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ON-ICE trial: Investigation of the combined effects of oxytocin and naltrexone on stress-induced and alcohol cue-induced craving in alcohol use disorder–Study protocol of a phase II randomised double-blind placebo-controlled parallel-group trial

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ABSTRACT

Introduction Although alcohol dependence (AD) is highly prevalent, only few medications are approved for its treatment. While currently approved medications, such as naltrexone (NTX), reduce craving and relapse risk to a certain extent, new approaches are needed to complement these pharmaca. One potential compound is oxytocin (OXY), which proved beneficial effects on alcohol craving and stress reactivity in preliminary clinical studies and synergism with NTX effects.

Methods and analysis This clinical phase II trial is a monocentre two-armed, placebo (PLC)-controlled, 1:1 randomised, double-blind, parallel-group study. 62 participants with AD will be randomised to receive either intranasal OXY spray (24 IU) or PLC spray plus oral NTX (50 mg) for 2 days, and alcohol craving will be assessed using a validated combined stress-exposure and cue-exposure experiments and MRI. The primary outcome will be the intensity of alcohol craving, assessed using the Alcohol Urge Questionnaire (AUQ), 60 min after OXY/PLC application, directly after the stress and cue exposures. Secondary outcomes include subjective stress, negative affect, cortisol and OXY plasma levels, and neural response to alcohol and emotional cues and natural rewards. Follow-up drinking data were collected over 90 days. The primary efficacy analysis will test the difference between the verum and the PLC group in the distribution of AUQ craving scores. Appropriate statistical analysis will be used for the evaluation of the secondary outcomes.

Ethics and dissemination This trial has been approved by the ethics committee of Heidelberg University and competent authority. All participants in the trial will provide written informed consent. The study will be conducted according to the principles of the Declaration of Helsinki and in accordance to the German Medicinal Products act. Results of this study will be disseminated in peer-reviewed scientific journals and deidentified data, and the statistical analysis plan will be made available via open-access online repositories.

Strengths and limitations of this study

- This is the first randomised controlled trial to examine the efficacy and safety of a novel combination of oxytocin (OXY) and naltrexone (NTX) in participants with alcohol dependence (AD).
- The inclusion of an active comparator treatment with NTX, which is approved for the treatment of an AD, will allow the assessment of the added value of OXY in treating alcohol craving.
- This study will include established experimental procedures, which have been validated for the assessment of pharmacological effects on alcohol craving.
- To optimise the generalisability of the findings, eligibility criteria were defined to reflect the group of patients undergoing pharmacological relapse prevention.
- The sample size calculation is based on the assumption that only medium to large effects of OXY on alcohol craving will be of clinical relevance and warrant further confirmatory trials; thus, smaller effects may not be detected.

Trial registration numbers EudraCT 2021-003610-40 and NCT05093296.

INTRODUCTION

Although alcohol dependence (AD, according to the International Classification of Diseases, 10th Revision) or alcohol use disorder (according to *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition) is highly prevalent, only a few medications are approved for its treatment, and randomised

