BMJ Open

Protocol of HOTFy: randomised clinical trial to hyperbaric oxygen therapy in fibromyalgia

José Mota Neto ,[1,2] Adriano Fernando Mendes Jr. ,[2,3] Anita Fernanda Magalhães Martins,[4] Aline Teixeira de Landa,[5] Rafael de Oliveira Fraga,[5] Viviane Angelina de Souza,[4,5] Nádia Rezende Barbosa Raposo[1,4]

To cite: Mota Neto J, Mendes Jr. AF, Martins AFM, *et al*. Protocol of HOTFy: randomised clinical trial to hyperbaric oxygen therapy in fibromyalgia. *BMJ Open* 2023;**13**:e069153. doi:10.1136/bmjopen-2022-069153

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-069153).

Received 14 October 2022
Accepted 19 December 2022

For numbered affiliations see end of article.

Correspondence to
Dr. José Mota Neto;
jose.jmota@ebserh.gov.br

ABSTRACT

Introduction Fibromyalgia is a polysymptomatic syndrome with a prevalence between 0.2% and 13% of the population and causes work disabilities in approximately half of affected patients. Several treatments to fibromyalgia have been proposed with partial improvement. This study aims to evaluate the efficacy of hyperbaric oxygen therapy and when it should be introduced to fibromyalgia.

Methods and analysis This is a protocol for an open-label, crossover, randomised clinical trial comparing treatment with hyperbaric oxygen therapy and standardised treatment to fibromyalgia. In the proposed study, 56 individuals with fibromyalgia will be randomised in a 1:1 ratio into a single, fixed, random block, in which one group will receive hyperbaric oxygen therapy and another will receive standard treatment. Subsequently, the groups will be crossed. Participants will be evaluated at baseline, eight and 16 weeks based on functional impairment assessed with the Fibromyalgia Impact Questionnaire—Brazilian Portuguese version, psychopathological symptoms questionnaire and short-form quality of life questionnaire. The improvement of symptoms concerning the moment of therapy used will be compared between groups. For sample size calculation, a moderate effect size, 80% power and 95% CI will be estimated, in a total of 46 patients. Considering a dropout of 20%, 56 patients should be recruited.

Ethics and dissemination The study was approved by the Universidade Federal de Juiz de Fora Teaching Hospital ethics committee and assigned the number 53058421.9.0000.5133 (version 3). The results will be disseminated via publications in peer-reviewed journals and presentations in medical meetings.

Trial registration number RBR-6prps8g)/UTN U1111-1278-3224.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Analysis of treatment in the same group and between treatment and no treatment in different groups.
⇒ Assess the impact of hyperbaric oxygen therapy on the quality of life of fibromyalgia patients.
⇒ Sample size was previously statistically calculated.
⇒ The protocol was previously published, minimising publication bias.
⇒ Due to the long-term nature of the treatment (40 sessions), participants may be lost to follow-up.

INTRODUCTION

Fibromyalgia (FM) is a polysymptomatic syndrome that consists of diffuse chronic pain, fatigue, sleep disturbances and autonomic disturbances, cognitive dysfunction, hypersensitivity to stimuli, somatic symptoms and psychiatric disorders.[1] The prevalence of FM in the general population is distinct in each country[2] and affects between 0.2% and 13% of the population and causes work disability in approximately half of affected patients.[3 4]

Due to the absence of accurate diagnostic tools and adequate biomarkers, a diagnosis based on constantly evolving clinical criteria remains the best option.[1] Treatment and prevention constitute knowledge gaps and move towards multimodal therapies.[5–12] According to the American College of Rheumatology, generalised bilateral pain above and below the waist for at least 3 months or 11 tender points are diagnostic criteria for FM.[13–15]

