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Title

Optimizing treatment expectations in chronic lower back pain through observing others: a study protocol for a randomised clinical trial

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Abstract

Introduction

Chronic lower back pain (CLBP) is a frequent cause of medical consultations worldwide, and it results in decreased quality of life and disability. Current treatments for CLBP are often not effective, and alternatives are urgently needed. Three promising possibilities have emerged: 1) results from an open-label placebo treatment, 2) placebo treatment is as efficacious as opioid treatment with a high correlation between patient expectation and treatment outcome, and 3) observing positive effects in another patient can improve functional capacity. We hypothesize that treatment expectations can be positively influenced through social observation and improve treatment outcome.

Methods and analysis

In our clinical trial, we will randomize CLBP patients into five groups. Two groups receive either a 3-week course of treatment with an analgesic (metamizole/dipyrone) or with open-label placebos (OLP). For one of each group, we will build treatment expectations through observational learning and assess its impact on the treatment. For this purpose, one group each will watch either a positive or a neutral video. The intervention groups will be compared to a control group that will not be given any medication or observational learning.
Participants will be recruited via all institutions in the Hamburg metropolitan area that treat patients with CLBP. Patients are eligible for inclusion if they are at least 18 years or older, have CLBP (of at least 3 months duration), and agree to potentially receive an active analgesic or an OLP. Patients with pain-related "red flags" will be excluded. The study requires 150 participants (30 participants per group) to assess the differences in the primary outcome, pain intensity. Secondary outcomes include changes in treatment expectations, anxiety, comorbid depression, stress-related neuroendocrine measures, functional and structural connectivity, functional capacity, and analgesic consumption. All outcomes and treatment expectations will be measured before and after the intervention and 3 months post-intervention.

Ethics and dissemination

Ethical approval was obtained in January 2020 from the Hamburg Medical Ethics Council (ref number PV7067). Outcomes will be disseminated through publications in peer-reviewed journals and presentations at national and international conference meetings.

Registration details

The approved trial protocol was registered at the German Clinical Trials Register (DRKS) and can be found at drks.de (Identifier: DRKS00024418).

Strengths and Limitations of this Study

- This randomised trial will investigate an innovative approach to treat patients with CLBP
- A randomized controlled design will be implemented to evaluate the effect of expectations on the efficacy of analgesics and open label placebos in combination with observational learning
- This is the first clinical study that will evaluate the influence of expectations on perceived efficacy of analgesics and OLPs in one study design
- The study design does not allow blinding of the therapist throughout the entire study.

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INTRODUCTION

Background

Back pain is one of the most frequent reason for medical consultations worldwide,[1-5] and it is a global concern. Lower back pain is the most common complaint, and it can be acute onset or a chronic issue. Back pain is regarded as chronic (chronic lower back pain; CLBP) if the pain lasts more than 12 weeks[6] and increases with age, and it is prevalent in 19.6% of women and men between the ages of 20 to 59.[7] CLBP results in decreased quality of life, can lead to disability, and is a financial burden for patients and communities.[8] Hence, effective treatment of CLBP is crucial and highly relevant. Unfortunately, current treatment options are unsatisfactory. Despite considerable efforts to improve CLBP, common front-line pharmacological therapies are often not significantly more effective than placebos.[9 10] Despite the unsatisfactory effect of analgesics, CLBP is often treated solely with medication. However, the (long-term) consumption of analgesics, especially opioids, can lead to severe side effects and addiction, as is currently being witnessed with the so-called "opioid crisis".[11] This lack of effective drug treatment partially explains the rising numbers of surgical and other interventional procedures CLBP patients undergo, despite little evidence of the long-term benefits.[12] National guidelines for the treatment of CLBP[13] recommend an interdisciplinary multimodal pain treatment approach, which is often also ineffective [10] and is only available to a limited number of patients because few institutions offer this intensive treatment. CLBP should be treated with a multimodal management strategy that includes the bio-psycho-social perspective.[14] Alternative treatment strategies are urgently required and current research findings regarding cognitive pain modulation should be exploited.[15]

Treatment Expectations

One possibility for the inclusion of the bio-psycho-social perspective to go beyond a pharmacological approach to enhance treatment effect is to integrate psychological mechanisms into CLBP treatment and to increase patient involvement in the treatment. A novel approach is to exploit the effect of treatment expectancy.[16-21] Positive expectations can enhance the treatment effect and play a key role in placebo effects.[9] Negative expectations can impair treatment effects and are relevant to the nocebo effect. For example, it has been shown that the expectation of impending pain substantially alters our perception of pain. Expectation of pain can turn an otherwise non-painful sensation to a painful experience[22] or substantially reduce or even block pain altogether.[9 23 24] Experimental studies suggest that positive expectations can modulate the perception and neural processing of pain and the response to placebos and active drugs. Hence, more systematic exploitation of the mechanisms and effects of expectations is necessary to improve the efficacy of treatment in clinical populations. Therefore, harnessing expectations in a therapeutic way might be promising to improve treatment for patients with CLBP in a safe and cost-effective way.[25 26]

Up to today, most evidence for the striking effect of expectations has come from experimental studies with healthy volunteers and not from studies that include patients with chronic pain. However, the desire for pain relief might be different for patients with chronic pain than for healthy volunteers. Therefore, a study that systematically investigates how to exploit the placebo effects is highly relevant.

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Influence of Treatment Expectation on Active Drug Treatment

Treatment expectation can enhance the effect of both placebos and active drugs.[27] Clinical and experimental evidence indicates that expectation can substantially modulate the efficacy and tolerability of active medical treatment, including pharmacotherapy.[27] Positive treatment expectation has been shown, for instance, to double the analgesic effect of the opioid remifentanil[28] and to substantially enhance the effect of the acute antimigraine drug rizatriptane.[29] Up to 50% of the response to analgesics can be attributed to expectation and not to the pharmacodynamic effect of the administered drug.[30 31] Similar effects have been reported for other medications, including psychotropic drugs.[27 32] The influence of the expectation of treatment outcome is not limited to pharmacological interventions. Positive expectations also affect outcomes in multimodal treatment programs for chronic pain,[33] the effect of deep brain stimulation on motor performance in Parkinson's disease,[27] and the outcome of surgical procedures.[34 35] Until now, the influence of expectations on active drugs has mainly been tested in experimental studies on healthy volunteers. The extent to which the effect of the medication for the treatment of chronic back pain can be influenced by expectancy manipulation has not yet been investigated. Pain medication recommended in the treatment guidelines for back pain is suitable for this purpose. Expectation manipulation to enhance active drug treatment in clinical samples is, therefore, a pivotal next step to advance the systematic use of treatment expectation in clinical practice.

Open Label Placebos

Classic clinical controlled placebo trials imply that patients receive the placebos deceptively, which means that patients do not know whether they receive active or inactive medication. This approach is possible and reasonable in trials because patients consent to the possibility of receiving a placebo instead of the active medication. However, in daily clinical practice, this is not ethically acceptable. One way to avoid this dilemma is to administer the placebo openly (Open Label Placebo; OLP) so that the patients are aware of what they are taking.[36 37] Recent research has revealed that CLBP patients have shown a clinically relevant response, even when they were aware that they were taking a placebo.[36 38] Initial studies showed that the administration of OLPs lead to significant improved effects over the usual treatment in regard to pain and disability and are well-accepted by the patients.[36 37 39] Patients are openly told that they are receiving a placebo and are informed about the underlying mechanisms of placebo effects. Treatment expectation might be the underlying mechanism for the effectiveness of OLPs. Therefore, the effect could be enhanced by utilizing the mechanisms underlying treatment expectation, which are, for example, conditioning or observational learning.[40] This systematic modulation of expectation could boost treatment effect and, in particular, enhance treatment for previously inadequate pain relief.[41]

Observational learning

Treatment expectation is generally formed in various ways, including conditioning via prior experiences,[42 43] therapeutic context, observational learning,[40 44 45] and verbal suggestions via instructions.[9 29] Furthermore, pain is influenced by social interaction and can be modulated by observing others.[44 46] Initial studies confirm that this effect can be achieved through the observation of the benefits of treatment in others.[40 47] However, these studies were conducted with healthy participants under laboratory conditions, meaning that the pain was induced and the participants did not suffer from chronic pain. One study with patients with chronic pain has revealed that intentional observational learning has an effect on disability in patients with CLBP.[48] However, especially for patients with chronic pain, further research is

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required because there are frequent changes in treatment expectations due to the circumstance that patients continuously interact with other patients, health care providers, and personal acquaintances. However, in clinical practice, a model patient who demonstrates the advantages of an intervention is not always available. Therefore, it is important to evaluate whether pre-recorded videos of patients who have benefitted from a treatment can alter treatment expectations and enhance effect of treatment.

