Hypnosis for the management of COPD-related anxiety and dyspnoea in pulmonary rehabilitation: rationale and design for a cluster-randomised, active-control trial (HYPNOBPCO_2)

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Abstract

Complementary psychological care is recommended for COPD, as it significantly reduces anxiety and boosts the pulmonary rehabilitation efficacy. In a precedent trial (HYPNOBPCO_1, ISRCTN10029862), administering a single hypnosis session was linked to reduced anxiety and improved breathing mechanics in intermediate and advanced COPD patients. However, whether hypnosis could improve self-management of anxiety and dyspnoea in COPD during pulmonary rehabilitation is yet to be investigated.

This is the protocol for HYPNOBPCO_2, a 2-arm, cluster-randomised, statistician-blinded superiority monocentre trial (NCT04868357). Its aim is to assess the efficacy of hypnosis as a tool to manage anxiety and dyspnoea during a pulmonary rehabilitation programme (PRP). Clusters of COPD patients eligible for the conventional hospital-based PRP at the Centre Hospitalier de Bligny (CHB) will be randomised and evenly allocated into two parallel arms: "Hypnosis" (treatment) and "Relaxation" (active control). "Hypnosis" will consist of the CHB's conventional 4-week group PRP, supplemented by two educational sessions for teaching self-hypnosis. "Relaxation" will be identical, except standard relaxation exercises will be taught instead. Primary end-point will consist of assessing weekly changes in anxiety throughout the PRP, additional to total anxiety change after treatment completion. Anxiety will be determined by the six-item version of the State-Trait Anxiety Inventory (STAI-6). Secondary outcomes will include change in the 6-min walk test and the COPD assessment test (CAT). Further follow-up outcomes will include CAT and STAI-6 retests, re-hospitalisation rate, action plan use and persistence in self-hypnosis use, throughout the 12 weeks ensuing PRP completion.

Introduction

Patients suffering from COPD often find themselves trapped in a vicious cycle of comorbidity. While dyspnoea, chest tightness and increased respiratory rate are known inducers of anxiety [1–3], emotional exertion and anxiety are known as common culprits for the acute worsening of chronic dyspnoea and other COPD symptoms [4]. Treatments addressing COPD together with its psychological comorbidities have been found generally to improve COPD prognosis in pulmonary rehabilitation programmes (PRPs) [5–8].

The 2021 edition of the Global Initiative for Obstructive Lung Disease (GOLD) report observes that antidepressant efficacy in the treatment of dyspnoea-related anxiety remains inconclusive [6] and suggests

the implementation of PRPs to address the condition. Multidisciplinary PRPs promote behavioural change and tackle physical and psychological symptoms associated with COPD in tandem [5, 8]. In particular, the complementary use of cognitive behavioural therapy and proprioceptive interventions, such as mindfulness-based therapy, have been found to reliably reduce anxiety and depression in COPD [5–8]. Interestingly, mind–body interventions have also been found to improve physical outcomes of the disease, such as lung function, exercise capacity and fatigue [6, 8].

As one such intervention, hypnosis is dotted with unique characteristics that can be of great service for COPD patients encumbered by anxiety and breathlessness. The key difference between hypnosis and meditation (or other attention exercises) is that patients experience suggestions capable of strategically altering the perception of their bodily sensations (*i.e.* proprioception) to achieve a therapeutic outcome [9]. During HYPNOBPCO_1 [10], the investigators hypothesised that these perceptual modulations could be used to regulate breath and reduce anxiety [11], by suggesting a feeling of "air effortlessly entering the lungs". The investigators found that a 15-min scripted hypnotic intervention positively impacted respiratory rate, arterial oxygen saturation, Borg scores (numeric scale) and anxiety (as assessed by State-Trait Anxiety Inventory – 6 items [12, 13]). In particular, anxiety decreased a mean 23.8% after hypnosis, *versus* only 3% after sham.

While these transient effects of a single hypnosis intervention hold promise, whether repeated hypnosis use would reliably produce these same benefits has not yet been investigated. Besides, whether the incorporation of hypnosis into a PRP would have a positive effect on patient anxiety beyond the baseline impact of the physical and educational components of standard rehabilitation remains unknown. Finally, hypnotic interventions can be adapted to a "self-hypnosis" format with relative ease. This begs the question of whether hypnosis could be used iteratively for the self-management of anxiety and dyspnoea throughout (and after) pulmonary rehabilitation.