Several factors are related to the results of the treatment of FM, such as genetic predisposition, personal experiences of pain, emotional-cognitive factors, mind–body relationships and psychological capacity to deal with stress. According to the European Alliance of Rheumatology Associations, the ideal treatment of FM must contain at least four pillars and may also use new adjuvant modalities.[1] It should begin with a pharmacotherapeutic modality with antidepressants, anticonvulsants, analgesics and adjuvant non-pharmacological measures, such as patient education about the disease, regular physical activity at least three times per week,

psychotherapy modalities, such as relaxation techniques, hypnosis and cognitive–behavioural therapy. With respect to adjuvant treatment modalities, positive results have been observed with the use of medical cannabis, low laser therapy, nature activity therapies, transcutaneous electrical nerve stimulation, acupuncture and hyperbaric oxygen therapy (HOT).[6 8 9 16]

The HOT treatment modality involves patients breathing nearly 100% oxygen while inside a closed chamber in which the pressure is two to three times higher than the atmospheric pressure at sea level.[12 17 18] HOT has led to promising results in preclinical models of nociceptive, inflammatory, and neuropathic pain and clinical benefits in the treatment of chronic pain, stroke sequelae, traumatic brain injury, spinal cord trauma and autism.[16 17 19] HOT may play a role in modulating the inflammatory response after tissue injury, resulting in a decrease in the nociceptive response by 80%–95% for up to 90 min after exposure to HOT. However, the antinociceptive effect of HOT in preclinical models appear to be unrelated to oxidative stress.[20] Randomised clinical trials on HOT for FM have shown reduction of pain, number of tender points, improvement of functional and neuropsychiatric questionnaires and quality of life.[16]

Several protocols for the treatment of FM with HOT have been applied with different pressure values, total number of sessions and time to begin the therapy.[16] Although the effectiveness of HOT has already been evaluated in other studies, doubts remain about the ideal time to introduce the technology and about the consistency of the results. This study aims to evaluate the efficacy of HOT and when it should be introduced for FM.

MATERIALS AND METHODS

Study design and settings

This protocol was written according to the Standard Protocol Items: Recommendations for Interventional Trials guidelines.[21] This work uses a randomised, crossover primary study protocol to conduct a clinical trial comparing treatment with hyperbaric oxygen and standardised treatment at a single research centre in the rheumatology department of a tertiary teaching hospital.

Recruitment

All participants will be referred from the Teaching Hospital Rheumatology outpatient clinic, after being diagnosed with FM according to the American College of Rheumatology diagnostic criteria[13–15] and enrol in the study according to the inclusion and exclusion criteria identified by a rheumatologist (figure 1). After being considered eligible as a participant, the patient will be informed verbally about the study and its objectives. Those who consent to participate will be offered the consent form (online supplemental appendix I); they will then be asked to sign the consent form, and a registration number will be incepted for the participant.

Inclusion and exclusion criteria

Patients will be included if they meet the following criteria: adults aged between ≥18 years and ≤70 years; diagnosis of FM at least 2 years before inclusion based on one of two criteria—bilateral symptoms of generalised pain occurring above and below the waist for at least 3 months without another somatic disorder that warrants the symptoms and/or the presence of at least 11 of the 18 tender points.[13–15] The exclusion criteria included the following: HOT contraindications (pregnancy, use of bleomycin, cisplatin, disulfiram and doxorubicin, middle ear surgery, untreated pneumothorax or pneumomediastinum, claustrophobia)[22]; associated autoimmune rheumatologic disease (rheumatoid arthritis, systemic lupus erythematosus, scleroderma and others) to avoid interference in the primary outcome due to the autoimune disease and inability to sign the consent form.

Withdraw from the study

The participants who wish to withdraw from the study before the completion of 32 sessions and/or interrupt the treatment for more than five consecutive sessions will