Objectives and Outcome

Primary objective

The primary objective of this study is to evaluate whether observational learning enhances positive treatment expectations and whether the positive expectations improve the treatment outcome of OLPs or active analgesics in CLBP patients in comparison to the usual treatment. We will randomize CLBP patients to either a 3-week treatment with an analgesic, metamizole, or a 3-week treatment with OLPs. We will build treatment expectations through observational learning and assess the impact on the two groups. For this purpose, patients will watch either a positive or a neutral video. We will assess the patients' treatment expectations pre and post the three weeks and again after three months, and we will evaluate the effect of these expectation on subjective and objective outcome measures.

The primary subjective outcome is the intensity of the CLBP after three weeks of treatment on a numeric rating scale (NRS) 0–10 (0 = no pain; 10 = worst pain imaginable). We hypothesize that observational learning enhances positive treatment expectations and that positive expectations improve treatment outcome, so both groups that received positive reinforcement through the positive video should experience more satisfactory outcomes from the treatment than those who saw the neutral videos.

Secondary objectives

A secondary objective is to determine whether positive expectations and analgesic treatment effects combine in an additive or synergistic manner. We hypothesize that the group receiving the positive reinforcement will have better outcomes than the group receiving no positive reinforcement. In addition, we will investigate to determine whether individual trait and state variables such as anxiety, comorbid depression, and stress-related neuroendocrine measures modulate treatment expectancy and the effect of this on treatment outcome. Moreover, another aim is to gain insight into whether the functional and structural connectivity of the prefrontal cortex with the pain-related regions at rest predicts the effects of expectation on analgesic treatment outcome.

Secondary subjective outcome measures will be the patients' self-ratings, while the objective outcome measures will be functional capacity, neuroendocrine measures, resting state functional magnet resonance imaging (rsfMRI), and diffusion tensor imaging (DTI). Subjective and objective outcome measures are described in detail in the paragraph titled "Outcome Measures".

METHODS AND ANALYSIS

Setting

The study will be part of an SFB 289/CRC (collaborative research centre) project. Therefore, some of the tests will be analysed across all participating projects. This study will be conducted at the University Medical Centre Hamburg-Eppendorf, Germany.

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Study aim

The proposed study will evaluate the expectations and effects of OLPs in contrast to active analgesics for the treatment of CLBP. The following are the proposed key questions.

Research aims in the present study

1. Can the effect of treatment expectation on pain be enhanced by observational learning?
2. Does positive treatment expectation enhance the analgesic effects of treatment (main effect of expectation)?
3. Do the effects of positive expectation and pharmacological treatment combine in an additive or multiplicative (synergistic) manner?

Research aims analysed within the SFB 289/CRC

4. Does the impact of treatment expectation on analgesic treatment outcome differ between subjective (pain, perceived limitation in mobility) and behavioural (functional capacity) outcome measures?
5. Do individual trait and state variables such as anxiety, comorbid depression, and stress-related neuroendocrine measures modulate the effect of treatment expectancy on treatment outcome?
6. Does the functional and structural connectivity of the prefrontal cortex with pain-related regions at rest predict expectation effects on analgesics treatment outcome?
7. Do salivary cortisol awakening response and salivary alpha-amylase predict expectations effects on analgesics treatment outcome?

Patient and public involvement

Patients should benefit from clinical studies, and this has been a priority for this project from the outset. The study grew out of the authors' clinical activity and therapy expertise with chronic pain patients. Therefore, the patients were already involved in the planning phase and were asked whether they would accept the study design, the deception condition, and what information they considered necessary to understand the procedure. The patients were able to provide valuable input. We discussed the study in an interview with the chairperson of the German pain organisation "UVSD SchmerzLOS" (independent association of active patients with pain in Germany, "Painless"). The "UVSD SchmerzLOS" has also published an interview that introduces the main aspects of the clinical applications of placebo effects in their journal.

The production of the videos for the observational learning for the treatment (analgesic or OLP) effects is of high importance for our study. We based the video script on the medical history of one of our patients with CLBP and hired a professional actor to perform in it. We carefully investigated satisfaction with the videos of patients with CLBP and distributed materials by interviewing patients who were not later enrolled in the study. In addition, patients will be asked for in-depth feedback on the materials and study design after their participation in the study. When the results of the study are published, they will be sent to all patients who provided written consent.

Target population

Participants will be eligible or not eligible for the study according to the following criteria.

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Inclusion criteria

- Age ≥ 18 years;
- Primary symptom CLBP (ICD-10) [49]
- Average pain intensity ≥ 4/10 on numeric rating scale (NRS) during past week
- Sufficient fluency in German language to understand and respond in German language and questionnaires

Exclusion criteria

- Severe acute or chronic mental health condition (e.g., psychosis)
- Chronic diseases with a dominant role in disability (e.g., rheumatic disorders, cancer, severe heart diseases)
- Pain-relevant "red flags" [6]
- Inflammatory or neuropathic back pain
- Unstable analgesic medication – dose and frequency of analgesic treatment should be stable for three weeks prior to screening
- Regular intake of metamizole (dipyrone)
- Known allergies or other contraindications for metamizole (dipyrone)
- Pregnancy and breastfeeding

Recruitment

Participants will be recruited via general practitioners, specialized institutions for back pain, orthopaedic surgeons, physiotherapists, pain therapists, and all institutions in the Hamburg metropolitan area that treat patients with CLBP.

Relevant contact partners in Hamburg, Germany will be contacted and informed about the study. They will receive a checklist to be able to do fast screening of the inclusion and exclusion criteria. Thereafter, potential participants will receive a flyer with all the relevant information and contact addresses. After the study team receives the contact information of potential participants, the study physician will assess the inclusion and exclusion criteria.

Study design

This study is based on a fully balanced within- and between-subject placebo study design (Figure 1). Treatment outcome will be assessed at the subjective (pain rating, limitation in mobility) and objective behavioural (functional capacity) levels. For this purpose, active analgesic (ANA), OLP, and expectation (positive = high vs. neutral = low) will be fully crossed. In addition, a control group (natural history; NH) will complement the design. The NH group will receive no intervention (no treatment, no videos). Treatment expectation (high/low) will be induced through observational learning of treatment benefits in a standardized video showing either positive or neutral treatment effects in another patient.

The study includes three visits over the course of three months, including a follow-up after three months. The baseline assessment of pain includes perceived limitation in functional capacity, treatment expectation, and further psychological assessment. If patients meet the inclusion criteria, they will be fully informed about the study and asked to provide written informed consent. All patients will be reminded to continue with their usual care (e.g. current medication), and they will be informed that they will be randomized to receive either an approved and widely used non-opioid analgesic or a placebo, or they will be assigned to the control group. Participants will also be informed that both the active analgesic and the placebo have shown beneficial effects for CLBP in previous studies, with varying responses between individuals.[36 39]

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After providing written consent, participants will complete a questionnaire and do certain physical exercises to assess baseline values. To assess and analyse predicting variables, patients will undergo rsfMRI scanning, 3D-MPRage T1 weighted sequence (T1), diffusion tensor imaging (DTI), and neuroendocrine measures (salivary cortisol awakening response and salivary alpha-amylase) at rest within one week after enrolment in the study. After the baseline assessment, patients will be randomly allocated to one of the five study groups. Participants will be randomized using block randomisation stratified by gender (ratio 1:1) to allocate the participants to one of the five study arms (ANA/high, ANA/low, OLP/high, OLP/low, NH). A member of staff who will not be involved in the trial will prepare sealed envelopes.

Once the study psychologist has obtained informed consent and baseline data regarding medical background, pain, and physical capacity, participants can choose a random sealed envelope, and the intervention and treatment will commence accordingly.

Before the corresponding medical treatment is started, participants will undergo a treatment expectation modulation by watching a brief (10-minute) video that is part of the general standardized study information. Alterations in treatment expectation will be assessed immediately after the intervention. On the following day, patients will start their treatment (ANA or OLP) at home. The NH group will be assessed in the same manner as the four experimental groups, but they will not undergo modulation of expectancy (video) or receive analgesic treatment (ANA or OLP). Participants in the NH group will be offered ANA or OLP after completion of the main observation period (three months) and after participating in the study.

In addition to the treatment, patients will be given a pain diary and questionnaires to complete within the three week phase. Patients will be contacted once a week and encouraged to update their pain diaries. At the follow-up sessions (at three weeks and three months), the assessment tools used for the baseline assessment will be repeated. Participants will be contacted to remind them of their appointments.