Here, the investigators present the protocol and rationale for HYPNOBPCO_2. This long-duration protocol will focus on the complementary use of hypnosis as a self-management strategy for chronic anxiety in COPD. The investigators will evaluate whether the positive effects of hypnosis improve anxiety, withstand repeated use and persist in cases where hypnosis is self-administered. Additionally, the general impact of hypnosis on the psychological and physical symptoms of COPD will be estimated. Self-hypnosis is considered a risk-free process with virtually no contraindications [14]. Further, it is fast, generally low-cost [15] and requires little physical effort on behalf of the patient [16].

Material and methods

Study guidelines

This protocol follows the Template for Interventions Description and Replication (TIDieR) checklist when describing interventions [17]. Completed trial reports will follow the non-pharmacological subsection of the Consolidated Standards of Reporting Trials statement (CONSORT) [18] (see figure 1).

Study design

The HYPNOBPCO_2 trial is a two-arm, cluster-randomised, statistician-blinded monocentre superiority trial (NCT04868357; 29/04/2021), taking place at the Centre Hospitalier de Bligny (CHB) in Briis-sous-Forges, France. Patients suffering from COPD, eligible for the conventional hospital-based PRP of the CHB, will be signed into a PRP group by order of admittance to the hospital (group capacity 4–7 patients per group). Each PRP group will then be treated as a cluster, and randomly allocated, with a 1:1 ratio, to one of two parallel arms: "Hypnosis" (treatment) and "Relaxation" (active control). "Hypnosis" will consist of the CHB's conventional 4-week group PRP, supplemented by two educational group sessions for teaching self-hypnosis. "Relaxation" will be identical, except standard relaxation exercises will be taught during the educational group sessions instead. Interventions will be delivered in both cases by A.D., C.M. and I.S., three experienced hypnosis practitioners specialised in complementary care during pulmonary rehabilitation. Primary end-point will consist of assessing weekly changes in anxiety throughout the PRP treatment, additional to total anxiety change after treatment completion. Anxiety will be assessed by the six-item version of the State-Trait Anxiety Inventory (STAI-6), which will be taken at baseline (*i.e.