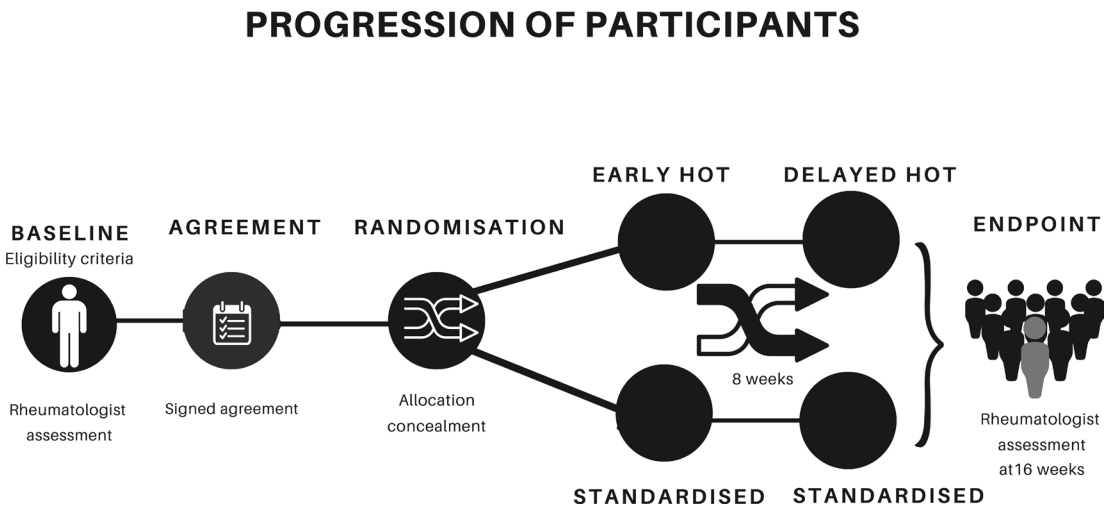

Figure 1 Participant progression flow chart. HOT, hyperbaric oxygen therapy.

be able to continue their assistance treatment without interruption at the rheumatology outpatient clinic and without prejudice to the usual recommended treatment, according to the orientation of the preparticipation recommendations.

Randomisation

All patients who give written consent to participate and meet the eligibility criteria, as assessed by a rheumatologist, will be randomised in a 1:1 ratio. Each participant will receive a number in sequential order. The randomisation sequence will be generated using computer software (randomizer.org). Participants will be allocated with equal probability to the intervention and will be randomised into a single, fixed, random block. The list will be prepared by an individual not belonging to the research group based in the musculoskeletal unit of the university hospital. This individual will prepare a sequence of opaque envelopes identified with the participant's registration number, containing only one intervention to be performed, according to the computer-generated sequence. In the participant researcher's allocation request, that independent individual will access the envelope and disclose its contents.

Blinding

Clinical findings will be assessed by a rheumatologist evaluator blinded to treatment allocation. Due to the nature of the intervention, evaluators, data collectors and care providers will be blinded.

Intervention

The participants will receive daily HOT sessions five times per week, totalling between 32 and 40 procedures at the end of the protocol. Each treatment will consist of 90 min of oxygen therapy with an inspired fraction of medicinal oxygen (purity >99%)[23] at 2.3 ATA (absolute atmospheres) of pressure in individualised hyperbaric equipment registered according to ECO BAR 800 (serial number: E4-034, manufactured in April 2015 and ECO BAR 800, serial number: E4-033, manufactured in November 2014). Each chamber will be up to date on maintenance.

The standard treatment will be offered by a rheumatologist and will consist of simultaneous patient education, physical activity and pharmacological treatment (antidepressants, anticonvulsants, analgesics and myorelaxants).[1] Both groups will complete the functional impairment questionnaire assessed with the Visual Analogue Scale (VAS),[24] Fibromyalgia Impact Questionnaire-Brazilian Portuguese version (FIQR-Br),[25] Psychopathological Symptoms Questionnaire (EAS-40)[26] and 12-Item Short-Form Quality of Life Questionnaire- (SF-12)[27] initially after randomisation. Consecutively, they will receive the same HOT protocol at different times. The early group will receive 40 sessions of HOT for 8 weeks and will be reassessed by the same rheumatologist and applied the same baseline questionnaires and will be crossed over to the standardised group, which will receive the standardised treatment alone now. The standardised group will now be crossed over to the delayed group will receive HOT for 8 weeks according to the same protocol and will be reassessed at 16 weeks by the same rheumatologist and the same baseline questionnaires will be applied (figure 2).

