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RESPIRATION AND THE AIRWAY

Inhaled Δ^9 -tetrahydrocannabinol does not enhance oxycodone-induced respiratory depression: randomised controlled trial in healthy volunteers

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Abstract

Background: In humans, the effect of cannabis on ventilatory control is poorly studied, and consequently, the effect of Δ^9 -tetrahydrocannabinol (THC) remains unknown, particularly when THC is combined with an opioid. We studied the effect of THC on breathing without and with oxycodone pretreatment. We hypothesised that THC causes respiratory depression, which is amplified when THC and oxycodone are combined.

Methods: In this randomised controlled crossover trial, healthy volunteers were administered inhaled Bedrocan® 100 mg (Bedrocan International B.V., Veendam, The Netherlands), a pharmaceutical-grade high-THC cannabis variant (21.8% THC; 0.1% cannabidiol), after placebo or oral oxycodone 20 mg pretreatment; THC was inhaled 1.5 and 4.5 h after placebo or oxycodone intake. The primary endpoint was isohypercapnic ventilation at an end-tidal P_{CO_2} of 55 mm Hg or 7.3 kPa (V_{E55}), measured at 1-h intervals for 7 h after placebo/oxycodone intake.

Results: In 18 volunteers (age 22 yr [3]; 9 [50%] female), oxycodone produced a 30% decrease in V_{E55} , whereas placebo was without effect on V_{E55} . The first cannabis inhalation resulted in V_{E55} changing from 20.3 (3.1) to 23.8 (2.4) L min⁻¹ ($P=0.06$) after placebo, and from 11.8 (2.8) to 13.0 (3.9) L min⁻¹ ($P=0.83$) after oxycodone. The second cannabis inhalation also had no effect on V_{E55} , but slightly increased sedation.

Conclusions: In humans, THC has no effect on ventilatory control after placebo or oxycodone pretreatment.

Clinical trial registration: 2021-000083-29 (EU Clinical Trials Register.)

Keywords: cannabinoid receptor; hypercapnic ventilatory response; opioid-induced respiratory depression; opioid receptor; ventilatory control; Δ^9 -tetrahydrocannabinol

Editor's key points

- Despite being commonly used as both a medical and recreational drug, the effect of cannabis on opioid-induced respiratory depression is unknown.
- The authors hypothesised that Δ^9 -tetrahydrocannabinol (THC) causes respiratory depression,

which is amplified when THC and oxycodone are combined.

- Healthy volunteers received a pharmaceutical-grade high-THC cannabis variant, after randomisation to placebo or oral oxycodone pretreatment.
- THC has no effect on ventilatory control after placebo or oxycodone pretreatment.

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Opioids and cannabis are widely used, both recreationally and in medical practice.^{1,2} Although there is substantial evidence that opioids suppress respiration,³ the effect of cannabis on respiration, particularly in humans, is sparsely investigated.^{4–15} Cannabinoid type 1 (CB1) and cannabinoid type 2 (CB2) receptors are found in brainstem respiratory networks, including the preBötzinger complex, the respiratory rhythm generator.^{9,16–18} Several, but certainly not all,^{4,5,7} studies suggest that CB1 activation is related to respiratory depression.^{6,8–13} In contrast, CB2 receptor activation has an excitatory effect on breathing, at least during opioid exposure.^{17,18} The main component of cannabis, Δ^9 -tetrahydrocannabinol (THC), is a partial agonist at CB1 and CB2 receptors. In tissues with low cannabinoid receptor density, THC can either inhibit or activate the receptors,¹⁹ which may cause a mixed inhibitory–excitatory effect on ventilatory control, as is observed in other behavioural assays.¹⁹

In pain management, the use of THC or its combination with an opioid can be advantageous, as the combination has an opioid-sparing effect.^{20–23} However, this is only of advantage provided the combination of these two drug classes does not exacerbate opioid-induced respiratory depression (OIRD). Because respiratory depression is potentially life-threatening, enhancement of the probability of OIRD by a CB1 agonist is unwanted.³ Previously, we showed that combining oxycodone with alcohol or with an antidepressant (paroxetine or tianeptine) augments OIRD.^{24–26} Deaths associated with opioid misuse are frequently linked with co-medication or abuse of other centrally acting depressants.^{27,28}

In this study, we examined the effect of inhaled medicinal-grade cannabis, containing a high THC dose, on ventilatory control in healthy human volunteers with placebo or oxycodone pretreatment. We aimed to answer two questions: (i) does inhaled THC induce respiratory depression? (ii) Will combining oxycodone and THC exacerbate respiratory depression? We hypothesised that inhaled THC causes respiratory depression, an effect that is amplified when THC and oxycodone are co-administered.

Methods

Study design

This study was a single-centre double-blind, randomised, placebo-controlled crossover trial, approved by the Leiden University Medical Research Ethics Committee (METC Leiden Den Haag Delft) in Leiden, The Netherlands and conducted from December 1, 2021 to August 1, 2022. Before enrolment, all subjects gave written informed consent after which their medical histories were taken and a physical examination was performed. The study was registered in the EU Clinical Trials Register (<https://www.clinicaltrialsregister.eu>; identifier 2021-000083-29; March 31, 2021).

Inclusion criteria

Healthy volunteers of either sex were recruited with the following inclusion criteria: age 18–45 yr, BMI <30 kg m⁻², and ability to give written consent form.

Exclusion criteria

Exclusion criteria were presence or history of any medical or psychiatric disease, including substance use disorder; presence of any chronic pain syndrome; use of >21 alcohol units

per week; use of cannabis in the 4 weeks before the study; a positive urine drug test at screening or on the morning of the experiment; and pregnancy, lactation, or a positive pregnancy test on the morning of the experiment. All participants in the study had prior experience with the use of cannabis in a recreational setting but were opioid-naïve.

Measurements

THC metabolites

At regular intervals, 5 ml blood was drawn from the arterial line for measurement of oxycodone, THC, the THC metabolite 11-OH-THC, and cannabidiol (CBD). Blood was collected in ethylenediaminetetraacetic acid (EDTA) tubes, centrifuged at 2000 g (4°C), and the separated plasma was stored at –80°C until analyses. The pharmacokinetic analyses, performed by Ardena Bioanalysis (Assen, The Netherlands), were performed using validated liquid chromatography with tandem mass spectrometer detection (LC-MS/MS) methods.²⁹ The analysis methods and acceptance criteria are available from ABL (ABL Standard Operating Procedure 0251).