* Week 1), then once a week every week throughout the entire duration of the PRP (4th week measurement considered here as final outcome). To ensure reliability, and maximise inclusion in future meta-analyses, STAI-6 values will be confirmed by two additional inventories: the Hospital Anxiety and Depression Scale, and the Multidimensional Dyspnoea Profile, to be taken at baseline and after PRP completion. Secondary outcomes will include assessing change in 6-min walk test (baseline *versus* PRP completion) and COPD assessment test (baseline *versus* PRP completion, then once every 4 weeks for 3 months after discharge). Further exploratory follow-up outcomes will include re-hospitalisation rate, action plan use and
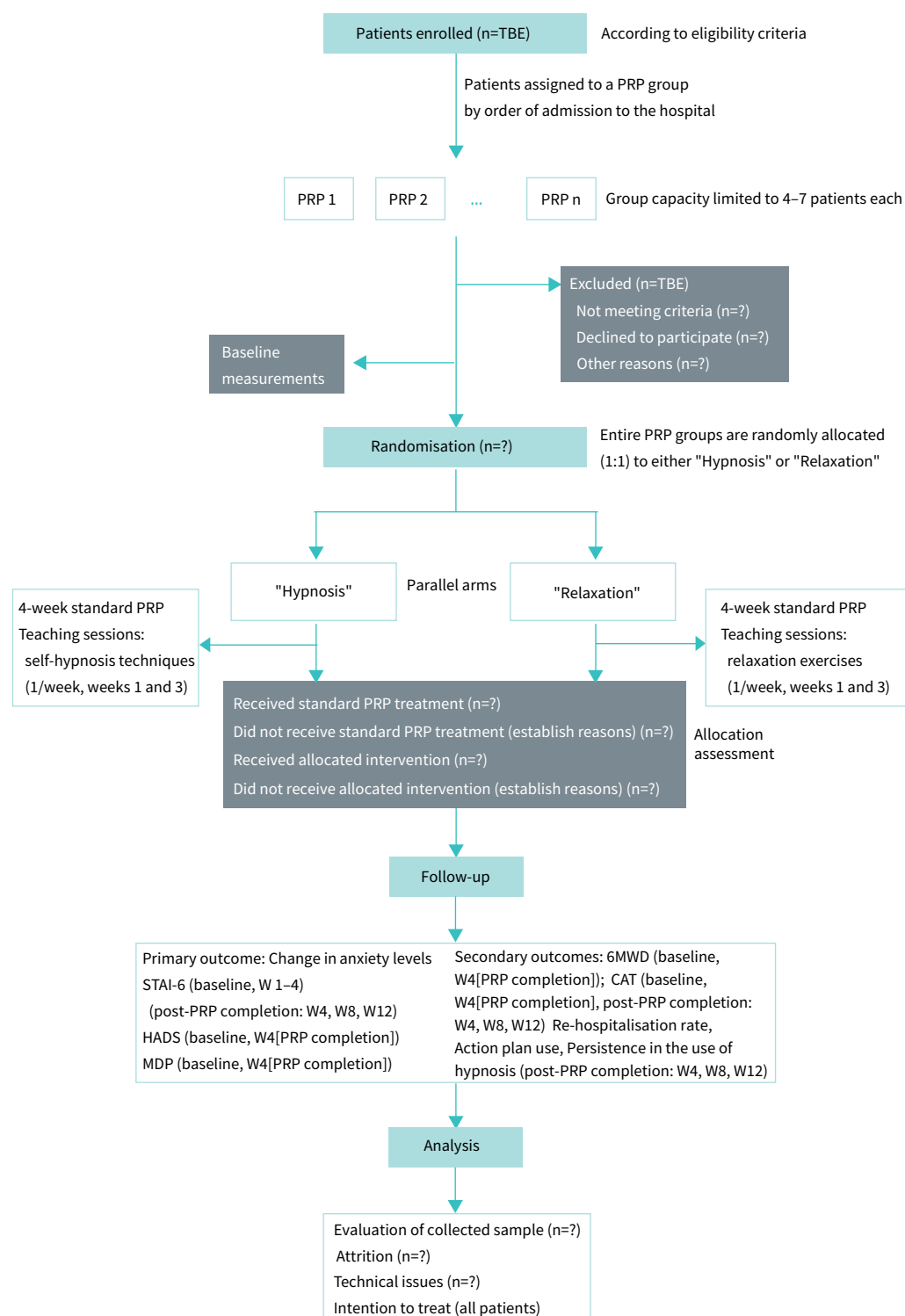
FIGURE 1 CONSORT flowchart for HYPNOBPCO_2. TBE: to be determined; PRP: pulmonary rehabilitation programme; PRP n: pulmonary rehabilitation programme group no. n; STAI-6: state-trait anxiety inventory, 6-items; HADS: Hospital Anxiety and Depression Scale; MDP: Multidimensional Dyspnoea Profile; 6MWD: 6-min walk distance; CAT: COPD assessment test.

persistence in the use of self-hypnosis/relaxation (at PRP completion, then 4, 8 and 12 weeks after discharge). All results will be reported in the same final publication (see table 1 for a full summary of collected measures).

TABLE 1 Study measures and outcomes to be collected							
Variable	Baseline (W1)	W2	W3	W4	1-M (W8)	2-M (W12)	3-M (W16)
Primary							
Anxiety (STAI-6 questionnaire)	x	x	x	x	x	x	x
Anxiety (HADS questionnaire)	x			x			
Anxiety (MDP questionnaire)	x			x			
Secondary							
6-min walking test	x			x			
COPD assessment test	x			x	x	x	x
Descriptive							
Charlson comorbidity index	x			x			
FEV_1	x			x			
FVC	x			x			
FEV_1/FVC	x			x			
BODE	x			x			
mMRC	x			x			
P_{aO_2}	x			x			
P_{aCO_2}	x			x			
GOLD (1–4/A–D)	x			x			
Oxygenotherapy (LTO *versus* ambulatory)	x			x			
Anxiety-related psychoactive drug intake (dosage/frequency) (*exploratory*)	x			x	x	x	x
Morphine (dosage/frequency)	x			x			
Anthropometric							
Age	x						
Weight	x						
Height	x						
Sex	x						
Body mass index	x						
Self-reported							
Smoking status (*exploratory*)	x			x	x	x	x
Use of self-hypnosis/relaxation (how many times)		x	x	x	x	x	x
Re-hospitalisations (how many times)					x	x	x
Action plan use (how many times)					x	x	x