Follow-up

Enrolled patients will undergo assessments by a blinded rheumatologist at baseline, 8 weeks and 16 weeks (figure 2). In addition, during the baseline, 8-week and 16-week appointments, they will be subjected to additional pain assessment with the VAS,[24] functional evaluation using the FIQR-Br,[25] psychopathological evaluation using the EAS-40[26] and the SF-12 quality of life questionnaire.[27]

Risks and modifications

The risks described in the literature in decreasing order of frequency will be considered those related to the treatment with HOT: hypoglycaemia in diabetic patients, barotraumas, central nervous system intoxication by oxygen (convulsive seizures), pulmonary toxicity related to a long time of exposure to oxygen, temporary changes in eye refraction and acceleration of the lens opacification process.[28–33] Before each HOT session, medical and nursing evaluations specialised in hyperbaric medicine will be carried out as risk reduction and control measures. The patient will be asked about possible side effects and situations that could trigger them, which will be recorded in a form preestablished by qualified professionals in hyperbaric medicine who will perform the treatment.

Adherence

Daily reminders are performed by the hyperbaric medicine team for adherence purposes and with the following approach: education on the importance of following study guidelines for treatment adherence; instructions on equalisation manoeuvres and their effects; guidelines in the first session on adverse effects and how to identify them; notification of exclusion from the study if there are more than five consecutive days of absence of treatment; importance of notifying the hyperbaric medicine team quickly about possible adverse effects reported in the informed consent; instruction on the flowchart of care in case of intercurrences in the first care of the hyperbaric medicine team.

Concomitant care

The use of antibiotic, hormonal and non-hormonal anti-inflammatory drugs for less than 10 days due to adverse effects should not be considered as a covariate, as well as the use of topical drugs in the ear, for example.

Concomitant drugs or therapies that will be considered prohibited will be potent analgesic drugs that are introduced during the research without justification or prior evaluation by the rheumatology medical team or other treatment methodology that was not introduced before randomisation such as hypnotherapy.

