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ORIGINAL ARTICLE

Dose-dependent naloxone-induced morphine withdrawal symptoms in opioid-dependent males—a double-blinded, randomized study

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Aims: Oral opioid preparations combined with naloxone are intended to induce a transient acute withdrawal syndrome to avoid intravenous misuse. This trial aimed to establish an appropriate morphine–naloxone dose ratio for an abuse-deterrent oral opioid formulation.

Methods: In a randomized, double-blinded, 2 × 2 cross-over trial, 43 patients with opioid use disorder were challenged with intravenous morphine HCl Ph.Eur. (75 mg; [morphine mono]) or morphine HCl Ph.Eur. and naloxone HCl Ph.Eur. at ratios of 100:1 (75 mg: 0.75 mg; [morphine–naloxone 100:1]) or 200:1 (75 mg: 0.375 mg; [morphine–naloxone 200:1]). Acute naloxone-induced opioid withdrawal was evaluated using subjective (Short Opiate Withdrawal Scale–German [SOWS-G]) and observer-rated (Objective Opiate Withdrawal Scale [OOWS], Wang scale) questionnaires, and physiological parameters. For statistical analysis, the area under the curve between baseline and 20 minutes after drug administration of the outcome variables was calculated.

Results: Intravenous morphine–naloxone caused rapid withdrawal symptoms. Coadministration of naloxone dose-dependently (morphine–naloxone 100:1 > morphine–naloxone 200:1) increased SOWS-G, OOWS and Wang Scale area under the curve when compared to morphine mono, respectively (all $P < .0001$). A similar response was detectable for changes of pupil diameter. Blood pressure and respiratory rate changed heterogeneously, and heart rate was unaltered by morphine without or with naloxone.

Conclusion: Morphine–naloxone 100:1 effectively suppresses the pleasurable effects of intravenous morphine and results in an aversive withdrawal reaction. A lower

The authors confirm that Principal Investigator for this paper is Christa Firbas and that she had direct clinical responsibility for patients.

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naloxone concentration as used in morphine–naloxone 200:1 does not appear to be appropriate to prevent intravenous morphine misuse.

KEYWORDS

morphine, naloxone, opioid maintenance treatment, opioid withdrawal syndrome, substance abuse—intravenous

1 | INTRODUCTION

Around 1.3 million people in the EU use opioids by high-risk pattern and/or by high risk routes of administration.[1] The harms associated with intravenous (i.v.) illicit opioid use have been well documented, including fatal overdose, blood borne viral and bacterial infections.[2] Opioid maintenance treatment (OMT) is the first-line treatment for opioid dependence.[3] However, although methadone—the most commonly prescribed medication for OMT[1]—has been shown to be effective and is approved for first-line OMT in many regions, its side effects limit compliance, which results in an increased risk for relapse.[4–7] Slow-release oral **morphine** (SROM) preparations with a longer elimination half-time than traditional morphine and with sustained therapeutic plasma concentrations after once daily dosing have become an alternative to methadone or buprenorphine due to improved tolerability and reduced opioid craving.[8–12] In addition, morphine maintenance does not influence QT interval to the extent of methadone with the increased risk of life-threatening arrhythmias. Considering the aging population of opioid maintained patients, as well as patients on multiple medication, the need for an alternative agonistic medication is evident.

However, special attention needs to be paid to the higher misuse potential of SROM,[13] which might be related to the pharmacology of SROM since morphine is the major product of heroin metabolism,[14] and i.v. injected doses of SROM are equivalent to several times the oral dose equivalent.[15] In Austria, SROM is the most commonly prescribed OMT medication (56% of patients).[1] Intravenous abuse of SROM has shown particularly severe side effects, exceeding the risks of needle sharing.[16]

SROM preparations that contain an additional competitive **opioid receptor** antagonist ([sequestered] naltrexone) have been developed to discourage diversion and misuse of oral opioids (e.g. ALO-01 for treatment of chronic pain[17]) but SROM medicines with **naloxone** are not yet available. Similar to naltrexone, naloxone exerts only a low systemic bioavailability after oral administration but will cause severe withdrawal symptoms upon i.v. administration.[17,18] Given that patients with opioid use disorder (OUD) may benefit from treatment with SROM compared to traditional methadone,[12,19] the development of new abuse-deterrent SROM preparations with fewer side effects as compared to other OMT medicines may be of particular interest, and may result in an increased retention rate as well as a possible reduction of oral opioid misuse.[20,21]

Pharmacological data and results of published (pre)clinical studies suggest that a morphine–naloxone 100:1 dose may be appropriate to suppress the pleasurable effects of i.v. morphine and precipitate an aversive withdrawal reaction.[22–26] This study aimed at confirming the theoretical findings in favour of the morphine–naloxone 100:1 dose. In addition, the efficacy of a smaller dose (200:1) was explored to establish the selected dose proportion. The assessment of a withdrawal reaction by using different psychometric scales was supported by additional measurement of an objectifiable physiological variable (changes in pupil diameter during treatment).