Exploratory variables are signalled with the note "*(exploratory)*" next to their name. Dotted line represents beginning of post-PRP follow-up. W1,… W4: week 1, … week 4; 1-M(W8): 1 month after PRP completion (Week 8 since PRP onset, Week 4 since PRP completion); 2-M(W12): 2 months after PRP completion (Week 12 since PRP onset, Week 8 since PRP completion); 3-M(W16): 3 months after PRP completion (Week 16 since PRP onset, Week 12 since PRP completion). STAI-6 score: state-trait anxiety inventory – six-item version; HADS: Hospital Anxiety and Depression Scale score; MDP: Multidimensional Dyspnoea Profile; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; FEV_1/FVC: Tiffeneau score; BODE: grading system based on a composite score from body mass index, airway obstruction, dyspnoea and exercise capacity; mMRC: Modified Research Council Questionnaire score; P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension; GOLD: Global Initiative for Obstructive Lung Disease criteria (1–4/A–D); age: in years; sex: male/female; Oxygenotherapy: Long term (LTO) or ambulatory.

Study hypotheses

The primary hypothesis of HYPNOBPCO_2 is that the addition of self-hypnosis to pulmonary rehabilitation will provide patients with an easy-to-use, powerful anxiety management tool. This will cause post-PRP anxiety levels to decrease significantly more than when PRP is complemented by simple relaxation (a 10% to 20% difference, given the precedent set by HYPNOBPCO_1). Additionally, HYPNOBPCO_2 entertains a secondary hypothesis. Namely, based on the proprioceptive nature of self-hypnosis and its similarity to other mind–body approaches [9], its repeated use will also contribute to the improvement of the physical COPD outcomes targeted by pulmonary rehabilitation.

Study setting and recruitment procedures

Enrollment will be limited to patients undergoing a PRP at the CHB, starting September 2021 until September 2024. All procedures have been authorised by the French National Ethics board of Hôtel Dieu in Paris, France (Approval Number: 2019-A02016-51). Care providers at the CHB will approach PRP patients and advertise the trial. Patients interested in the trial will be provided with a detailed leaflet explaining the trial's layout and goal (partially masking hypothesis to prevent motivation biases). Patients who decide to participate will be screened for inclusion criteria. Those who fall into the scope of the inclusion criteria will be asked to sign an informed consent form. They will be informed that they will be

included in either the Hypnosis Arm or the Relaxation Arm. A unique random 3-digit numerical ID will be assigned to each patient to ensure participant anonymity throughout the trial.

Critically, the CHB can only conduct one PRP at a time. Patients participating in the same PRP group are typically in contact with each other during group activities, weekends and down time. Hence, it was deemed impractical to conduct both arms of the study simultaneously within the same PRP group. Main concerns included patients sharing self-hypnosis and relaxation techniques across arms, the generation of motivation biases or increased attrition out of wanting to switch groups. For these reasons, it was decided that randomisation would be conducted at the cluster level, with each PRP group constituting a cluster (see Randomisation for details).

