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Intranasal Naloxone Reversal of Opioid-induced Respiratory Depression in Opioid-naive Individuals and Self-reported Daily Opioid Users

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Naloxone, particularly in its intranasal formulation, is widely used to reverse respiratory depression from opioid overdoses, with proven efficacy against heroin-induced respiratory depression
- However, concerns remain about its effectiveness against newer, more potent synthetic opioids like fentanyl and its analogs, which have higher affinity for the opioid receptor and are increasingly implicated in overdose deaths

What This Article Tells Us That Is New

- This study demonstrated that a single 4-mg dose of intranasal naloxone rapidly reversed moderate respiratory depression caused by both fentanyl and sufentanil in opioid-naive individuals and daily opioid users, but recovery of carbon dioxide levels was delayed, especially during sufentanil exposure
- These findings reveal variable effectiveness depending on the physiologic endpoint and opioid receptor affinity, indicating that a single intranasal naloxone dose may be insufficient for reversing respiratory instability in cases involving high-affinity or high-dose synthetic opioids

ABSTRACT

Background: Since current opioid overdose deaths occur mainly from potent synthetic opioids with high affinity for the opioid receptor, such as fentanyl and carfentanil, it is important to determine the efficacy of naloxone, particularly the intranasal formulation, in reversing opioid-induced respiratory depression. This study evaluated effectiveness of 4 mg intranasal naloxone (Narcan; Adapt Pharma Inc., USA) in reversing moderate respiratory depression induced by fentanyl and sufentanil in opioid-naive individuals and self-reported daily opioid users. Sufentanil was compared to fentanyl because of its higher affinity for the opioid receptor.

Methods: In this prospective, crossover trial, 12 opioid-naive individuals and 18 daily opioid users (morphine milligram equivalent, 291; range, 60 to 2,250 mg/day) received continuous fentanyl or sufentanil infusions, titrated to achieve 30 to 40% reduction in minute ventilation ($\dot{V}_E$). Participants were administered Narcan during steady-state respiratory depression. Primary endpoints included time to reversal of diminished $\dot{V}_E$ and elevated end-tidal carbon dioxide concentration (pCO_2).

Results: Narcan restored $\dot{V}_E$ within 2 to 4 min across all participants but showed delayed reversal of end-tidal pCO_2 (11 to 17 min), with pCO_2 recovery during sufentanil exposure in just 8 opioid-naive individuals and 10 daily opioid users. Hysteresis analysis showed for $\dot{V}_E$ reversal onset/offset times (blood-effect-site equilibration half-lifes) of 0 to 1 min and for end-tidal pCO_2 2 to 11 min. Because of withdrawal symptoms, 7 of 18 daily opioid users participated once in the study. Study limitations included continuous opioid infusions that do not occur in real-world overdose settings.

Conclusions: A single Narcan dose reversed moderate fentanyl- and sufentanil-induced respiratory depression, although effectiveness varied by endpoint and opioid receptor affinity. Rapid $\dot{V}_E$ recovery suggests clinical utility of intranasal naloxone, but delayed and sometimes incomplete recovery of end-tidal pCO_2, particularly during exposure to the high-affinity opioid sufentanil, indicates reversal inefficacy and persistence of respiratory instability. Further studies are needed to address optimal naloxone doses and alternative formulations to address high-dose potent opioid threats.

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Abbreviations: **ΔT**, complete reversal time; **ETpco$_2$**, end-tidal carbon dioxide concentration; **OIRD**, opioid-induced respiratory depression; **t½k$_{e0}$**, arterial concentration-effect-site equilibration half-life; $\dot{V}_E$, minute ventilation

Opioids, intended for severe pain relief, have serious side effects that complicate their use. Among the many opioid adverse effects, the potential to cause dependency, abuse, and respiratory depression are particularly concerning and have contributed to the current opioid crisis in the United States. In the past 2 decades, an estimated 800,000 people in the United States have died from drug overdoses, primarily due to potent opioids.[1,2] These drugs bind to mu-opioid receptors within the brainstem, suppressing brainstem respiratory centers, and consequently depress minute ventilation ($\dot{V}_E$), potentially to the level of apnea when consumed at high doses.[3–6] Particularly overdoses from opioids with high affinity for the mu-opioid receptor, such as the synthetic opioid fentanyl or its congeners (*e.g.,* sufentanil, carfentanil), may cause respiratory depression that results in hypoxia and bradycardia, progressing to cardiac arrest and, when no intervention is initiated, death.[7]

Intranasal naloxone (Narcan; Adapt Pharma Inc., USA), approved as an over-the-counter medication by the U.S. Food and Drug Administration (Silver Spring, Maryland) in 2023, is currently the most applied treatment of an opioid overdose in the community setting (*i.e.*, outside the hospital) by first responders and bystanders. Effectiveness of intranasal naloxone in reversing heroin-induced respiratory depression has been demonstrated with success rates ranging from 74 to 83% using a 2-mg intranasal dose.[8–12] However, heroin's receptor affinity is significantly lower than that of fentanyl, which raises concerns whether adequate reversal can be achieved with intranasal naloxone when faced with a more potent synthetic opioid such as fentanyl or sufentanil. An opioid with a high receptor affinity, carfentanil, is rather difficult to reverse with naloxone, as observed in primate laboratory studies and human case reports.[13–15]

In this observational, prospective, crossover trial, we evaluated the effectiveness of the US Food and Drug Administration–approved, over-the-counter intranasal naloxone hydrochloride spray (4 mg in 0.1 ml; Narcan) in reversing respiratory depression induced by fentanyl and sufentanil in opioid-naive individuals and daily opioid users in terms of speed of onset as well as speed of offset (*i.e.*, renarcotization). Sufentanil was selected for its approximately 10-fold higher affinity for the mu-opioid receptor relative to fentanyl, Ki (inhibitor constant) 0.14 *versus* 1.35 nM,[7] serving as a model for ultra-potent synthetic opioids such as carfentanil. We hypothesized that a single 4-mg intranasal dose naloxone would reverse fentanyl- or sufentanil-induced respiratory depression within 5 min of administration on all three measured endpoints: $\dot{V}_E$, end-tidal carbon dioxide concentration ($ETpCO_2$), and pupil diameter. Change in pupil size is an easy-to-measure clinical sign that is considered a surrogate of respiratory depression. A second hypothesis is that the naloxone-induced changes in pupil diameter may be used to predict induced ventilatory changes with similar dynamics.

Materials and Methods

Ethics and Subjects

This single-center, crossover, open-label trial evaluated the effect of intranasal naloxone to reverse opioid induced respiratory depression. All subjects were scheduled to visit the laboratory on two separate occasions, at least 1 week apart. In opioid-naive individuals, the treatment sequence was fentanyl on the first occasion and sufentanil on the second occasion. The study was approved by the regional medical research ethics committee, Leiden Den Haag Delft (Leiden, The Netherlands). The protocol was registered at the clinicaltrials.gov registry under identifier NCT05338632 on April 14, 2022. Before enrollment, all participants gave written informed consent. All study procedures were performed according to good clinical practice guidelines and the Declaration of Helsinki. The study was conducted from June 15, 2022, to October 30, 2023.