controlled trials point towards a limited mean effect size and high relapse rates.[1] Relapse to alcohol consumption results in negative impacts on patient's health and quality of life.[2] While currently available medications, such as naltrexone (NTX), reduce craving and relapse risk to a certain extent,[1] new approaches are needed to complement these pharmaca. One potential new compound for the treatment of AD is oxytocin (OXY), which has shown beneficial effects on alcohol craving,[3] stress-reactivity[4] and neural response to alcohol cues[5] in preliminary clinical studies. These processes are relevant to patient outcome, because all three show strong associations to relapse risk.[6 7] OXY also seems to be a particularly promising candidate for the enhancement of NTX's effects because of the synergistic interactions between opioid antagonists and OXY. Specifically, opioid antagonists enhance OXY release in the central nervous system.[8] OXY release, in turn, blocks dopamine release within the brain reward system, which has been shown to be a neurobiological correlate of reduced alcohol consumption and preference in animal models.[9] Synergistic effects of NTX and OXY are also supported by recent studies demonstrating supralinear effects of both compounds on social behaviour in macaque monkeys.[10] OXY administration in animal models of binge drinking dose-dependently reduced ethanol consumption in mice[11] and prairie voles.[12] In line with this preclinical data, preliminary clinical studies have shown the beneficial effects of intranasal OXY administration on alcohol craving. Specifically, a randomised parallel-group study comparing the effects of repeated intranasal administrations of OXY (24 IU two times per day over 3 days) against placebo (PLC) in a group of n=11 alcohol-dependent patients has shown that OXY reduced alcohol craving and withdrawal symptom severity.[3] Another randomised double-blind, crossover study in n=32 patients with alcohol use disorder compares the effects of a single intranasal administration of OXY (40 IU) against a single PLC administration (1 week apart). Results show a significant effect of OXY on craving in patients with anxious attachment style.[13] A randomised PLC-controlled parallel-group trial in n=16 patients with cannabis use disorder investigated the effects of a single intranasal administration of OXY (40 IU) against a single PLC administration on experimental stress, cortisol levels and craving. Results demonstrate that OXY reduces cortisol levels and craving in cannabis users after stress exposure.[4] Our own group investigated the effects of a single intranasal administration of 24 IU OXY against a single PLC administration in n=15 heavy social drinkers using a randomised PLC-controlled crossover design. Results demonstrate that intranasal administration of 24 IU. OXY reduces alcohol cue-induced brain response in the brain reward system, which is associated with a reduction in alcohol craving.[5] The aforementioned clinical studies have also established the safety of intranasal administration of OXY in doses of 24–40 IU in individuals using alcohol and patients with AD. In addition, previous work demonstrated central nervous penetrance after intranasal application[14 15] and a maximal effect on brain response and behaviour between 40 and 78 min after application with a maximal effect of a dose of 24 IU.[14 16] A recent study showed a maximal stress-reducing and craving-reducing effect at 60 min after OXY application, directly after the 15 min Trier Social Stress Test (TSST).[4] Taken together, existing lines of evidence support the safety of intranasal OXY administration in humans and the potential of OXY to reduce alcohol craving and yield additional effects in combination with opioid antagonists.[8]

This paper describes the protocol and presents the rationale for an adequately powered, stratified, randomised, double-blind, parallel-arm, PLC-controlled, phase II clinical trial investigating the added value of OXY in combination with NTX in reducing alcohol craving. This phase II study aimed to improve the evidence base for the pharmacological treatment of alcohol craving in patients with AD. This paper complies with the SPIRIT recommendations (Standard Protocol Items: Recommendations for Interventional Trials) for protocol reporting.[17 18] The study will report considering the CONSORT guidelines.[19]

METHODS

Clinical trial design

This clinical phase II trial will be conducted as a monocentre, two-armed, PLC-controlled, 1:1 randomised, double-blind, parallel-group study with two treatment arms (OXY plus NTX vs PLC plus NTX). A PLC-controlled study implementing an active comparator background treatment with NTX in the dose recommended for AD treatment was chosen because any new medication should provide additional effects on craving that are not achieved by the current recommended standard treatment with NTX, whose safety and efficacy in reducing craving were established in previous clinical trials (see[1] for review).

Following assessment of eligibility and informed consent, a total of 62 participants with AD will receive NTX and will be randomised to receive either a single dose of 24 IU OXY 40 min prior to a combined stress-exposure and alcohol cue-exposure experiments[20] during study visits 3 and 40 min prior to a functional MRI (fMRI) measurement during study visit 4 or a PLC nasal spray instead of OXY at the same time points during study visit 3 (day 0, ie, relative time point to visit 3) and study visit 4 (days 1–3). Participants can continue treatment with NTX during and after study participation, without limitations, in the framework of standard treatment. For each patient, the trial consists of a screening visit (day −7 to 0), a baseline visit (day 0), two treatment visits (visit 3 at day 0 and visit 4 at day 1 to 3) with OXY or PLC administration and two follow-up visits (visit 5 at day 30±7 and visit 6 at day 90±7 after study visit 3; see figure 1), in order to assess follow-up drinking data and participant safety and adverse effects.