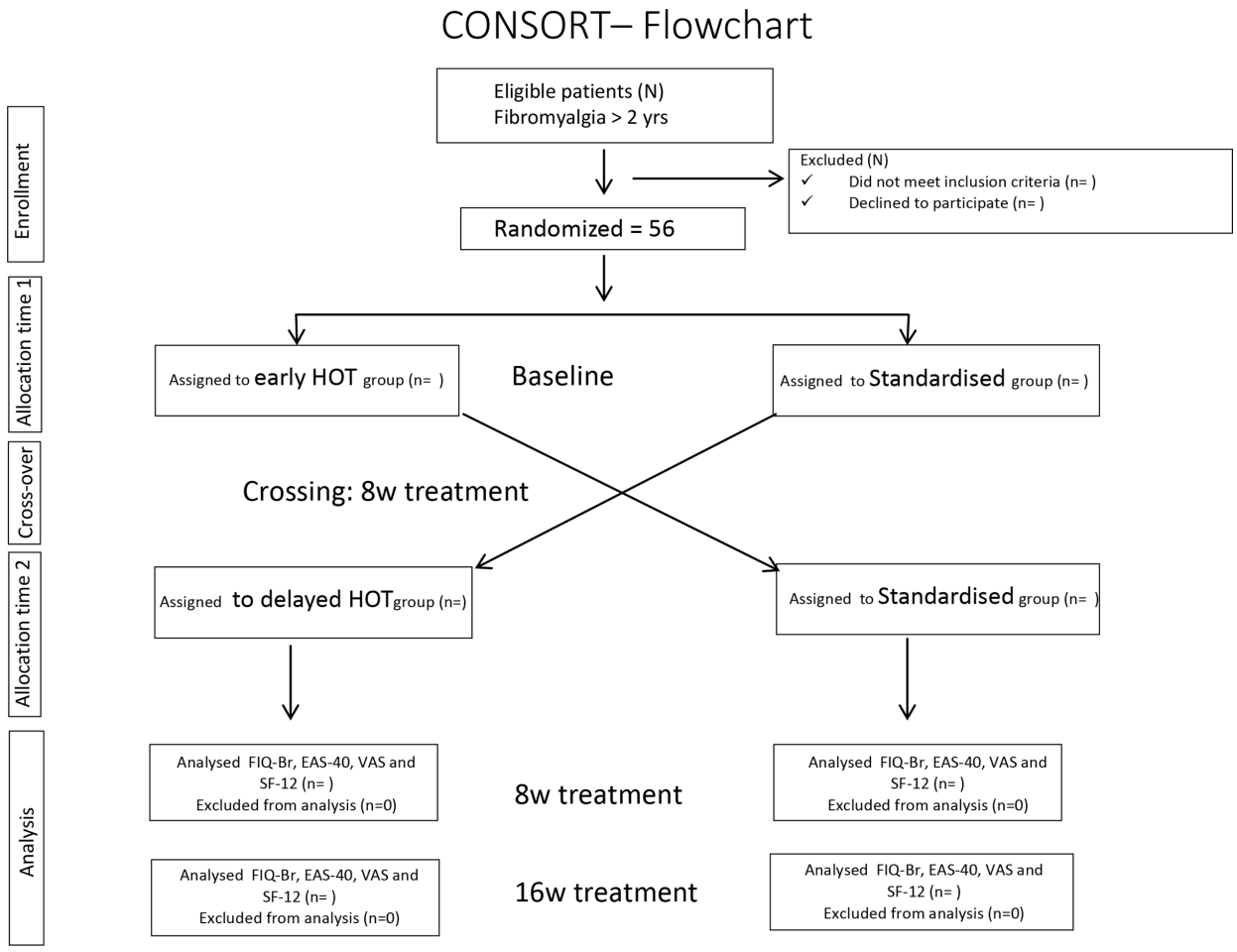

Figure 2 Enrolment flow chart. EAS-40, Psychopathological Symptoms Questionnaire; FIQ-Br, Fibromyalgia Impact Questionnaire-Brazilian Portuguese version; HOT, hyperbaric oxygen therapy; SF-12, 12-Item Short-Form; VAS, Visual Analogue Scale.

Outcomes

The primary outcome will be the improvement in the pain VAS, the functional impairment FIQR-Br and the psychopathological symptoms EAS-40 evaluations of patients with FM and to identify the best moment of application through the analysis of the results of the questionnaires applied at different times and in different groups conducted by the same rheumatologist at different times evaluation (0-8-16 weeks).

The improvement in the quality of life of the participants after the intervention will be assessed by a blinded rheumatologist through the analysis of the SF-12 score as a secondary outcome.

Data collection and management

Participant data will be collected through the study forms (online supplemental appendixs II–IV) and stored on the RedCap platform, which will be used as the study repository. The original study forms will be inserted and kept on file with the principal investigator. Participants' files must be stored in numerical order and in a safe and accessible place. Participant files will be kept in storage for a period of 5 years after the conclusion of the study. The principal investigator will supervise the completion of the electronic spreadsheet and will be responsible for its security and correct completion. Incorrect or missing data will be evaluated by the principal investigator and corrected where necessary. During the study, a committee consisting of the main researcher, a coresearcher, the cosupervisor and the main supervisor will monitor the data. The verification by one of the coresearchers of the adequate completion of the questionnaires that will be used may contribute to a strategy to avoid data loss. A loss of up to 20% of the sample was estimated, and patients considered drop-outs will be analysed in the groups in which they were initially allocated.

Confidentiality

Each participant will receive a number on inclusion in the study, which will be used for their identification in the trial. All data will be stored in the RedCap repository, and only the main researchers will have access to it. The set of data for statistical analysis will not use personalised identifications, thereby protecting the patient's individuality. All the data of the participants will be protected in the dissemination of the results, both in publication and at academic conferences. All information collected will

be used only for this research and will not be exchanged with other institutions.