Blinding

The researcher conducting the primary data analysis will be blinded to group allocation. Due to the nature of the study, the researcher conducting the intervention will not be blinded to group allocation.

Intervention

After providing written informed consent for participation in the study and the fMRI scanning, the participants will be randomly assigned to one of the five study groups and receive treatment-specific information that is largely similar for the ANA and OLP treatment (Figure 2).

Video-based treatment expectation manipulation

Upon randomisation to the study medication and the substance-specific/adjusted verbal information, patients will be asked to carefully watch a 10-minute video that will be introduced as part of the general standardized study information. Patients in the high expectation groups will watch a video in which an actor introduced as a fellow patient describes and demonstrates the improvement in their back pain and pain-related functional impairments, following ANA or OLP treatment. In the first part of the video, the patient executes a number of different movements with visible signs of discomfort (pre-treatment). In the second part, the same movements are repeated, but the patients shows no signs of

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discomfort (post-treatment). The videos are identical except for the treatment, which will be either an analgesic or an OLP. Participants in the neutral expectation groups, "OLP/low expectation" and "ANA/low expectation", will watch a control video of the same length, in which the same actor will provide neutral information regarding CLBP without any reference to the course of treatment. The age of the fellow patient is approximately 60 years, which best reflects the mean age of this patient group.[39]

Treatment: active analgesic vs. OLP

The non-opioid metamizole (dipyrone) will be used for the active analgesic treatment, as it is generally well-tolerated and has no known central nervous system side effects that could interfere with treatment expectation. According to the guidelines,[50 51] metamizole (dipyrone) can be used to treat CLBP at the lowest effective dose and for as short a duration as possible when non-steroidal anti-inflammatory drugs are contraindicated or not effective, which applies to the majority of patients with CLBP who present at tertiary referral centres such a university clinic. Metamizole (dipyrone) and OLP will be provided as film-coated tablets with an identical appearance. Patients randomized to the ANA group will receive 3x2 tablets (= 3,000 mg), and the OLP groups will receive the same number of placebo tablets. The NH group will receive no treatment other than the medication already prescribed before the trial. To rule out the possibility of agranulocytosis, blood samples will be taken from all patients before the study and after the three-week intervention.

Outcome measures

Treatment outcome will be assessed at the subjective (pain rating, perceived limitation in mobility) and observed (physical capacity) levels three weeks and three months after randomization and compared to the baseline assessment. The following variables will be recorded (Table 1).

Table 1. Outcome measures

Domain	Measures	Time point*	Method	Comment
Patient reported outcomes				
Pain (Primary Outcome)	Pain intensity: 0–10 NRS	0–21, 90	Pain diary	
Mobility	Hannover Functional Ability Questionnaire (FFbH-R[52])	0, 21, 90	Survey	
Mobility	Pain Disability Inventory[53]		Survey	
Treatment expectations	Stanford expectation treatment scale (SETS[54])	0	Survey, Pain Diary	
	Difference values of current and expected pain[9]	0, 14, 90	Survey	
	Generic rating for treatment pre-experiences, treatment expectations, and treatment effects (G-EEE[55])	0, 7, 14, 21	Survey, Pain Diary	Will be assessed in the whole CRC/relevant for other CRC projects
	Pain-related self-instructions (FSS[56])	7, 14, 21	Pain diary	
Objective behavioural outcomes				
Mobility	Back performance scale[57]	0, 21, 90	Experimental	Exercises will be video-taped and assessed by a blinded rater

Mobility	Schober's test and Ott's sign	0, 21, 90	Via Study Physician	
Exploratory Outcomes				
Side effects	Generic assessment of side effects (GASE-P[58])	0, 21, 90	Survey, Pain Diary	Will be assessed in the whole CRC/relevant for other CRC projects
Psychometric and neuroendocrine measures				
Sociodemographic	Pain-related items of German Pain Questionnaire (Deutscher Schmerzfragebogen; DSF)	0	Survey	Will be assessed in the whole CRC/relevant for other CRC projects
Psychological trait and state	Pain Catastrophizing Scale (PCS[59])	0	Survey	
	State-Trait-Anxiety-Depression inventory (STADI[60])	0	Survey	
	Somatosensory amplification scale (SSAS[61])	0	Survey	
	Behavioural inhibition system/behavioural approach system (BIS/ BAS[62])	0	Survey	
	Perceived Stress Scale (PSS-10[63])	0	Survey	
	Big-five-inventory (BFI-10[64])	0	Survey	
	Fear of Pain questionnaire iii[65]	0	Survey	
Emotional states	Pain and state of health inventory (PHI[66])	0, 21, 90	Survey	
Attitudes	General Attitude Towards Medication Questionnaire (GAMQ[67])	0	Survey	
Neuroendocrine measures				
	Salivary cortisol awakening response	0	Patient	Will be assessed in the whole CRC/relevant for other CRC projects
	Salivary alpha-amylase (sAA)	0, 1	Patient	
fMRI imaging and analyses				
	rsfMRI, DTI, T1	0	n.a.	Will be assessed in the whole CRC/ relevant for other CRC projects

*Time points: 0 = baseline; 1 = 1 day after baseline; 90 = 3 months after baseline
NRS = numeric rating scale

Sample size calculations

Our previous studies have shown large to even larger effects from placebo interventions in patients with CLBP with similar paradigms, d = 1.83[38] and d = 1.56.[9] Furthermore, the existing OLP studies in patients with back pain have revealed lower, but still substantial, effects on pain and reported disability with d = 0.44[39] and d = 0.76.[36] Accordingly, we expect a difference in the effect on primary outcome (pain intensity) between high and low expectation conditions, and this difference is expected to exceed an effect size of Cohen's d = 0.40. This effect should be shown for at least the pre-post comparison. The corresponding power analysis was based on F-statistics for the calculation of analyses of variance (ANOVA) with repeated measures (interaction effect of within and between factor, effect sizes of d = 0.4, α

= 0.05, power 1-ß = 0.9, 5 groups, 2 assessments with G*Power).[68] This requires 125 participants, and with consideration of the expected drop-out rates, a cell size of 30 participants (N = 150) per group is considered sufficient.

Statistical analysis

Between and within differences in clinical outcomes and group allocation will be studied for the different outcome measures with analyses of variance (ANOVA) tests. The data will be analysed as intention-to-treat by a researcher blinded to group allocation. Exploratory post hoc analysis will be applied in the event that significant main results are found. The analyses will be performed with IBM SPSS Statistics software version 25.0 (IBM Corp., Armonk, NY, USA) and data will be reported as means with 95% confidence intervals, unless otherwise specified. Greenhouse-Geisser or Huynh-Feldt correction for the F-Test will be used to adjust the degrees of freedom for deviation from sphericity, if necessary. For all performed analyses, two sided P-values of $P < 0.05$ will be considered statistically significant.

Outlook and Perspective

CLBP is highly prevalent, and it is a major cause of decreased quality of life and disability. The number of prescriptions for opioid medications for CLBP has increased dramatically.[10] This trend has been accompanied by significantly increased levels of prescription opioid overdoses, abuse, addiction, and diversion.[10] Therefore, strategies that exploit the potential of expectation to enhance analgesic treatment outcomes are urgently needed. If the observation of treatment benefits prove to enhance the response to OLP and/or active analgesic treatment, this could have fundamental implications for routine clinical care, as it may be used as an ethically acceptable[69] and cost-effective add-on or an alternative to current treatment modalities. The balanced placebo design used in this study will also shed light on the as yet unexplored question of whether the effects of expectation and of the drug combine in an additive or multiplicative manner. The insights gained in this study will pave the way for future studies that evaluate whether and how these results generalize to other (chronic) pain conditions and analgesic treatments. The thorough clinical and psychological assessment in combination with brain imaging (rsfMRI, DTI, T1) and neuroendocrine measures also promises to identify subgroups of patients who are particularly likely to benefit from such interventions and can be systematically targeted in defined patient subgroups in future studies. The brain imaging performed in this study can lay the foundation for not only identifying predictors but also the mechanisms underlying the beneficial effects of expectation in patients in future funding periods, as these may differ fundamentally from those in healthy volunteers.

Protocol and registration

This study is registered with drks.de (Identifier: DRKS00024418).

Ethics and dissemination

The study has been approved by the Hamburg Medical Ethics Council. The results of this trial will be reported in relevant academic journals and conferences.

Contributors

RK und JS jointly wrote the manuscript. RK, JS, MS und TF designed the study design. MS and CZ critical reviewed the manuscript and provided important intellectual content. RK obtained funding and supervised the whole study.

