Hyperbaric oxygen treatment of fibromyalgia: a prospective observational clinical trial

F. Atzeni1, R. Casale2, A. Alciati3,4, I.F. Masala5, A. Batticciotto6, R. Talotta6, M.C. Gerardi6, F. Salaffi7, P. Sarzi-Puttini6

1Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Messina; 2Habiliata Hospitals & Research Rehabilitation Unit, Zingonia, Bergamo; 3Department of Clinical Neurosciences, Villa San Benedetto Menni, Hermannas Hospitalarias, FoRiPsi, Albese con Cassano, Como; 4Humanitas Clinical and Research Centre, Rozzano (Milan); 5Orthopaedic and Trauma Unit, Santissima Trinità Hospital, Cagliari; 6Department of Rheumatology, ASST Fatebenefratelli-Sacco, Milan; 7Polytechnic University of Marche, C. Urbani Hospital, Jesi, Ancona, Italy. F. Atzeni*, MD, PhD Roberto Casale*, MD Alessandra Alciati*, MD Ignazio Francesco Masala, MD Alberto Batticciotto, MD, PhD Rossella Talotta, MD Maria Chiara Gerardi, MD Fausto Salaffi, MD, PhD Piercarlo Sarzi-Puttini, MD *These authors contributed equally to this paper.

Please address correspondence to: Fabiola Atzeni, MD, PhD, Rheumatology Unit, University of Messina, Via C. Valeria 1, 98100 Messina, Italy. E-mail: atzenifabiola@hotmail.com

Received on August 7, 2018; accepted in revised form on December 17, 2018. Clin Exp Rheumatol 2019; 37 (Suppl. 116): S63–S69.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2019.

Key words: fibromyalgia, hyperbaric oxygen therapy, pain

ABSTRACT

Objective. Fibromyalgia (FM) is a syndrome of unknown aetiology that is characterised by widespread musculoskeletal pain, fatigue and disordered sleep, and often associated with neuropsychiatric and cognitive symptoms. Current treatment options are only partially effective, but hyperbaric oxygen therapy (HBOT) seems to be capable of relieving some of the symptoms. The aim of this study was to evaluate the efficacy and safety of HBOT after fewer sessions than generally used, chosen on the basis of pre-clinical and clinical data showing its rapid and sustained antinociceptive effect.

Methods. Patients with FM underwent HBOT (100% oxygen at 2.5 ata with air breaks) administered on three days per week for a total of twenty 90-minute sessions. Pain, fatigue, the quality of sleep, symptoms of anxiety and depression, and the patients’ health-related quality of life were prospectively assessed before and after ten and twenty sessions.

Results. Twenty-eight of the 32 study patients completed the 20 HBOT sessions. Pain scores and the symptoms of anxiety (but not those of depression) significantly improved after both 10 and 20 sessions, whereas fatigue and FM symptom severity scores significantly improved only after 20 sessions. There was no significant change in the quality of sleep. The adverse effects were limited.

Conclusion. These findings support the view that HBOT is an effective, rapid and safe means of treating various symptoms of FM.

Introduction

Fibromyalgia (FM) is a chronic pain syndrome that has a prevalence of 1-5%, and is characterised by widespread musculoskeletal pain, extreme fatigue and sleep disturbances (1). These core features are often accompanied by neuropsychiatric manifestations such as cognitive impairment, and mood and anxiety symptoms or syndromes. FM can have a profoundly negative physical and psychological impact on the patients’ lives at an age that is critical for reaching personal and career goals. Many patients are physically disabled to the point that they are unable to accomplish various occupational, domestic and social tasks, and experience a dramatically impaired quality of life (QoL) (2).