Hypercapnic ventilatory response

The hypercapnic ventilatory response (HCVR) was measured 30–45 min before taking placebo or oxycodone, and at 1-h intervals after oxycodone/placebo administration (last measurement 7 h after oxycodone/placebo intake). The HCVR was measured using a modified Read rebreathing method.²⁵ During the respiratory tests, the subjects breathed into a face mask that was attached to a pneumotachograph and pressure transducer system (Hans Rudolph Inc., Kansas City, MO, USA) and a three-way valve that linked to a 6 L rebreathing bag. Gas was sampled from the face mask to measure inspired and expired oxygen and CO₂ concentrations (Datex Capnomac, Helsinki, Finland). Breath-to-breath respiratory data were collected using the custom-made ACQ/RESREG software package (Leiden University, Leiden, the Netherlands).^{24,26}

Protocol

Subjects were studied twice with 2 weeks between visits, randomised to assess the effect of THC inhalation, which was examined after oral oxycodone or after a placebo tablet. THC was inhaled 1.5 and 4.5 h after the intake of the tablets. Upon arrival in the research unit and after passing urine drug and pregnancy tests, the subjects received an i.v. line for fluid administration (NaCl/glucose 50–100 ml h⁻¹) and a 20-G arterial line in the left or right radial artery for blood sampling. A pulse oximeter (Masimo Corporation, Irvine, CA, USA) and ECG electrodes were placed on the subject to monitor oxygen saturation (SpO₂) and heart activity.

We administered one oral oxycodone 20 mg tablet (Mundipharma Pharmaceuticals B.V., Hoevelaken, The Netherlands) or a placebo tablet that was identical to the oxycodone tablet in form and taste (Leiden University Medical Center pharmacy). The pharmaceutical-grade high-THC cannabis was the Bedrocan[®] cannabis cultivar (Bedrocan International B.V., Veendam, The Netherlands), which contained 21.8% THC and 0.1% CBD.²⁹ It is made from the dried flowers of the plant *Cannabis sativa* L.,²⁹ cultivated under Good Manufacturing Practices. Each subject inhaled 100 mg of the grinded flower material after it was vapourised using a vapouriser (Volcano Medic 2; Storz & Bickel GmbH & Co.,

Tuttlingen, Germany).³⁰ In the vapouriser, cannabis flower 100 mg was heated to 210°C, allowing the THC acid to be converted into the active THC. The vapour was collected in an 8 L bag, and the subject inhaled the complete content of the bag through a mouthpiece in 3–7 min; after each inhalation, the subject was instructed to hold the breath for 5 s.

When the test started, the subjects first inhaled room air for 4–5 min, after which they were coached to hyperventilate for 2–3 min while breathing 100% oxygen, followed by relaxed breathing for 20–30 s (still inhaling oxygen).²⁵ Next, they were connected to the rebreathing bag that initially contained 7% CO₂ and 93% oxygen. Rebreathing of the gas content in the balloon continued for 3–4 min. Throughout the test, we collected the following variables: minute ventilation, end-tidal P_{CO₂}, and oxygen saturation. The HCVR was calculated in R by fitting the ventilation and end-tidal CO₂ data points of the linear increasing part of the response curve to the following equation^{24–26}:

$$V_E = S \times [\text{end-tidal } P_{\text{CO}_2} - B] \quad (1)$$

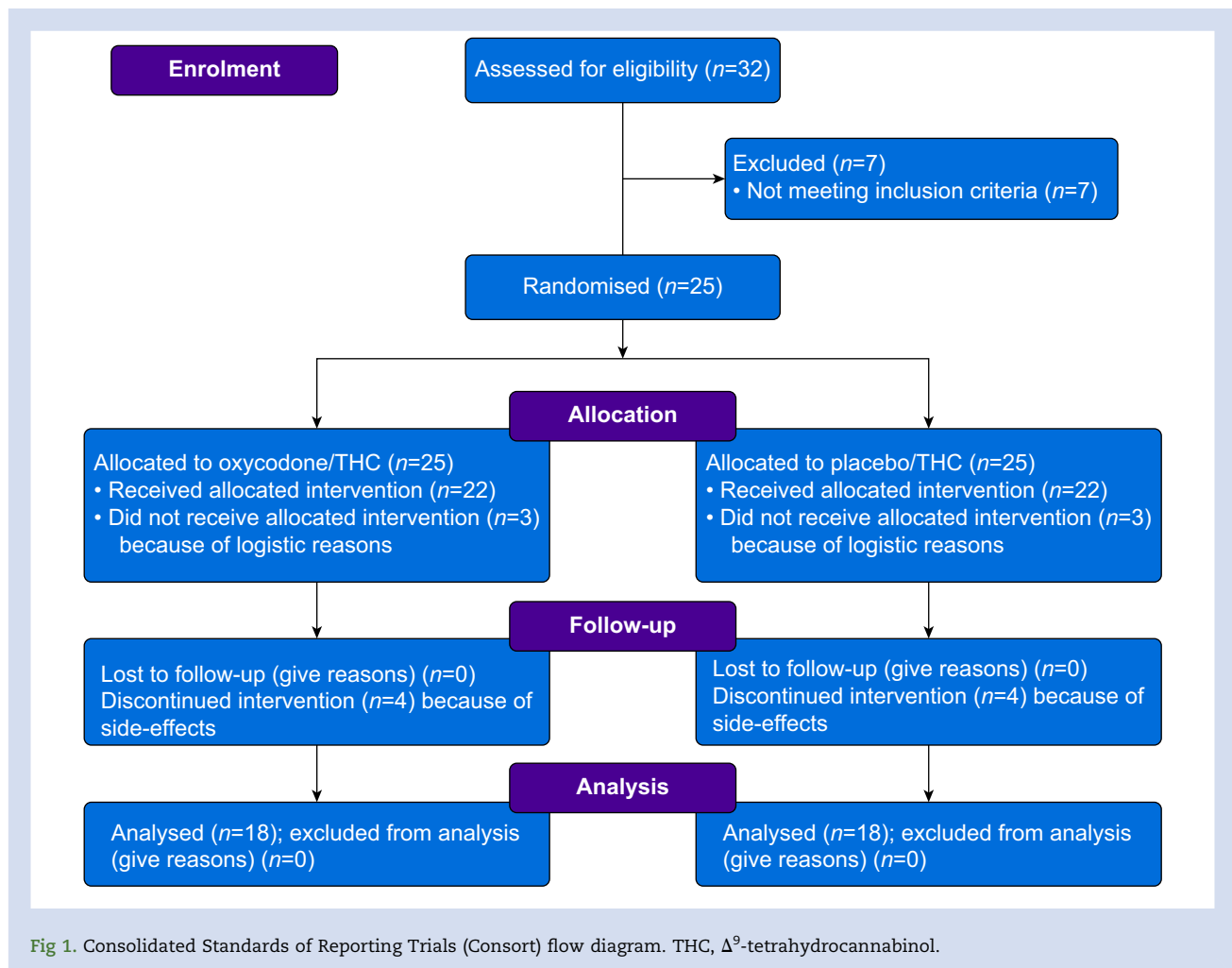
where V_E is minute ventilation, S is the slope of the HCVR, and B is the extrapolated P_{CO₂} at zero ventilation (i.e. the apnoeic threshold).^{24–26} The HCVR has a so-called 'dog leg' shape with an initial horizontal part, where ventilation is unaffected by