Inclusion criteria
1. Aged >30
2. Affiliated to a social security scheme or beneficiary of such a scheme
3. Absence of cognitive disease questioning the validity of patient-reported outcomes
4. Ability to give free, informed consent
5. Adult patients with severe COPD, dyspnoea; with distension
6. Hospitalised at the CHB
7. Predicted forced expiratory volume in 1s (FEV_1) and FEV_1/forced vital capacity (FVC) percentages consistent with moderate and severe COPD according to GOLD standards (from 70%)
8. Modified Research Council Questionnaire ⩾2
9. Exposure to tobacco ⩾10 pack-years

Exclusion criteria
1. Pregnancy
2. Known severe cardiac insufficiency
3. Known severe pulmonary arterial hypertension
4. Evolutive-cancer diagnosis
5. Significant cognitive impairment (*i.e.* inability to follow intervention instructions or understand the investigator), hypercapnic encephalopathy or confusional syndrome
6. Deafness
7. Anaemia ⩽8 g·dL^{-1}
8. Psychotic pathology

Randomisation
Randomly numbered sealed envelopes equal to the total number of clusters (24) were prepared before the beginning of the trial. Half of the envelopes assign patients to the "Active Control: Relaxation" arm, and half to the "Treatment: Hypnosis" arm. These envelopes were separated into 12 Control–Treatment pairs. Before the beginning of each PRP, one pair of envelopes is drawn at random by a hospital representative independent of the study. One envelope from the pair is then randomly selected. This envelope determines whether the educational sessions for that PRP will be about dynamic relaxation (Control) or self-hypnosis (Treatment). The other envelope is put aside and reserved for the subsequent PRP, to ensure a 1:1 allocation ratio. Allocation is conducted in this fashion to ensure that, in case of having to stop the trial early, the sample will remain balanced. Neither caregivers, investigators or patients will have any influence on which envelope is drawn, nor will they have the possibility to refuse the drawing outcome.

Blinding
It is not possible to blind patients, caregivers or the investigators responsible for delivering interventions, considering the evident differences between hypnosis and standard dynamic relaxation techniques. However, assessors in charge of data collection, digitalisation and analysis, as well as all other medical agents involved in regular participant care during the PRP, will be blinded to arm identity. This will be ensured by reporting envelope identity to data collectors and biostatisticians instead of arm identity (*e.g.* "PRP group 1, envelope N° 30″ instead of "PRP group 1, Hypnosis arm"). Unblinding will take place after results are analysed and presented to all authors.

Sample size
Power estimations
Prior power and sample-size calculations were simulation-based [19]. Simulation-based power estimations are an optimal technique to use alongside mixed models, due to their flexibility concerning statistical

assumptions (see Statistical analyses). The simulation's primary end-point consisted of change in anxiety symptoms, as measured by the STAI-6. Alpha was set to 5%. Previous literature [5, 20] and the investigators' precedent trial [10] were used to estimate the size of the effect. It was determined that the PRP+Hypnosis intervention would yield an additional 10% decrease in anxiety scores when compared to controls. Simulations showed that a sample of n=100 (*i.e.* 10 clusters per arm, five participants per cluster) had a power of 83% (95% CI 80–86) to detect this effect. In anticipation of a 20% attrition level, the target sample was set at n=120 (*i.e.* 12 clusters per arm). For further details on how the simulation was computed, see supplementary Methods – Power analyses.

Study groups

Base pulmonary rehabilitation programme (hypnosis and relaxation groups)

The standard multidisciplinary PRP conducted at the CHB has been subjected to previous scrutiny, and its efficacy has been documented [21]. All patients undergo a tailored in-person, 4-week comprehensive programme, in groups of four to seven people. Patients participate 5 days a week, for an average of 30 h per week. The PRP includes four main dimensions, outlined in table 2.

Hypnosis group (treatment) - PRP complemented with hypnosis

Delivered twice during the 4-week PRP programme (weeks 1, 3), it will consist of in-person 45-min sessions of group hypnosis. These will include a general explanation on how hypnosis and self-hypnosis works, one hypnotic induction, multiple suggestions of relaxation and feelings of air entering the lungs, and a closing exercise. The intervention includes a prescription to use these exercises freely throughout the PRP as a tool for self-managing discomfort and inducing calmness. This arm is structured following the classic format of didactic hypnosis interventions, where patients discover the exercise by doing it, and learn behavioural routines allowing them to recreate the hypnotic state on their own. The first session is introductory. The second session addresses concerns that patients may have identified after using self-hypnosis. Both sessions include group hypnosis exercises. Both sessions are to be administered in an identical manner and require the same motor and communication responses from the patient (*i.e.* concentrate on the practitioner's voice, eye closure, relaxation, nodding). Patients are asked to concentrate on nature-themed metaphors, memories of movement and hypnotic suggestions of pure air entering their lungs. Both sessions end with a round of questions, instructions and motivation to use self-hypnosis throughout the duration of the PRP and beyond.