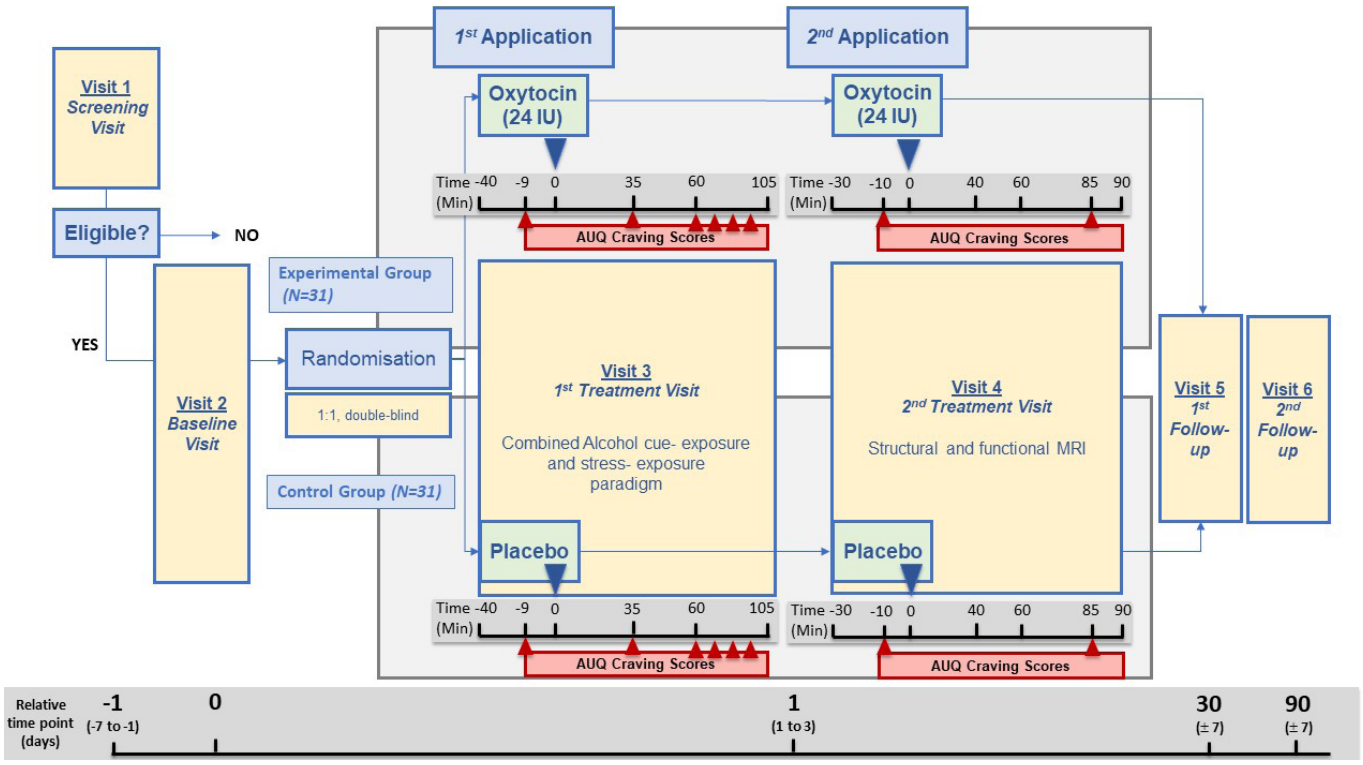

Figure 1 Clinical trial design.

Study objectives

The main purpose of the clinical trial was to assess the effect of an intranasal administration of 24 IU. OXY spray, in addition to standard treatment with 50 mg oral NTX on the reduction of alcohol craving (primary endpoint, assessed by using the Alcohol Urge Questionnaire (AUQ)) compared with the effects of a PLC plus NTX.

Secondary objectives are depicted in box 1.

Box 1 Secondary objectives

Comparison of the effects of OXY versus placebo administration on

- Alcohol craving, subjective stress, positive and negative affects during repeated assessments at visits 3 and 4.
- Cortisol plasma levels at visit 3.
- Neural brain activation (blood oxygenated level-dependent response, during presentation of alcohol cues, natural reward cues, emotional faces and shapes and during inhibition of motor responses) at visit 4.
- Alcohol craving, response times, rates of errors, rates of correct responses and omission rates during the four paradigms of the functional MRI session at visit 4.
- Cumulative alcohol consumption and % heavy drinking days during the follow-up period of 90 days (±7 days) and time from randomisation to first relapse to alcohol drinking during follow-up of 90 days (±7 days).
- Quality of life indices (WHO Quality of Life Questionnaire scores) at days 30 (±7 days) and 90 (±7 days).