What is already known about this subject

- Methadone and buprenorphine, the most common prescribed medicines for opioid maintenance therapy, have several side effects that limit compliance of opioid use disorder individuals.
- Slow-release oral morphine combined with naloxone may be a promising alternative due to improved tolerability and a lower misuse potential.

What this study adds

- Intravenous naloxone causes a rapid and transient withdrawal reaction with an attenuation of the pleasurable effects of intravenous morphine.
- Administration of morphine–naloxone at a ratio of 100:1 appears to effectively prevent intravenous opioid misuse as assessed by psychometric scales as compared to morphine–naloxone at a ratio of 200:1.

2 | METHODS

The study protocol and all related documents provided to study participants were approved by the Ethics Committee of the Medical University of Vienna, Austria (EK 1238/2012) and the national competent authority. The study conforms to the principles outlined in the Declaration of Helsinki including current revisions and the ICH Good Clinical Practice Guidelines. The trial is registered at the European Clinical Trials database (EudraCT 2011–005903-34). Written informed consent was obtained from all subjects before enrolment.

2.1 | Recruitment procedure

Participants were recruited using posters and flyers with brief information about the study, which were placed in waiting rooms of general practitioners who prescribe OMT, and pharmacies which dispense OMT. In addition, advertisements were placed in daily newspapers.

Patients were male and over the age of 18 years, met the DSM-IV criteria for the diagnosis of OUD, were undergoing OMT with SROM (with experience of injecting opioids) with a stable dose for ≥1 month, and were in otherwise good health. In addition, patients were excluded from participation if their alcohol consumption exceeded 100 g/d during the last 4 weeks, or if they used any other illicit substances apart from opioids and cannabis.

A personal briefing at the Department of Psychiatry and Psychotherapy with a psychiatrist was scheduled for potential study participants who met the inclusion criteria according to a telephone screening, to evaluate their addiction and mental health status. Seventy-nine patients met the inclusion criteria and were referred to the Department of Clinical Pharmacology for further screening. Twenty-three patients did not attend screening.

2.2 | Patient population

In total, 56 OUD patients, aged between 19 and 61 years, with a history of regular opioid abuse (DSM IV 304.0) and under OMT were included in the study, and 43 subjects were randomized (Figure 1). Study participants were given a complete health examination. They were excluded if a positive urine drug test apart from tetrahydrocannabinol or opioids was provided, or if they had somatic diseases other than stable chronic hepatitis. Other main exclusion criteria included a history of heart failure or cardiac arrhythmia.

2.3 | Study design and study drugs

This phase II clinical trial was conducted in a prospective, randomized, double-blinded, 2 × 2 cross-over fashion at the Department of Clinical Pharmacology, Medical University of Vienna, Austria between September 2012 and January 2016. Subjects were randomly allocated to 2 different study periods to 1 of 2 treatment sequences (period 1: morphine–naloxone ratio 100:1 and morphine i.v.; period 2: morphine–naloxone ratio 200:1 and morphine i.v.; Figure 1). A