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Competing interests None declared

Patient consent for publication Not required

Ethics approval This study protocol has been ethically approved by the Hamburg Medical Ethics Council (PV7067). The approved trial protocol was registered at the German Clinical Trials Register (DRKS) and can be found at drks.de (Identifier: DRKS00024418).

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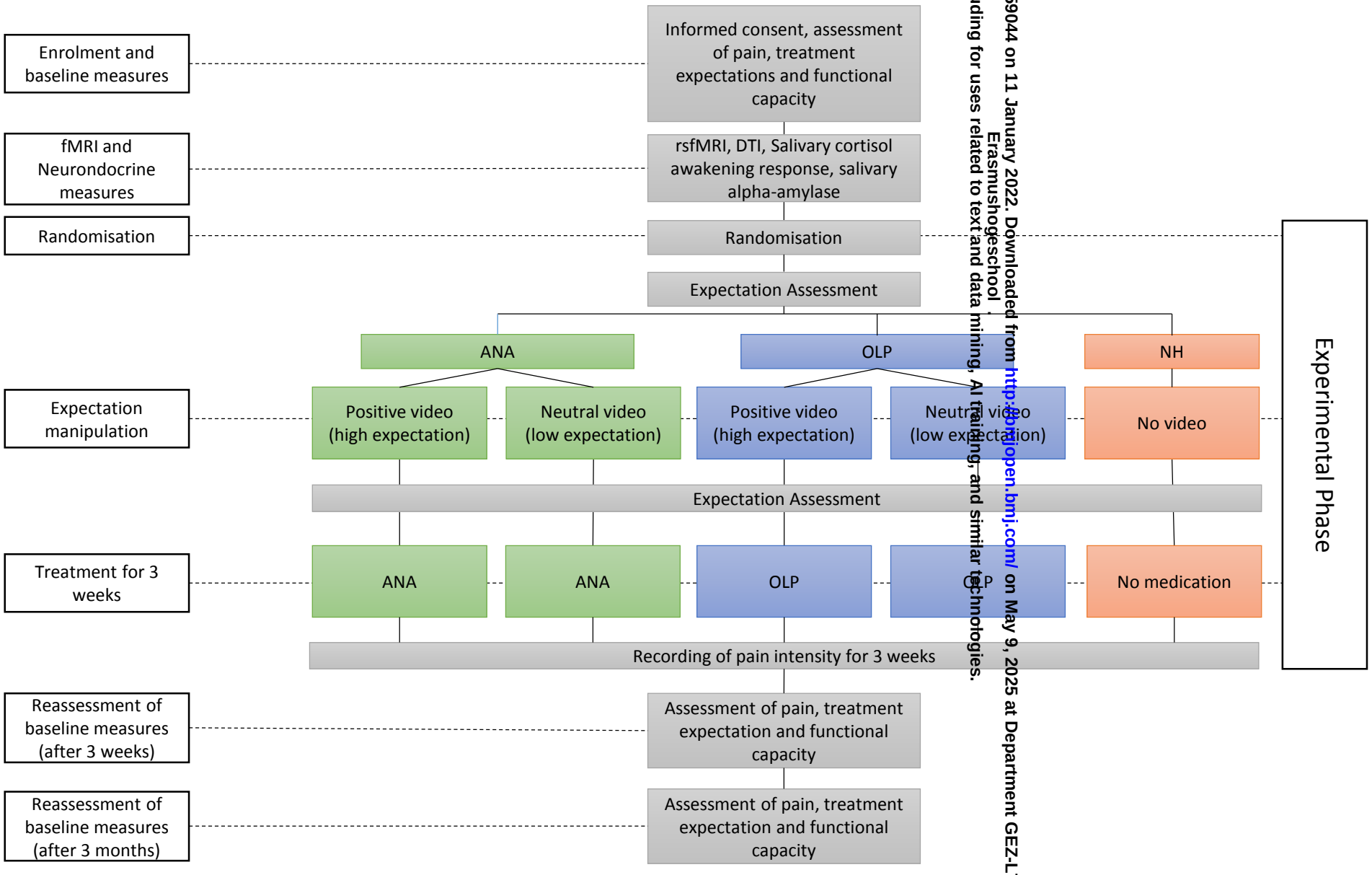
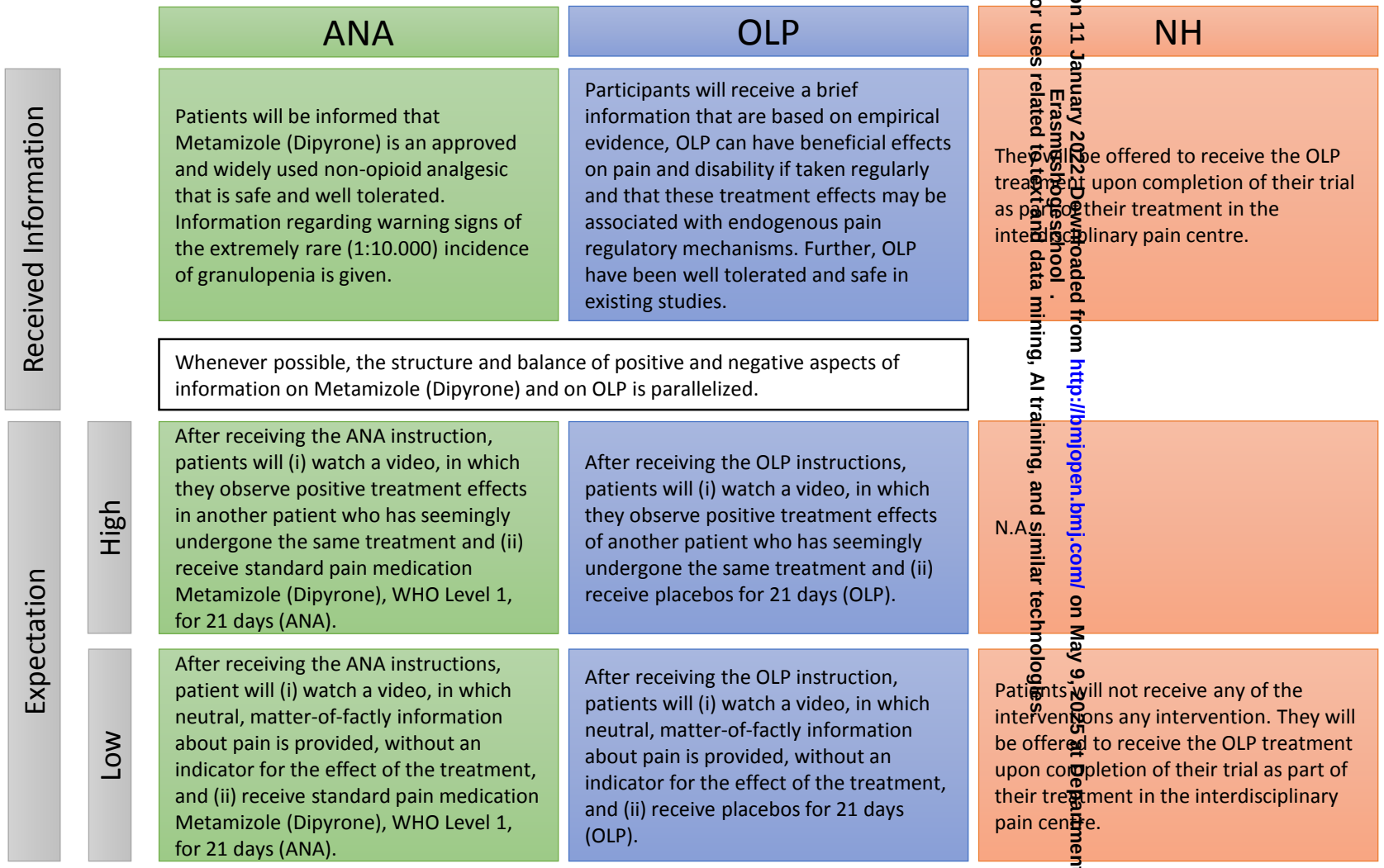
Figure and table legend

Figure 1. Study design

Figure 2. Treatment information

Table 1. Outcome measures





Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	11

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	12
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	5

		be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7

Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.	9

		Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events	n/a

		and other unintended effects of trial interventions or trial conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the	6

		public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Optimizing treatment expectations in chronic lower back pain through observing others: a study protocol for a randomised clinical trial

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Title

Optimizing treatment expectations in chronic lower back pain through observing others: a study protocol for a randomised clinical trial

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Word count

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Abstract

Introduction

Chronic lower back pain (CLBP) is a frequent cause of medical consultations worldwide, and it results in decreased quality of life and disability. Current treatments for CLBP are often not effective, and alternatives are urgently needed. Three promising possibilities have emerged: 1) open-label placebo treatment reduces chronic pain, 2) placebo treatment is as efficacious as opioid treatment with a high correlation between patient expectation and treatment outcome, and 3) observing positive effects in another patient can improve functional capacity. We hypothesize that treatment expectations can be positively influenced through social observation and improve treatment outcome.