Assessment of the safety of combined OXY and naltrexone administration in patients with alcohol dependence.

OXY, oxytocin.

Study population

The trial will enrol patients of both sexes with AD currently undergoing standard inpatient treatment at the study centre (Central Institute of Mental Health (CIMH), Mannheim), since that is the target group for pharmacologically assisted relapse prevention and craving reduction according to current German treatment guidelines. The inclusion and exclusion criteria (see table 1) were chosen in accordance to previous trials[21–23] and define a group of patients with AD which is representative for those patients receiving pharmacological treatment, hence allowing generalisation to this group.

Recruitment and consent

Potentially eligible participants will be informed about the study by their treating clinicians at the Central Institute of Mental Health in Mannheim, Germany. Before being admitted to the clinical trial, the subject must consent to participate after being fully informed by the investigator or a designated member of the investigating team about the nature, importance, risks and individual consequences of the clinical trial and their right to terminate the participation at any time. After reading the informed consent document, the subject must give consent in writing. The informed consent to participate in the clinical trial may be withdrawn by the subject verbally in the presence of, or in written form directed to, the investigator or a physician member of the investigating team at any time during the clinical trial without any disadvantage for the participant.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
► Age between 18 and 70 years.	► Current psychotic or bipolar disorder or current severe depressive episode with suicidal ideations.
► Diagnosis of an alcohol dependence (International Classification of Diseases, 10th Revision).	► Positive drug screening (amphetamines/ecstasy, opiates, cocaine and barbiturates).
► Ability to understand character and individual consequences of the clinical trial. ► Written informed consent. ► At least moderate craving (ie, ≥15 points on the AUQ (range 8–56 points) craving scale) or increase in AUQ scores by ≥50% after exposure to visual alcohol cues (ie, minimum increase of ≥4 points).	► Current treatment with any investigational medicinal product, opioid-containing analgesics, anorexics, anticonvulsants, opioid-containing antidiarrhoeal agents, antineoplastics, antipsychotics (exception: episodic use of melperone, pipamperone and quetiapine are allowed), antidepressants (exception: allowed, when being taken in stable dose for a minimum of 14 days prior to enrolment and/or doxepine in low doses (maximum of 75 mg/day), opioid-containing cough/cold agents, systemic steroids (see also table 3).
► Consent to random assignment.	► Pregnancy, lactation or breast feeding.
► Women with childbearing potential: highly effective birth control method until 24 hours after visit 4 and negative pregnancy test.	► Current severe somatic comorbidities: liver cirrhosis or impaired renal function, severe heart insufficiency, pre-existing epilepsy, long-QT syndrome or cardial arrhythmia.
	► History of hypersensitivity to the investigational medicinal product OXY and/or NTX or to any drug with similar chemical structure or to any excipient present in the pharmaceutical form of the investigational medicinal product OXY and/or NTX.
	► Participation in other clinical trials or observation period of competing clinical trials, respectively.
	► Acute suicidal tendency or acute endangerment of self and others.

AUQ, Alcohol Urge Questionnaire; NTX, naltrexone; OXY, oxytocin.

Randomisation

Participants will be sequentially allocated a unique identifying number to be used for all subsequent study documentation. This will ensure confidentiality is maintained. The randomisation request will be generated after consent and completion of the baseline visit. Eligible patients are randomised in a concealed fashion to one of the two treatment arms in a 1:1 ratio. Block randomisation stratified for sex (male/female) will be applied. Randomisation is done using a centralised web-based tool (www.randomizer.at) by which randomisation for double-blind clinical trials can easily be handled. Study medication containers (Syntocinon/PLC) are blinded to patients and investigators. For all trial personnel, including the biometricians, patient treatment remains blinded from the time of randomisation until final database lock. At the end of the study and after data verification and database lock, the assigned blinded codes are broken for the final analysis of study data.