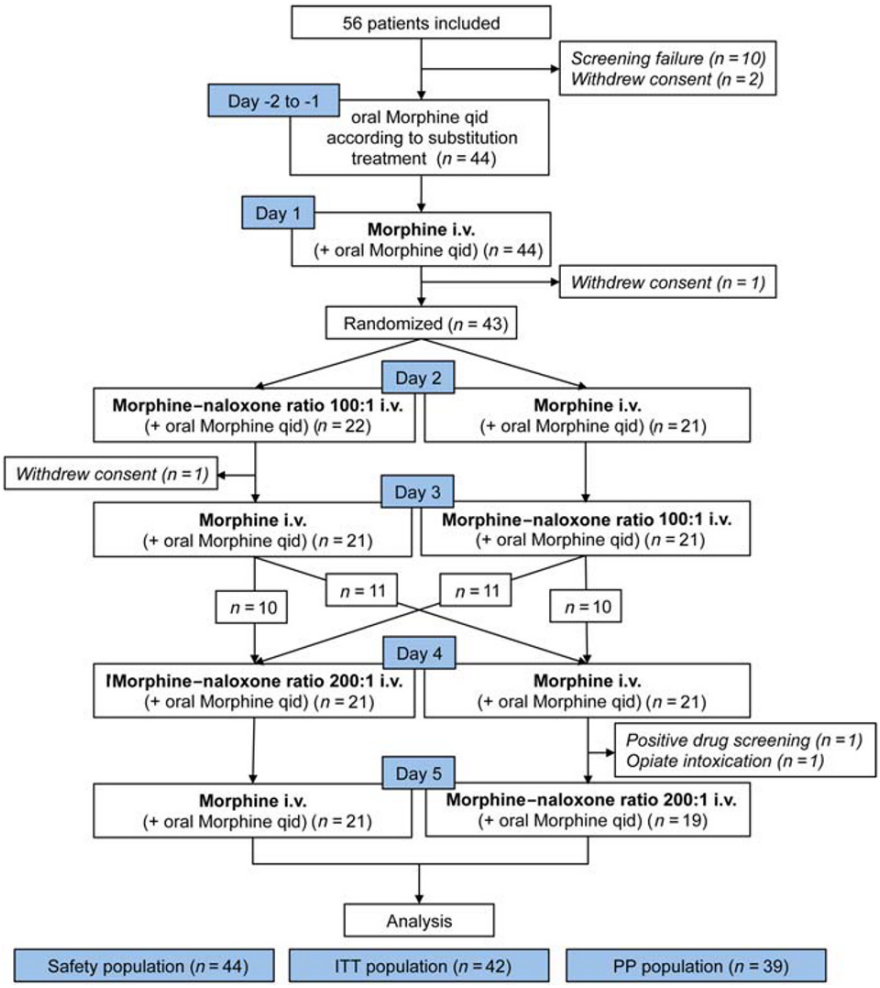

FIGURE 1 Study flow chart. qid = 4 times daily; i.v. = intravenous; ITT = intention to treat; PP = per protocol

predefined 1:1 cross-over randomization in balanced blocks was performed separately for different treatment periods by Bioconsult GmbH, Breitenfurt, Austria. The split design with morphine–naloxone 100:1 administration in the first investigational period was chosen as this ratio was of primary interest, and the number of OUD subjects meeting the inclusion criteria is low and a high dropout rate was expected due to hospitalization for several days. All study staff were unaware of the randomization code until clinical database lock in August 2016.

The trial comprised a run-in period (days −2 to −1) followed by a dose confirmation phase (day 1) and a double-blinded provocation phase with the 2 treatment periods. During run-in phase patients were transferred from once daily SROM maintenance treatment to oral immediate release morphine (Vendal Oral Solution, G. L. Pharma GmbH, Lannach, Austria) 4 times daily. On day 1 in the morning subjects received 75 mg morphine HCl Ph.Eur. (G. L. Pharma GmbH; [morphine mono]) i.v. to confirm the i.v. opioid dose that was going to be administered from day 2 to 5. During the provocation phase on day 2 or 3, patients received either morphine HCl Ph.Eur. and naloxone HCl Ph.Eur. at a ratio of 100:1 i.v. (75 mg: 0.75 mg; [morphine–naloxone 100:1]; G. L. Pharma GmbH) or morphine HCl Ph.Eur. i.v. (75 mg; G. L. Pharma GmbH). On day 4 or 5, either morphine HCl Ph.Eur. and naloxone HCl Ph.Eur. at a ratio of 200:1 (75 mg: 0.375 mg; [morphine–naloxone 200:1]; G. L. Pharma GmbH) or morphine HCl Ph.Eur. i.v. (75 mg; G. L. Pharma GmbH) were administered intravenously. Additionally, patients received immediate release oral morphine 4 times daily from day 1 to 5 to maintain stable substitution treatment conditions throughout the trial. Study participants remained in hospital during the trial and a urine drug test was scheduled on days 1, 3 and 5 to monitor compliance. Between days 1 and 3, a standardized psychiatric assessment was performed by a clinical research psychologist, who applied the European Addiction Severity Index. An end-of-study examination was performed on day 5.

2.4 | Outcome parameters

2.4.1 | Psychometric scales

Three different questionnaires for the evaluation of subjective and objective opiate withdrawal symptom severity were used to assess the impact of the medicines under study.[27–30] The Short Opiate Withdrawal Scale–German (SOWS-G) is a shortened version of the opiate withdrawal scale and a self-administered tool for assessment of opioid withdrawal symptoms. It includes 12 symptoms that have to be subjectively rated by the patient from 0 (not at all) to 3 (extremely). The Objective Opiate Withdrawal Scale (OOWS) and the Wang scale, which was additionally implemented during the study, were used to observe withdrawal symptoms by the study staff. The OOWS assesses the presence or absence of 13 withdrawal signs. The Wang scale utilizes 10 symptoms and their severity. The scores of the different scales ranges from 0–36 (SOWS-G), 0–13 (OOWS), and 0–45 (Wang scale), depending on the magnitude of opioid withdrawal.

2.4.2 | Pupil diameter assessment

Changes of the pupil diameter of both eyes were used as an objectifiable physiological parameter of opioid-induced effects during treatment with i.v. morphine ± naloxone. Pupillometry recordings were performed under standardized dimmed light conditions for 5 seconds at a sampling rate of 50 Hz with a binocular infrared photo refractor (PowerRef 3 plusoptiX R09; Plusoptix GmbH, Nuremberg, Germany) as described previously.[31–33]

2.4.3 | Vital signs

Blood pressure and heart rate were measured with an Infinity Delta monitoring system (Drägerwerk AG & Co. KGaA, Lübeck, Germany). The respiratory rate was assessed by observation of the patient.