Inclusion criteria were age 18 to 70 yr and body mass index 18 to 32 kg/m^2. In addition, all participants were required to be in a good health based on a medical evaluation conducted by an independent physician, including the subject's medical history, physical examination, and vital signs. For opioid users, a 12-lead electrocardiogram and blood tests (hematology, renal and liver functions) were obtained and required to be clinically normal. Exclusion criteria included illicit drug use; a history or current presence of significant medical or psychiatric disease (excluding licit opioid use disorder); pregnancy or lactation; any drug or food allergy; a positive alcohol breath test on screening and study days; and for opioid-naive individuals, a positive drug urine dipstick on screening and study days. Self-reported daily opioid users who met the criteria for diagnosis of a substance use disorder according to the Diagnostic and Statistical Manual of Mental Disorders 5 other than opioids, caffeine, or nicotine were excluded, as well as those individuals who received medication-assisted treatment for their opioid use, including treatment with mixed agonists–antagonists, such as buprenorphine. The medication regimen of

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daily opioid users was not altered to prevent any withdrawal during the study unrelated to the naloxone intervention. All subjects received a financial compensation (240 euros per session) for their participation in the study.

Study Design and Measurements

The study was conducted in the Anesthesia and Pain Research Unit at Leiden University Medical Center (Leiden, The Netherlands). Upon arrival in the unit, two intravenous access lines were placed in the cubital fossa of both arms, one for the infusion of the opioid and the other for immediate intravenous access in case of an emergency. Furthermore, an arterial line was placed in the radial artery of the nondominant arm for continuous blood pressure measurements and blood sampling.

Throughout the study, the subjects breathed through a facemask that was connected to a pneumotachograph and pressure transducer system (Hans Rudolph Inc., USA) to measure flow; corrections were in place for the effect of the density of the gas on volume. Inspired and expired gas concentrations and oxygen saturation measured by pulse oximetry were measured using the Masimo Root ISA OR plus capnograph (Masimo, USA). The subjects breathed 4 to 6 l oxygen in room air.[16]

After a 10- to 15-min period of steady-state breathing through the facemask, a continuous infusion of either fentanyl or sufentanil was initiated. The opioid was titrated to achieve approximately 40% depression of $\dot{V}_E$ (as observed in real-life on screen), after which the infusion rate was maintained constant. This was achieved by administration of an initial fentanyl dose of 75 μg/min for 1.5 min, followed by 13 μg/min for 14 min, after which the infusion was set at 7.7 μg/min. For sufentanil, the equivalent infusion rates were 8.0 μg/min for 1.5 min, 1.41 μg/min for 40 min, and 0.8 μg/min thereafter. The infusion rates and times of infusion were adapted on an individual basis depending on the effects on $\dot{V}_E$. After approximately 30 to 40 min of opioid infusion and when $\dot{V}_E$ had reached the target level, intranasal Narcan was administered by briefly removing the facemask and spraying the drug into a single nostril, in accordance with the manufacturer's instructions. $\dot{V}_E$ and inspired and expired carbon dioxide concentrations were continuously measured during the opioid infusion that was maintained as indicated above. We here present data of the first 180 min of opioid infusion.

Pupillometry data were obtained using a PLR-3000 pupillometer (NeurOptics, USA) at t = 0 (predrug infusion), 2, 5, 10, 15, 20, 30 (Narcan administration), 32, 35, 40, 50, 60, 75, 90, 105, 120, 150, and 180 min after the initiation of the opioid infusion. In cases where pupil measurements coincided with blood sampling, blood sampling preceded pupillometry.

Study Drugs, Blood Sampling, and Drug Measurements. All study drugs were prepared by the local pharmacy: fentanyl citrate 50 μg/ml (Hameln Pharma GmbH, Germany), sufentanil citrate 5 μg/ml (Eurocept BV, The Netherlands), and intranasal naloxone hydrochloride 4 mg in 0.1 ml (Narcan). The drugs were dispensed on the morning of the experimental session.

Blood samples were obtained for measurement of naloxone, fentanyl, and sufentanil concentrations in arterial blood. Naloxone samples were obtained at t = 0 (prenaloxone), 2, 5, 10, 15, 20, 30, 45, 60, 75, 90, 120, and 150 min after the intranasal spraying; fentanyl or sufentanil samples were obtained at t = 0, 2, 5, 10, 15, 20, 30 (time of Narcan administration), 35, 40, 45, 60, 75, 90, 120, 150, and 180 min after the initiation of opioid infusion. The samples were centrifuged within 15 min of withdrawal, and plasma was separated and stored at −70°C until analysis.

The samples were analyzed by KCAS Bio (USA) using validated liquid chromatography tandem mass spectrometry assays. The naloxone lower limit of quantitation was 0.020 ng/ml with between-run accuracy 100%, between-run precision 3.3%, within-run accuracy 99%, and within-run precision 5%. Fentanyl lower limit of quantitation was 0.01 ng/ml with between-run accuracy 100%, between-run precision 4%, within-run accuracy 102%, and within-run precision 2%. Sufentanil lower limit of quantitation was 0.01 ng/ml with between-run accuracy 94%, between-run precision 6%, within-run accuracy 94%, and within-run precision 7%.

Safety

Intravenous naloxone (0.4 mg) could be given as rescue medication if any of the following occurred: $ETpCO_2$ greater than 9 kPa (68 mmHg), oxygen saturation measured by pulse oximetry less than 85% for 2 min or longer, apnea for more than 90 s despite tactile or verbal stimulation, or any other condition that compromised the subject's health, as determined by the attending anesthesiologist. In case of withdrawal symptoms that needed treatment according to the attending anesthesiologist, we applied the local protocol. This consists of an initial treatment with clonidine or midazolam, sublingual nitroglycerin in case of hypertension, and low-dose propofol sedation in case the symptoms persisted.

Sample Size, Protocol Modification, and Data Analysis. Given the absence of previous data, no formal sample size calculation was performed. The target enrollment (n = 24 with 12 opioid-naive individuals and 12 daily opioid users) was based on precedent from analogous respiratory antagonist trials (8 to 12 participants) and should be considered a convenience sample.[16,17]

All healthy participants received fentanyl on their first visit followed by sufentanil on their second visit. All daily opioid users also initially received fentanyl first, followed by sufentanil. After we observed that several subjects withdrew consent after their first visit, we allowed participants

to participate only once after the first study round, and we switched the treatment sequence (sufentanil on their first visit followed by fentanyl). While this caused an unbalanced design, in the end, the number of daily opioid users who received fentanyl and sufentanil was comparable: fentanyl n = 14, sufentanil n = 12, with 8 participants receiving both treatments.

In the data analyses and graphs, opioid administration started at t = −30 ± 10 min. The time of the 4-mg intranasal naloxone administration was indexed at t = 0 min, with t greater than 0 min considered fully exposed to reversal treatment. The graphical data are presented as 5-min ensemble averages, *i.e.*, mean values ± 95% CI.[18] To determine the reversal times, we used the first 90 min after naloxone of individual data and calculated reversal times (complete reversal time [ΔT] ± SD) as the time between t = 0 (baseline) and the first breath that differed from baseline no more than 10%. For the graphs, the data from all subjects were included. No between-drug or between-group statistical analyses were performed.