Intervention

A single dose of 24 IU OXY (Syntocinon, Oxytocin, ATC code: H01BB02, contents: 40 IU of OXY/ 1.0 mL) nasal spray will be administered two times (ie, maximum treatment duration: two times on two separate days 1–3 days apart; maximum dose allowed: 24 IU/dose and 48 IU. in total), in addition to background treatment with NTX (50 mg oral tablet per days) 40 min prior to (i) a combined stress-exposure and alcohol cue-exposure experiment[20] during study visit 3 and 40 min prior to (2) the fMRI-based assessment of alcohol cue reactivity, reward processing, emotion processing and assessment of inhibitory performance during study visit 4.[24] This route and timing are chosen because previous work demonstrated central nervous penetrance after intranasal OXY application[14 15] and a maximal effect on brain response and behaviour between 40 and 78 min after application with a maximal effect of a dose of 24 IU.[14 16] Preliminary studies supported the safety of OXY (Syntocinon) administration in patients with AD.[3 13] A recent study showed a maximal stress-reducing and craving-reducing effect at 60 min after OXY application, directly after the 15 min TSST.[4] Hence, this schedule was adapted. A second assessment day (ie, study visit four with fMRI-based assessment of alcohol cue reactivity) and OXY (Syntocinon) administration are necessary due to the short half-life time of OXY (about 2 hours) and findings that repeated administration on a single day might result in carryover effects.

A PLC spray containing the same ingredients as the OXY (Syntocinon) nasal spray, except for the active ingredient OXY, will be administered in addition to background treatment with NTX. NTX is approved for AD treatment, and clinical trials established its safety and efficacy in reducing craving (see Rösner *et al*[1] for review). All patients receive 50 mg NTX daily, irrespective of participation in the trial, as part of standard treatment. Patients who have already received NTX before inpatient treatment and patients with newly started NTX treatment are included in this trial. NTX is administered to each of the clinical trial participants, either before or on the day of visit 3 (ie, first treatment visit with OXY/PLC

administration) and will be continued for up to 90 days (±7 days) after visit 3, regardless of randomisation group, to treat the indication which is the object of the study. NTX is considered standard care for treating AD. In the trial, OXY or PLC is given in addition to the background treatment and safety is assessed.

In accordance to previous trials,[21–23] all patients will receive state-of-the-art treatment according to current German guidelines that consist of medically supervised treatment of any withdrawal symptoms (not overlapping with trial procedures). Patients will remain in inpatient treatment for at least 24 hours after the fourth study visit, which leaves a large safety corridor for occurrence of any acute side effects, due to the short half-life time of OXY.

Combined stress-exposure and alcohol cue-exposure experiment

The combined stress-exposure and alcohol cue-exposure experiment is a combination of the TSST[25] and an alcohol cue-exposure, which has been established and validated in previous studies.[20] This procedure is necessary, in order to assess cue-induced and stress-induced alcohol craving.

Data collection and outcome measures

The AUQ will be used to assess alcohol craving, which serves as primary outcome measure. The AUQ score is determined by calculating the sum over all AUQ items. The AUQ is a suitable tool for measuring craving. It shows high internal consistency and test–retest reliability,[26] was used and validated by multiple pharmacological trials in patients with AD, and additionally showed strong associations with relapse susceptibility.[20 27] In case that items of the primary endpoint (AUQ score) are missing, they will be imputed using a predefined multiple imputation strategy. The AUQ will also be used to assess alcohol craving longitudinally at different time points relative to administration of the study medication.

Secondary outcomes will be assessed by completion of a number of validated measures at various time points throughout the study period. Box 2 gives an overview of the questionnaires and scales used in this study, and table 2 provides an overview of the study timeline and the outcome measures recorded at each visit. The range of assessment tools will ensure quantitative and qualitative assessment of participants' symptom severity and ensure measurement of quality of life.