Relaxation group (active control) – PRP complemented with relaxation

Delivered twice during the 4-week PRP programme (weeks 1, 3), it will consist of in-person 45-min sessions of group dynamic relaxation. It includes six exercises to increase proprioception, calmness and regulate breath. Both sessions include group relaxation exercises. Both sessions are to be administered in an identical manner and require the same motor and communication responses from the patient (*i.e.* concentrate on the practitioner's voice, stretching, breathing exercises, nodding). Both sessions end with a round of questions, instructions and motivation to use relaxation throughout the duration of the PRP and beyond. The intervention includes a prescription to use these exercises freely throughout the PRP, as a tool for self-managing discomfort and inducing calmness. It is important to underscore that a "usual care"

TABLE 2 Structure of base pulmonary rehabilitation at Centre Hospitalier de Bligny
Exercise
• Physical activity to determine cycle exercise endurance at a constant work rate beginning at ∼75% of the peak work rate (WR peak) obtained during incremental tests performed at initiation of the pulmonary rehabilitation programme
• Strength training, including progressive resistance exercises with free weights, resistance bands and weight machines
Education
• Instruction and participation in pedagogical lessons on the topics of pulmonary disease
• Lessons on the therapeutic, nutritional and physical issues of COPD
• Self-management strategies against COPD exacerbations (**treatment and active-control sessions for the HYPNOBPCO_2 trial will be part of this item**)
Workshops
• Workshops dedicated to helping patients desensitise to dyspnoea
• A wide range of organised group sessions including speech therapy and singing therapy
Psychological care
• Interventions on an individual basis (counselling with a psychologist and/or social worker; smoking cessation management when needed)

control would have added important reference values for comparing against treatment. However, standard care at CHB has always included complementary relaxation routines and mind–body exercises, with positive results [19]. Thus, the investigators decided against making changes that could affect the quality of standard care and opted for an active control instead. Nonetheless, the use of an active control has several advantages:

1. Providing additional care that motivates the patients to participate in the control group, reducing attrition.
2. Controlling for the number of additional interventions across arms.
3. Controlling for motivation and attention.
4. Allowing the disentanglement of hypnosis and relaxation effects. This is crucial, as hypnosis too includes physical relaxation and breathing exercises, but these are not the main active principles of the intervention (*i.e.* induction and suggestions).

Patient and self-intervention logs

Each patient has a patient log and a self-hypnosis log. The patient log contains all of the medical and behavioural information to be collected during the trial. It is completed by the investigator during weekly in-person patient interviews (except for self-assessment questionnaires, which will be completed by the patient during the interview). This log also contains the questionnaires to be filled during the telephone interviews in the months ensuing PRP completion. The first part of the self-intervention log is to be filled by patients throughout PRP. Here they will report the number of times a week self-hypnosis/relaxation was utilised to manage anxiety and dyspnoea, and whether self-intervention effects were satisfactory. The second part of this log consists of the same questions but will be filled by the investigator during the telephone interviews.

Outcomes

Primary and secondary outcome measures are outlined in detail in table 3.

Statistical analyses

Analyses will be performed using R. Primary outcomes will consist of changes in anxiety symptoms, as measured mainly by the STAI-6. Score changes will be observed weekly throughout the duration of the PRP (*i.e.* timepoints: Week 1, Week 2, Week 3, Week 4). Changes in anxiety as tracked by the Hospital Anxiety and Depression Scale (HADS) and Multidimensional Dyspnoea Profile (MDP), on the other hand, will be assessed between treatment onset and completion only (*i.e.* timepoints: Week 1, Week 4).

Analyses will be conducted using mixed-effect modelling: outcomes will be regressed against Intervention type (2-level factor: relaxation/hypnosis) and instance of measurement (with levels equivalent to data collection timepoints). Nested random intercepts per participant, and per participant/cluster, will be added to account for cluster effects [26, 27]. Secondary outcomes will be modelled in the same fashion, except for the instance of measurement factor, which will be adapted to reflect the timepoints of data collection for each outcome (see time frame in table 3).