CO₂, and a part in which ventilation increases.³¹ The analysis of our current study focuses on the linear increasing part of the study. The main endpoint of the study, V_{E55} or ventilation at an extrapolated end-tidal P_{CO₂} of 55 mm Hg or 7.3 kPa (unit L min⁻¹), was calculated from the slope and apnoeic threshold of the HCVR as follows:^{24–26}

$$V_{E55} = S \times [55 - B] \quad (2)$$

Assessment of sedation and alertness

The subjects were queried at regular intervals for various subjective experiences before and after drug administration. The following two endpoints were obtained using a 10-cm VAS: sedation and drug high. The scale ranged from 0 (no experience of sedation or drug high) to 10 (greatest experience imaginable). For sedation, this meant that the subject was unable to stay awake. Additionally, the subjects filled out the Bond and Lader³² questionnaire. The questionnaire contains 16 scales (10 cm) for several subjective domains with the left and right anchors set at antonymous word pairs, such as 'alert–drowsy', 'well coordinated–clumsy', 'mentally slow–quick witted', and 'incompetent–proficient' (i.e. the two anchors reflect the greatest extent of subjective experience of that domain). The study participant's task was to place a mark



on each scale at the point that best described how they felt at that time. In the current study, we report on two domains: energetic (10=lethargic → 0=energetic) and coordinated/alert (0=alert → 10=drowsy). The queries were obtained 5 min before blood sampling and 10 min before THC inhalation.

Primary outcome

The primary endpoint of the study was the effect of cannabis inhalation on V_{E55} after oxycodone 20 mg or placebo intake.

Secondary outcomes

The secondary outcomes of the study were resting V_E , resting end-tidal P_{CO_2} and SpO_2 (measured before hyperventilation while breathing room air), and sedation/alertness.

Statistical analysis

Data analysis was performed in R (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria). A linear mixed model analysis was performed using the lme4 package (Bates and colleagues³³). The main endpoint V_{E55} was included as a dependent variable, and fixed effects time, treatment, session, and treatment × time as fixed effects were added; subject was included as random effect. In case of significant main effects contrast between oxycodone vs placebo treatment arms, post- vs pre-cannabis inhalation was examined. *P*-values <0.01 were considered significant. Secondary ventilatory parameters were analysed in a similar manner. However, these analyses should be considered exploratory.

For the subjective secondary endpoints, sedation, outcome of the Bond and Lader³² questionnaire, and drug high, we calculated the mean differences (95% confidence intervals) between the two treatment arms to detect whether the effect size after the combination of oxycodone and THC would differ from just THC. These analyses should be considered exploratory.

Sample size

Because there are no prior data on the interactive effect of cannabis and oxycodone on isohypercapnic ventilation (V_{E55}), we extrapolated the results of an earlier study from our laboratory on the interactive effect of ethanol and oxycodone on V_{E55} .²⁵ We hypothesised that THC reduces ventilation by 5 (6) $L \text{ min}^{-1}$ (mean [standard deviation]) post- versus pretreatment in the two treatment arms. We estimated an effect size of 18 with $\alpha=0.05$ and $1-\beta=0.90$. To consider any uncertainties regarding effect size or possible dropouts, we increased the group size to 20 individuals of either sex.

Results

Study characteristics

After screening 32 volunteers, 25 (mean age: 22 yr [3]; 9 [50%] female) were randomised (Fig 1). Inhalation of the cannabis vapour from the balloon occurred within 5 min (~20 inhalations), without any adverse events. There was no effect of oxycodone on plasma concentrations of THC, 11-OH-THC, and CBD (Fig 2).

Primary outcome

Oxycodone reduced V_{E55} by 30% from baseline (pre-drug) to $t=1$ h, whereas placebo had no effect on V_{E55} (Fig 3a). Based on the likelihood ratio test (that compares the models with and

without treatment effect), there was a significant difference in the mean profiles between the two treatment groups (main effect: $P<0.001$; Fig 3). No carry-over effect between visits (visit by treatment interaction) was detected. In both treatment arms, THC had no effect on V_{E55} after the first inhalation (Fig

