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SUMMARY WITH CRITICAL APPRAISAL

Hyperbaric Oxygen Therapy for the Treatment of Chronic Pain: A Review of Clinical Effectiveness and Cost-Effectiveness

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Abbreviations

ACR	American College of Rheumatologists
AE	adverse event
ATA	atmospheric absolute
BA	Brodmann area
FIQ	Fibromyalgia Impact Questionnaire
FMS	Fibromyalgia Syndrome
HBOT	hyperbaric oxygen therapy
HRQoL	health-related quality of life
MPS	myofascial pain syndrome
O_2	oxygen
PDI	Pain Disability Index
QoL	quality of life
RCT	randomized controlled trial
SAE	serious adverse event
SCL-90	Symptom Check List
SD	standard deviation
SF-12	MOS 12-item Short-Form Health Survey
SF-36	MOS 36-item Short-Form Health Survey
SPECT	single photon emission computed tomography
VAS	visual analog score

Context and Policy Issues

Hyperbaric oxygen therapy (HBOT) involves the intermittent inhalation of 100% oxygen (O_2) while being exposed to an increase in atmospheric pressure inside of a hyperbaric chamber.[1,2] During HBOT, hemoglobin saturation increases thus increasing the O_2 available and able to be delivered to tissues.[1,2] Different hyperbaric chambers are available for HBOT treatment, including low pressure single-person chambers, high pressure single-person chambers, and high pressure multi-person chambers. HBOT was originally developed to treat decompression illness due to accidents experienced during diving.[1,3] In recent years, it has been investigated for its use to treat numerous different injuries and conditions, some examples of which include necrotizing soft tissue injuries, chronic wounds, traumatic ischemia, radiation injury,[1,2] chronic pain, dysfunctional syndromes, fibromyalgia, chronic fatigue, headaches,[1,3,4] and complex regional pain syndrome.[5] HBOT is not without accompanying risks and can be associated with O_2 toxicity, central nervous system O_2 toxicity,[2] and barotrauma.[6]

Chronic pain is described as pain that persists well past the usual course of disease or injury and can persist for many months to years in a continuous or intermittent manner.[4] Pain can additionally occur without any identifiable cause. It can be difficult to treat, often requires a multidisciplinary approach,[3] and is one of the more frequent reasons patients visit healthcare professionals.[4] Due to the chronicity of pain (particularly musculoskeletal pain) and the lack of effective therapeutic options, other treatment paradigms (such as pharmacotherapy) on their own or as adjuncts to pre-existing therapies are being examined. HBOT has been postulated to be effective as adjunctive treatment for the treatment of chronic pain in many conditions.[1-5] and could be a viable option for patients experiencing chronic musculoskeletal pain.

With the increase interest in alternative treatment paradigms to address the lack of therapeutic effectiveness for chronic musculoskeletal pain, this review aims to examine the clinical effectiveness and cost-effectiveness of HBOT for the treatment of chronic musculoskeletal pain in adults.

Research Questions

1. What is the clinical effectiveness of hyperbaric oxygen therapy for the treatment of chronic musculoskeletal pain in adults?
2. What is the cost-effectiveness of hyperbaric oxygen therapy for the treatment of chronic musculoskeletal pain in adults?

Key Findings

One randomized controlled trial with a crossover active comparator and one prospective non-randomized cohort study formed the evidence base for this review. The RCT provided evidence to suggest that two months of hyperbaric oxygen therapy (HBOT) increases pain thresholds, physical functionality, and health-related quality of life, while decreasing tender points and psychological distress in female patients with Fibromyalgia Syndrome (FMS) at three months post-treatment. In addition, according to single photon emission computed tomography analyses, the majority of patients were classified as responders to HBOT and were assessed as having beneficial changes in brain activity within the specific regions of the brain known to be previously associated with abnormal activity in patients with FMS.

However, the generalizability of HBOT to the Canadian population and in the male population with FMS remains uncertain.

The prospective preliminary non-randomized study identified provided evidence to suggest that two weeks of hyperbaric oxygen therapy increased pain thresholds and health-related quality of life and decreased disability in patients with myofascial pain syndrome (MPS) at three months post-treatment. However, the generalizability of HBOT to the Canadian population with MPS is unclear as is its long-term effectiveness.

No evidence was identified regarding the cost-effectiveness of HBOT for the treatment of chronic musculoskeletal pain.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Medline, PubMed, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD), Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2008 and August 14, 2018.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults with chronic musculoskeletal pain
Intervention	Hyperbaric oxygen therapy

Comparators	• Treatment as usual, including but not limited to:
	  ○ Pharmacological interventions
	  ○ Non-pharmacological interventions (e.g., exercise, manual therapies, physiotherapy, massage, osteopathy, chiropractor services)
	• Placebo or sham interventions
	• Wait list
	• No treatment

Outcomes	Q1: Clinical effectiveness (e.g., improvement of symptoms, safety) Q2: Cost-effectiveness
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2008.

Critical Appraisal of Individual Studies

The included randomized and non-randomized studies were critically appraised by one reviewer using Downs and Black instrument[7] as a guide. Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 304 citations were identified in the literature search. Following screening of titles and abstracts, 275 citations were excluded and 29 potentially relevant reports from the electronic search were retrieved for full-text review. Fourteen potentially relevant publications were retrieved from the grey literature and hand search for full text review. Of these potentially relevant articles, 41 publications were excluded for various reasons, and two publications met the inclusion criteria and were included in this report. These comprised one RCT and one non-randomized study. Appendix 1 presents the PRISMA[8] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Study characteristics are summarized below and additional details are available in Appendix 2 Table 2.

Study Design

The included RCT was published in 2015 and was a prospective single center control crossover trial.[6]

One prospective non-randomized cohort study was included and published in 2009.[9]

No relevant economic evaluations were identified.