Methods and analysis

In our clinical trial, we will randomize CLBP patients into five groups. Two groups receive either a 3-week course of treatment with an analgesic (metamizole/dipyrone) or with open-label placebos (OLP). For one of each group, we will build treatment expectations through observational learning and assess its impact on the treatment. For this purpose, one group each will watch either a positive or a neutral video. The intervention groups will be compared to a control group that will not be given any medication or observational learning.

Participants will be recruited via all institutions in the Hamburg metropolitan area that treat patients with CLBP. Patients are eligible for inclusion if they are at least 18 years or older, have CLBP (of at least 3 months duration), and agree to potentially receive an active analgesic or an OLP. Patients with pain-related "red flags" will be excluded. The study requires 150 participants (30 participants per group) to assess the differences in the primary outcome, pain intensity. Secondary outcomes include changes in treatment expectations, anxiety, comorbid depression, stress-related neuroendocrine measures, functional and structural connectivity, functional capacity, and analgesic consumption. All outcomes and treatment expectations will be measured before and after the intervention and 3 months post-intervention.

Ethics and dissemination

Ethical approval was obtained in January 2020 from the Hamburg Medical Ethics Council (ref number PV7067). Outcomes will be disseminated through publications in peer-reviewed journals and presentations at national and international conference meetings.

Registration details

The approved trial protocol was registered at the German Clinical Trials Register (DRKS) and can be found at drks.de (Identifier: DRKS00024418).

Strengths and Limitations of this Study

- This randomised trial will investigate an innovative approach to treat patients with CLBP
- A randomized controlled design will be implemented to evaluate the effect of expectations on the efficacy of analgesics and open label placebos in combination with observational learning
- This is the first clinical study that will evaluate the influence of expectations on perceived efficacy of analgesics and OLPs in one study design
- The study design does not allow blinding of the therapist throughout the entire study.

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INTRODUCTION

Background

Back pain is one of the most frequent reason for medical consultations worldwide,[1-5] and it is a global concern. Lower back pain is the most common complaint, and it can be acute or chronic. Back pain is regarded as chronic (chronic lower back pain; CLBP) if the pain lasts more than 12 weeks[6]. It increases with age, and it is prevalent in 19.6% of women and men between the ages of 20 to 59.[7] CLBP results in decreased quality of life, can lead to disability, and is a financial burden for patients and communities.[8] Hence, effective treatment of CLBP is crucial and highly relevant. Unfortunately, current treatment options are unsatisfactory. Despite considerable efforts to improve CLBP, common front-line pharmacological therapies are often not significantly more effective than placebos.[9 10] Despite the unsatisfactory effect of analgesics, CLBP is often treated solely with medication. However, the (long-term) consumption of analgesics, especially opioids, can lead to severe side effects and addiction, as is currently being witnessed with the so-called "opioid crisis".[11] This lack of effective drug treatment partially explains the rising numbers of surgical and other interventional procedures CLBP patients undergo, despite little evidence of the long-term benefits.[12] National guidelines for the treatment of CLBP[13] recommend an interdisciplinary multimodal pain treatment approach, which is often also ineffective [10] and is only available to a limited number of patients because few institutions offer this intensive treatment. CLBP should be treated with a multimodal management strategy that includes the bio-psycho-social perspective.[14] Alternative treatment strategies are urgently required and current research findings regarding cognitive pain modulation should be exploited.[15]

Treatment Expectations

One possibility for the inclusion of the bio-psycho-social perspective to go beyond a pharmacological approach to enhance the treatment effect is to integrate psychological mechanisms into CLBP treatment and to increase patient involvement in the treatment. A novel approach is to exploit the effect of treatment expectancy.[16-21] Positive expectations can enhance the treatment effect and play a key role in placebo effects.[9] Negative expectations can impair treatment effects and are relevant to the nocebo effect. For example, it has been shown that the expectation of impending pain substantially alters our perception of pain. Expectation of pain can turn an otherwise non-painful sensation to a painful experience[22] or substantially reduce or even block pain altogether.[9 23 24] Experimental studies suggest that positive expectations can modulate the perception and neural processing of pain and the response to placebos and active drugs. Hence, more systematic exploitation of the mechanisms and effects of expectations is necessary to improve the efficacy of treatment in clinical populations. Therefore, harnessing expectations in a therapeutic way might be promising to improve treatment for patients with CLBP in a safe and cost-effective way.[25 26]

So far, most evidence for the striking effect of expectations has come from experimental studies with healthy volunteers and not from studies that include patients with chronic pain. However, the desire for pain relief might be different for patients with chronic pain than for healthy volunteers. Therefore, a study that systematically investigates how to exploit the placebo effects is highly relevant.

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Influence of Treatment Expectation on Active Drug Treatment

Treatment expectation can enhance the effect of both placebos and active drugs.[27] Clinical and experimental evidence indicates that expectation can substantially modulate the efficacy and tolerability of active medical treatment, including pharmacotherapy.[27] Positive treatment expectation has been shown, for instance, to double the analgesic effect of the opioid remifentanil[28] and to substantially enhance the effect of the acute antimigraine drug rizatriptane.[29] Up to 50% of the response to analgesics can be attributed to expectation and not to the pharmacodynamic effect of the administered drug.[30 31] Similar effects have been reported for other medications, including psychotropic drugs.[27 32] The influence of the expectation of treatment outcome is not limited to pharmacological interventions. Positive expectations also affect outcomes in multimodal treatment programs for chronic pain,[33] the effect of deep brain stimulation on motor performance in Parkinson's disease,[27] and the outcome of surgical procedures.[34 35] Until now, the influence of expectations on active drugs has mainly been tested in experimental studies on healthy volunteers. The extent to which the effect of the medication for the treatment of chronic back pain can be influenced by expectancy manipulation has not yet been investigated. Pain medication recommended in the treatment guidelines for back pain is suitable for this purpose. Expectation manipulation to enhance active drug treatment in clinical samples is, therefore, a pivotal next step to advance the systematic use of treatment expectation in clinical practice.

Open Label Placebos

Classic clinical controlled placebo trials imply that patients receive the placebos deceptively, which means that patients do not know whether they receive active or inactive medication. This approach is possible and reasonable in trials because patients consent to the possibility of receiving a placebo instead of the active medication. However, in daily clinical practice, this is not ethically acceptable. One way to avoid this dilemma is to administer the placebo openly (Open Label Placebo; OLP) so that the patients are aware of what they are taking.[36 37] Recent research has revealed that CLBP patients have shown a clinically relevant response, even when they were aware that they were taking a placebo.[36 38] Initial studies showed that the administration of OLPs lead to significant improved effects over the usual treatment in regard to pain and disability and are well-accepted by the patients.[36 37 39] Patients are openly told that they are receiving a placebo and are informed about the underlying mechanisms of placebo effects. Treatment expectation might be the underlying mechanism for the effectiveness of OLPs. Therefore, the effect could be enhanced by utilizing the mechanisms underlying treatment expectation, which are, for example, conditioning or observational learning.[40] This systematic modulation of expectation could boost treatment effect and, in particular, enhance treatment for previously inadequate pain relief.[41]

Observational learning

Treatment expectation is generally formed in various ways, including conditioning via prior experiences,[42 43] therapeutic context, observational learning,[40 44 45] and verbal suggestions via instructions.[9 29] Furthermore, pain is influenced by social interaction and can be modulated by observing others.[44 46] Initial studies confirm that this effect can be achieved through the observation of the benefits of treatment in others.[40 47] However, these studies were conducted with healthy participants under laboratory conditions, meaning that the pain was induced and the participants did not suffer from chronic pain. One study with patients with chronic pain has revealed that intentional observational learning has an effect on disability in patients with CLBP.[48] However, especially for patients with chronic pain, further research is

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required because there are frequent changes in treatment expectations due to the circumstance that patients continuously interact with other patients, health care providers, and personal acquaintances. However, in clinical practice, a model patient who demonstrates the advantages of an intervention is not always available. Therefore, it is important to evaluate whether pre-recorded videos of patients who have benefitted from a treatment can alter treatment expectations and enhance treatment effects.