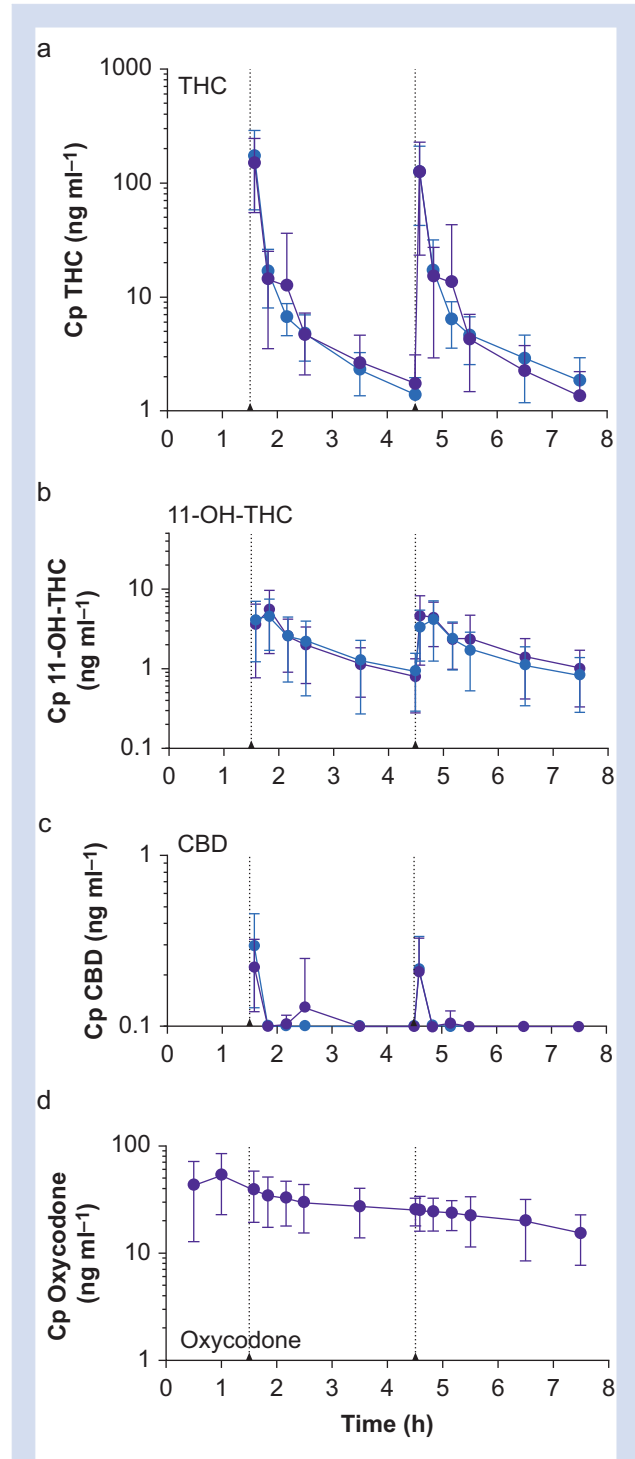


Fig 2. Plasma concentrations of (a) THC, (b) 11-OH-THC, (c) CBD, and (d) oxycodone. In purple, plasma concentrations observed after oxycodone; in blue, after placebo pretreatment. CBD, cannabidiol; THC, Δ^9 -tetrahydrocannabinol.

3a). The first THC inhalation did not increase ventilation after placebo (from 20.3 [3.1] to 23.8 [2.4] L min⁻¹; $P=0.06$) or oxycodone pretreatment (from 11.8 [2.8] to 13.0 [3.9] L min⁻¹; $P=0.83$). After the second THC inhalation ($t=4.5$ h; Fig 2), no effect of THC was observed in either treatment group (placebo/THC $P=0.94$; oxycodone/THC $P=0.99$).

Secondary outcomes

Ventilation, gas exchange, and oxygenation

The main effects of oxycodone/THC vs placebo/THC on V_E , end-tidal P_{CO_2} , and SpO_2 were consistent with the primary outcome (Fig. 3b–d). Only oxycodone reduced resting

ventilation and SpO_2 , accompanied by an increase in end-tidal P_{CO_2} (from 4.2 [0.2] to 4.5 [0.2] kPa). The small declines in SpO_2 in both groups were deemed clinically insignificant in this group of healthy, young volunteers.

Sedation

Significant subjective symptoms were observed after placebo/THC (Fig 4), an effect that was amplified when THC and oxycodone were combined. Compared with placebo/THC, the degree of sedation increased by 30% (from $t=1$ to $t=8$ h) and drug high by 10% (from $t=2$ to $t=4$ h) in the oxycodone/THC treatment arm. Compared with placebo/THC, the energy state