To get an indication of the hysteresis in the naloxone on and off responses, we constructed loops of naloxone plasma concentration *versus* effect and used a nonparametric approach to collapse the loop and to give the relationship between effect-site or steady-state naloxone concentration and effect. To that end, we applied the ke0obj program, kindly provided by S. Shafer, M.D. (Department of Anesthesiology, Stanford University, Palo Alto, California), rewritten in R (https://www.R-project.org/, accessed June 14, 2025) closing the loops gives the arterial concentration-effect-site equilibration half-life ($t½k_{e0}$).[19]

Results

A total of 38 individuals were evaluated for study eligibility, 17 opioid-naive individuals and 21 daily opioid users (fig. 1). All 17 opioid-naive participants were enrolled in the study and completed their first visit. Thereafter, five subjects dropped out due to logistical reasons (n = 4) or because of persistent nausea (n = 1). The remaining twelve participants completed their second visit with sufentanil, and their data (12 fentanyl, 12 sufentanil data sets) were included in the analysis.

Nineteen opioid users were allocated to treatment receiving either fentanyl (n = 12) or sufentanil (n = 7) on their first visit. One subject indicated serious discomfort from the facemask after receiving fentanyl and withdrew consent; she did not receive Narcan. Of the remaining 18 subjects, 8 returned for a second visit, of whom 5 received fentanyl and 3 sufentanil. Ten subjects withdrew consent after their first visit: seven because of the severity of withdrawal symptoms after Narcan, two because of logistic issues, and one because of discomfort unrelated to withdrawal. This resulted in 15 fentanyl and 12 sufentanil data sets that were analyzed.

The 12 opioid-naive participants (6 men/6 women) had a mean ± SD age of 24 ± 2 yr with range 22 to 27 yr and body mass index 22 ± 3 kg/m^2 with range 18 to 26 kg/m^2. The 18 daily opioid users (9 men/9 women) who completed at least 1 study day had a mean age of 51 ± 10 yr with range 39 to 67 yr and body mass index 27 ± 3 kg/m^2 with range 20 to 32 kg/m^2 (table 1). The opioids users consumed a daily amount of oral morphine milligram equivalents of 291 ± 521 mg (median, 135 mg); in table 2, the opioids that were daily consumed by the participants are given.

Pharmacokinetics

Plasma concentrations of naloxone, fentanyl, and sufentanil are given in figure 2. Peak naloxone concentrations (mean ± SD) were 6.7 ± 1.4 mg/ml occurring at t = 15 min in opioid-naive individuals and 5.5 ± 1.3 ng/ml at t = 20 min in daily opioid users. The area under the concentration time curve was 607 (95% CI, 547 to 667) min · ng/ml in opioid-naive individuals *versus* 476 (95% CI, 397 to 555) min · ng/ml in daily opioid users ($P < 0.001$), indicating an almost 30% greater naloxone exposure in the opioid-naive population.

The steady-state fentanyl concentration in the first 3 h after naloxone administration, required to induce approximately 40% depression of $\dot{V}_E$, was 3.6 ± 0.7 ng/ml in opioid-naive individuals and 5.1 ± 1.1 ng/ml in daily opioid users, *i.e.*, a 42% higher level ($P < 0.001$), reflective of the opioid tolerance in daily opioid users. Equivalent values for sufentanil were 0.54 ± 0.05 and 0.66 ± 0.09 ng/ml, respectively, opioid-naive individuals and daily opioid users, *i.e.,* a 22% higher concentration level in daily opioid users ($P < 0.001$). The variability in the data (fig. 2, C to F) reflects the need for up–down titration before Narcan administration to ensure a constant level of respiratory depression.

The infusion schemes were optimized to achieve stable plasma concentrations and further refined through individualization. This was expected to result in stable plasma and effect-site concentrations after approximately 30 min. In order to get an indication of the effect-site opioid concentrations, we added these concentrations to figure 2. These concentrations were derived from simulated pharmacokinetic models using data sets from Algera *et al.* for fentanyl[20] and Gepts *et al.* for sufentanil.[21] The effect-site concentrations are in close agreement with stable plasma opioid concentrations causing 30 to 40% respiratory depression, indicative that naloxone was given under steady-state conditions.

$\dot{V}_E$ and $ETpCO_2$

Baseline Values and Opioid Effects. In both populations, mean baseline $\dot{V}_E$ ($\dot{V}_E$ before any drug administration) ranged from 7.3 to 7.9 l/min, with corresponding $ETpCO_2$ values of 4.6 to 4.8 kPa (35 to 36 mmHg). Infusions of fentanyl and sufentanil reduced $\dot{V}_E$ to 4.4 to 5.5 l/min, a 30 to 40% reduction, while $ETpCO_2$ increased to 5.9 to 6.7 kPa (44 to 50 mmHg), reflecting a 22 to 28% increase (fig. 3). The effects of fentanyl and sufentanil infusions were comparable in the two populations, with a trend in greater effects from

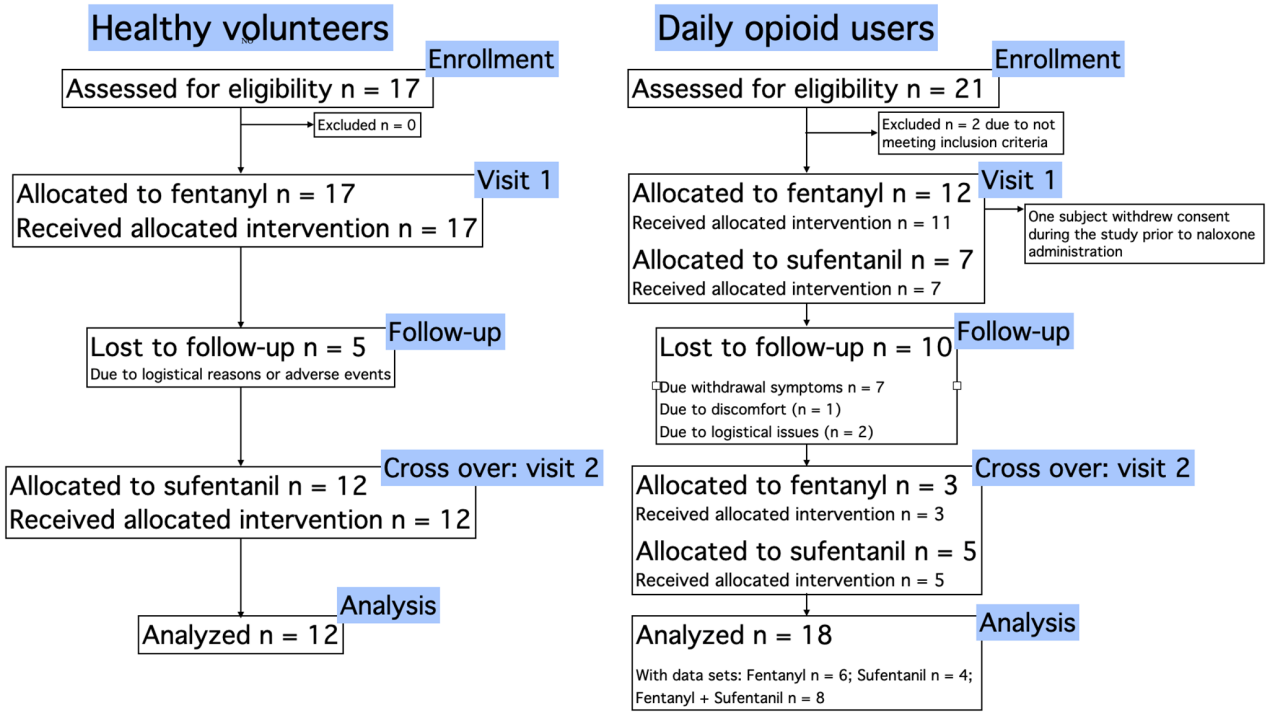

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagrams.