2.4.4 | Outcome parameter assessment

During the run-in phase (day −2 to −1), SOWS-G, OOWS and Wang scale were assessed 3 times daily (9 a.m., 3 p.m., 9 p.m.) prior to the administration of oral immediate release morphine to determine signs of opiate withdrawal. The pupil diameter and vital signs were assessed once daily in the morning (9 a.m.).

From study day 1 to 5 vital signs (blood pressure, pulse rate, respiratory rate), pupillometry and opiate withdrawal signs (SOWS-G, OOWS, Wang scale) were assessed at predose (before morphine ± naloxone i.v.) and at 5, 20, 40, 60, 90 and 120 minutes after study drug administration. After the last evaluation, subjects received the first dose of oral immediate release morphine for maintenance treatment.

2.4.5 | Study endpoints

Co-primary endpoints were the area under the curve (AUC) of SOWS-G total score between 0 and 20 minutes after application ($SOWS\text{-}G_{AUC(0-20)}$) and the AUC of the pupil diameter measurements between 0 and 20 minutes after application ($pupillometry_{AUC(0-20)}$). Data of pupil diameter (mean of both eyes) were baseline adjusted before calculation of AUC.

Comparisons were done between i.v. morphine–naloxone 100:1 *vs* morphine to assess naloxone-precipitated acute withdrawal. In addition, the dose-dependent opioid withdrawal effect was examined by evaluation of morphine + naloxone at a ratio of 200:1. Secondary endpoints included assessment of OOWS ($OOWS_{AUC(0-20)}$), Wang scale ($Wang_{AUC(0-20)}$) and vital signs $AUC_{(0-20)}$. The AUC between

baseline and 20 minutes after administration was chosen as previous evidence suggests that peak withdrawal symptoms occur shortly after i.v. administration of the opioid antagonist.[34] Safety was examined by assessment of adverse events and vital signs.

2.4.6 | Statistics, analysis population and sample size estimation

SPSS 23 (IBM Cooperation, New York, NY, USA) and Excel 2013 for Windows (Microsoft Corporation, Redmond, WA, USA) were used for statistical analysis and graphical presentation. The AUCs between 0 and 20 minutes of the outcome variables were derived according to the linear trapezoidal rule. Three data points (predose, 5 and 20 min) were used. For assessment of the AUC of opioid withdrawal scales the individual total score at corresponding time points was used. The pupil diameter was calculated from the mean of the right and left eyes and adjusted to baseline value (change of pupil diameter from predose). AUCs of blood pressure, heart rate and respiratory rate were also calculated from baseline adjusted values. Comparison of study endpoints was performed by means of Wilcoxon matched pairs signed rank test.

A 2-sided *P* value <.05 was considered to be statistically significant. For the co-primary study endpoints, a Bonferroni adjustment was performed to keep a global α of .05. Secondary study objectives were analysed exploratory. Values are provided as mean and standard deviation unless indicated otherwise.

The safety population (*n* = 44) included all randomized subjects (*n* = 43) and 1 study participant who received morphine i.v. on day 1 (Figure 1). The intention to treat population (*n* = 42) was defined as randomized patients who were challenged with the investigational medicinal products in study period 1 (morphine–naloxone ratio 100:1 *vs* morphine) with available data of at least 1 co-primary endpoint. The per-protocol population (*n* = 39) comprised subjects with SOWS-G and pupillometry data in both study periods (days 2–5). A separate analysis of intention to treat and per-protocol population was not performed due to a subject difference of <5% between populations.

Sample size calculation was based on the composite endpoint SOWS-$G_{AUC(0-20)}$ and pupillometry$_{AUC(0-20)}$ between morphine–naloxone ratio 100:1 and morphine. A mean difference of 50% (SOWS-$G_{AUC(0-20)}$) and 20% (pupillometry$_{AUC(0-20)}$) between treatments was considered to be clinically relevant. We assumed a standard deviation of 50% for the SOWS-G score and 20% for pupillometry data, respectively. Thus, a sample size of 40 subjects was sufficient to detect a significant difference with 80% power using the Wilcoxon signed ranks test at a significance level of 2.5% (2-sided) for the co-primary endpoints SOWS-$G_{AUC(0-20)}$ and pupillometry$_{AUC(0-20)}$.

2.4.7 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

3 | RESULTS

3.1 | Study population

Demographic data, screening laboratory characteristics and concomitant diseases of patients who entered the dose confirmation phase (day 1) are presented in Table 1.