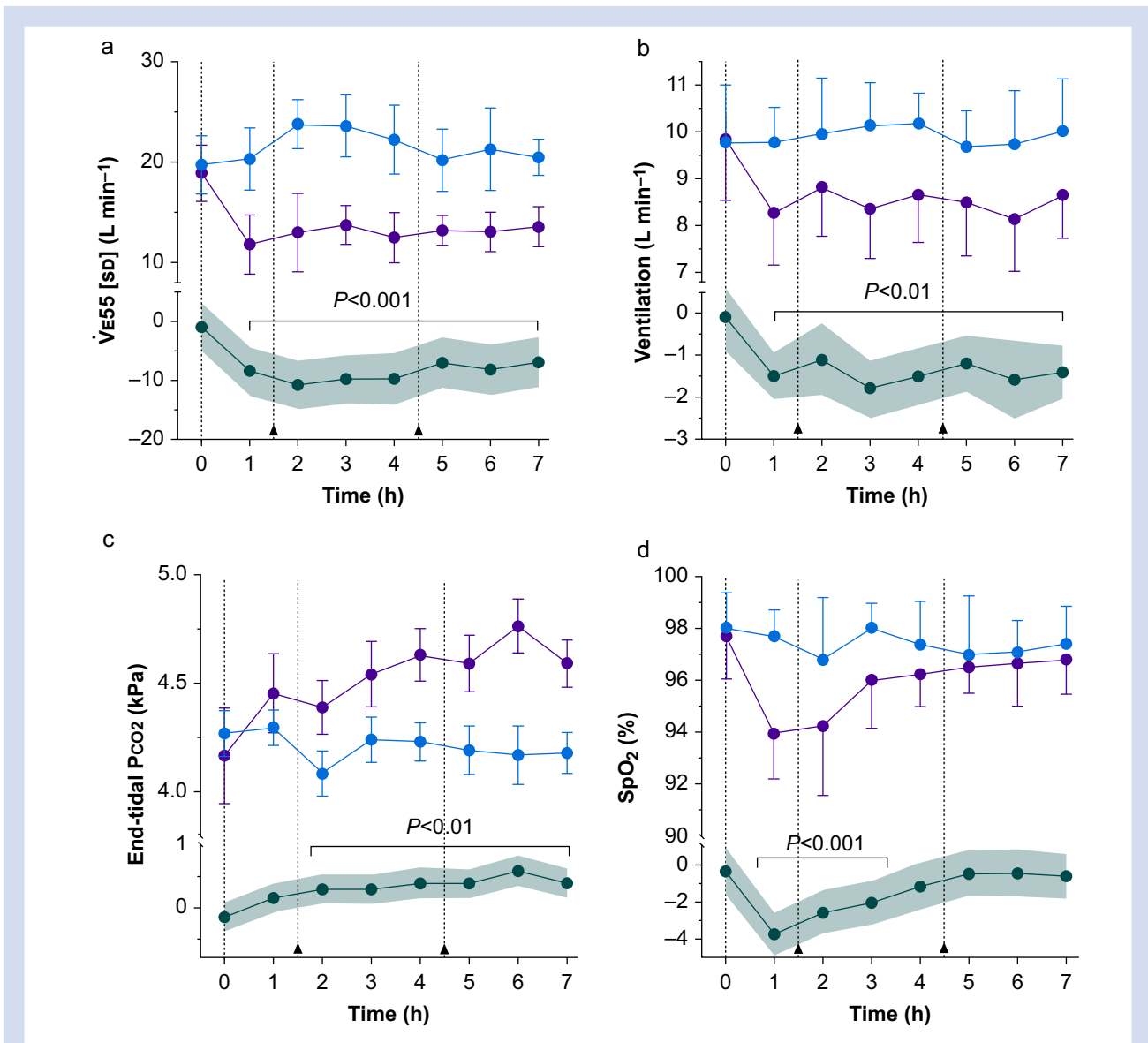


Fig 3. Influence of two inhalations of THC 22.4 mg at $t=1.5$ and 4.5 h after ingestion of 20 mg oral oxycodone or placebo at $t=0$ h on respiratory variables. Blue symbols depict mean placebo data (SD); purple symbols depict mean oxycodone data (SD). Green symbols depict the mean differences in the data (oxycodone – placebo) (95% confidence interval; blue shaded area). Arrows indicate the timing of the THC inhalation. P -values indicate the level of significance of the difference between treatment arms. (a) V_{E55} , (b) resting ventilation, (c) resting end-tidal P_{CO_2} , and (d) oxygen saturation. SD , standard deviation; THC, Δ^9 -tetrahydrocannabinol.

(energetic vs lethargic) and the state of alertness (alert vs drowsy) were further reduced in the oxycodone/THC treatment arm by, respectively, 30% (from $t=2$ to $t=6$ h) and 40% (from $t=1$ to $t=8$ h). Spontaneously observed or reported adverse events are given in Table 1.

Discussion

In this randomised crossover study, we found that THC did not reduce ventilation in healthy volunteers after pretreatment with placebo or oral oxycodone 20 mg, using HCVR as a sensitive biomarker of drug effect.^{24–26} The excitatory THC effect was small, short-lived, variable, and not consistent.

THC is a partial agonist at the CB1 and CB2 receptors, and both receptors are expressed within brainstem respiratory pathways, with opposing effects on ventilatory control.^{9,16–19} Because THC is the primary component of the Bedrocan variety, the lack of (consistent) respiratory effects of THC may be attributable to THC activation of both cannabinoid receptor systems, whereby the respiratory depressant effect from CB1 receptor activation was counteracted by stimulation from CB2 receptor activation (i.e. a mixed stimulatory–inhibitory THC effect).¹⁹ Another possibility is that the expression of CB receptors within the human brainstem respiratory circuits is low, and consequently, their activation was insufficient to interact with ventilatory control. Our protocol, however, was