Country of Origin

The RCT originated in Israel[6] and the non-randomized study likely occurred in Turkey due to the authors' affiliations with Turkish hospitals.[9]

Patient Population

The prospective control crossover RCT by Efrati et al.[6] included female patients who had been diagnosed with Fibromyalgia Syndrome (FMS) (according to the 1990 FMS American College of Rheumatologists [ACR] criteria) at least two years prior to study inclusion. Sixty patients were included with ages ranging between 21 and 67 years (mean of 50.4 years and 48.1 years in the HBOT and crossover treatment groups, respectively). Enrollment of patients occurred between May 2010 and December 2012.

The prospective non-randomized study by Kiralp et al.[9] included patients newly diagnosed with myofascial pain syndrome (MPS) according to the Simons Criteria (having to have all five major criteria and one of the three minor criteria (as described in Table 2 of Appendix 2). Thirty patients were included in the study; 20 in the HBOT treatment group and 10 in the

control group. The male to female ratios per treatment group were as follows: 8:12 in the HBOT treatment group and 3:7 in the control group.

Interventions and Comparators

Efrati et al.[6] compared the HBOT treatment group (who received HBOT for two months) with a crossover group (comprised of patients receiving no treatment during the first two months that the treatment group was receiving HBOT and then receiving two months of HBOT treatment after the control period). The HBOT treatment was comprised of patients receiving 100% oxygen with air breaks at 2 ATA for 90 minutes (considered one session) for five days per week. This continued for 40 sessions (the equivalent of two months). The HBOT evaluations were performed more than one week (ranging between one and four weeks) post-HBOT.

Kiralp et al.[9] compared the HBOT treatment group with a control group. Patients, regardless of treatment group, were placed in a hyperbaric chamber capable of holding up to 16 patients. Those patients in the treatment group experienced a gradual (10 minute) increase in pressure from 1 ATA to 2.4 ATA, while patients in the control group experienced an increase in pressure from 1 ATA to 1.3 ATA. At this time, all patients breathed 100% oxygen through face masks for three 30-minute periods which were interrupted with two 5-minute air breaks. The pressure then decreased to 1 ATA over a period of 10 minutes, concluding the session. Sessions took place on five days per week (Monday through to Friday), with a total of 10 sessions being performed (two weeks total time).

Outcomes

The primary outcome both trials was the evaluation of pain (either as evaluation of tender point count[6] or as an assessment of pain threshold[9]). Efrati et al.[6] used a dolorimeter and physician assessment to ascertain the pressure required to sense pain and tender point count, respectively, while the physiatrists in Kiralp et al.[9] used an algometer to assess the pain threshold and the patients self-assessed their pain using visual analog scores (VAS) for pain.

Secondary outcomes examined by Efrati et al.[6] included an assessment of functional impairment (using the Fibromyalgia Impact Questionnaire [FIQ], symptom severity and psychological distress (using the Symptom Checklist [SCL-90], quality of life (using the MOS 36-item Short-Form Health Survey [SF-36]), and metabolic imaging of brain activity (using single photon emission computed tomography [SPECT]). In addition, they sought to assess whether there was correspondence between SPECT-observed changes in brain activity and improvements in FMS symptoms.[6] The Hebrew version of the FIQ has been validated in the FMS population, with the first portion of the questionnaire focusing on the ability of the patient to perform daily tasks. It contains 10 items with a ranking of 0 to 3 , indicating always to never able, respectively. Scores are then normalized from 0 to 10, with the higher scores representing worse physical functioning, and the mean of the items then provides a physical functioning score.[6] The SCL-90 has been validated in Hebrew and used extensively to assess psychological distress or general psychiatric symptom severity. It consists of 90 questions that measure nine clinical psychiatric subscales. Patients rate their subscale experience on a 5-point Likert scale from 0 to 4 (never to frequently, respectively), with a higher score indicating more distress.[6] The SF-36 has been validated in the general population and the Hebrew language version has also been validated. It measures the health-related quality of life (HRQoL) across three domains; well-being, functional status, and an overall measure of health. Scores vary between 0 and 100, with a higher score

indicating better health and functionality.[6] SPECT analyses were also performed on every patient in order to ascertain regional blood flow changes and perfusion changes in each Brodmann area (BA). No minimal clinically important differences were provided in this study for any of the secondary outcomes. Safety was also assessed in terms of adverse events (AEs) and serious adverse events (SAEs); both defined within their protocol.[6]

The secondary outcomes examined by Kiralp et al.[9] included an assessment of disability (using the Pain Disability Index [PDI]) and HRQoL (using the MOS 12-item Short-Form Health Survey [SF-12]). The PDI is used to assess disability caused by pain by examining seven daily psychosocial function/activities. An 11-point scale is used by the patient to rate their experience, with higher scores indicating increasing disability.[9] The SF-12, like the SF-26 is used to assess HRQoL but instead is a shortened version of the original. It measures eight domains, with higher scores indicating better health. Like the SF-36, it yields a total score and both physical and mental summary scores.[9] No minimal clinically important differences were provided in this study for any of the secondary outcomes.