Plasma samples for determination of oxytocin and cortisol levels are collected at three and two time points, respectively, before and after OXY/PLC administration and are determined using enzyme-linked immune assays. The *neural response to alcohol cues* is measured using a validated paradigm[24] and by recording the blood oxygenated level-dependent response (BOLD) using fMRI using a Siemens MAGNETOM Prisma 3 Tesla MRI scanner (Siemens, Erlangen, Germany) and contrasting alcohol against neutral conditions using a general linear model (GLM). In addition, neural responses during a validated face-matching task,[28] stop signal task[29] and natural rewards task will be recorded in order to determine the neurobiological effects of OXY. Alcohol use during the 90 days prior to baseline visit and between successive follow-up visits will be assessed using the Form-90 semi-structured interview.[30] Demographics including age, gender, ethnicity, ability to read and speak German will be recorded. In addition, medical history, current diagnoses, as well as concomitant medication and use of addiction-specific treatment and aftercare will be recorded. Further, a physical examination, drug urine screening and blood sampling are performed at predefined time points (see table 2) to determine standard parameters of clinical chemistry, haematology and clotting and to perform a pregnancy test in order to validate inclusion and exclusion criteria, respectively. In addition, 12-lead ECG is performed to rule out clinically relevant cardiac pathologies.

Adverse events will be interrogated for at each contact between the responsible investigator and the clinical trial participant. Furthermore, occurrence of new pathological and clinically relevant findings or aggravation of pre-existing symptoms will be documented as adverse events/serious adverse events.

Sample size calculation

To date, no study investigated the combined effects of OXY+NTX on craving in AD. Therefore, no firm prediction of the expected effect size can be made. However, according to previous work investigating new compounds in AD, we assume that only large effects on craving will be of clinical relevance and warrant further confirmatory trials. Hence, the current trial is designed to detect such effects using the AUQ at 60 min after OXY/PLC application (AUQ_{60min}). The AUQ has a range between 8 and 56 and has a considerably skewed distribution; thus, methods assuming a normally distributed outcome are not applicable. Instead, non-parametric methods will be used. We assume a distribution shift of $\delta=4$ (ie, 4 points on the AUQ craving scale) in the experimental group, corresponding to an effect that would reflect clinical significance for patients with high craving values. Under these assumptions, a sample size of n=29 patients per group yields a power of $1-\beta=0.90$ when using Mann-Whitney U test at a two-sided significance level of $\alpha=5\%$ (according to the sample size formula proposed by Zhao *et al*.[31] The exact values for the cumulative distribution functions assumed under H_1, which we used for calculating the sample size, are shown in online supplemental

Box 2 Questionnaires and psychometric scales that are incorporated in the study

- Beck Depression Inventory.[35]
- Positive and Negative Affect Schedule.[36]
- State–Trait Anxiety Inventory.[26]
- Primary Appraisal and Secondary Appraisal Questionnaire.[37]
- WHO Quality of Life Questionnaire.[38]

Table 2 Schedule of clinical trial visits

	Screening	Baseline	Treatment		Follow-up	
Measurement (relative time point in days)	***Visit 1* (-7 to –1)**	***Visit 2* (0)**	***Visit 3* (0)**	***Visit 4* (1 to 3)**	***Visit 5* (30±7)**	***Visit 6* (90±7)**
General patient characteristics	x					
AD symptoms and drinking habits	x					
Medical history	x					
Concomitant medication	x		x	x	x	x
Physical examination	x				x	x
Vital signs	x				x	x
ECG	x					
Breath alcohol concentration			x	x	x	x
Drug urine screening	x					
Ethylglucuronide in urine samples					x	x
Blood sampling (routine parameters)	x					
Pregnancy test	x					
Screening for psychiatric comorbidities (SCID)	x					
Alcohol Urge Questionnaire	x		x	x	x	x
Edinburgh Inventory of Handedness	x					
Assessment of alcohol use during the past 90 days or since last visit (Form-90)		x			x	x
Fagerstrøm Test for Nicotine Dependence		x				
Beck Depression Inventory		x				
State–Trait Anxiety Inventory		x				
Positive and Negative Affect Schedule			x	x		
Primary Appraisal and Secondary Appraisal			x	x		
Alcohol Dependence Severity		x				
Quality of life and patient-reported outcomes (WHO-QOL-BREF)		x			x	x
Naltrexone compliance		x		x	x	x
Oxytocin nasal spray application			x	x		
Trier Social Stress Test and alcohol cue exposure			x			
Blood sampling (oxytocin and cortisol plasma levels)			x			
Structural and functional MRI assessment				x		
AEs/ SAEs			x	x	x	x
Assessment of the use of addiction-specific treatment and use of aftercare					x	x