Significance tests will be computed by means of likelihood ratio tests that compare our models to simpler models, in which the relevant predictor will be removed [28, 29]. ANOVA tables will be computed through analysis of deviance (Type II Wald χ^2 test), and *post hoc* pairwise comparisons through Tukey contrasts of least-squares means, setting a 95% confidence interval. Findings will be considered statistically significant when $p < 0.05$.

To prove lack of effect the investigators will calculate an approximation of the Bayes factor (BF) from the Bayesian information criterion (BIC), for the saturated and null models implicated in the contrast (BIC approximation to BF, so that BF=exp ((BICnull−BICfull)/2)) [30]. The BF will account for the strength of evidence in favour of the full model, meaning BF <1 equals virtual lack of effect, and BF >2 equals a strong, noteworthy effect [31].

Compliance

Both interventions will be presented as equally relevant to the patients, so as to prevent prior differences in compliance or motivation. For the same reason, no statements regarding possible differential therapeutic effects between interventions will be made. Data will be analysed following the intention-to-treat principle, as recommended for superiority trials [32].

TABLE 3 Primary and secondary outcomes for the trial		
Outcome	Description	Time frame
Primary		
Change in anxiety scores (STAI-6) [12, 13]	Anxiety, as determined by the State-Trait Anxiety Inventory (six-item version, STAI-6). Takes around 30 s to complete. It rates anxiety with a score between 20 and 80 points. The cut-off score for a clinical anxiety diagnosis is 39 points. Lower scores mean lower anxiety levels. To be obtained during an interview with an assessor	• Baseline • W2 • W3 • W4 • M1 • M2 • M3
Change in anxiety and depression scores (HADS) [22]	Anxiety, as determined by the Hospital Anxiety and Depression inventory (HADS). Takes around 4 min to complete. It rates anxiety and depression tendencies with a score between 0 and 21. The cut-off score for a clinical mild anxiety diagnosis is 8–10 points. Lower scores mean lower anxiety and depression levels. To be obtained during an interview with an assessor	• Baseline • W4
Change in anxiety and quality of life scores (MDP) [23]	Anxiety and quality of life as measured by the Multidimensional Dyspnoea Profile (MDP). Takes about 6 min to complete. The MDP consists of 11 items divided into three domains (discomfort breathing by intensity, discomfort breathing by description, anxiety and distress coming from breathing difficulties). In all domains, intensity is rated from 0 (negligible) to 10 (worst possible condition). In the second domain in particular, the respondent selects from between five descriptors the one that better represents their breathing discomfort, and then rates its intensity. Lower levels mean less discomfort and better quality of life. To be obtained during an interview with an assessor	• Baseline • W4
Secondary		
6-min walk test [24]	This exercise test measures the distance the patient can walk quickly on a flat, hard surface in 6 min. It reflects the patient's ability to perform daily physical activities. Measured as part of patient care	• Baseline • W4
COPD assessment test (CAT) [25]	Short eight-item patient-completed questionnaire, particularly responsive to change in treatment. To be obtained during an interview with an assessor	• Baseline • W4 • M1 • M2 • M3
Re-hospitalisation rate	Enquiring whether the patient has been hospitalised again after the PRP, in connection to dyspnoea, exacerbation or anxiety. To be obtained through monthly telephonic interviews with an assessor	• M1 • M2 • M3
Use of self-hypnosis (treatment)/ relaxation (control)	A questionnaire developed at the Hospitalier de Bligny asking simply whether patients used hypnosis to manage their anxiety and breathlessness, how many times a week, and whether they felt satisfied with hypnosis effects	• Baseline • W2 • W3 • W4 • M1 • M2 • M3
Action plan	Occurrences of use of an action plan including corticosteroids and/or antibiotics after PRP. Delivered at discharge, detailed explanations on the use of this plan having been done during dedicated workshops, as part of the PRP	• M1 • M2 • M3

Baseline: week 1 of the PRP. W2 to W4: weeks 2 to 4 of the PRP, measures will be taken once a week during the week; M1–3: months 1 to 3 after PRP completion, measures will be taken once a month, towards the end of the month. PRP: pulmonary rehabilitation programme.