Data access and dissemination

The study protocol will be available on request. Study data will be collected for academic and non-commercial use, and any participant will have access to their data per their request. The researchers involved in the study will have access to the summary data of the research at the end, and they will be able to publish the study and present it at a scientific event. To ensure confidentiality, data dispersed to project team members will be masked from any information identifying the participants. This work will be disseminated by the publication of peer-reviewed manuscripts, presentation in abstract form at national and international scientific meetings and data sharing with other investigators.

Patient and public involvement

Patients participating in the study will not be involved in the development of this protocol. The results of the study will be made available to patients on request.

Sample size

The software G*Power V.3.1[34] was used to calculate the sample size. The study by Efrati *et al*[16] guided the calculation when considering the hypothesis for a clinical improvement of the somatic and neuropsychiatric symptoms of FM, associated with a moderate effect size (f=0.25)[35]; the correlation between measurements (r=0.30), correction for non-sphericity (ε=1.0), 80% power and 95% CI were also included in the calculation. Ultimately, a total of 46 patients will be required. Considering a lost to follow-up ('drop-out') of 20%, 56 patients should be recruited, with 28 patients in each group.

Statistical analysis

Descriptive statistics will be expressed as the mean±SD (continuous data) or numbers and percentages (categorical data). Data will be analysed with the SPSS software (V.24.0, IBM). To test differences between groups (early vs delayed), a 2×3 analysis of variance of repeated measures will be performed based on a crossover design with a sequence effect. Post hoc comparisons will be performed with unpaired t tests for intergroup comparisons and paired t-tests for intragroup comparisons. The significance level adopted will be 5% ($p<0.05$).[35]

DISCUSSION

The presented protocol intends to study the adjuvant effect of HOT in patients with FM. The hypotheses about the pathogenic mechanism of FM lead to the multifactorial comprehension of the disease and still has points to clarify; but data show that genetic factors, stressful events, peripheral (inflammatory) and central (cognitive-emotional) mechanisms are associated with neuromorphological and nociplastic changes, leading to pain misperception.[1]

The multimodal treatment has been rapidly growing as the ideal option for FM.[9] In this strategy, the combination of pharmacological and non-pharmacological treatment strategies, such as education in pain neuroscience, physical activity, psychological support, physical therapy techniques and nature exposure, offers option that may improve the adherence of the treatment. In this sense, the introduction of other adjuvant therapeutic modality as oxygen therapy improves the effectiveness.

HOT consists of a treatment modality with a low risk of complications and few contraindications[28 31] that can greatly reduce the pain symptoms of FM patients, due to its immunomodulatory action on several cells of the immune system and by acting on the inflammatory pathways of different tissues. Furthermore, the role of HOT in inducing neuroplasticity in FM patients was endorsed by studies showing clinical and brain functionality improvement through single photon emission CT.[16 18 19]

The strengths of this study are the possibility of evaluating the best time to apply HOT based on functional and neuropsychiatric scores, in addition to ratifying the effectiveness of the method as an adjuvant treatment for FM at Brazilian population. The risk of losing participants due to the long period of the intervention and the moderate power of the sample size ratio for the primary outcome should be mentioned as limitations. The study may generate new hypotheses for the application of HOT in FM and its effects on neuroplasticity and the modulation of the inflammatory process.

Author affiliations
[1]Núcleo de Pesquisa e Inovação em Ciências da Saúde (NUPICS), Universidade Federal de Juiz de Fora, Juiz de Fora, Brazil
[2]Serviço de Ortopedia e Traumatologia, Universidade Federal de Juiz de Fora Hospital Universitário, Juiz de Fora, Brazil
[3]Departamento de Cirurgia, Faculdade de Medicina da Universidade Federal de Juiz De Fora, Juiz de Fora, Minas Gerais, Brazil
[4]Programa de Pós Graduação em Saúde, Faculdade de Medicina da Universidade Federal de Juiz de Fora, Juiz de Fora, Minas Gerais, Brazil
[5]Departamento de Reumatologia, Universidade Federal de Juiz de Fora, Juiz de Fora, Minas Gerais, Brazil