Summary of Critical Appraisal

Randomized Controlled Trials

The study by Efrati et al.[6] included robust methods with appropriate considerations regarding the regular limitations associated sham comparisons in HBOT studies. The authors performed their due diligence by using a crossover control as their comparator as there is no true “sham” HBOT procedure that would act as an appropriate control. It would be insufficient for patients to believe they were receiving treatment if they were in the hyperbaric chamber and the pressure was not increased; therefore, this would not act as a true placebo. However, if the pressure increases even a small amount (as is needed for patients to feel as though the pressure is increasing) there are physiological responses that begin to occur, thereby precluding an actual sham procedure.[2] Therefore, the investigators added a control period whereby patients in the crossover arms would not be treated with anything. This control period was followed by a HBOT treatment period, thus allowing an investigation of a control and a treatment period with the treatment group. However, even with this design, patients were not blinded to their treatment groups; hence there was the potential for patient bias. In addition, the HBOT physicians remained unblinded (mainly for safety reasons), thus adding to the potential for investigator bias. The physicians assessing pain and evaluating the secondary and SPECT outcomes were all blinded to the patient treatment groups, thus precluding the possibility of assessor bias. In addition, previously validated (along with being validated in Hebrew) and extensively used instruments were used to assess functionality, psychological distress, and HRQoL and dolorimetry appears to be an accepted method of evaluating pain in other studies.[5,10]

The patients included in the study had all been diagnosed with the 1990 ACR FMS criteria; however, at the time that the study had already started, the new 2010 ACR FMS criteria were published. Therefore, the authors did not adhere strictly to the 2010 ACR FMS criteria. However, they noted this limitation in their study and ascertained that their methods could be considered as a combination of the ACR 1990 and 2010 FMS criteria. In addition, while FMS has a disease predominance in women,[11] only women were enrolled into this study. Therefore, these results cannot necessarily be generalized to the male population with FMS. The study included patients with FMS from Israel, potentially limiting the generalizability to other patients of different ethnicities, races, and from other cultures.

There were 60 patients enrolled in the study with 50 participating in the trial. An appropriate sample size calculation was performed based on achieving 80% power to detect an improvement rate (using the dolorimeter) of at least 0.62 (according to a previous study)[10] in the threshold of tender sites. While the appropriate sample size was used, the authors also noted that larger studies will be needed in order to corroborate their findings. In addition, no confidence intervals were provided, only p-values; therefore, only hypothesis testing can be discussed with any accuracy.

Non-Randomized Studies

The prospective non-randomized study by Kiralp et al.[9] assessed patients with MPS according to the Simons Criteria which was based on the five major criteria (of which patients had to exhibit all five) and three minor criteria (of which patients had to exhibit at least one). Therefore, there was a standard that patients with MPS had to meet. However, detailed baseline characteristics and inclusion criteria were lacking, making it difficult to ascertain the comparability of the patients. In addition, there were 30 patients included, no evidence of an accompanying power calculation; and only p-values were provided (with no accompanying confidence intervals [CI]). All of these study limitations may decrease the confidence in the effectiveness results. Of particular significance is the use of the control group, whereby patients were placed in the hyperbaric chamber and the pressure increased to 1.3 ATA. As previously noted, any increase in atmospheric pressure elicits a physiological response,[2] thereby precluding these patients from acting like a true control and decreasing the confidence of the effectiveness evaluations. Additionally, the patients included in the this study had a mean disease duration of between 24.10 and 37.37 months indicating that this population may not have been suffering from chronic MPS.

Additional details regarding the strengths and limitations of the included publications are provided in Appendix 3.

Summary of Findings

Findings are summarized below and details, along with authors' conclusions, are provided in Appendix 4, Table 4.

Clinical Effectiveness of HBOT

The clinical effectiveness findings are based on the RCT by Efrati et al.[6] and the prospective non-randomized cohort study by Kiralp et al.[9]

Clinical Effect on Pain

In Efrati et al.,[6] the clinical effect on pain was examined by tender point counts and dolorimeter pain thresholds in patients treated with 2.0 ATA for two months. After two months of HBOT treatment, statistically significant improvements in the mean scores of both the number of tender points and dolorimeter pain thresholds were observed in both treatment groups ($P < 0.001$; no CIs provided). No improvements in either dolorimtery pain thresholds or tender point counts were observed in the crossover group following the control period.

In Kiralp et al.,[9] the clinical effect on pain was examined by assessing the pain threshold (using an algometry device) and a self-assessment of pain (using VAS for pain) in patients treated with 2.4 ATA or 1.3 ATA (treatment or control groups, respectively) for two weeks. After two weeks and after three months, pain thresholds were significantly increased ($P < 0.001$; no CIs provided) in the HBOT treatment group. Pain thresholds did not change in the

control group after two weeks or three months (*P* = 0.847 and *P* = 0.385, respectively; no CIs provided).

Physical Functioning

Efrati et al.[6] assessed physical functioning using the FIQ, which significantly increased in both treatment groups after two months of HBOT. No improvement in physical functioning was observed in the crossover group following the control period.

Psychological Distress

Psychological distress was measured using the SCL-90 in the Efrati trial.[6] Significant improvements in the SCL-90 mean changes were observed following two months of treatment group and the crossover group after HBOT treatment (*P* < 0.01 and *P* = 0.05, respectively; no CIs provided). No improvements in the SCL-90 scores were observed in the crossover group following the control period.

Quality of Life

QoL was assessed using the SF-36 in the Efrati trial.[6] In the treatment and crossover group post-HBOT, significant improvements in the SF-36 scores were observed (*P* < 0.01 and *P* = 0.05, respectively). No improvements in the SF-36 scores were observed in the crossover group following the control period.

The SF-12 was used to assess QoL in the Kiralp trial.[9] Both the mental and physical health scores improved at month three post-HBOT (*P* < 0.001; no CIs provided) as did the physical health score in the control group (*P* = 0.008). The mental health score did not change after three months in the control group (p=0.591). The improvement in the SF-12 score in the control group suggests that increasing the atmospheric pressure to 1.3 ATA in the hyperbaric chamber elicits a physiological response.