Table 1. Participant Characteristics

	Opioid-naive Participants	Daily Opioid Users
Sex (F/M)	n = 6/6	n = 9/9
Age,* yr	24 ± 2 [22–27]	53 ± 8 [39–67]
Body mass index,* kg/m^2	22 ± 3 [18–26]	27 ± 4 [20–32]
MME,* mg	—	291 ± 521 [60–2,250]

*Values given are mean ± SD [range]; n = number of subjects.
F, female; M, male; MME, morphine milligram equivalent.

sufentanil (10 to 20% greater changes in $\dot{V}_E$ and $ETpCO_2$; fig. 3).

Narcan Effects in Opioid-naive Individuals. The intranasal 4-mg naloxone spray increased $\dot{V}_E$ while simultaneously decreasing $ETpCO_2$, with divergent effects for fentanyl and sufentanil (fig. 3). During fentanyl infusion, intranasal naloxone restored $\dot{V}_E$ and $ETpCO_2$ to baseline values after 2.5 ± 1.4 min (ΔT ± SD) and 11.0 ± 10.5 min (table 3), respectively. One subject did not show reversal of $ETpCO_2$. In contrast, during sufentanil infusion, while ventilation recovered after 3.0 ± 1.9 min in all subjects, $ETpCO_2$ did return to baseline in just eight subjects (ΔT 16.5 ± 19.2 min), while values were more than 90 min in the remaining five subjects; the ensemble average shows no reversal (fig. 3). The nadir of $ETpCO_2$ was 5.3 ± 0.7 kPa (40.5 mmHg) at t = 30 min after naloxone, after which $ETpCO_2$ slowly increased.

Narcan Effects in Daily Opioid Users. Intranasal naloxone restored fentanyl-exposed $\dot{V}_E$ after 2.5 ± 3.2 min (n = 14) and end-tidal pCO_2 within 13.0 ± 7.3 min (n = 14). Equivalent values during sufentanil exposure were 4.0 ± 2.5 min (n = 11) and 15.0 ± 7.9 min (n = 10), respectively.

Pupil Diameter

Baseline pupil diameter values were 4.2 ± 0.4 mm (mean ± SD) in opioid-naive individuals and 3.5 ± 0.7 mm in daily opioid users ($P < 0.01$), a difference we relate to the opioids already consumed by the opioid users on the morning of testing. In the opioid-naive population, fentanyl and sufentanil reduced the pupil diameter to 2.6 ± 0.3 mm and 2.3 ± 0.1 mm at t = 20 and 30 min, respectively. In daily opioid users, equivalent values were 2.2 ± 0.4 mm and 2.0 ± 0.5 mm at t = 30 min (for both fentanyl and sufentanil). These data indicate similar changes in pupil diameter from baseline between populations (fig. 4).

Although after administration of intranasal naloxone, reversal of pupil constriction was observed, opioid-naive individuals did not experience full reversal. Full naloxone-induced reversal was observed in four opioid-naive participants during fentanyl infusion (ΔT 62 ± 31 min) and sufentanil infusion (ΔT 20 ± 10 min). Full reversal was

Table 2. Individual Data from Daily Opioid Users Including Self-reported Daily Opioid Consumption

Subject	Sex	BMI	Visit	Withdrawal Symptoms	Home Opioid Use	MME, mg
A	Male	20	Fentanyl + sufentanil	No	Oxycodone	60
B	Female	29	Fentanyl + sufentanil	No	Oxycodone	90
C	Female	32	Fentanyl + sufentanil	Yes	Oxycodone	60
D	Male	26	Fentanyl	Yes	Morphine	180
E	Male	26	Fentanyl + sufentanil	No	Tramadol	150
F	Female	24	Fentanyl + sufentanil	No	Oxycodone	90
G	Male	28	Fentanyl	Yes	Fentanyl + morphine	200
H	Female	23	Fentanyl	Yes	Oxycodone	120
I	Male	24	Fentanyl	No	Oxycodone + methadone	2,250
J	Female	30	Fentanyl	Yes	Oxycodone + fentanyl	225
K	Female	32	Fentanyl	No	Fentanyl	60
L	Female	32	Fentanyl + sufentanil	Yes	Oxycodone + fentanyl	285
M	Female	27	Fentanyl + sufentanil	No	Oxycodone	75
N	Male	29	Sufentanil	Yes	Methadone	80
O	Male	23	Sufentanil	Yes	Methadone	840
P	Male	27	Sufentanil	No	Methadone	60
Q	Male	24	Sufentanil	Yes	Oxycodone + fentanyl	225
R	Female	30	Fentanyl + sufentanil	No	Fentanyl	180

BMI, body mass index; MME, morphine milligram equivalent.