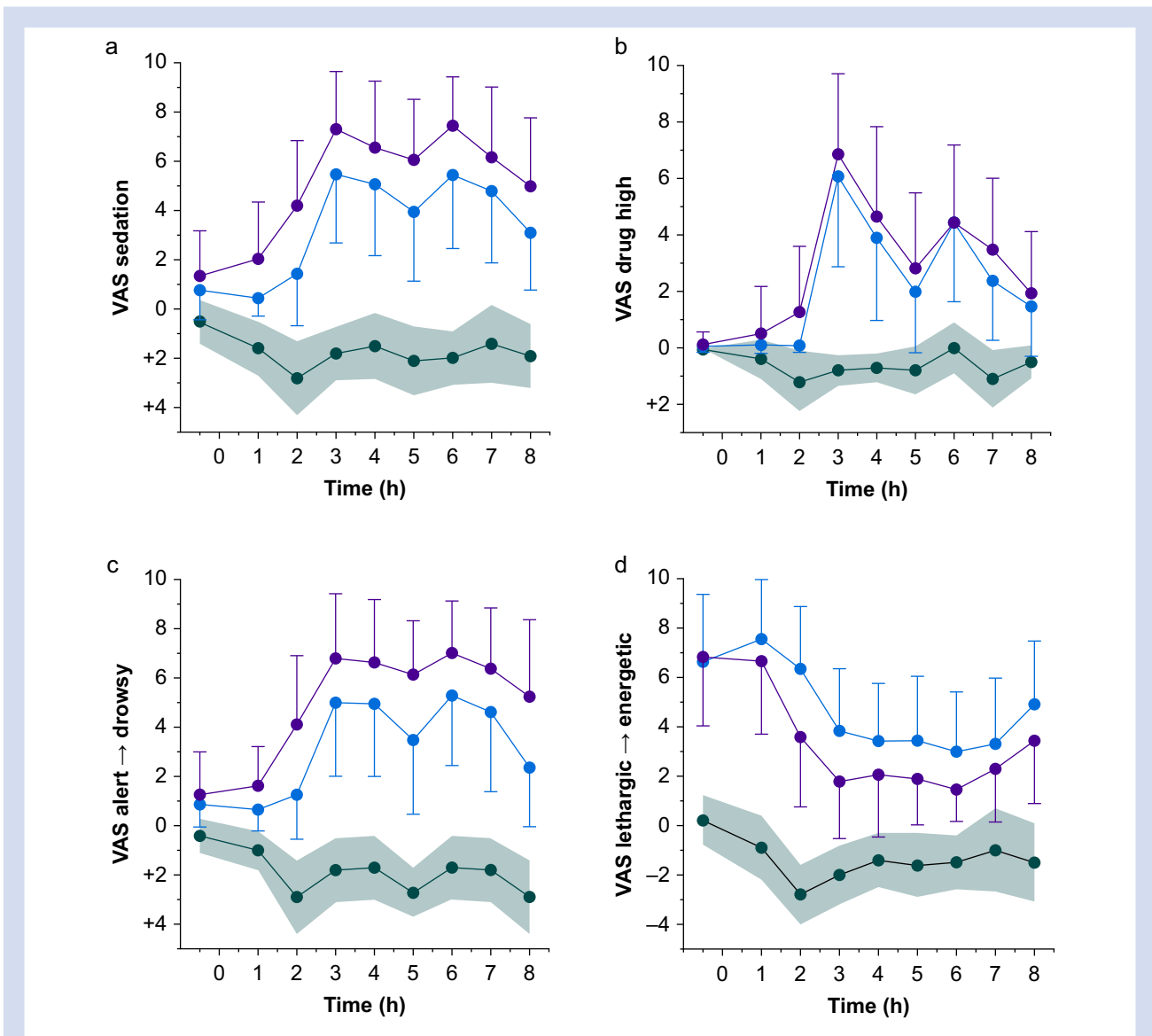


Fig 4. Influence of two inhalations of 22.4 mg THC at $t=1.5$ and 4.5 h after ingestion of 20 mg oral oxycodone or placebo at $t=0$ h on subjective effects. Blue symbols depict mean placebo data (SD); purple symbols depict mean oxycodone data (SD). Green symbols depict the mean differences in the data (oxycodone – placebo) (95% confidence interval; blue shaded area). (a) Sedation, (b) drug high, (c) transition from alert to drowsy, and (d) transition from energetic to lethargic. SD, standard deviation; THC, Δ^9 -tetrahydrocannabinol.

Table 1 Spontaneously reported or observed adverse events. THC, Δ^9 -tetrahydrocannabinol.

Adverse event	Placebo/THC, n	Oxycodone/THC, n
Nausea	4	10
Vomiting	1	1
Dizziness	12	15
Lightheadedness	17	17
Vertigo	4	5
Headache	8	4
Somnolence	17	17
Pruritis	1	4
Flushing	2	1
Dry mouth	17	17
Apnoea	1	3
Total	84	94

not designed to explore the underlying mechanism of THC effect on ventilatory control; hence, we are unable to confirm these hypothesised mechanisms. Further research, using specific CB1 and CB2 antagonists, is required to comprehend our findings and additionally establish the role of partial agonism of THC at the cannabinoid receptor systems.

The human literature is equivocal regarding the effect of THC on ventilatory control. THC at escalating doses of 5–10 mg produced dose-dependent moderate respiratory depression with a maximum ΔV_{E55} of -6 L min^{-1} .⁵ However, some subjects also experienced periods of respiratory stimulation. In another study, 35 mg THC administered by smoking, caused mild but consistent respiratory depression in experienced marijuana consumers; the effect declined with continued marijuana administrations.⁶ In a third study,⁷ 10 mg inhaled THC increased hypercapnic and hypoxic ventilatory responses in experienced marijuana smokers. Despite differences in study protocol, population, dose, administration mode, and experimental setup, we argue that the differences in outcome amongst these studies, and our study, are small. We, therefore, conclude that the effect of THC on ventilatory control in healthy humans is limited, and serious respiratory depression does not occur. However, these experimental data contrast real-world evidence on synthetic CB1 cannabinoids, which are widely available and a cheap alternative to natural THC.^{12,13} Two reports mention that, after synthetic cannabinoid use, some individuals needed medical attention because of severe respiratory depression. Evidently, differences in potency between natural THC and these synthetic CB1 agonists, underlying disease, and simultaneous abuse of other illicit substances or alcohol are accountable for these exacerbated effects. A meaningful comparison with the experimental studies is therefore not realistic.

Animal studies are similarly unclear. In the non-human primate, THC had a variable effect on resting ventilation with a modest respiratory depressant effect in non-human primates.¹⁴ In contrast, in spontaneously breathing anaesthetised rats, THC produced marked respiratory depression.¹⁰ Most other studies used synthetic cannabinoids. Although CB1 agonists were consistently inhibitory,^{9,11,15} CB2 agonists were without effect.^{17,18} These later findings suggest that THC might be without effect at the CB2 receptor or only becomes active when the system is exposed to an opioid.^{17,18} Such a particular effect has also been observed for ketamine and amphetamines.³⁴ These drugs stimulate breathing only when

there is noticeable OIRD. This is possibly related to the fact that these stimulants act on brain areas that control CO₂-dependent ventilation, the major site of action of opioids, and not on areas that regulate CO₂-independent resting ventilation.³⁴

We found that THC did not further enhance oxycodone-induced depression of V_{E55} , neither after the first nor after the second inhalation. The small excitatory effect present in the data was again short-lived, variable, inconsistent, and not significant in the post versus pre comparison pre-test. For example, THC was unable to improve SpO₂ levels that were modestly reduced by oxycodone. Because oxygen saturation is a measure of gas exchange in the lungs and not of ventilation, other mechanisms related to ventilatory control may be involved, such as opioid-induced atelectasis. Our data do imply that oxycodone was solely responsible for the respiratory depression in the oxycodone/THC arm of the study.