Disability

Disability was assessed using the PDI in the Kiralp et al. trial.[9] Compared with pre-treatment scores, PDI scores were significantly reduced after three months in the HBOT treatment group (*P* < 0.001; no CIs provided). The PDI scores did not change significantly in the control group after three months.

Assessment of Brain Activity

Brain activity was assessed using SPECT analyses in the Efrati trial.[6] Forty-one of 48 patients with SPECT analyses were classified as responders to HBOT (defined as physiologically improved) and assigned to the response group, while seven patients were classified as non-responders and assigned to the non-response group. Normalized changes in brain activity were observed in many distinct BAs following treatment with HBOT, with hyper-perfusion observed in 10 BAs and hypo-perfusion observed in five BAs. In contrast, the normalized mean changes after the control period ranged between -0.6 and 0.6 in the BAs. Elevated activity in the BAs of the frontal lobe were observed in the responders after HBOT treatment, while reduced activity was observed in the posterior brain in these same responders. The authors noted that HBOT treatment appeared to lead to beneficial changes in brain activity within the specific regions of the brain that have been previously observed to have abnormal activity in patients with FMS.

Safety

AEs and SAEs were assessed in the Efrati trial.[6] Five patients stopped HBOT due to AEs associated with the treatment itself (including claustrophobia, ear pressure issues, and dizziness). Mild barotrauma, which spontaneously resolved was experienced by 13 patients during HBOT treatment. The authors also noted that 14 patients (29%) experienced an increase in pain sensation during the first 10 to 20 sessions; however, their pain sensations were subsequently reduced after the 40 HBOT sessions.

In summary, evidence from both the RCT crossover trial and the prospective non-randomized study suggests that (based on the multiple outcome measures) HBOT offered some clinical benefit to patients experiencing chronic pain associated with FMS and MPS, respectively. The authors of the Efrati trial noted that a good association was observed between changes in brain functionality (detected using SPECT) and improvements in brain physiology, suggesting that HBOT can help in the rectification of abnormal brain activity observed in patients with FMS (as it has been hypothesized that their pain perceptions might be associated with hyper-excitability of the pain processing pathways). Adverse effects were observed with HBOT treatment; however, they tended to be mild or resolve spontaneously.

Cost-Effectiveness

No relevant economic evaluations were identified regarding hyperbaric oxygen therapy for the treatment of chronic musculoskeletal pain in adults; therefore, no summary can be provided.

Limitations

Very few studies were identified assessing HBOT treatment for chronic musculoskeletal pain. The paucity of evidence regarding its use as a treatment for pain suggests that it has not been examined in a number of potential indications, it may be a difficult treatment to access, and it may be too limited a treatment paradigm to assess many indications.

While the two identified studies provided some evidence of benefit of HBOT in reducing pain in patients with FMS and MPS, these studies did not include large numbers of patients, one was a preliminary study,[9] the results may not be generalizable to the Canadian population (as one study was done exclusively in patients from Israel[6] and the other appears to have been performed in Turkish patients[9]), and the results likely cannot be generalized to male patients with FMS (as the Efrati trial exclusively recruited women only). The lack of reliable control or sham procedures to compare with HBOT is also very limiting, as there is no way to appropriately assess the potential for a placebo effect. Any changes to atmospheric pressure (no matter how small) appear to have a physiological effect[2] and patients can sense when there is no increase in atmospheric pressure in the hyperbaric chamber, thus increasing the potential for patient bias. In addition, hyperbaric chambers may not be available in many regions, particularly in more remote or land-locked areas, as they were originally developed to treat decompression sickness. This lack of availability could also influence how often this treatment may be assessed in studies.

This review set out to identify if HBOT was effective at relieving chronic pain. The RCT by Efrati et al.[6] in addition to the non-randomized prospective trial by Kiralp et al.[9] looked at the effectiveness of relieving pain for up to two and three months, respectively. Therefore, neither identified trial was able to provide evidence that HBOT would be effective in their respective populations any longer than three months. In addition, the lack of trials identified

for other conditions causing chronic musculoskeletal pain (particularly in the veteran, military, or para-military populations) impedes anyone from knowing if HBOT can be used for any other indications. It is possible that studies assessing chronic musculoskeletal pain have been performed outside of the date range specified for this report and therefore have not been formally identified.

No relevant cost-effectiveness analyses were identified that examined HBOT in any indication whose patients may suffer from chronic (musculoskeletal) pain.

Conclusions and Implications for Decision or Policy Making

Two eligible publications[6,9] were identified that examined the clinical effectiveness of hyperbaric oxygen therapy (HBOT) for the treatment of chronic musculoskeletal pain. One was a prospective, active comparator, crossover RCT[6] while the other was a prospective non-randomized cohort trial.[9] No relevant economic evaluations were identified. Overall, there is the potential for bias in both of these studies, with the possibility of patient bias due to the lack of patient blinding in Efrati et al.[6] and investigator bias due to the lack of blinding of the HBOT physician in both studies.[6,9] Additionally, none of the study authors indicated whether or not their statistically significant findings were clinically significant.

Evidence from the RCT[6] suggested that HBOT had a positive clinical effect on pain experienced by female patients with Fibromyalgia Syndrome (FMS). After two months of HBOT treatment, patients observed significantly increased pain thresholds and a decreased number of tender points. In addition, patients observed increased physical functionality, decreased psychological distress, and increases in their health-related quality of life. According to SPECT analyses, the majority of patients were classified as responders to HBOT and were assessed as having beneficial changes in brain activity within the specific regions of the brain known to be previously associated with abnormal activity in patients with FMS. Few and mild adverse events were associated with HBOT, with the mild barotrauma experienced by thirteen of the patients resolving spontaneously. While this study does provide evidence for the usefulness of HBOT in the treatment of FMS, larger RCTs with inclusion criteria that reflect a more diverse population with FMS is required in order to corroborate the aforementioned results and increase its generalizability. In addition, studies should incorporate longer assessment time points in order to ascertain the long-term effectiveness of HBOT in patients with FMS.