AE, adverse event; SAE, severe adverse event; SCID, Structured Clinical Interview for DSM-5; WHO-QOL-BREF, WHO Quality of Life Questionnaire.

table S1. In order to validate this analytically computed sample size, we conducted a power analysis using PASS V.16 with 1 000 000 simulation runs. These simulations confirmed the result of the analytical sample size calculation, yielding a simulated power of 0.92 for a sample size of 29 patients per group. Based on previous trials at our clinic,[21 23] we assume a dropout rate of 5% for the primary endpoint. Hence, n=62 patients (n=31 per group) have to be enrolled and randomised. Using the non-parametric sex-adjusted van Elteren test and the implementation of a predefined imputation strategy, we expected to yield an additional increase in power.

Statistical analysis

The full-analysis population includes all randomised patients with treatment groups assigned in accordance with the randomisation, regardless of the treatment actually received. The analysis of data using the full-analysis population therefore follows the principles of intention to treat. This will be the primary analysis population for the primary and secondary efficacy endpoints.

Analysis of the primary endpoint

Primary outcome is the AUQ score 60 min after OXY or PLC administration at visit 3 (right after the combined

Table 3 List of non-permitted concomitant medication

Drug class	Disallowed prior to the screening visit	Disallowed during the trial from screening visit until after visit 4 for		
		Chronic use	Episodic use	Comments or exceptions
Any investigational medicinal product	Within 30 days or five half-lives (whichever is longer)	X	X	
Opioid-containing Analgesics	Within 1 week for opioid agonists and partial agonists	X	X	Non-opioid analgesics are allowed.
Anorexics		X	X	
Anticonvulsants	Within 30 days or five half-lives (whichever is longer)	X	X	
Opioid-containing antidiarrhoeal agents		X	X	
Antineoplastics	Within 30 days or five half-lives (whichever is longer)	X	X	
Antipsychotics	Within 8 weeks	X	X	Use of melperone (maxmum of 75 mg/day), pipamperone (maximum of 80 mg/day) and quetiapine (maximum of 50 mg/day) is allowed.
Antidepressants		X	X	Antidepressants are allowed, when being taken in stable dose for a minimum of 14 days prior to enrolment and episodic use of doxepine in low doses (maximum of 75 mg/day) is permitted.
Opioid-containing cough/cold agents		X	X	
Steroids–systemic–topical–inhalant		X	X	Systemic corticosteroids are not allowed. Topical and inhalant use is allowed.

challenge task), which will be analysed using the non-parametric van Elteren test stratified for sex at a two-sided significance level of α=5% to assess the null hypothesis that AUQ_{60min} distributions are equal in both groups against the alternative that AUQ_{60min} distributions are different. The summary measure within the sex strata is the relative treatment effect according to Brunner and Munzel.[32] The global summary measure is the weighted mean of the stratum-specific relative treatment effect sizes. The weights are proportional to the size of the strata. A 95% CI will be given for the treatment effect using a t-distribution approximation.[32] Missing data for the primary outcome are assumed to be 'missing at random' and will be replaced on the item level using multiple imputation using the fully conditional specification (FCS) method[33] and predictive mean matching (PMM), taking the variables treatment group, sex and all previously measured AUQ values into account. FCS was chosen as multiple imputation method since no multivariate distribution needs to be assumed for the imputation variables, while PMM was chosen as suitable due to the fact that the primary outcome is highly skewed and no parametric distribution can reasonably be assumed. The SAS (V.9.4 or higher) procedure PROC MI will be used to generate multiply imputed datasets, which relies on multiple imputation chained equations; the number of burn-in iterations for the algorithm is set to n=20.

Analysis of the secondary endpoints

Secondary outcomes are evaluated with adequate summary measures of the empirical distribution. P values of appropriate statistical tests and 95% CIs will be reported for all secondary outcomes; p values will solely be interpreted in a descriptive manner and thus, no adjustment for multiple testing will be done.