In a previous study in healthy male volunteers, who were all experienced cannabis consumers, Johnstone and colleagues⁴ combined increasing i.v. THC doses (2.2–10.7 mg) with oxymorphone 1 mg kg^{-1} and measured the HCVR. Oxymorphone reduced V_{E55} by about 10 L min^{-1} , with a further decrease of 9 L min^{-1} after adding THC. In contrast, in non-human primates, THC did not further impair respiratory depression induced by morphine or fentanyl.¹⁴ Although they did not study THC, the study from Wiese and colleagues¹⁵ is of interest, as they show that while a brain-penetrant CB1 agonist enhanced OIRD, a peripherally restricted CB1 agonist attenuated morphine-induced respiratory depression. This was possibly attributable to an effect at CB1 receptors outside the CNS, such as in lung tissue and in vagal or glossopharyngeal nerves.¹⁵ An effect at the carotid bodies, an important target for reversal of OIRD,³⁵ seems unlikely, as CB1 expression within the carotid body is low.³⁶ Further studies are needed to determine whether the results from Wiese and colleagues¹⁵ apply to humans. Possibly receptor-specific differences may exist between non-human primates and humans. Finally, two animal studies addressed the effect of synthetic CB2 agonists on OIRD. The first study¹⁷ showed that a biased CB2 agonist reduced fentanyl-induced respiratory depression, whereas the second independent study¹⁸ showed that a selective CB2 agonist reversed morphine-induced respiratory depression. These animal data suggest that our inability to show enhancement of oxycodone-induced respiratory depression by THC may be related to a central CB2 effect or a peripheral CB1 effect, or both (but see also above, where we suggest absence of involvement of CB receptors in ventilatory control in humans).^{17,18} These assumptions are presently purely hypothetical and need further proof. The discrepancy between our findings and those of Johnstone and colleagues⁴ remains unexplained but may relate to differences in THC dose, study population, opioids studied, THC origin, presence of terpenes in our preparation (i.e. the entire cannabis 'cocktail'), administration mode (i.v. vs inhalation), or to other unreported methodological issues.

THC produced several subjective experiences (Fig 3), including sedation, reduced alertness and energy state, and the sensation of drug high. These are well-known effects of THC and were earlier reported also in pain patients.²⁹ Of interest is the observation that oxycodone pretreatment had just a relatively small additive effect on these symptoms; drug high was least affected by oxycodone (Fig 3b). Our findings show that subjective effects and changes in ventilatory control are differentially affected by THC and oxycodone. Although

oxycodone had an exclusive effect on ventilation, THC had a dominant (but not exclusive) effect on subjective experiences. We relate this to the differences in activated brain sites by THC and oxycodone. It is somewhat unexpected that the increase in sedation by THC had no effect on ventilation. This may possibly be related to the excitatory effect of THC at CB2 receptors.

A limitation of our study was that there was no study arm examining the effect of oxycodone/placebo. The design avoided exposing our subjects to multiple oxycodone administrations and reduced the likelihood of addictive behaviour. Although the subjects were screened for illicit opioid abuse and all stated that they were opioid-naïve, some of them were recreational cannabis users. We and the ethics committee argued that in such a relatively young adult population, the restrictive use of potent agents that may induce addictive behaviour is warranted. Additionally, the oxycodone/THC group and the post-*vs* pre-test analysis gave sufficient information to detect an effect of THC on OIRD.

Another important limitation of the study was that we did not investigate the addictive properties of the opioid–THC combination. Because both agents have strong addictive tendencies, it is possible that problems might arise from this specific combination in terms of abuse, diversion, dependence, and problems with withdrawal. In a recently completed study, we compared the effect of long-term treatment with cannabis *vs* oxycodone *vs* cannabis combined with oxycodone on adverse effects, including drug craving, likability, and withdrawal (unpublished data; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT05235503) ID: NCT05235503). The first results suggest that, at least in our well-chosen study population of patients with chronic pain, no serious adverse effects occurred and abuse or addiction did not occur. However, in real life where no inclusion or exclusion criteria apply, such problems may indeed arise. Hence, caution is warranted with the current combination.

In summary, in human volunteers, THC has no significant effect on ventilatory control after placebo or oxycodone pretreatment. This suggests that cannabinoid receptors do not interact with respiratory pathways in the brainstem, or that CB1 receptor activation is offset by an opposing effect at CB2 receptors.

Authors' contributions

Study design: AD, RvdS, MN, MvV, MAK, CK

Subject recruitment: JvD

Experimentation: JvD, MvL, PS, KWKK, SJ

Data analysis: EO, AD, JvD, MN

Writing of first version of manuscript: JvD, AD, MvV, RvdS, MN, CK, MAK

Approval of final version: all authors.

Declaration of interest

The authors declare that they have no conflicts of interest.