The evidence from the preliminary prospective cohort study of HBOT for the treatment of patients with myofascial pain syndrome (MPS)[9] suggests that HBOT can increase the pain threshold at three months post-treatment. In addition, these patients also experienced decreases in their disability and increases in their health-related quality of life. However, larger studies that incorporate patients from many different countries are required in order to build on these preliminary results and increase its generalizability.

While HBOT has been shown to provide clinical benefit in the treatment of pain in indications other than FMS and MPS such as headaches,[1,3,4] complex regional pain syndrome,[1,3,4] and trigeminal neuralgia,[1] there is a paucity of evidence of the effectiveness of HBOT in other indications that cause chronic musculoskeletal pain. Therefore, studies in patients with this type of pain are warranted in order to reduce uncertainty. Economic evaluations with Canadian inputs are needed in order to determine the cost-effectiveness of HBOT for the treatment of chronic musculoskeletal pain in the Canadian setting.

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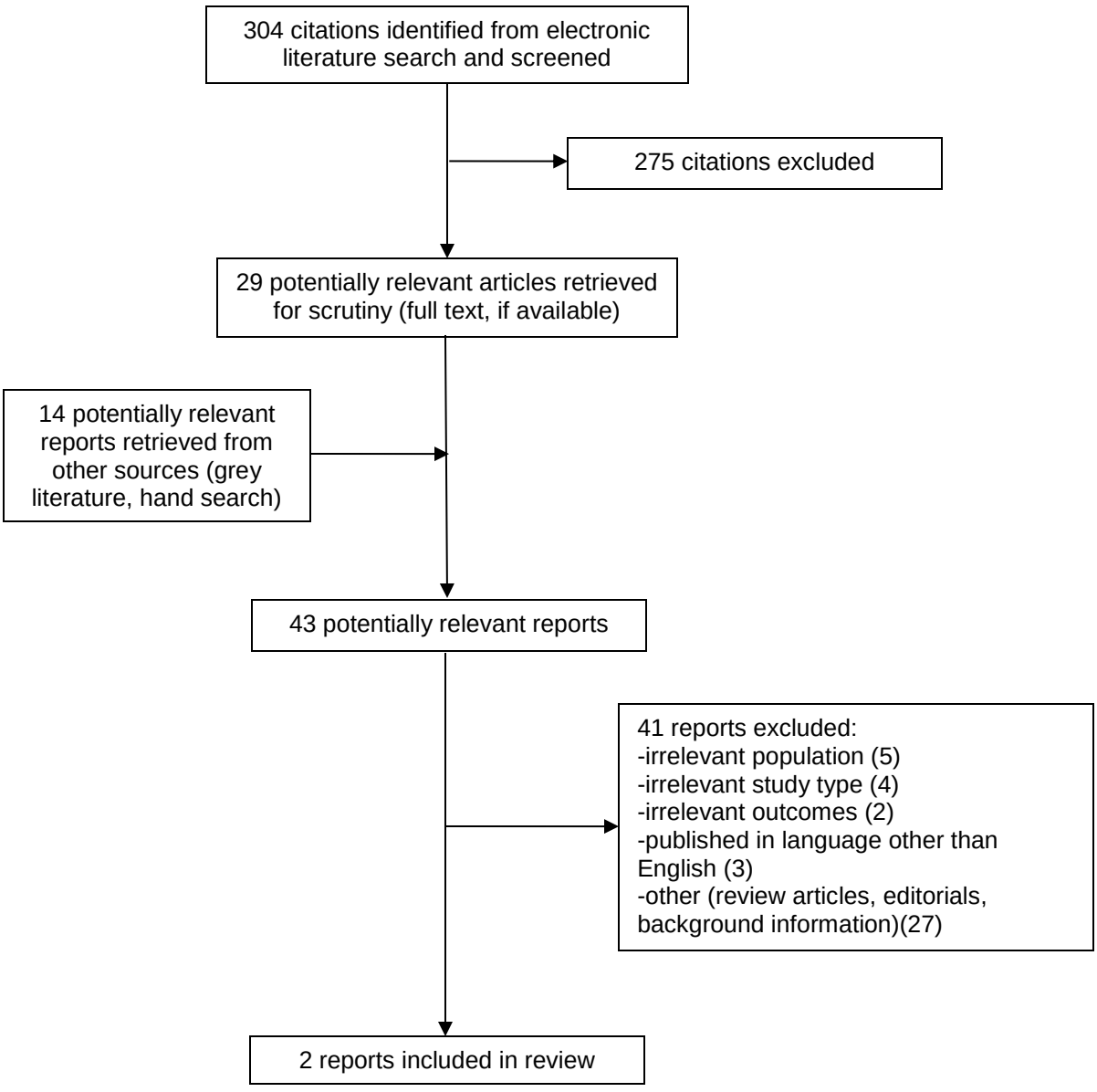
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Randomized Controlled Trial				
Efrati, 2015[6] Israel	Prospective, randomized control-crossover trial (1:1 randomization) Setting: hyperbaric chamber in the research and development unit of the Assaf Harofeh Medical Center	Patients with chronic FMS Diagnosis of FMS included: • Widespread pain that occurs both above and below waist and affecting both left and right side of body • Physical findings of ≥ 11 of 18 tender points N=60; (n=24 in HBOT treated and n=26 Crossover group) 100% patients female Patients had a diagnosis of FMS at least 2 years prior to trial inclusion (mean 6.5 years, range 2-22 years)	HBOT treatment comprised of 40 daily sessions, 5 days/week, 90 minutes per session, 100% oxygen at 2 ATA Treatment group: HBOT treatment for 2 months Control cross-over group: No treatment during first 2 months (control period) then cross-over to receive HBOT sessions for 2 months	***Primary outcome:*** Pain evaluation (tender point count and dolorimetry of 9 tender points) ***Secondary outcomes:*** Functional impairment (FIQ)[c] Symptoms severity, psychological distress (SCL-90 questionnaire)[c] QoL (SF-36)[c] Metabolic imaging (SPECT analysis) Safety Correspondence between SPECT-observed changes in brain activity and improvements in FMS symptoms ***Length of Follow-Up:*** • HBOT group evaluated at baseline and then after 2 months of HBOT treatment) • Cross group evaluated at baseline, after 2 months control period,[d] and then received 2 months of HBOT sessions • All post-HBOT evaluations performed ≥ 1 week (range 1 – 4 weeks)