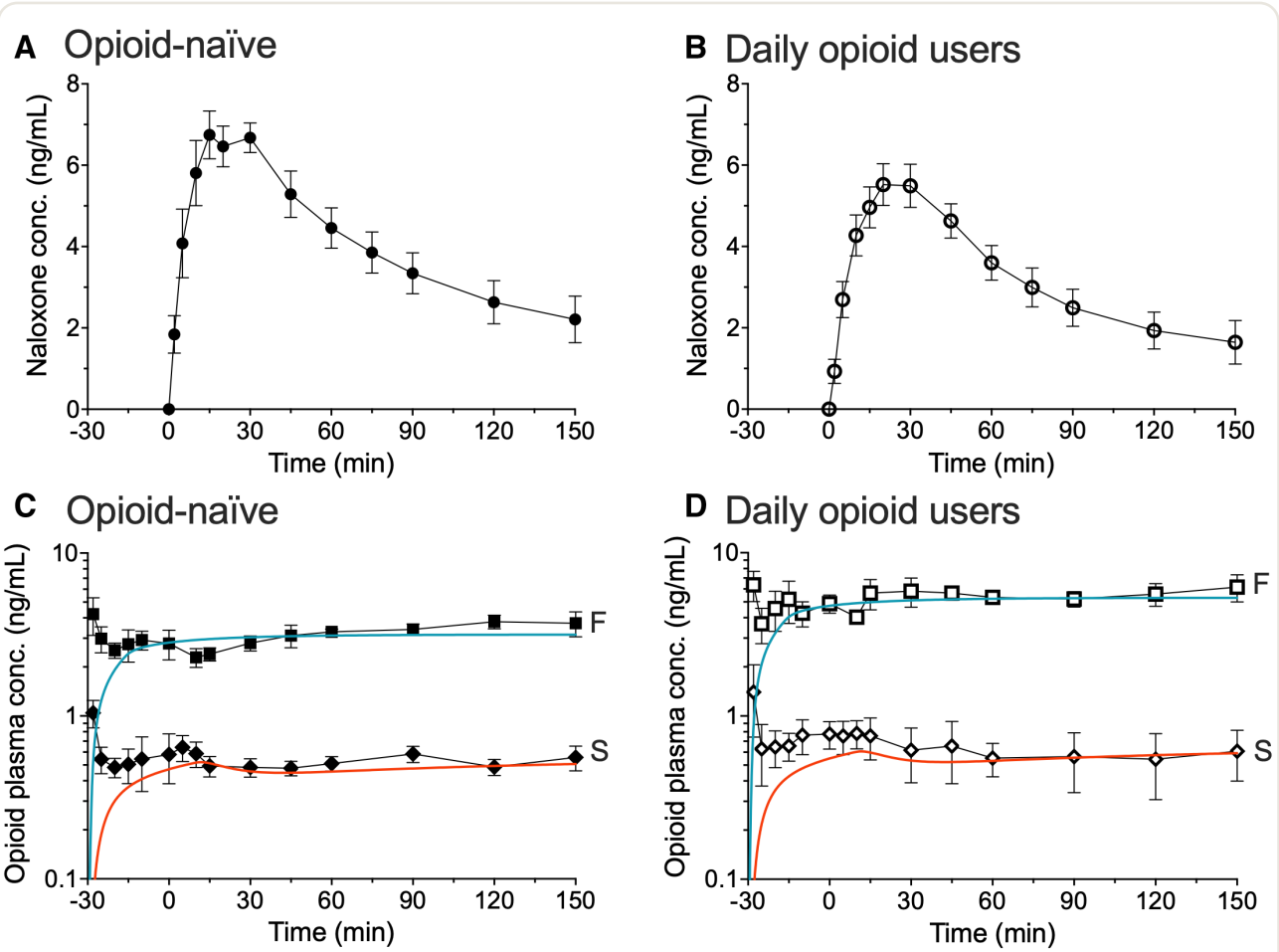

Fig. 2. Naloxone (*A* and *B*) and opioid (*C* and *D*) concentrations in opioid-naive individuals (*A* and *C*) and daily opioid users (*B* and *D*). S, sufentanil (*squares*); F, fentanyl (*diamonds*). Intranasal naloxone was given at t = 0 min. Values are mean ± SD. The *colored lines* are the simulated effect-site concentrations for fentanyl (*blue lines*) and sufentanil (*orange lines*). conc., concentration.

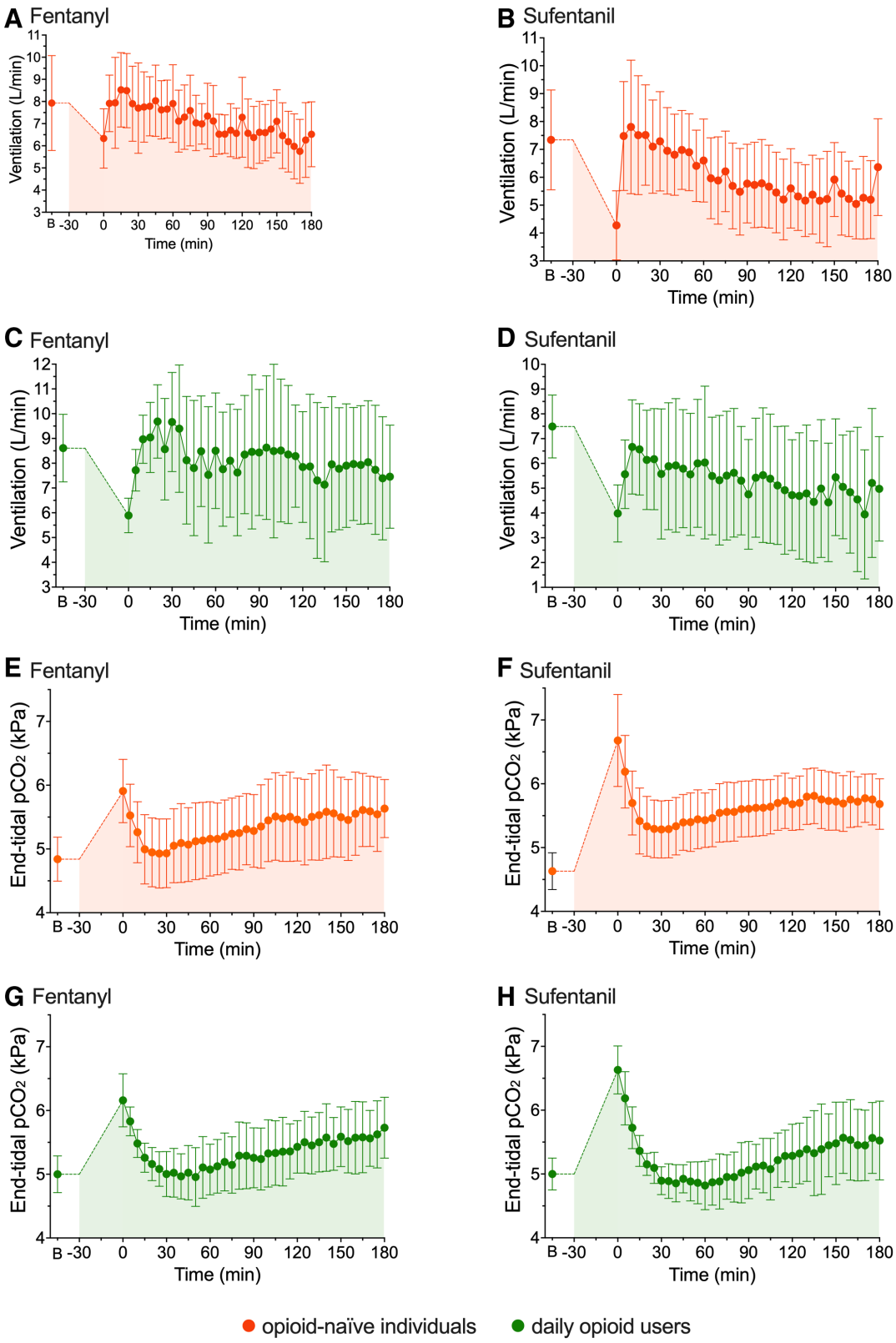

Fig. 3. Mean ventilation and end-tidal carbon dioxide concentration (pCO_2) before any drug administration (*B* on the *x-axis*) and during opioid (fentanyl or sufentanil) infusion (*shaded areas*) in opioid-naive individuals (*orange symbols*, *A*, *B*, *E*, and *F*) and daily opioid users (*green symbols*, *C*, *D*, *G*, and *H*). Intranasal naloxone was given at t = 0 min. Values are mean ± 95% CI.

Table 3. Recovery Times (ΔTs) after Intranasal Reversal of Fentanyl- and Sufentanil-induced Respiratory Depression

Recovery Times, min	Opioid-naive Participants ΔT ± SD (n, %)	Daily Opioid Users ΔT ± SD (n, %)
Recovery of ventilation		
Fentanyl	2.5 ± 1.4 (12, 100)	2.5 ± 3.2 (14, 100)
Sufentanil	3.0 ± 1.9 (12, 100)	4.0 ± 2.5 (11, 92)
Recovery of $ETpCO_2$		
Fentanyl	11.0 ± 10.5 (11, 92)	13.0 ± 7.3 (14, 100)
Sufentanil	16.5 ± 10.2 (8, 67)	15.0 ± 7.9 (10, 82)
Recovery of miosis		
Fentanyl	62 ± 31 (4, 33)	15.4 ± 8.5 (14, 100)
Sufentanil	30 ± 10 (4, 33)	11.0 ± 9.7 (7, 50)

Recovery was defined as ±10% from baseline value. n is number of participants in the analysis.
$ETpco_2$, end-tidal carbon dioxide concentration.

observed in all daily opioid users during fentanyl exposure with ΔT 15.4 ± 8.5 min (n = 14) for fentanyl and in half of the participants following during sufentanil dosing with (ΔT = 11.0 ± 9.0 min).