3.2 | Pharmacodynamics

Data of opiate withdrawal scales and pupillometry analysis are summarized in Table 2. The effect of morphine ± naloxone on outcome parameters from predose to 2 hours after investigational medicinal product application are illustrated in Figure 2 and Figure 3, respectively. Intravenous administration of morphine–naloxone at a ratio of 100:1 or 200:1 induced rapid and severe opioid withdrawal symptoms with maximum changes from baseline at 5 minutes after administration. Severity of withdrawal symptoms was naloxone dose-dependent with a greater magnitude at morphine–naloxone ratio of 100:1.

TABLE 1 Characteristics of study participants (*n* = 44). Data are presented as median (interquartile range) or *n* (%)

Demographic and screening characteristics	
Age, y	33 (29–38)
Body mass index, kg/m^2	25.1 (22.4–28.2)
Haemoglobin, g/dL	14.9 (14.0–15.3)
White blood cell count, ×10^9/L	7.0 (5.9–8.4)
Platelet count, ×10^9/L	219 (181–252)
Prothrombin time, %	109 (91–129)
Activated partial thromboplastin time, s	34.8 (33.3–37.1)
Serum creatinine, mg/dL	0.8 (0.8–0.9)
Aspartate aminotransferase, U/L	30 (21–39)
Alanine aminotransferase, U/L	31 (21–55)
Gamma-glutamyl transferase, U/L	30 (20–60)
Alkaline phosphatase, U/L	79 (67–97)
Systolic blood pressure, mmHg	133 (121–142)
Diastolic blood pressure, mmHg	81 (72–89)
Concomitant diseases	
Hepatitis C	18 (41%)
Chronic obstipation	3 (7%)
Psoriasis	1 (3%)
Allergic asthma	1 (3%)
Chronic gastritis	1 (3%)
Headache	1 (3%)

TABLE 2 Area under the curve (AUC; period: 0–20 min) of short opiate withdrawal scale - German (SOWS-G), objective opiate withdrawal scale (OOWS) or Wang scale total score or pupil diameter change after morphine + naloxone at ratios of 100:1 or 200:1 or morphine alone. Data are presented as mean and standard deviation

	Primary endpoints			
	SOWS-$G_{AUC(0-20)}$ (total score*min)		Pupillometry$_{AUC(0-20)}$ (mm*min)	
		n		*n*
Morphine–naloxone ratio 100:1	239 (127)*,***	42	17.1 (10.5)*	41
Morphine period 1	21 (37)	42	−10.2 (8.2)	41
Morphine–naloxone ratio 200:1	104 (110)**	40	13.7 (11.2)**	40
Morphine period 2	18 (36)	40	−10.6 (10.3)	40
	Secondary endpoints			
	OOWS$_{AUC(0-20)}$ (total score*min)		Wang scale$_{AUC(0-20)}$ (total score*min)	
		n		*n*
Morphine–naloxone ratio 100:1	131 (43)*,***	42	253 (148)*,***	23
Morphine period 1	7 (11)	42	2 (7)	23
Morphine–naloxone ratio 200:1	68 (42)**	40	67 (77)**	21
Morphine period 2	5 (9)	40	1 (2)	21

*P < .05 *vs* morphine period 1,
**P < .05 *vs* morphine period 2,
***P < .05 *vs* morphine–naloxone ratio 200:1 (Wilcoxon test).

During administration of morphine alone, scores of psychometric scales remained unchanged.

3.3 | SOWS-G

Following morphine–naloxone 100:1, mean SOWS-$G_{AUC(0-20)}$ was 239 ± 127 *vs* 21 ± 37 score*minutes with morphine alone (P < .0001). Following morphine–naloxone ratio 200:1, mean SOWS-$G_{AUC(0-20)}$ was 104 ± 110 *vs* 18 ± 36 score*minutes with morphine alone (P < .0001). The mean SOWS-$G_{AUC(0-20)}$ of morphine–naloxone 100:1 challenge was 2.3-fold greater than that after administration of the smaller naloxone dose (P < .0001). Intravenous morphine alone did not induce aversive feelings and the AUC was similar between study periods (P = .194).

3.4 | Pupil diameter

As expected, morphine treatment caused miosis while coadministration of naloxone induced transient mydriasis in all subjects under study. Following morphine–naloxone 100:1, mean pupil diameter$_{AUC(0-20)}$ was 17.1 ± 10.5 *vs* −10.2 ± 8.2 mm*minutes with morphine alone (P < .0001). Following morphine–naloxone 200:1, mean pupil diameter$_{AUC(0-20)}$ was 13.7 ± 11.2 *vs* −10.6 ± 10.3 mm*minutes with morphine alone (P < .0001). The mydriatic changes in pupil diameter were comparable between different naloxone doses (P = .056). Additionally, i.v. administration of morphine alone induced miosis at a similar degree between different study periods (P = .619).