Table 2: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
				after end of HBOT sessions
Non-Randomized Study				
Kiralp, 2009[9] Turkey	Prospective study with treatment and placebo control group Objective: To assess the use of HBOT in patients with MPS	Patients with newly diagnosed[a] MPS[b] N=30 (n=20 HBOT group and n=10 control group) Male:female ratio (8:12 HBOT group and 3:7 control group)	***HBOT:*** Total of 10 HBOT sessions in HBOT chamber (able to house 16 patients); patients received 100% oxygen via face masks at 2.4 ATA for 3 30-minute periods 5 days /week (2 weeks total) ***Placebo control:*** Total of 10 placebo session in HBOT chamber, patients received 100% oxygen via face masks at 1.3 ATA for 3 30-minute periods 5 days/week (2 weeks total)	***Primary outcome:*** Pain threshold (measured using algometry device) ***Secondary outcomes:*** Disability (PDI) QoL (SF-12) ***Length of Follow-Up:*** HBOT and Placebo control groups assessed at pretreatment, 2 weeks, and 3 months

ATA = atmospheric absolute; FIQ = Fibromyalgia Impact Questionnaire; FMS = Fibromyalgia Syndrome; HBOT = hyperbaric oxygen therapy; MPS = myofascial pain syndrome; QoL = quality of life; SCL-90 = Symptom Check List; SF-12 = MOS 12-item Short-Form Health Survey; SF-36 = MOS 36-item Short-Form Health Survey; SPECT = single photon emission computed tomography.

[a] Diagnosed by a physiatrist.

[b] Diagnosis made according to Simons Criteria (5 major criteria [Major: 1) spontaneous localized pain, 2) referred pain in expected area for a given trigger point, 3) taut and palpable muscle band, 4) localized pain in precise point along taut muscle band, 5) measurable reduced range of motion] and at least one of the 3 minor criteria [Minor: 1) reproduction of pain /altered sensation with pressure on trigger point, 2) local muscular twitch response by snapping or needling affected area, 3) pain relief upon stretching or needing trigger point]).[9]

[c] Validated Hebrew version.

[d] No treatment.

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Clinical Studies Using Downs and Black[7]

Strengths	Limitations
Randomized Controlled Trial	
Efrati, 2015[6]	
• Background into the reasoning for examining the effect of HBOT on FMS provided • Objective clearly stated • Appropriate trial design to assess efficacy of HBOT (taking into account the appropriateness of the crossover approach to circumvent the problems with a true sham group using HBOT) • Primary and secondary outcomes clearly described and validated tools were used to examine these endpoints • The majority of tools used to examine the secondary outcomes had been validated in Hebrew • Inclusion and exclusion criteria provided in detail • Definitive FMS diagnosis required for inclusion based on ACR diagnostic criteria • Sample size considerations provided; power considerations and calculations were described • Physicians performing the pain evaluation were blinded to the patient's treatment group • All patients receiving therapy (regardless of dropout during the study) were assessed for safety (AE and SAE; in addition to definitions of both being provided) • No significant differences in the baseline patient characteristics between groups were apparent • Patients were randomized 1:1 into treatment and crossover groups	• Lack of blinding of the patients to their treatment; hence potential for patient bias • Lack of blinding of the HBOT physicians providing HBOT; hence potential for investigator bias • Only hypothesis testing results were provided (p-values); no CIs were provided, hence uncertain if the null hypothesis value of no difference is contained within the 95% CI • The characteristics of the patients who dropped out of the treatment (n=2 in treatment and n=2 in crossover group) not provided • While there is a predominance of women suffering from FMS,[11] no men included in the study; thereby limiting generalizability to all patients with FMS • This study was specifically carried out in Israel; therefore, generalizability may be compromised to individuals of other ethnic/racial descent • Findings were from a total of 50 patients • The 1990 ACR diagnostic criteria for FMS was used instead of that of the newly formed 2010 ACR diagnostic criteria (as the protocol was finalized well in advance of the release of the 2010 criteria) • Lack of appropriate sham control • Trial limited to 2 months post-HBOT treatment; therefore, cannot ascertain the effectiveness of HBOT longer than this in patients with FMS
Non-Randomized Study	
Kiralp, 2009[9]	
• Hypothesis clearly stated with appropriate rationale for performing the study (HBOT in patients with MPS) provided • MPS diagnosis made using Simons Criteria • Inclusion and exclusion criteria provided • Patients with contraindications to HBOT were excluded from therapy • Physiatrists blinded to patient group allocation • Patients blinded to pain threshold values • Multiple time-point assessments performed to ascertain short and long-term effects	• Lack of blinding of the HBOT physicians providing HBOT; hence potential for investigator bias • Potential for patient bias as the hyperbaric chamber accommodated 16 individuals; therefore, there is potential for the patients to "discuss" their outcomes • Findings were from a total of 30 patients • Patients not randomized; although placed in a 2:1 ratio into HBOT: Control groups, respectively • Control group ultimately not a true "control" group as they did receive 100% oxygen at a slightly increased pressure in the hyperbaric