Contributors JdMN was the main researcher involved in the study concept and design, data collection and drafting of the manuscript. VAdS, AFM, AFMM, ATdL, RdOF and NRBR initiated the study design. ATdL, RdOF, VAdS and AFMM will take part in the implementation and data collection. JdMN, VAdS, AFM, AFMM and NRBR provided statistical insights into the clinical trial design. VAdS, AFM, AFMM, ATdL, RdOF and NRBR will perform primary statistical analysis. All authors contributed to the refinement of the study protocol and approved the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been

ORCID iDs
José Mota Neto http://orcid.org/0000-0003-2919-0971
Adriano Fernando Mendes Jr. http://orcid.org/0000-0003-1877-8155

REFERENCES

1 Sarzi-Puttini P, Giorgi V, Marotto D, *et al*. Fibromyalgia: an update on clinical characteristics, aetiopathogenesis and treatment. *Nat Rev Rheumatol* 2020;16:645–60.
2 Heidari F, Afshari M, Moosazadeh M. Prevalence of fibromyalgia in general population and patients, a systematic review and meta-analysis. *Rheumatol Int* 2017;37:1527–39.
3 Henriksson CM, Liedberg GM, Gerdle B. Women with fibromyalgia: work and rehabilitation. *Disabil Rehabil* 2005;27:685–94.
4 Alberti F, Blatt C, Pilger D. Direct and indirect costs of fibromyalgia: a scoping review. *J Bras Econ Saúde* 2021;13:338–44.
5 Geneen LJ, Moore RA, Clarke C, *et al*. Physical activity and exercise for chronic pain in adults: an overview of cochrane reviews. *Cochrane Database Syst Rev* 2017;4:CD011279.
6 Khurshid H, Qureshi IA, Jahan N, *et al*. A systematic review of fibromyalgia and recent advancements in treatment: is medicinal cannabis a new hope? *Cureus* 2021;13:e1733.
7 Farag HM, Yunusa I, Goswami H, *et al*. Comparison of amitriptyline and US food and drug Administration-approved treatments for fibromyalgia: a systematic review and network meta-analysis. *JAMA Netw Open* 2022;5:2212939.
8 Yeh S-W, Hong C-H, Shih M-C, *et al*. Low-level laser therapy for fibromyalgia: a systematic review and meta-analysis. *Pain Physician* 2019;22:241–54.
9 Serrat M, Almirall M, Musté M, *et al*. Effectiveness of a multicomponent treatment for fibromyalgia based on pain neuroscience education, exercise therapy, psychological support, and nature exposure (NAT-FM): a pragmatic randomized controlled trial. *J Clin Med* 2020;9:3348.
10 Udina-Cortés C, Fernández-Carnero J, Romano AA, *et al*. Effects of neuro-adaptive electrostimulation therapy on pain and disability in fibromyalgia: a prospective, randomized, double-blind study. *Medicine* 2020;99:e23785.
11 Larsson A, Palstam A, Löfgren M, *et al*. Resistance exercise improves muscle strength, health status and pain intensity in fibromyalgia--a randomized controlled trial. *Arthritis Res Ther* 2015;17:161.
12 Atzeni F, Casale R, Alciati A, *et al*. Hyperbaric oxygen treatment of fibromyalgia: a prospective observational clinical study. *Clin Exp Rheumatol* 2019;37 Suppl 116:63–9.
13 Wolfe F, Smythe HA, Yunus MB, *et al*. The American college of rheumatology 1990 criteria for the classification of fibromyalgia. Report of the multicenter criteria committee. *Arthritis Rheum* 1990;33:160–72.
14 Wolfe F, Clauw DJ, Fitzcharles M-A, *et al*. The American college of rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res* 2010;62:600–10.
15 Wolfe F, Clauw DJ, Fitzcharles M-A, *et al*. 2016 revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Semin Arthritis Rheum* 2016;46:319–29.