Data management

Data will be recorded first in the patient and self-treatment logs (on paper), during weekly in-person interviews, to be conducted by trained assessors. Interviews will take place every 5 working days. Telephone follow-up interviews will be conducted monthly (towards the end of the month) during the 3 months ensuing completion, in order to obtain information on the remaining variables. All paper records will be digitalised by the assessors using secure data-entry tools available at the CHB, and subsequently stored for a 10-year period. All stored data will be kept anonymous.

The investigators will conduct statistical analyses using linear mixed-effect models. Mixed models are better than classic inferential approaches, as they are tolerant to missing datapoints and out-of-range results. In particular, they allow for the control of random effects that stem from individual patient differences, as well as the trials' cluster structure.

Changes to initial plan

Continuation of the trial and modifications to the original protocol will be subject to deliberation between the sponsor and the investigators. Reasons to stop the trial either temporarily or permanently include (but are not limited to) a resurgence in the coronavirus disease 2019 (COVID-19) sanitary crisis, massive participant desertion, large-scale technical failure or material inability to recruit the desired sample.

Adverse event reporting

Special adverse effect forms have been made available to care providers. A pipeline with the sponsor has been established. This pipeline will be used to report adverse events, enact the unblinding of the trial and conduct a potential emergency stop. The protocol distinguishes between adverse events directly attributable to the study interventions and the live monitoring of independent adverse events. The medical team involved in patient care will be immediately notified. The principal investigator, as well as the sponsor's in-house ethics committee, quality control department and medical director, will be notified within 24 h. However, it should be noted that due to the nature of the interventions included in the trial, the probability of associated adverse events are negligible [14, 15].

Dissemination

The results of this trial will be presented to the international clinical audience through conferences and peer-reviewed publications. The general public will also be made aware of the trial's findings through a press release.

Discussion

Clinical hypnosis interventions have several proven therapeutic benefits that adequately fit the specific needs of COPD patients [10]. To our knowledge, HYPNOBPCO_2 is the first randomised controlled trial study aimed at assessing whether hypnosis would be beneficial for managing anxiety and dyspnoea during pulmonary rehabilitation in COPD. HYPNOBPCO_2 incorporates hypnosis into a rehabilitation programme of proven efficacy [21], while controlling for contextual effects and the general benefits of relaxation. It also explores whether hypnosis' projected benefits will wane with repeated use. The primary end-point is tracked through three popular indexes for quantifying anxiety and depression symptoms (the STAI-6 as main index, and the HADS and the MDP as supporting indexes). Observing changes in anxiety symptoms through all three measurements will allow investigators to assess consistency. It will also render the trial compatible with a broader range of meta-analyses. Finally, HYPNOBPCO_2 includes the assessment of intervention effects outside of the hospital (*i.e.* after PRP completion), which will allow for the consideration of hypnosis' potential as a self-management tool.

Currently, PRPs suffer from logistical and methodological limitations, including elevated financial cost, lengthy duration, lack of sufficient personalisation and even geographical inaccessibility. If deemed effective, hypnosis could significantly contribute to solving these issues. First, because its costs are low: it requires no material investment other than trained caregivers applying the technique (often one or two sessions suffice [15, 16]). Second, because its implementation is fast, and its effects are both immediate and long-lasting: patients can be inconvenienced for as little as 15 min [10], either in person or online [33], and obtain a clinically significant relief that can be revisited through self-hypnosis at later times. This could significantly contribute to delocalising PRPs, conducting online PRPs [34] and reducing general rehabilitation duration without compromising output quality [35]. Finally, owing to the nature of its therapeutic mechanisms, hypnosis is always highly personalised, as it is based on a patients' own memories, behaviours and proprioception [36].

Given this array of advantages, the investigators propose that understanding how the effects of hypnosis and self-hypnosis interact with those of a standard PRP could grant the medical community an opportunity to use this technique for the complementary management of COPD's physical and psychological symptoms, to both patient and caregiver benefit.

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