3.5 | OOWS and Wang scale

Following morphine–naloxone 100:1, mean OOWS$_{AUC(0-20)}$ was 131 ± 43 vs 7 ± 11 score*minutes with morphine alone (P < .0001). Following morphine–naloxone 200:1, mean OOWS$_{AUC(0-20)}$ was 68 ± 42 *vs* 5 ± 9 score*minutes with morphine alone (P < .0001). The mean OOWS$_{AUC(0-20)}$ of morphine–naloxone 100:1 challenge was 1.93-fold greater than that after administration of the smaller naloxone dose (P < .0001). Intravenous morphine alone did not induce aversive feelings and the AUC was similar between study periods (P = .408).

Following morphine–naloxone 100:1, mean WANG$_{AUC(0-20)}$ was 253 ± 148 *vs* 2 ± 7 score*minutes with morphine alone (P < .0001). Following morphine–naloxone 200:1, mean WANG$_{AUC(0-20)}$ was 67 ± 77 *vs* 1 ± 2 score*minutes with morphine alone (P < .0001). The mean WANG$_{AUC(0-20)}$ of morphine–naloxone 100:1 challenge was 3.8-fold greater than that after administration of the smaller naloxone dose (P < .0001). Intravenous morphine alone did not induce aversive feelings and the AUC was similar between study periods (P = .445).

3.6 | Vital signs

Data of vital signs are provided in the online supplemental material. Table S1 summarizes AUC_{0-20} of vital sign changes. Figures S1–S4 show the baseline adjusted changes of vital signs. $AUC_{(0-20)}$ of respiratory rate and blood pressure differed significantly between morphine + naloxone *vs* morphine alone, while $AUC_{(0-20)}$ of respiratory rate and systolic blood pressure was comparable on study days with morphine administration alone (P > .05, morphine period 1 *vs* period

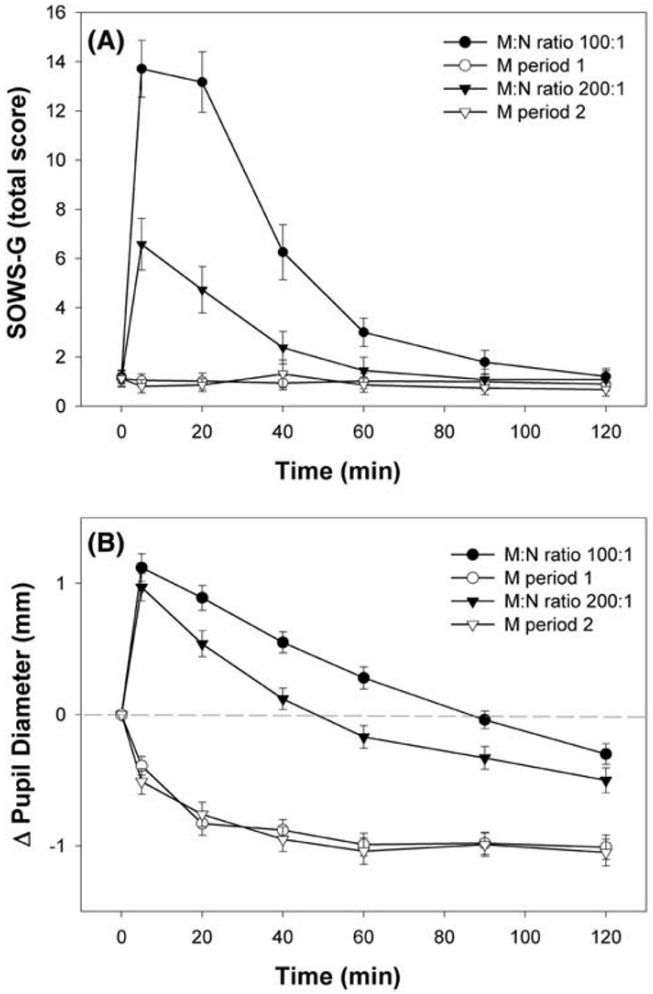

FIGURE 2 Total score of Short Opiate Withdrawal Scale–German (SOWS-G; A) or baseline adjusted changes of pupil diameter (B) after intravenous administration of morphine–naloxone at a ratio of 100:1 (M:N ratio 100:1) or 200:1 (M:N ratio 200:1) or during treatment with morphine alone (M period 1, M period 2) from predose to 120 minutes after administration. Data are presented as mean and standard error of the mean