The optimal management of FM requires a multidisciplinary approach utilizing a combination of pharmacological treatments and non-pharmacological (educational, physical, psychological, and physiotherapeutic) interventions (3, 4). Analgesic, non-steroidal anti-inflammatory drugs, opioids, anti-convulsants, serotonin and noradrenaline reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRI), and muscle relaxants can help to improve the patients’ QoL by reducing pain and other key symptoms to varying extents (5). However, it has been shown that the three drugs approved by the American Food and Drug Administration (FDA) for the treatment of FM (the antidepressants duloxetine and milnacipram, and the anticonvulsant pregabalin [PGB]) are only moderately (6, 7) or even questionably (8) more beneficial than placebo. The revised European League Against Rheumatism (EULAR) recommendations (9) suggest that non-pharmacological treatment should be the first-line approach to FM as exercise is the only ‘strong’ therapy-based recommendation. Similarly, a systematic review and meta-analysis of randomised clinical trials (RCTs) (10) has concluded that aerobic and muscle strengthening...
exercises are the most effective way of reducing pain and improving global well-being. Furthermore, the short- and long-term efficacy of balneotherapy (11) has recently been demonstrated in a 6-month double-blind RCT (12) and, although not conclusive, the evidence supporting the efficacy of cognitive behavioural therapy and mindfulness meditation is encouraging (10).

One effective alternative or additional treatment options is hyperbaric oxygen therapy (HBOT), which involves patients’ breathing nearly 100% oxygen while inside an enclosed chamber in which the pressure is 2–3 times greater than at sea level (one atmosphere absolute [ata] or 760 mmHg). HBOT was initially used to treat patients with decompression sickness but, over the years, its indications have been extended to include the treatment of diabetic and ischemic ulcers, chronic osteomyelitis, radiation injury, failed surgical grafts or flaps, carbon monoxide poisoning, necrotising soft tissue infections, and central retinal artery occlusion (13).

Its therapeutic effects are based on increasing the partial pressure of arterial oxygen to supra-physiological levels (>1,000 mmHg), which facilitates oxygen delivery to hypoxic tissues (14). HBOT has led to promising results in animal models of nociceptive, inflammatory and neuropathic pain (15) and animal models of nociceptive, inflammatory and neuropathic pain (15). HBOT has been shown to improve key symptoms, psychological distress, the QoL, and abnormal activity in pain-related brain areas (19). The evidence coming from animal (20, 21) and human studies (17) suggests that the anti-nociceptive activity of HBOT has a rapid onset and is long lasting.

The primary endpoints of this study were the effects of HBOT on the core symptoms of FM (pain, fatigue and disturbed sleep), the Fibromyalgia Impact Questionnaire (FIQ) score, and Fibromyalgia Assessment Status (FAS). The secondary endpoints were its effects on the QoL, anxiety and depressive symptoms, and its safety profile. We also investigated whether its putative positive effects on a vast array of FM symptoms could be achieved using fewer than 40 HBOT sessions.

**Methods**

**Patients**

The inclusion criteria were an age of 21-67 years and the fulfilment of both the 1990 and 2010 American College of Rheumatology (ACR) diagnostic criteria for fibromyalgia (22, 23) for at least two years. The 1990 criteria are a history of widespread musculoskeletal pain on the right and left sides of the body, and above and below the waist, for a minimum of three months, and pain at 11 or more of 18 specific tender points, with moderate or greater tenderness reported upon digital palpation (22); the 2010 criteria are a widespread pain index (WPI) of ≥7 and symptom severity (SS) of ≥5, or a WPI of 3-6 and SS ≥9, without a disorder that would otherwise explain the pain (23). The exclusion criteria were: 1) inflammatory causes of pain; 2) alcohol/drug abuse or dependence; 3) significant difficulty in maintaining attention or understanding clinimetric evaluation instructions; 4) any clinical condition that may interfere with the assessment; 5) pregnant women or potentially childbearing women not using an adequate method of birth control; and 6) any of the following medical conditions that preclude safe HBOT treatment: a) severe cognitive impairment; b) current mood episodes, claustrophobia or seizure disorder; c) active or severe pulmonary disease, previous thoracic surgery or pneumothorax; d) a history of severe heart disease; e) chronic or acute sinusitis/otitis media or major eardrum trauma; and f) a history of bleomycin-including chemotherapy or current chemotherapy.

**Study design and procedures**

This prospective, observational clinical trial was approved by the institutional review boards of L. Sacco University Hospital, Milan, and Habilita Care & Research Hospitals, Zingonia–Bergamo (Italy). All of the subjects gave their written informed consent after receiving a complete description of the study. Their clinical and socio-demographic data (age, gender, years of education, marital and occupational status, duration of FM and body mass index) were collected by means of a structured interview using interviewer-administered questionnaires. The eligible patients completed baseline clinimetric assessments of pain, fatigue, sleep, depression, anxiety, symptom severity, functional impairment, and their QoL, and were re-evaluated using the same instruments after 10 and 20 HBOT sessions.

