannick Guillon. "Paroxetine: a review". In: *CNS drug reviews* 7.1 (2001), pp. 25–47.
27. Rébecca Robillard et al. "Selective serotonin reuptake inhibitor use is associated with worse sleep-related breathing disturbances in individuals with depressive disorders and sleep complaints: a retrospective study". In: *Journal of Clinical Sleep Medicine* 17.3 (2021), pp. 505–513.

28. Angelo Bertani et al. “Pharmacologic effect of imipramine, paroxetine, and sertraline on 35% carbon dioxide hypersensitivity in panic patients: a double-blind, random, placebo-controlled study”. In: *Journal of clinical psychopharmacology* 17.2 (1997), pp. 97–101.
29. Giampaolo Perna et al. “Modification of 35% carbon dioxide hypersensitivity across one week of treatment with clomipramine and fluvoxamine: a double-blind, randomized, placebo-controlled study”. In: *Journal of clinical psychopharmacology* 17.3 (1997), pp. 173–178.
30. Angelo Bertani et al. “The 35% CO 2 hyperreactivity and clinical symptomatology in patients with panic disorder after 1 week of treatment with citalopram: an open study”. In: *Journal of clinical psychopharmacology* 21.3 (2001), pp. 262–267.
31. Giampaolo Perna et al. “Modulation of hyperreactivity to 35% CO2 after one week of treatment with paroxetine and reboxetine: a double-blind, randomized study”. In: *Journal of clinical psychopharmacology* 24.3 (2004), pp. 277–282.
32. Jack M Gorman et al. “Effect of antipanic treatment on response to carbon dioxide”. In: *Biological Psychiatry* 42.11 (1997), pp. 982–991.
33. V Bocola et al. “Antipanic effect of fluoxetine measured by CO2 challenge test”. In: *Biological psychiatry* 43.8 (1998), pp. 612–615.
34. David D Gummin et al. “2020 annual report of the American association of poison control centers’ national poison data system (NPDS): 38th annual report”. In: *Clinical toxicology* 59.12 (2021), pp. 1282–1501.
35. Holly Hedegaard et al. “Drugs most frequently involved in drug overdose deaths: United States, 2011-2016”. In: (2018).
36. Barbara Zedler et al. “Development of a risk index for serious prescription opioid-induced respiratory depression or overdose in Veterans’ Health Administration patients”. In: *Pain Medicine* 16.8 (2015), pp. 1566–1579.
37. Barbara K Zedler et al. “Validation of a screening risk index for serious prescription opioid-induced respiratory depression or overdose in a US commercial health plan claims database”. In: *Pain Medicine* 19.1 (2018), pp. 68–78.
38. Ismaeel Yunusa et al. “Risk of opioid overdose associated with concomitant use of oxycodone and selective serotonin reuptake inhibitors”. In: *JAMA Network Open* 5.2 (2022), e220194–e220194.
39. David J Nutt et al. “Mechanisms of action of selective serotonin reuptake inhibitors in the treatment of psychiatric disorders”. In: *European neuropsychopharmacology* 9 (1999), S81–S86.
40. Janet F Czachura and Kurt Rasmussen. “Effects of acute and chronic administration of fluoxetine on the activity of serotonergic neurons in the dorsal raphe nucleus of the rat”. In: *Naunyn-Schmiedeberg’s archives of pharmacology* 362 (2000), pp. 266–275.