Hysteresis

Figure 5 gives the 12 concentration-effect loops with plasma naloxone concentration *versus* effect (black lines/circles) and effect-site naloxone concentration *versus* effect (green lines/circles) in a single panel and $t½k_{e0}$ values in table 4. Twelve loops were constructed with clear differences in hysteresis among the three measured effects. In the two populations, the plasma concentration-ventilation loops had $t½k_{e0}$ values ranging from of 0 to 1 min, irrespective of opioid. This indicates that the naloxone onset/offset times closely followed changes in naloxone plasma concentration. For end-tidal pCO_2, the hysteresis was a factor of 2 to 3 greater for daily opioid users than for opioid-naive individuals, with $t½k_{e0}$ values of 2.2 min (fentanyl) and 5.5 min (sufentanil) in opioid-naive participants *versus* 6.7 (fentanyl) and 11.3 min in daily opioid users. The largest hysteresis was observed for pupil diameter with for this endpoint greater hysteresis in opioid-naive individuals: 24.4 (fentanyl) and 35.6 min (sufentanil) *versus* 4.2 (fentanyl) and 12.8 min (sufentanil; table 4).

Withdrawal and Dropouts

No withdrawal symptoms were observed in opioid-naive individuals; however, in opioid-dependent participants, withdrawal symptoms ranging from mild to moderate were observed in half those who received Narcan (n = 9). First withdrawal symptoms appeared 20 min after intranasal naloxone administration, with peak intensity at around 30 min. Due to the excitation experienced by these participants, respiratory measurements were discontinued, and symptoms were initially treated with intravenous clonidine (maximum intravenous dose, 300 μg). In two subjects, low-dose propofol was subsequently administered, while one subject received midazolam. Additionally, one participant who experienced hypertension received sublingual nitroglycerin. The observed symptoms included agitation, pain, hypertension, tachycardia, vomiting, and diarrhea; all symptoms resolved within 2 h.

All data collected before the occurrence of withdrawal symptoms were used in the data analysis. During fentanyl exposure, the number of subjects included in the data sets was 14 until t = 20 min, n = 13 until t = 30 min, n = 11 until t = 45 min, n = 10 until t = 80 min, and thereafter n = 9. During sufentanil exposure, these numbers were n = 12 until t = 5 min, n = 0 until t = 20 min, n = 9 until t = 25 min, n = 8 until t = 35 min, and thereafter n = 7.

Renarcotization

The reversal effect of a single Narcan spray did not persist with a slow return of the measured indices toward the opioid level (fig. 3), irrespective of opioid, endpoint measured, and population studied, indicative of renarcotization. This exemplifies the short duration of action of intranasal naloxone under conditions of persistent opioid exposure.

Discussion

We evaluated the effectiveness of 4 mg intranasal naloxone in reversing moderate, continuously infused fentanyl- and sufentanil-induced respiratory depression under controlled experimental conditions. Our study included both opioid-naive individuals and daily opioid users with mean morphine milligram equivalents of 291 mg/day (tables 1 and 2). The primary endpoints measured were $\dot{V}_E$, end-tidal pCO_2, and pupil diameter. Our results demonstrate that Narcan gradually reversed respiratory depression, although with highly variable reversal times (table 3). Ventilatory recovery occurred within 2 to 4 min for opioid-naive

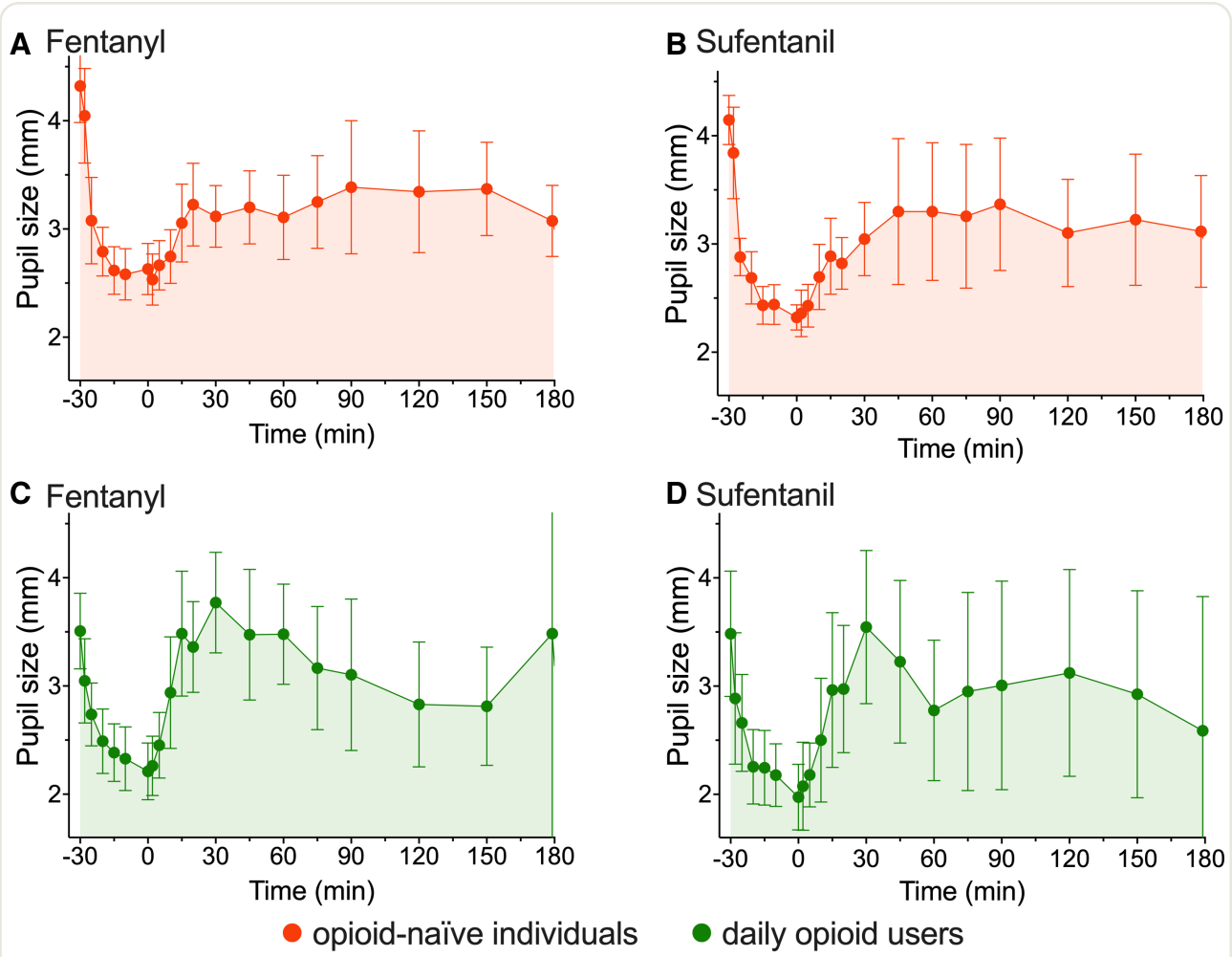

Fig. 4. Effect of 4 mg intranasal naloxone on pupil diameter during either fentanyl (*A* and *C*) or sufentanil (*B* and *D*) infusion (*shaded areas*) in opioid-naive individuals (*orange symbols*) and daily opioid users (*green symbols*). t = −30 min is a predrug baseline measurement; intranasal naloxone was given at t = 0 min. Data are mean ± 95% CI.

individuals and daily opioid users, with no significant difference between opioids. However, end-tidal pCO_2 showed slower recovery times: opioid-naive individuals exhibited a ΔT of 11 min during fentanyl exposure and 16.5 min with sufentanil, while daily opioid users had ΔT values of 13 and 15 min for fentanyl and sufentanil, respectively. Pupil diameter showed partial recovery in opioid-naive individuals and showed only a slow reversal (ΔT = 11 to 15 min) in daily opioid users.