16 Efrati S, Golan H, Bechor Y, *et al*. Hyperbaric oxygen therapy can diminish fibromyalgia syndrome--prospective clinical trial. *PLoS One* 2015;10:e0127012.
17 Yildiz S, Kiralp MZ, Akin A, *et al*. A new treatment modality for fibromyalgia syndrome: hyperbaric oxygen therapy. *J Int Med Res* 2004;32:263–7.
18 Atzeni F, Masala IF, Cirillo M, *et al*. Hyperbaric oxygen therapy in fibromyalgia and the diseases involving the central nervous system. *Clin Exp Rheumatol* 2020;38 Suppl 123:94–8.
19 Efrati S, Fishlev G, Bechor Y, *et al*. Hyperbaric oxygen induces late neuroplasticity in post stroke patients--randomized, prospective trial. *PLoS One* 2013;8:e53716.
20 Liu S, Shirachi DY, Quock RM. The acute antinociceptive effect of hyperbaric oxygen is not accompanied by an increase in markers of oxidative stress. *Life Sci* 2014;98:44–8.
21 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al*. Spirit 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
22 Kindwall EP, Whelan HT. Contraindications and side effects to hyperbaric oxygen treatment. In: Joiner J, ed. *Hyperbaric medicine practice*. 3a. Flagstaff: Best Publishing Company, 2008: 273–88.
23 Associação Brasileira de Normas Técnicas. *Pressure vessel for human occupancy (PVHO) for therapeutical purposes – minimum requirements for manufacturing, installation, and operation. ABNT NBR 15949*. Rio de Janeiro, 2011: 1–18.
24 Hawker GA, Mian S, Kendzerska T, *et al*. Measures of adult pain: visual analog scale for pain (vas pain), numeric rating scale for pain (NRS pain), McGill pain questionnaire (MPQ), short-form McGill pain questionnaire (SF-MPQ), chronic pain grade scale (CpGs), short form-36 bodily pain scale (SF-36 BPs), and measure of intermittent and constant osteoarthritis pain (ICOAP). *Arthritis Care Res* 2011;63 Suppl 11:240–52.
25 Lupi JB, Carvalho de Abreu DC, Ferreira MC, *et al*. Brazilian portuguese version of the revised fibromyalgia impact questionnaire (FIQR-Br): cross-cultural validation, reliability, and construct and structural validation. *Disabil Rehabil* 2017;39:1650–63.
26 Yoshida EMP, Silva FCS. Escala de Avaliação de Sintomas-40 (EAS-40): validade E precisão em amostra não-clínica Validade E precisão dA EAS-40. *Rev ABRAPPE* 2007;2:89–9.
27 Damásio BF, Andrade TF, Koller SH. Psychometric properties of the Brazilian 12-Item short-form health survey version 2 (SF-12v2). *Paidéia* 2015;25:29–37.
28 Plafki C, Peters P, Almeling M, *et al*. Complications and side effects of hyperbaric oxygen therapy. *Aviat Space Environ Med* 2000;71:119–24.
29 Hadanny A, Meir O, Bechor Y, *et al*. Seizures during hyperbaric oxygen therapy: retrospective analysis of 62,614 treatment sessions. *Undersea Hyperb Med* 2016;43:21–8.
30 Al-Waili NS, Butler GJ, Beale J, *et al*. Influences of hyperbaric oxygen on blood pressure, heart rate and blood glucose levels in patients with diabetes mellitus and hypertension. *Arch Med Res* 2006;37:991–7.
31 Stevens SL, Narr AJ, Claus PL, *et al*. The incidence of hypoglycemia during HbO2 therapy: a retrospective review. *Undersea Hyperb Med* 2015;42:191–6.
32 Hadanny A, Zubari T, Tamir-Adler L, *et al*. Hyperbaric oxygen therapy effects on pulmonary functions: a prospective cohort study. *BMC Pulm Med* 2019;19:148.
33 McMonnies CW. Hyperbaric oxygen therapy and the possibility of ocular complications or contraindications. *Clin Exp Optom* 2015;98:122–5.
34 Faul F, Erdfelder E, Lang A-G, *et al*. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods* 2007;39:175–91.
35 Cohen J. A power primer. *Psychol Bull* 1992;112:155–9.