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References

1. National Institute on Drug Abuse. *What is the scope of cannabis (marijuana) use in the United States?*. Available from: <https://nida.nih.gov/publications/research-reports/marijuana/what-scope-marijuana-use-in-united-states>. (accessed 31 August 2022)
2. US Department of Health and Human Services. Opioid crisis statistics. Available from: <https://www.hhs.gov/opioids/statistics/index.html> (Accessed 20 January 2023).
3. Dahan A, Niesters M, Smith T, Overdyk F. Opioids. In: Barash PG, Cullen BF, Stoelting RK, et al., editors. *Clinical anesthesia*. 9th Edn. Philadelphia, PA: Wolters Kluwer; 2023. p. 505–26
4. Johnstone RE, Lief PL, Kulp RA, Smith TC. Combination of Δ^9 -tetrahydrocannabinol with oxymorphone or pentobarbital: effects on ventilatory control and cardiovascular dynamics. *Anesthesiology* 1975; **42**: 674–84
5. Malit LA, Johnstone RE, Bourke DI, Kulp RA, Klein V, Smith TC. Intravenous Δ^9 -tetrahydrocannabinol: effects on ventilatory control and cardiovascular dynamics. *Anesthesiology* 1975; **42**: 666–73
6. Bellville JW, Gasser JC, Miyake T, Aqleh K. Tolerance to the respiratory effects of marijuana in man. *J Pharmacol Exp Ther* 1976; **197**: 326–31
7. Zwillich CW, Doekel R, Hammill S, Weil JV. The effects of smoked marijuana on metabolism and respiratory control. *Am Rev Resp Dis* 1978; **118**: 885–91
8. Mathew RJ, Wilson WH, Humphreys DF, Lowe JV, Wiethe KE. Regional cerebral blood flow after marijuana smoking. *J Cereb Blood Flow Metab* 1992; **12**: 750–8
9. Padley JR, Li Q, Pilowsky PM, Goodchild AK. Cannabinoid receptor activation in the rostral ventrolateral medulla oblongata evokes cardiorespiratory effects in anaesthetised rats. *Br J Pharmacol* 2003; **140**: 384–94
10. Schmid K, Niederhoffer N, Szabo B. Analysis of respiratory effects of cannabinoids in rats. *Naunyn Schmiedebergs Arch Pharmacol* 2003; **368**: 301–8
11. Pfitzer T, Niederhoffer N, Szabo B. Central effects of the cannabinoid receptor antagonist WIN55212-2 on respiratory and cardiovascular regulation in anaesthetized rats. *Br J Pharmacol* 2004; **142**: 943–52
12. Jinwala FN, Gupta M. Synthetic cannabis and respiratory depression. *J Child Adolesc Psychopharmacol* 2012; **22**: 459–62
13. Alon MH, Saint-Fleur MO. Synthetic cannabinoid induced acute respiratory depression: case series and literature review. *Resp Med Case Rep* 2017; **22**: 137–41
14. Weed PF, Gerak LR, France CP. Ventilatory-depressant effects of opioids alone and in combination with cannabinoids in rhesus monkeys. *Eur J Pharmacol* 2018; **833**: 94–9
15. Wiese BM, Liktov-Busa E, Couture SA, et al. Brain penetrant, but not peripherally restricted, synthetic cannabinoid 1 receptor agonists promote morphine-mediated respiratory depression. *Cannabis Cannabinoid Res* 2022; **7**: 621–7
16. Van Sickel MD, Duncan M, Kingsley PJ, et al. Identification and functional characterization of brainstem cannabinoid CB₂ receptors. *Science* 2005; **310**: 329–32
17. Zavala CA, Thomaz AC, Iyer V, Mackie K, Hohmann AG. Cannabinoid CB₂ receptor activation attenuates fentanyl-induced respiratory depression. *Cannabis Cannabinoid Res* 2021; **6**: 389–400

18. Wiese BM, Liktor-Busa E, Levine A, et al. Cannabinoid-2 agonism with AM2301 mitigates morphine-induced respiratory depression. *Cannabis Cannabinoid Res* 2021; **6**: 401–12
19. Pertwee GB. The diverse CB₁ and CB₂ receptor pharmacology of three plant cannabinoids: Δ^9 -tetrahydrocannabinol, cannabidiol and Δ^9 -tetrahydrocannabivarin. *Br J Pharmacol* 2008; **153**: 199–215
20. Naef M, Curatolo M, Petersen-Felix S, Arendt-Nielsen L, Zbinden A, Brenneisen R. The analgesic effect of oral delta-9-tetrahydrocannabinol (THC), morphine, and a THC-morphine combination in healthy subjects under experimental pain conditions. *Pain* 2003; **105**: 79–88
21. Cooper ZV, Bedi G, Ramesh D, Balter R, Comer SD, Haney M. Impact of co-administration of oxycodone and smoked cannabis on analgesia and abuse liability. *Neuropsychopharmacol* 2018; **43**: 2046–55
22. Chen X, Cowan A, Inan S, et al. Opioid-sparing effects of cannabinoids on morphine analgesia: participation of CB₁ and CB₂ receptors. *Br J Pharmacol* 2019; **176**: 3378–89
23. O'Connell M, Sandgren M, Frantzen L, Bower E, Erickson B. Medical cannabis: effects on opioid and benzodiazepine requirements for pain control. *Ann Pharmacother* 2019; **53**: 1081–6
24. van der Schrier R, Roozkrans M, Olofsen E, et al. Influence of ethanol on oxycodone-induced respiratory depression: a dose-escalating study in young and elderly volunteers. *Anesthesiology* 2017; **126**: 534–42
25. Florian J, van der Schrier R, Gershuny V, et al. Effect of paroxetine or quetiapine combined with oxycodone on ventilation: a randomized clinical trial. *JAMA* 2022; **328**: 1405–14
26. Algera H, van der Schrier R, Cavalla D, et al. Respiratory effects of the atypical tricyclic antidepressant tianeptine in human models of opioid-induced respiratory depression. *Anesthesiology* 2022; **37**: 446–58
27. Chen TC, Knaggs RD, Chen LC. Association between opioid-related deaths and prescribed opioid dose and psychotropic medicines in England: a case-crossover study. *Br J Anaesth* 2021; **127**: 789–97
28. Boon M, van Dorp E, Broens S, Overdyk F. Combining opioids and benzodiazepines: effects on mortality and severe adverse respiratory effects. *Ann Palliat Med* 2020; **9**: 542–57
29. van de Donk T, Niesters M, Kowal MA, Olofsen E, Dahan A, van Velzen M. An experimental randomized study on the analgesic effects of pharmaceutical-grade cannabis in chronic pain patients with fibromyalgia. *Pain* 2019; **160**: 860–9
30. Hazekamp A, Ruhaak R, Zuurman L, van Gerven J, Verpoorte R. Evaluation of a vaporizing device (Volcano) for the pulmonary administration of tetrahydrocannabinol. *J Pharm Sci* 2006; **95**: 1308–17
31. Nielsen M, Smith H. Studies on the regulation of respiration in acute hypoxia. *Acta Physiol Scand* 1951; **4**: 293–313
32. Bond A, Lader M. The use of visual analogue scales in rating of subjective feelings. *Br J Med Psychol* 1974; **47**: 211–8
33. Bates D, Maechler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. *J Stat Softw* 2015; **67**: 1–48
34. Jonkman K, van Rijnsoever E, Olofsen E, et al. Esketamine counters opioid-induced respiratory depression. *Br J Anaesth* 2018; **120**: 1117–27
35. Roozkrans M, Olofsen E, van der Schrier R, et al. Reversal of opioid-induced respiratory depression by BK-channel blocker GAL021: a pharmacokinetic-pharmacodynamic modelling study in healthy volunteers. *Clin Pharmacol Ther* 2015; **97**: 641–9
36. De Caro R, Macchi V, Sfriso MM, Porzionato A. Structural and neurochemical changes in maturation of the carotid body. *Respir Physiol Neurobiol* 2013; **185**: 90–9

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