Overall, our findings do show effectiveness of 4 mg intranasal naloxone in reversing *moderate* levels of opioid-induced respiratory depression (OIRD; 30 to 40% decrease in $\dot{V}_E$) with faster reversal of $\dot{V}_E$ than end-tidal pCO_2 by a factor of at least 3. The induced OIRD levels align with those seen in the perioperative anesthesia and pain care settings.[22] It is important to realize that $\dot{V}_E$ and arterial carbon dioxide concentration are inherently interconnected, and under closed loop ventilatory control conditions, the depression of $\dot{V}_E$ causes a rise in arterial carbon dioxide concentration, which in turn stimulates breathing as a compensatory mechanism.[23] We therefore assume that full reversal of respiratory depression is reached only when both physiologic variables reach baseline steady-state levels. While the rapid restoration of breathing is critical for oxygen uptake and survival, care must be taken in interpreting these results as recovery of $\dot{V}_E$ before consolidation of carbon dioxide reversal, does not necessarily mean complete reversal of respiratory instability.

Comparison with an Earlier Narcan Study on Naloxone-induced Recovery after Fentanyl-induced Apnea

Our current findings contrast with those of a separate experimental study after a 2-min apneic episode caused by high-dose intravenous fentanyl.[16] In that study, all participants, opioid-naive individuals and daily opioid users, required two to four Narcan doses to restore rhythmic and

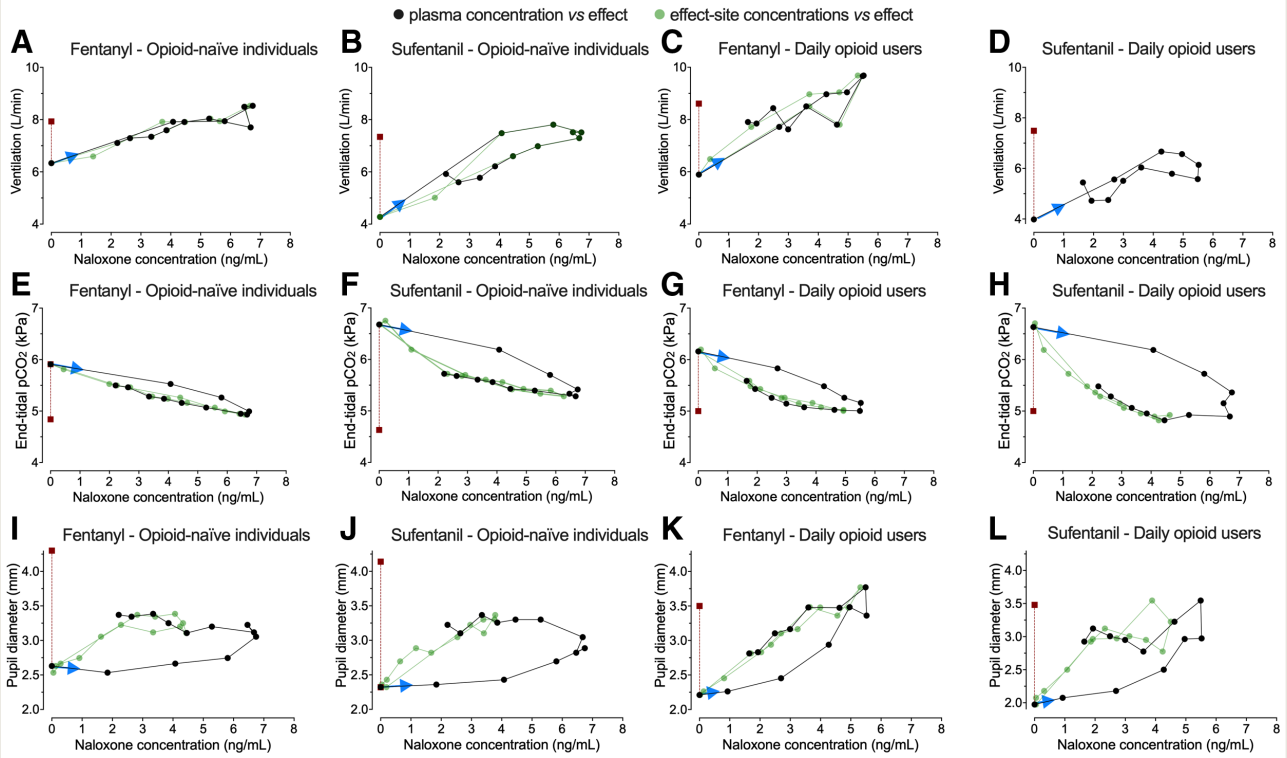

Fig. 5. Naloxone concentration *versus* effect. *Black lines and dots* represent measured plasma naloxone concentration *versus* effect; *green lines and dots* represent estimated effect-site or steady-state concentration *versus* effect. Effect data are ventilation (*A* to *D*), end-tidal pCO_2 (*E* to *H*), and pupil (*I* to *L*) during fentanyl or sufentanil exposure in opioid-naive individuals and daily opioid users. The *red squares* are the measurement values before the start of opioid infusion. Data start just before naloxone dosing (first data point linked to *blue arrow*, which also gives the direction of the loop). The *green lines and dots* represent the collapsed loops. For ventilation/sufentanil in daily opioid users, no further collapse of the loop was deemed possible beyond the loops in *black* indicative of absence of significant hysteresis between plasma concentration and effect.

Table 4. Hysteresis ($t½k_{e0}$) between Naloxone Plasma Concentration and Effect

Hysteresis ($t½k_{e0}$), min	Opioid-naive Participants	Daily Opioid Users
Ventilation		
Fentanyl	0.3	1.2
Sufentanil	0.001	NA
$ETpCO_2$		
Fentanyl	2.2	6.7
Sufentanil	5.5	11.3
Miosis		
Fentanyl	24.4	4.2
Sufentanil	35.6	12.8

$ETpCO_2$, end-tidal carbon dioxide concentration; NA, not applicable as no further collapse possible; $t½k_{e0}$, blood-effect-site equilibration half-life.

adequate breathing. We relate the difference in outcomes to the differences in the level of OIRD, moderate in the current study with a reduction in $\dot{V}_E$ of 40% *versus* apnea in all participants after an intravenous bolus dose of 0.7 to 1 mg fentanyl. This suggests that naloxone's effectiveness depends on several factors, including the severity of OIRD. At higher opioid exposures leading to apnea, a single dose of intranasal naloxone will not be sufficient for restoring normal breathing.