Table 3: Strengths and Limitations of Clinical Studies Using Downs and Black

Strengths	Limitations
• Additional secondary outcomes used to assess QoL and disability • Statistical plan provided • No significant differences between patients at baseline	chamber (1.3 ATA); thus experiencing some physiological response[2] • VAS self-perceived pain scale highly subjective • Only hypothesis testing results were provided (p-values); no CIs were provided, hence the reader is uncertain if the null hypothesis value of no difference is contained within the 95% CI • Actual values not provided for primary outcome (only figure provided) • Not many baseline characteristics were provided along with no additional discussion pertaining to the types of patients included in the study • Inclusion criteria very brief with not a lot of detail; therefore, this precluded the ability to ascertain any generalizability to other patients • The study appeared to take place in Turkey; therefore, these results may not be generalizable to other patients of different ethnicities/races • Power calculation to detect clinically meaningful effect not performed • Trial limited to 3 months post-HBOT treatment; therefore, cannot ascertain the effectiveness of HBOT longer than this in patients with MPS

ACR = American College of Rheumatology; ATA = atmospheric absolute; CI = confidence intervals; FMS = Fibromyalgia Syndrome; HBOT = hyperbaric oxygen therapy; MPS = myofascial pain syndrome; QoL = quality of life; VAS = visual analog score.

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Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Randomized Controlled Trial	
Efrati, 2015[6]	

Primary Outcome:
Clinical Effect on Pain:

Measurement	Treated Group		Crossover Group		
	Baseline	After HBOT Treatment	Baseline	Control – No Treatment Period	After HBOT Treatment
Dolorimetry threshold (kg): 9 tender sites, mean (SD)	0.55 (1.7)	1.65 (0.81)	0.72 (0.46)	0.58 (0.46)	1.86 (0.76)
Mean change (SD)	1.11 (0.79)		1.29 (0.76)[a]		
Before and after comparison, p-value	<0.001		0.037		<0.001[a]
Between-group comparison, p-value	<0.001				
Dolorimetry threshold (kg): 4 control sites, mean (SD)	2 (0.75)	3.24 (1.05)	2.19 (0.51)	1 (0.53)	2.29 (0.76)
Before and after comparison, p-value	<0.001		0.05		<0.001[a]
Between-group comparison, p-value	<0.001				
Tender point count (out of a total of 18), mean (SD)	17.33 (1.4)	8.87 (6.03)	17.71 (0.69)	17.24 (1.15)	5.35 (4.47)
Mean change (SD)	8.46 (5.36)		11.54 (4.93)[a]		
Before and after comparison, p-value	<0.001		0.56		<0.001[a]
Between-group comparison, p-value	<0.001				

[a] Comparison after control group, before and after HBOT in the crossover group.
Adaptations to the tables based on the specific criteria for this review were made using the tables and information from Efrati S, Golan H, Bechor Y, Faran Y, Daphna-Tekoah S, Sekler G, et al. (2015) Hyperbaric Oxygen Therapy Can Diminish Fibromyalgia Syndrome – Prospective Clinical Trial. PLoS ONE 10(5): e0127012. doi:10.1371/journal.pone.0127012.

Secondary Outcomes:

Effect on Pain, Physical Function, Symptoms, and Quality of Life:
The authors noted, "*The changes in all measures (pain threshold, number of tender points, FIQ, SCL-90 and SF-36) were assessed by detailed computerized evaluations and were compared to changes in brain activity obtained by SPECT imaging. The HBOT in both groups led to similar significant improvements. No significant changes were detected during the non-treatment period in the crossover group.*" page 18

Functionality of the Brain:
The authors noted, "*What makes the results particularly convincing is the good correspondence between the physiological improvements and the changes in brain functionality as detected by the SPECT scans, as well as the good agreement with the abnormal brain activity of FMS patients….. The specially devised analyses of the HBOT imaging revealed that the improvements in the syndrome status went hand-in-hand with changes in the patterns of brain activity towards those of healthy subjects. More specifically, for the response patients, HBOT sessions led to reduction in brain activity in the somatosensory cortex and enhancement of the brain activity in the frontal, cingulate, medial temporal and cerebellar cortices*." page

Table 4: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion

Assessment of Physical Function, Symptoms (Psychological Distress), and Quality of Life

Measurement	Treated Group		Crossover Group		
	Baseline	After HBOT Treatment	Baseline	Control – No Treatment Period	After HBOT Treatment
Physical Functional Assessment					
FIQ Score, mean (SD)	3.76 (0.73)	2.51 (1.14)	3.76 (1.06)	3.7± (1.15)	2.71 (1.12)
Before and after comparison, p-value	<0.001		0.876		0.02[a]
Between-group comparison, p-value	0.001				
Symptom Assessment (Psychological Distress)					
SCL-90 Score, mean (SD)	0.88 (0.47)	0.66 (0.4)	1.23 (0.64)	1.08 (0.62)	0.71 (0.27)
Before and after comparison, p-value	0.004		0.296		0.009[a]
Between-group comparison, p-value	0.009				
Quality of Life					
SF-36 Score, mean (SD)	3.15 (0.44)	3.48 (0.45)	2.89 (0.47)	3.03 (0.38)	3.32 (0.36)
Before and after comparison, p-value	<0.001		0.1		0.01[a]
Between-group comparison, p-value	<0.001				

[a] Comparison after control group, before and after HBOT in the crossover group

Adaptations to the tables based on the specific criteria for this review were made using the tables and information from Efrati S, Golan H, Bechor Y, Faran Y, Daphna-Tekoah S, Sekler G, et al. (2015) Hyperbaric Oxygen Therapy Can Diminish Fibromyalgia Syndrome – Prospective Clinical Trial. PLoS ONE 10(5): e0127012. doi:10.1371/journal.pone.0127012

SPECT Assessment of Brain Activity Changes

Evaluations of all BAs were undertaken in each patient (Treated group had 2 assessments [baseline and post-HBOT], while Crossover group had 3 assessments [baseline, post-control, and post-HBOT])

Responders (response group): Significant improvements in FMS symptoms were observed in 41 patients (of 48 total patients with SPECT analyses) from the Treatment and Crossover groups.