Differences between treatment arms in AUQ, positive and negative affect schedule and primary appraisal and secondary appraisal stress scores at specified time points, as well as also oxytocin plasma levels are analysed using non-parametric F2-LD-F1 models, taking treatment group and sex as fixed factors and time as repeated factor into account.[34] Alcohol use (eg, cumulative alcohol consumption) and response times during the four paradigms of the fMRI session will all be analysed using (descriptive) van Elteren tests stratified for sex. fMRI data will be analysed by modelling the separate task conditions within the framework of a GLM using the statistical non-parametric mapping software (SnPM13) toolbox for MATLAB. Within the framework of the software package, a GLM will be used to construct pseudo *t*-statistic images from individual BOLD contrast images, which are then assessed using a non-parametric multiple comparison procedures based on permutation testing to assess the difference in the magnitude of the BOLD responses between treatment groups, stratified by sex. The assessment of safety

is based mainly on the frequency of adverse and serious adverse events. Statistical analysis is performed using SAS V.9.4 or higher.

Patient and public involvement

A trial advisory board (TAB) has been established, composed of one representative of the CIMH advisory board of affected, one representative of self-help groups, one expert in the field of addiction research and one expert in psychopharmacology to balance and diversify perspectives. The tasks of the TAB are to consult with the clinical trial team and solicit input into continuous improvement opportunities with areas of focus, such as design of patient-facing materials, communication (eg, potential alternative treatment, risks and results) with patients and the scientific field, clinical trial procedures, patient recruitment procedures, trial execution simulations and recommendations on reducing strain on participants.

ETHICS AND DISSEMINATION

Ethical considerations

The clinical trial is conducted in accordance with local legal and regulatory requirements and in compliance with the ICH Good Clinical Practice Guidelines, the Declaration of Helsinki and the German Medicinal Product Act. All study documents were submitted to the local Ethics Committee (Ethics Committee II of the Medical Faculty Mannheim, Heidelberg University, ID 2021–6-AMG ff) and the competent authority, which approved to conduct of the trial. Before trial admission, each participant provides written informed consent to participate in the study, after the risks and alternative therapies have been explained in detail. Subjects will be insured and an independent Data and Safety Monitoring Board. Monitoring and Pharmacovigilance will be provided by an independent specialised institution. We previously investigated both study drugs (NTX,[22] OXY[5] in separate trials with minimal rates of adverse events and no severe adverse events. Hence, risk of any physical impairment or severe adverse events is reduced to a minimum and the potential patient benefit outweighs the risks. All patients additionally receive state-of-the-art care according to current German guidelines and receive NTX, such that no effective treatment is withheld.

Confidentiality

Data will be retained in accordance with the principles of Good Clinical Practice. Participants will be allocated a unique identification (ID) number at entry. The master list linking participant personal information and ID number will be maintained in a separate locked cabinet and password-protected hard drive. Data will be analysed by ID number only. Records will be retained for 15 years after study completion.

Dissemination

Individual de-identified data will be shared, specifically individual participant data that underlie the results of the trial (ie, primary outcome data (AUQ scores)) will be made available with a respective data dictionary. Secondary Outcome data (eg, fMRI data) will be made available on aggregated group level (eg, for the purpose of meta-analyses). Related documents, specifically the study protocol, statistical analysis plan and analytic code will be shared in open-access online repositories. Data will be available on publication of the results until 3 years after that. Individual data will be shared with researchers who provide a methodologically sound proposal (sent to the Principal Investigator of the Trial). Aggregated data will be made available to publicly accessible online repositories, for example, for the purpose of meta-analyses.

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SUPPLEMENTS

Supplementary Table S1: Assumed cumulative distribution functions for the primary outcome, $F_E(z)$ and $F_C(z)$, in experimental and control group under H_1

z	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25-26	27	28-39	40-43	44-56
$F_E(z)$	.02	.12	.43	.47	.49	.57	.61	.69	.80	.84	.86	.90	.90	.92	.92	.94	.98	.98	98	.98	1	1
$F_C(z)$	.00	.00	.00	.00	.02	.12	.43	.47	.49	.57	.61	.69	.80	.84	.86	.90	.90	.92	.94	.98	.98	1