Miosis

While μ-opioid receptors expressed on neurons within brainstem respiratory networks are responsible for OIRD, opioid-induced miosis results from mu-opioid receptor activation in the Edinger–Westphal nucleus *via* activation of the parasympathetic fibers of the oculomotor nerve and ciliary ganglia and subsequent contraction of the sphincter pupillary muscles.[24] We observed that opioid-naive individuals exhibited only 70 to 75% reversal at 15 to 30 min after Narcan, whereas daily opioid users experienced complete pupil reversal at 15 min, although this effect was not sustained (fig. 4). The absence of full reversal in opioid-naive individuals contrasts with the full reversal seen for respiratory indices. It may reflect differences in mu-opioid receptor kinetics within distinct brain regions. We relate the full

reversal observed in daily opioid users to the occurrence of precipitated withdrawal, with its increase in sympathetic activity, that was then followed by renarcotization due to the decrease in naloxone concentration. These data suggest that the pupil data do not fully capture naloxone's respiratory effects. Further studies are needed to improve our understanding of the utility of the pupil diameter in assessing naloxone's respiratory reversal efficacy, particularly during precipitated withdrawal in daily opioid users.

Hysteresis

In both study populations, the reversal of the different physiologic endpoints showed distinct dynamics. In order to quantify these dynamics, we plotted mean ventilation data, mean end-tidal pCO_2 data, and mean pupil diameter data against mean naloxone plasma concentrations (fig. 5). We then collapsed the loops to estimate the blood-effect-site equilibration half-life, ($t½k_{e0}$).

Hysteresis was observed for the reversal of miosis, which was more pronounced in opioid-naive individuals than in daily opioid users (table 4; range, 24 to 36 min in opioid-naive individuals and 4 to 13 min in daily opioid users). A somewhat lower degree of hysteresis was observed for end-tidal pCO_2 (2 to 6 min in opioid-naive individuals and 7 to 11 min in daily opioid users). The hysteresis was more pronounced during sufentanil infusion compared to fentanyl, which we attribute to sufentanil's higher opioid receptor affinity, making it more difficult for naloxone to displace the opioid from the receptor. In contrast to the other endpoints, $\dot{V}_E$ reversal followed naloxone plasma concentrations closely ($t½k_{e0}$ 0 to 1 min) with in some subjects even signs of acute opioid tolerance, *i.e.*, the decline in $\dot{V}_E$ after peak reversal preceded the decline in naloxone plasma concentrations (fig. 5, B and D). While this suggests a rapid onset of reversal, the hysteresis in end-tidal pCO_2 should be considered as well. Additionally, it is important to acknowledge that the level of OIRD in this study was moderate, which might have favored the efficacy of naloxone. We expect more pronounced hysteresis loops at higher opioid doses.

Study Limitations

Some study limitations should be discussed:

1. Several participants withdrew consent due to withdrawal symptoms, which could have influenced both reversal dynamics and magnitude. Still, since the opioid-naive population did not experience withdrawal, we were able to isolate naloxone's pharmacologic effects and determine the influence of withdrawal *per se* on reversal indices. Interestingly, pupil effects were most affected by withdrawal, whereas respiratory endpoints showed no significant differences.
2. A key distinction of our experimental design with real-world conditions was the continuous opioid infusion that was maintained at 30 to 40% reduction in $\dot{V}_E$ with stable opioid plasma and effect-site concentrations (fig. 2). This deviates from real-world overdose scenarios, where opioid plasma levels are initially high and typically decline over time.[16,25] These declining opioid concentrations will improve ventilation as well. While the persistent opioid administration seems potentially more challenging, in our experimental study, ventilatory depression was moderate (30 to 40% depression of baseline ventilation), while in the community setting, overdose victims might experience more severe respiratory depression, including apnea.
3. While we aimed to assess naloxone's effectiveness against high-affinity synthetic opioids, carfentanil is unavailable for human research. Instead, we compared fentanyl to sufentanil, which has slower receptor kinetics than fentanyl but faster than carfentanil. The receptor dissociation constant for sufentanil is $1.07 \cdot 10^{-3}$ nM; fentanyl, $4.33 \cdot 10^{-3}$ nM; and carfentanil, $2.47 \cdot 10^{-4}$ nM.[26] The affinity constant for sufentanil is 0.14 nM; fentanyl, 1.35 nM; and carfentanil, 0.05 nM.[7]
4. Due to the expected withdrawal of consent in half the opioid users, we allowed participants to participate only once after the first study round and reversed the sequence of opioid administration. Ultimately, 6 participants completed both visits, while 12 completed a single visit (table 2). Due to participant withdrawal, the number of subjects analyzed over time gradually decreased from n = 15 to n = 9 (at t = 60 min) in the fentanyl-exposed groups and from n = 12 to n = 11 (at t = 30 min) in the sufentanil-exposed population. Such reductions are inherent to studies investigating naloxone in individuals with opioid dependence. Given the observed responses, particularly the observation that the respiratory data were comparable across study groups, we argue that this decline in sample size did not impact our conclusions.
5. All subjects who used daily opioids received extensive information on the possibility that withdrawal symptoms could occur, apart from other side effects that could occur. They were informed that withdrawal symptoms would be treated upon request or when deemed necessary by attending staff. Before the study day, all subjects were made aware of their right to withdraw from the study at any time without consequences. This was reiterated on the morning of the study. Nine of 18 subjects experienced some degree of withdrawal symptoms (table 2). Four received treatment, including one case solely for hypertension. The most burdensome symptom was agitation; minor symptoms were pain, nausea/vomiting, or diarrhea. Symptoms in all subjects resolved within 2 h of onset. In the days after the initial visit, all subjects were closely monitored. They reported

no persistent issues and resumed their usual opioid regimens without complications. Seven participants chose to withdraw further consent, primarily due to the withdrawal symptoms they experienced. Two subjects returned for a second visit despite withdrawal symptoms experienced after their first visit. The occurrence of withdrawal symptoms was expected and a significant concern for the research team and was not taken lightly. However, we believe that all participants were adequately informed, the symptoms were manageable, and the duration was brief. Overall, we contend that the value of the information gained justifies the temporary discomfort experienced by participants. Finally, the study of withdrawal symptoms is an important topic and deserves further study. Our approach may serve as a template for such studies.

In conclusion, we evaluated the efficacy of a single 4-mg Narcan intranasal spray on the reversal of OIRD in opioid-naive individuals and daily opioid users. We show that Narcan is able to reverse moderate levels of OIRD. However, reversal dynamics and magnitudes vary across physiologic endpoints. Ventilation recovers faster than end-tidal pCO_2 and pupil diameter, and no recovery in end-tidal pCO_2 was observed in opioid-naive individuals exposed to sufentanil. Our current data suggest that a single dose of Narcan is unlikely to serve as an adequate countermeasure in the event of exposure to high-dose or high-affinity opioids.

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Competing Interests

Dr. Dahan received consultancy or speaker fees from Enalare Therapeutics (Princeton, New Jersey), Trevena Inc (Chesterbrook, Pennsylvania), and ZMI Pharma (Carlsbad, California) and an award from the U.S. Food and Drug Administration (Silver Spring, Maryland). The other authors declare no competing interests.

Reproducible Science

Full protocol available at: r.m.van_der_schrier@lumc.nl. Raw data available at: r.m.van_der_schrier@lumc.nl.

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