Non-Responders: No significant improvements in FMS symptoms were observed in 7 patients (of 48 patients with SPECT analyses).

Pearson correlations (Normalized[b] mean changes in BA response – histograms of mean relative changes)[a]:

- Between vectors of mean relative changes for response group and crossover group (control period): **-0.28**

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Rectification of Abnormal Brain Activity by HBOT:

The authors noted, "*In the present study we found that HBOT can rectify chronically abnormal brain activity – decrease the activity of hyperactive regions (mainly posterior regions) and increase the activity of underactive regions (mainly frontal areas), in good agreement with the current knowledge regarding the brain's response to pain*." page 19

In addition, the authors noted, "*It [the study] shows for the first time that HBOT can induce neuroplasticity and significantly rectify brain activity in pain related areas of FMS patients*." page 21

Table 4: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
• Between mean relative changes for 41 responders and 7 non-responders (during treatment): **-0.09** • Between mean relative changes for whole response group and responders from the Treated Group (during treatment): **0.66** • Between mean relative changes for the whole response group and the responders from the Crossover Group (during treatment): **0.61** **Safety:** N=30 5 patients stopped HBOT treatment due to AEs (problems adjusting to ear pressure, dizziness, and claustrophobia) 13 patients had mild barotrauma (they completed treatment and all cases resolved) During the first 10 to 20 sessions, 14 patients (29%) experienced an increase in pain sensations before seeing a benefit	
Non-Randomized Study	
Kiralp, 2009[9]	
Primary Outcome: **Pain threshold values (compared with pre-treatment):** HBOT treatment group: statistically significantly increase at 2 weeks and 3 months post-HBOT (both *P* < 0.001) Control group: unchanged after 2 weeks (*P* = 0.847) and 3 months (*P* = 0.385) **VAS of pain (compared with pre-treatment::** HBOT treatment group: statistically significantly increase at 2 weeks and 3 months post-HBOT (both *P* < 0.001) Control group: unchanged after 2 weeks (*P* = 0.573) and 3 months (*P* = 0.249) ***Secondary Outcomes:*** **PDI** HBOT treatment group, mean (SD) • Pre-treatment: 30.15 (14.51) • 3 months post-treatment: 14.90 (10.18) • Statistically significant reduction in scores (*P* < 0.001) Control group, mean (SD) • Pre-treatment: 34.30 (10.19) • 3 months post-treatment: 32.90 (9.03) • Statistically significant reduction in scores (*P* = 0.205)	The authors noted, "*In light of the preliminary findings of this placebo controlled study, HBO therapy for 2 weeks significantly reduced pain intensity and pain-related disability and improved the quality of life in patients with MPS.*" page 80 In addition, the authors noted, "*In our study, patients also reported less pain and improved quality of life on the third month of follow-up.*" page 80

Table 4: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
SF-36 ***Mental Health*** HBOT treatment group, mean (SD) • Pre-treatment: 16.30 (2.39) • 3 months post-treatment: 18.80 (2.60) • Statistically significant reduction in scores (*P* < 0.001) Control group, mean (SD) • Pre-treatment: 16.90 (2.42) • 3 months post-treatment: 16.60 (2.27) • Statistically significant reduction in scores (*P* = 0.591) ***Physical Health*** HBOT treatment group, mean (SD) • Pre-treatment: 11.35 (2.58) • 3 months post-treatment: 15.50 (2.50) • Statistically significant reduction in scores (*P* < 0.001) Control group, mean (SD) • Pre-treatment: 11.60 (2.17) • 3 months post-treatment: 12.60 (2.63) • Statistically significant reduction in scores (*P* = 0.008) ***Total*** HBOT treatment group, mean (SD) • Pre-treatment: 27.65 (4.15) • 3 months post-treatment: 34.30 (5.21) • Statistically significant reduction in scores (*P* < 0.001) Control group, mean (SD) • Pre-treatment: 28.50 (3.44) • 3 months post-treatment: 29.20 (4.28) (*P* value not reported)_	

AE = adverse event; BA = Brodmann areas; FIQ = Fibromyalgia Impact Questionnaire; FMS = Fibromyalgia Syndrome; HBOT = hyperbaric oxygen therapy; PDI = Pain Disability Index; SCL-90 = Symptom Check List; SD = standard deviation; SF-36 = MOS 36-item Short-Form Health Survey; SPECT = single photon emission computed tomography; VAS = visual analog scores.

[a] Shown in the BA histograms of the original article.

[b] Each BA mean relative change was normalized by its corresponding significant index.

Appendix 5: Additional References of Potential Interest

Identified References Outside of the Inclusion Criteria Date Range

Kiralp MZ, Yildiz S, Vural D, et al. Effectiveness of hyperbaric oxygen therapy in the treatment of complex regional pain syndrome. *J Int Med Res*. 2004; 32:258-262.

Yildiz S, Kiralp MZ, Akin A, et al. A new treatment modality for fibromyalgia syndrome: hyperbaric oxygen therapy. *J Int Med Res*. 2004;32:263-267.