Objectives and Outcome

Primary objective

The primary objective of this study is to evaluate whether observational learning enhances positive treatment expectations and whether the positive expectations improve the treatment outcome of OLPs or active analgesics in CLBP patients in comparison to the usual treatment. We will randomize CLBP patients to either a 3-week treatment with an analgesic, metamizole, or a 3-week treatment with OLPs. We will build treatment expectations through observational learning and assess the impact on the two groups. For this purpose, patients will watch either a positive or a neutral video. We will assess the patients' treatment expectations before and after three weeks and again after three months, and we will evaluate the effect of these expectation on subjective and objective outcome measures.

The primary subjective outcome is the intensity of the CLBP after three weeks of treatment on a numeric rating scale (NRS) 0–10 (0 = no pain; 10 = worst pain imaginable). A composite pain intensity score (mean of minimum, maximum and average pain intensity) will be assessed at baseline and 3 weeks after the baseline on a NRS 0-10. This well-established outcome measure has also been used I the two existing studies of OLP treatments for CLBP and will allow comparing the results [36] [39]. We hypothesize that observational learning enhances positive treatment expectations and that positive expectations improve treatment outcome, so both groups that received positive reinforcement through the positive video should experience more satisfactory outcomes from the treatment than those who saw the neutral videos.

Secondary objectives

A secondary objective is to determine whether positive expectations and analgesic treatment effects combine in an additive or synergistic manner. We hypothesize that the group receiving the positive reinforcement will have better outcomes than the group receiving no positive reinforcement. In addition, we will investigate whether individual trait and state variables such as anxiety, comorbid depression, and stress-related neuroendocrine measures modulate treatment expectancy and consequently the effect of this on treatment outcome. Moreover, another aim is to gain insight into whether the functional and structural connectivity of the prefrontal cortex with the pain-related regions at rest predicts the effects of expectation on analgesic treatment outcome. This will be investigated through resting state functional magnet resonance imaging (rsfMRI) and diffusion tensor imaging (DTI).

Consequently, the secondary outcomes consists of subjective and objective outcome measures. Subjective outcome measures will be the patients' self-ratings. Whereas, the objective outcome measures will be functional capacity, neuroendocrine measures, and functional and structural connectivity of the prefrontal cortex. Subjective and objective outcome measures are described in detail in the paragraph titled "Outcome Measures".

METHODS AND ANALYSIS

Setting

The study will be part of a collaborative research centre (CRC) project (SFB 289).Therefore, some of the tests will be analysed across all participating projects. This study will be conducted at the University Medical Centre Hamburg-Eppendorf, Germany.

Study aim

The proposed study will evaluate the expectations and effects of OLPs in contrast to active analgesics for the treatment of CLBP. The following are the proposed key questions.

Research aims in the present study

1. Can the effect of treatment expectation on pain be enhanced by observational learning?
2. Does positive treatment expectation enhance the analgesic effects of treatment (main effect of expectation)?
3. Do the effects of positive expectation and pharmacological treatment combine in an additive or multiplicative (synergistic) manner?
4. Does the impact of treatment expectation on analgesic treatment outcome differ between subjective (pain, perceived limitation in mobility) and behavioural (functional capacity) outcome measures?

Research aims in the present study which are also analysed as part of other projects within the SFB 289/CRC

5. Do individual trait and state variables such as anxiety, comorbid depression, and stress-related neuroendocrine measures modulate the effect of treatment expectancy on treatment outcome?
6. Does the functional and structural connectivity of the prefrontal cortex with pain-related regions at rest predict expectation effects on analgesics treatment outcome?
7. Do salivary cortisol awakening response and salivary alpha-amylase predict expectations effects on analgesics treatment outcome?

Patient and public involvement

Patients should benefit from clinical studies, and this has been a priority for this project from the outset. The study grew out of the authors' clinical activity and therapy expertise with chronic pain patients. Therefore, the patients were already involved in the planning phase and were asked whether they would accept the study design, the deception condition, and what information they considered necessary to understand the procedure. The patients were able to provide valuable input. We discussed the study in an interview with the chairperson of the German pain organisation "UVSD SchmerzLOS" (independent association of active patients with pain in Germany, "Painless"). The "UVSD SchmerzLOS" has also published an interview that introduces the main aspects of the clinical applications of placebo effects in their journal.

The production of the videos for the observational learning for the treatment (analgesic or OLP) effects is of high importance for our study. We based the video script on the medical history of one of our patients with CLBP and hired a professional actor to perform in it. We carefully investigated satisfaction with the videos of patients with CLBP and distributed

materials by interviewing patients who were not later enrolled in the study. In addition, patients will be asked for in-depth feedback on the materials and study design after their participation in the study. When the results of the study are published, they will be sent to all patients who provided written consent.

Target population

Participants will be eligible or not eligible for the study according to the following criteria:

Inclusion criteria

- Age ≥ 18 years
- Primary symptom CLBP (ICD-10) [49]
- Average pain intensity ≥ 4/10 on numeric rating scale (NRS) during past week
- Sufficient fluency in German language to understand and respond in German language and questionnaires

Exclusion criteria

- Severe acute or chronic mental health condition (e.g., psychosis)
- Chronic diseases with a dominant role in disability (e.g., rheumatic disorders, cancer, severe heart diseases)
- Pain-relevant "red flags" [6] (e.g. tumour, active rheumatologic disorder)
- Inflammatory or neuropathic back pain
- Unstable analgesic medication – dose and frequency of analgesic treatment should be stable for three weeks prior to screening
- Regular intake of metamizole (dipyrone)
- Known allergies or other contraindications for metamizole (dipyrone)
- Pregnancy and breastfeeding

Notably, if patients are not eligible to participate in the MRI scanning, they will not be excluded from participation for the study itself.

Recruitment

Participants will be recruited via general practitioners, specialized institutions for back pain, orthopaedic surgeons, physiotherapists, pain therapists, and all institutions in the Hamburg metropolitan area that treat patients with CLBP.
Relevant contact partners in Hamburg, Germany will be contacted and informed about the study. They will receive a checklist to be able to do fast screening of the inclusion and exclusion criteria. Thereafter, potential participants will receive a flyer with all the relevant information and contact addresses. After the study team receives the contact information of potential participants, the study physician will assess the inclusion and exclusion criteria.

Study design

This study is based on a fully balanced within- and between-subject placebo study design (Figure 1). Treatment outcome will be assessed at the subjective (pain rating, limitation in mobility) and objective behavioural (functional capacity) levels. For this purpose, active analgesic (ANA), OLP, and expectation (positive = high vs. neutral = low) will be fully crossed. In addition, a control group (natural history; NH) will complement the design. The NH group will receive no intervention (no treatment, no videos). Treatment expectation (high/low) will be induced through observational learning of treatment benefits in a standardized video showing either positive or neutral treatment effects in another patient.

The study includes three visits over the course of three months, including a follow-up after three months. The baseline assessment of pain includes perceived limitation in functional capacity, treatment expectation, and further psychological assessment. If patients meet the inclusion criteria, they will be fully informed about the study and asked to provide written informed consent. All patients will be reminded to continue with their usual care (e.g. current medication), and they will be informed that they will be randomized to receive either an approved and widely used non-opioid analgesic or a placebo, or they will be assigned to the control group. Participants will also be informed that both the active analgesic and the placebo have shown beneficial effects for CLBP in previous studies, with varying responses between individuals.[36 39]

After providing written consent, participants will complete a questionnaire and do certain physical exercises to assess baseline values. To assess and analyse predicting variables, patients will undergo rsfMRI scanning, 3D-MPRage T1 weighted sequence (T1), diffusion tensor imaging (DTI), and neuroendocrine measures (salivary cortisol awakening response and salivary alpha-amylase) at rest within one week after enrolment in the study. After the baseline assessment, patients will be randomly allocated to one of the five study groups. Participants will be randomized using block randomisation stratified by gender (ratio 1:1) to allocate the participants to one of the five study arms (ANA/high, ANA/low, OLP/high, OLP/low, NH). A member of staff who will not be involved in the trial will prepare sealed envelopes.

Once the study psychologist has obtained informed consent and baseline data regarding medical background, pain, and physical capacity, participants can choose a random sealed envelope, and the intervention and treatment will commence accordingly.

Before the corresponding medical treatment is started, participants will undergo a treatment expectation modulation by watching a brief (10-minute) video that is part of the general standardized study information. Alterations in treatment expectation will be assessed immediately after the intervention. On the following day, patients will start their treatment (ANA or OLP) at home. The NH group will be assessed in the same manner as the four experimental groups, but they will not undergo modulation of expectancy (video) or receive analgesic treatment (ANA or OLP). Participants in the NH group will be offered ANA or OLP after completion of the main observation period (three months) and after participating in the study.