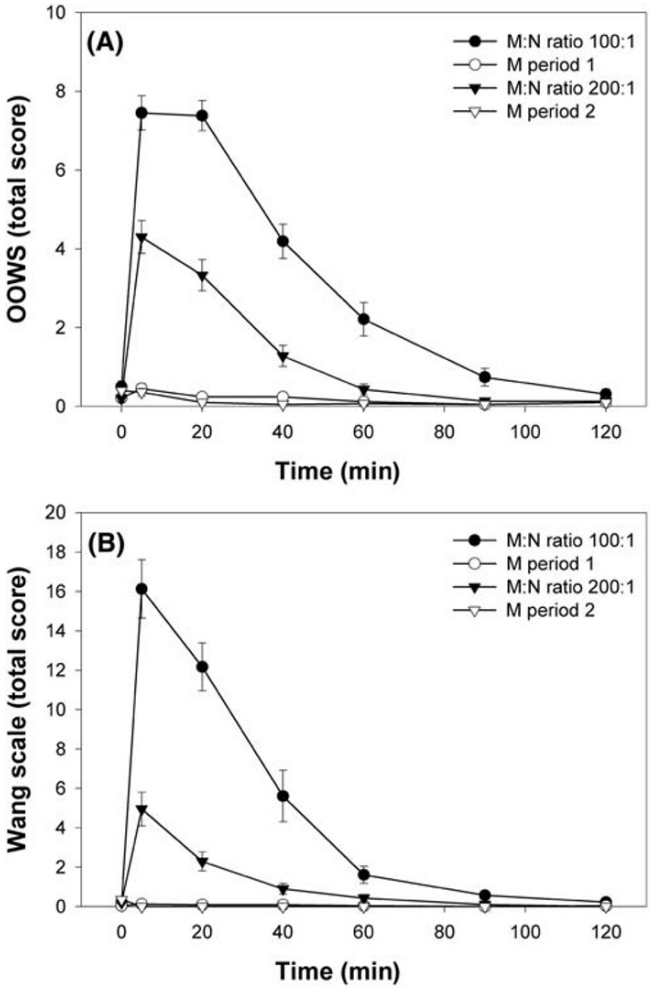

FIGURE 3 Total score of Objective Opiate Withdrawal Scale (OOWS; A) or Wang scale (B) after intravenous administration of morphine–naloxone at a ratio of 100:1 (M:N ratio 100:1) or 200:1 (M:N ratio 200:1) or during treatment with morphine alone (M period 1, M period 2) from predose to 120 minutes after administration. Data are presented as mean and standard error of the mean

2). A naloxone dose-dependent effect was observed in vital sign parameters (all $P < .05$ 100:1 *vs* 200:1). However, heart rate $AUC_{(0-20)}$ was similar across all study days and no effect of naloxone could be detected (all $P > .05$).

3.7 | Safety

For 21 subjects of the safety population ($n = 44$) at least 1 adverse event (AE) was reported. In total, 45 AEs were documented that were mild (minimal discomfort, no pharmacological intervention; 56%) or moderate (interference with normal daily activities, pharmacological treatment needed; 44%) in severity and recovered without sequelae. The most frequent AEs were related to gastrointestinal disorders ($n = 21$) with diarrhoea ($n = 9$), flatulence ($n = 3$), constipation, enteritis, vomiting and abdominal cramps ($n = 2$ for each) and nausea ($n = 1$). Thirteen AEs were related to the administration of the study drug with injection site urticaria and erythema. Other AEs included headache ($n = 2$), sinus tachycardia ($n = 1$), fatigue ($n = 1$), abscess of the limb ($n = 1$), opiate intoxication ($n = 1$), coma ($n = 1$), dysgeusia ($n = 1$), sleep disorder ($n = 1$), cough ($n = 1$) and dyspnoea ($n = 1$). The majority of AEs were classified to be unrelated (47%) or probably unrelated (7%) to the study drugs; 40% of AEs were rated as possibly or probably related, and 6% had definite causality to the study drug.

4 | DISCUSSION

In this prospective, randomized, double-blinded, cross-over study, i.v. administration of morphine in combination with naloxone at a ratio of 100:1 or 200:1 rapidly induced withdrawal symptoms in OUD patients undergoing OMT. Self-rated (SOWS) and observer-rated

(OOWS, Wang scale) psychometric questionnaires indicate that the severity of withdrawal symptoms was naloxone dose-dependent. Morphine challenge was accompanied with miosis while after naloxone coadministration a transient mydriasis that was comparable between different naloxone doses was detectable by pupillometry.

Our data indicate that i.v. administered morphine–naloxone at a ratio of 100:1 induced an aversive withdrawal reaction and was more appropriate to effectively suppress the pleasurable effects of i.v. morphine as compared to the ratio of 200:1. In contrast to trials in nondependent opioid users who assessed the mitigation of pleasurable morphine effects (*drug-liking*) after naltrexone administration,[17,35] this study evaluated the severity of subjective and objective withdrawal symptoms using psychometric scales that do not consider drug-liking effects. The difference between morphine + naloxone *vs* morphine alone might be more pronounced using a methodological approach that detects a change of positive morphine-induced effects in this population. However, for the development of abuse-deterrent SROM it appears more useful to measure the degree of withdrawal symptoms than differences in drug-liking effects.