In addition to the treatment, patients will be given a pain diary and questionnaires to complete within the three week phase. Patients will be contacted once a week and encouraged to update their pain diaries. At the follow-up sessions (at three weeks and three months), the assessment tools used for the baseline assessment will be repeated. Participants will be contacted to remind them of their appointments.

Blinding

The researcher conducting the primary data analysis will be blinded to group allocation. Due to the nature of the study, the researcher conducting the intervention will not be blinded to group allocation. Therefore the possibility of an experimenter effect cannot completely be excluded but should be minimized due to the study design.

Intervention

After providing written informed consent for participation in the study and the fMRI scanning, the participants will be randomly assigned to one of the five study groups and receive

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treatment-specific information that is largely similar for the ANA and OLP treatment (Figure 2).

Video-based treatment expectation manipulation

Upon randomisation to the study medication and the substance-specific/adjusted verbal information, patients will be asked to carefully watch a 10-minute video that will be introduced as part of the general standardized study information. Patients in the high expectation groups will watch a video in which an actor introduced as a fellow patient describes and demonstrates the improvement in their back pain and pain-related functional impairments, following ANA or OLP treatment. In the first part of the video, the patient executes a number of different movements with visible signs of discomfort (pre-treatment). In the second part, the same movements are repeated, but the patients shows no signs of discomfort (post-treatment). The videos are identical except for the treatment, which will be either an analgesic or an OLP. Participants in the neutral expectation groups, "OLP/low expectation" and "ANA/low expectation", will watch a control video of the same length, in which the same actor will provide neutral information regarding CLBP without any reference to the course of treatment. The age of the fellow patient is approximately 60 years, which best reflects the mean age of this patient group.[39]

Treatment: active analgesic vs. OLP

The non-opioid metamizole (dipyrone) will be used for the active analgesic treatment, as it is generally well-tolerated and has no known central nervous system side effects that could interfere with treatment expectation. According to the guidelines,[50 51] metamizole (dipyrone) can be used to treat CLBP at the lowest effective dose and for as short a duration as possible when non-steroidal anti-inflammatory drugs are contraindicated or not effective, which applies to the majority of patients with CLBP who present at tertiary referral centres such a university clinic. Metamizole (dipyrone) and OLP will be provided as film-coated tablets with an identical appearance. Patients randomized to the ANA group will receive 3x2 tablets (= 3,000 mg), and the OLP groups will receive the same number of placebo tablets. The NH group will receive no treatment other than the medication already prescribed before the trial. To rule out the possibility of agranulocytosis, blood samples will be taken from all patients before the study and after the three-week intervention.

Outcome measures

Treatment outcome will be assessed at the subjective (pain rating, perceived limitation in mobility) and observed (physical capacity) levels three weeks and three months after randomization and compared to the baseline assessment. The following variables will be recorded (Table 1).

Table 1. Outcome measures

Domain	Measures	Time point*	Method	Comment
Patient reported outcomes				
Pain (Primary Outcome)	Pain intensity: 0–10 NRS	0–21, 90	Pain diary, Survey	
Mobility	Hannover Functional Ability Questionnaire (FFbH-R[52])	0, 21, 90	Survey	
Mobility	Pain Disability Inventory[53]		Survey	

Treatment expectations	Stanford expectation treatment scale (SETS[54])	0	Survey, Pain Diary	
	Difference values of current and expected pain[9]	0, 14, 90	Survey	
	Generic rating for treatment pre-experiences, treatment expectations, and treatment effects (G-EEE[55])	0, 7, 14, 21	Survey, Pain Diary	Will be assessed in the whole CRC/relevant for other CRC projects
	Pain-related self-instructions (FSS[56])	7, 14, 21	Pain diary	
Objective behavioural outcomes				
Mobility	Back performance scale[57]	0, 21, 90	Experimental	Exercises will be video-taped and assessed by a blinded rater
Mobility	Schober's test and Ott's sign	0, 21, 90	Via Study Physician	
Exploratory Outcomes				
Side effects	Generic assessment of side effects (GASE-P[58])	0, 21, 90	Survey, Pain Diary	Will be assessed in the whole CRC/relevant for other CRC projects
Psychometric and neuroendocrine measures				
Sociodemographic	Pain-related items of German Pain Questionnaire (Deutscher Schmerzfragebogen; DSF)	0	Survey	Will be assessed in the whole CRC/relevant for other CRC projects
Psychological trait and state	Pain Catastrophizing Scale (PCS[59])	0	Survey	
	State-Trait-Anxiety-Depression inventory (STADI[60])	0	Survey	
	Somatosensory amplification scale (SSAS[61])	0	Survey	
	Behavioural inhibition system/behavioural approach system (BIS/ BAS[62])	0	Survey	
	Perceived Stress Scale (PSS-10[63])	0	Survey	
	Big-five-inventory (BFI-10[64])	0	Survey	
	Fear of Pain questionnaire iii[65]	0	Survey	
Emotional states	Pain and state of health inventory (PHI[66])	0, 21, 90	Survey	
Attitudes	General Attitude Towards Medication Questionnaire (GAMQ[67])	0	Survey	
Neuroendocrine measures				
	Salivary cortisol awakening response	0	Patient	Will be assessed in the whole CRC/relevant for other CRC projects
	Salivary alpha-amylase (sAA)	0, 1	Patient	
fMRI imaging and analyses				
	rsfMRI, DTI, T1	0	n.a.	Will be assessed in the whole CRC/ relevant for other CRC projects

*Time points: 0 = baseline; 1 = 1 day after baseline; 90 = 3 months after baseline
NRS = numeric rating scale

Sample size calculations

Our previous studies have shown large to even larger effects from placebo interventions in patients with CLBP with similar paradigms, d = 1.83[38] and d = 1.56.[9] Furthermore, the existing OLP studies in patients with back pain have revealed lower, but still substantial, effects on pain and reported disability with d = 0.44[39] and d = 0.76.[36] Accordingly, we expect a difference in the effect on primary outcome (pain intensity) between high and low expectation conditions, and this difference is expected to exceed an effect size of Cohen's d = 0.40. This effect should be shown for at least the pre-post comparison. The corresponding power analysis was based on F-statistics for the calculation of analyses of variance (ANOVA) with repeated measures (interaction effect of within and between factor, effect sizes of d = 0.4, α = 0.05, power 1-ß = 0.9, 5 groups, 2 assessments with G*Power).[68] This requires 125 participants, and with consideration of the expected drop-out rates, a cell size of 30 participants (N = 150) per group is considered sufficient.

Statistical analysis

Between and within differences in clinical outcomes and group allocation will be studied for the different outcome measures with analyses of variance (ANOVA) tests. The data will be analysed as intention-to-treat by a researcher blinded to group allocation. Exploratory post hoc analysis will be applied in the event that significant main results are found. The analyses will be performed with IBM SPSS Statistics software version 27.0 (IBM Corp., Armonk, NY, USA) and data will be reported as means with 95% confidence intervals, unless otherwise specified. Greenhouse-Geisser or Huynh-Feldt correction for the F-Test will be used to adjust the degrees of freedom for deviation from sphericity, if necessary. For all performed analyses, two sided P-values of $P < 0.05$ will be considered statistically significant.

Outlook and Perspective

CLBP is highly prevalent, and it is a major cause of decreased quality of life and disability. The number of prescriptions for opioid medications for CLBP has increased dramatically.[10] This trend has been accompanied by significantly increased levels of prescription opioid overdoses, abuse, addiction, and diversion.[10] Therefore, strategies that exploit the potential of expectation to enhance analgesic treatment outcomes are urgently needed. If the observation of treatment benefits prove to enhance the response to OLP and/or active analgesic treatment, this could have fundamental implications for routine clinical care, as it may be used as an ethically acceptable[69] and cost-effective add-on or an alternative to current treatment modalities. The balanced placebo design used in this study will also shed light on the as yet unexplored question of whether the effects of expectation and of the drug combine in an additive or multiplicative manner. The insights gained in this study will pave the way for future studies that evaluate whether and how these results generalize to other (chronic) pain conditions and analgesic treatments. The thorough clinical and psychological assessment in combination with brain imaging (rsfMRI, DTI, T1) and neuroendocrine measures also promises to identify subgroups of patients who are particularly likely to benefit from such interventions and can be systematically targeted in defined patient subgroups in future studies. The brain imaging performed in this study can lay the foundation for not only identifying predictors but also the mechanisms underlying the beneficial effects of expectation in patients in future funding periods, as these may differ fundamentally from those in healthy volunteers.

Protocol and registration

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This study is registered with drks.de (Identifier: DRKS00024418).