The study personnel graded the magnitude of acute naloxone-induced symptoms after challenge with morphine–naloxone 100:1 using the Wang scale with similar maximum total scores as compared to subjective withdrawal feelings reported by the study participants (SOWS-G: 14/36 *vs* 16/45 for Wang scale). Interestingly, the severity of acute withdrawal appeared to differ disproportionately with the OOWS (total score at 5 min after administration: 8/13). This discrepancy may be explained by a more precise discrimination of each individual withdrawal symptom in the SOWS-G and Wang questionnaire while the OOWS only provides information of the presence or absence of symptoms.[27–30] Nonetheless, all psychometric scales detected a statistically significant naloxone dose-dependent effect of acute aversive feelings, favouring a morphine–naloxone ratio of 100:1. Specifically, the OOWS response appeared to be inappropriately small at a ratio of 200:1 to avoid misuse effectively. It cannot be excluded that this finding was affected by expectations as study periods were not randomized in this trial (Figure 1) and that subjective (and observer-rated) scores would be more pronounced at a ratio of 200:1 in a randomized setting of study periods. In addition, the morphine–naloxone ratio of a crushed abuse deterrent SROM tablet formulation may differ from that of the study medicines. To ensure subject safety in accordance with the ethics committee requirements, the medicines for this trial were provided in ampoules for i.v. use.

Assessment of pupil diameter by pupillometry confirmed the results derived from withdrawal questionnaires with an expected morphine-induced miosis that was similar between different study periods following morphine alone. In addition, The observed re-establishment of miosis at 60–90 minutes after morphine + naloxone is consistent with the short half-life of naloxone.[36] These findings indicate that pupillometry measurement is an objective method for the assessment of morphine- (and naloxone-) induced effects, yielding highly reproducible results, while changes in other physiological parameters (heart rate, blood pressure, respiratory rate) were more heterogeneous. However, there was only a trend towards a greater transient mydriatic response after morphine–naloxone at a ratio of 100:1 as compared to the ratio of 200:1. This may be due to the limited power of this study to detect differences of smaller effect size between different ratios. It is more likely, however, that the smaller naloxone dose is sufficient to induce a submaximal change in pupil diameter.[35] The small power of this study for secondary endpoints with a high between-subject variability may also explain that no statistical significant differences could be detected in heart rate changes as compared to other vital signs. Overall, the objectifiable changes in pupil diameter appear to be less important to prevent drug misuse as compared to subjective symptoms of acute withdrawal as assessed by the SOWS.

Safety data demonstrate that the administered morphine–naloxone combination product was well tolerated with no unexpected AEs or AEs leading to trial discontinuation except for 1 subject who experienced an opiate intoxication and coma following morphine mono administration due to illicit opiate intake prior to the respective study day. Study drug-related AEs were mild or moderate in severity and the majority of AEs was associated with known precipitated (gastrointestinal) withdrawal symptoms. The observed injection site reactions with urticaria may be explained by local histamine release caused by morphine.[37]

This trial was conducted in OUD individuals experienced in i.v. administration of opioids rather than in i.v.-unexperienced subjects to avoid encouragement of future i.v. misuse. It remains unclear if results of acute withdrawal can be extrapolated to other populations (i.e. nondependent recreational opioid users), and the duration of withdrawal symptoms may differ in individuals with impaired liver function due to a decreased hepatic clearance of naloxone.[38]

Given the particularly high risk for severe side effects such as organ damage due to microembolism exerted by SROM when abused intravenously,[16] it appears useful to introduce OMT products containing an antagonist to provide a safe diversification of pharmacological treatment options for OUD individuals and to reduce i.v. abuse, respectively. This view is supported by a lower misuse rate of a combined film formulation of buprenorphine and naloxone.[39,40] Our results indicate that a fixed combination of morphine–naloxone solution of 100:1 is sufficient to abrogate morphine effects after i.v. administration in subjects with a confirmed diagnosis of opioid use disorder, and thus has the potential to considerably reduce the abuse liability of SROM.

5 | CONCLUSION

Administration of i.v. naloxone induces a rapid and transient acute withdrawal syndrome in OUD individuals. Morphine–naloxone at a ratio of 100:1 is effective to suppress the pleasurable effects of i.v. morphine and results in an aversive withdrawal reaction. Assessment of pupil diameter appears to be more sensitive to assess morphine–naloxone-induced physiological changes than measurement of heart rate, blood pressure or respiratory rate.

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COMPETING INTERESTS

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CONTRIBUTORS

S. Weisshaar: drafting of the manuscript, acquisition and interpretation of data, G. Fischer and M. Wolzt: study concept and design, interpretation of data, critical revision of the manuscript for important intellectual content, B. Litschauer, S. Sheik-Rezaei, C. Firbas, G. Gouya and L. Moser: acquisition of data, L. Brandt drafting of the manuscript, acquisition of data, G. Nirnberger: analysis and interpretation of data, E. Kühberger and U. Bauer: study concept and design.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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