Ethics and dissemination

The study has been approved by the Hamburg Medical Ethics Council. The results of this trial will be reported in relevant academic journals and conferences.

Contributors

RK und JS jointly wrote the manuscript. RK, JS, MS und TF designed the study design. MS and CZ critical reviewed the manuscript and provided important intellectual content. RK obtained funding and supervised the whole study.

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Competing interests None declared

Patient consent for publication Not required

Ethics approval This study protocol has been ethically approved by the Hamburg Medical Ethics Council (PV7067). The approved trial protocol was registered at the German Clinical Trials Register (DRKS) and can be found at drks.de (Identifier: DRKS00024418).

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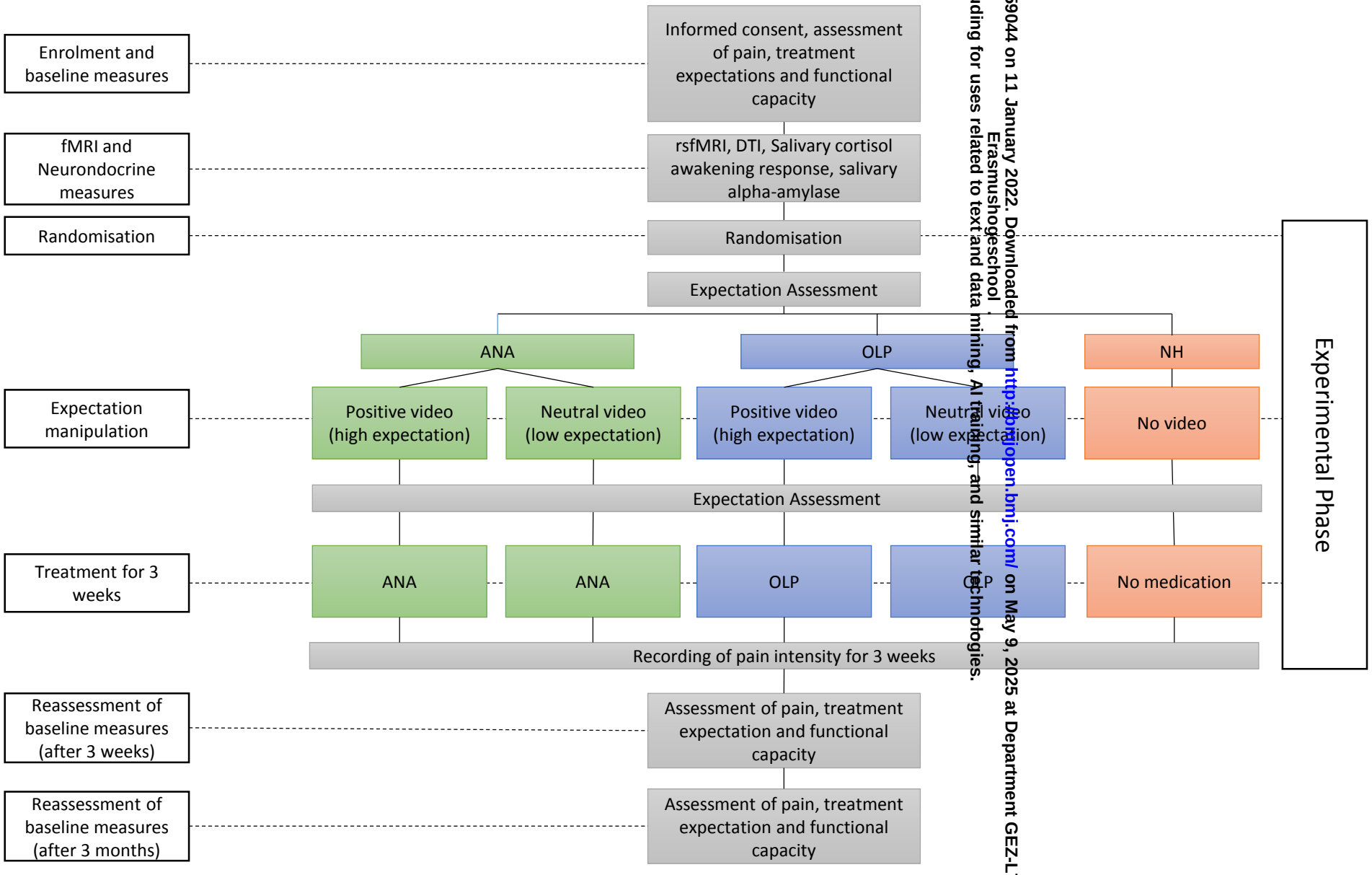
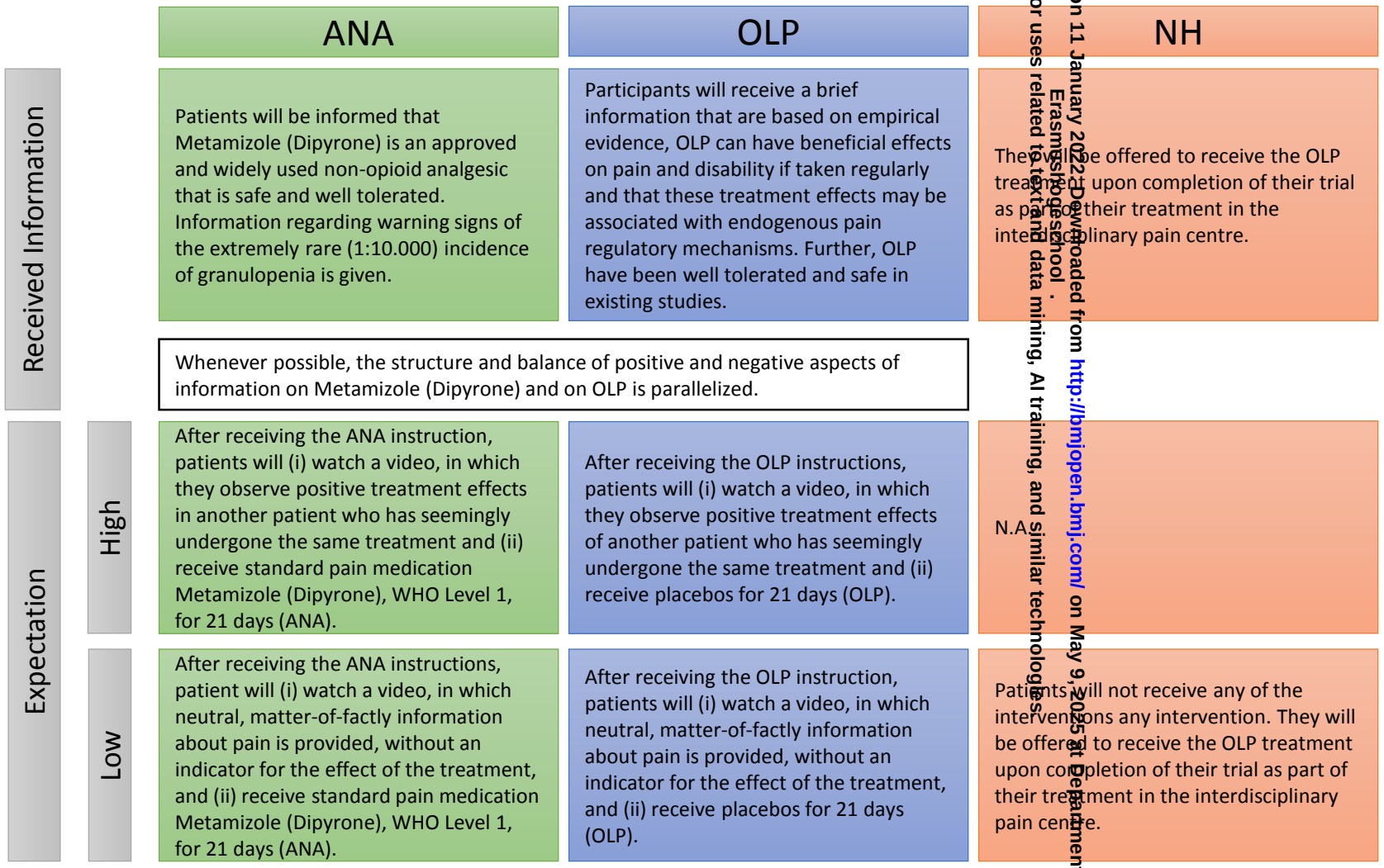
Figure and table legend

Figure 1. Study design

Figure 2. Treatment information

Table 1. Outcome measures





Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	11

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	12
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	5

		be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7

Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.	9

		Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events	n/a

		and other unintended effects of trial interventions or trial conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the	6

		public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a