**Clinimetric evaluations – Primary outcome measures**

**Pain:** Pain was assessed using a visual analogue scale (VAS) in the form of a 10 cm line numbered from 0 to 10 at regular intervals, with 0 representing no pain and 100 the most extreme pain. The subjects were asked to make a single mark at the appropriate place in the scale.

**Fatigue:** The Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scale is a 13-item questionnaire that measures the level of fatigue experienced during usual daily activities over the previous week using a four-point Likert-type scale (4 = not at all fatigued to 0 = very much fatigued) (24).

The scale has demonstrated equivalence in terms of its administration (interview vs self-report), reliability and sensitivity to change in a variety of populations and clinical settings.

**Sleep:** The Pittsburgh Sleep Quality Index (PSQI) retrospectively measures sleep quality and disturbances (25), discriminates good and poor sleepers, and provides a brief assessment of multiple sleep disturbances. It consists of 24 items, 19 of which are self-reported and five require secondary feedback from a room or bed partner. Only the self-reported items (15 scored 0-3 and 4 open-ended) are used for the quantitative evaluation of sleep and generate seven component scores, the sum of which provides a global measure of sleep quality (range 0–21), with
higher scores indicating poorer sleep (>5 indicates sleep disturbance). The component scores assess a broad range of domains associated with the quality of sleep, including its duration and latency, the frequency and severity of specific sleep-related problems, and the perceived impact of poor sleep on daytime functioning (25).

Symptom severity: The Fibromyalgia Impact Questionnaire (FIQ) is a 10-item self-report questionnaire that was developed to measure the physical and psychological symptoms of FM, and their impact on daily activities and the QoL. The first item includes 10 sub-items regarding physical functioning, each of which is rated using a 4-point Likert-type scale; items 2 and 3 ask the patients to indicate the number of days they felt well and the number of days they were unable to work because of FM symptoms; and items 4–10 rate work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety and depression using horizontal linear scales marked with 10 increments. The maximum possible total score is 100, and severely affected patients usually score >70. We used the validated Italian version (26).

Fibromyalgia Assessment Status (FAS) (27) is an index that provides a single measure (range: 0–10) combining patient assessments of fatigue, sleep disturbances, and pain evaluated on the basis of the 16 non-articular sites listed in the Self-Assessment Pain Scale (SAPS). It is based on 20 items designed to assess the frequency of FM symptoms such as pain, dyspnea, sleep disorders using 4-point Likert-type scale ranging from 1 (none or little of the time) to 4 (most or all of the time).

Secondary outcome measures
Depression: Depression was evaluated using the Italian version of the Zung Self-Rating Depression Scale (ZSDS) (28), which consists of 20 items that assess depression-related affective, cognitive, behavioural and physiological symptoms during the previous week using a 4-point scale ranging from 1 (none or little of the time) to 4 (most or all of the time). The total score ranges from 20 to 80, with higher scores representing greater symptom severity.

Anxiety: The Zung Self-Rating Anxiety Scale (ZSAS) (29) is a 20-item self-report instrument that was developed to assess the severity of anxiety symptoms. Subjects have to indicate the extent to which each of the 20 statements applied during the previous week using a 4-point Likert-type scale (1 = little of the time, 2 = some of the time, 3 = a good part of the time, and 4 = most of the time). Some questions are negatively worded to avoid the problem of set responses. The overall assessment is made on the basis of the total score (range 20–80), with higher scores representing more severe anxiety symptoms.

Quality of life: The patients’ QoL was evaluated using the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) (30) whose 36 items assess the extent to which health interferes with physical activities (physical functioning - 10 items), social aspects (social functioning - 2 items), working or other daily activities relating to their physical role (physical - 4 items) and emotional roles (role emotional - 3 items), energy level (vitality - 4 items), pain intensity (bodily pain - 5 items), psychopathology (mental health - 5 items), and subjective perception of health (general health - 5 items). The scores for each of these eight domains range from 0 to 100, with higher scores indicating a better quality of life. Algorithms have also been developed to calculate two psychometrically-based summary measures: the physical component summary (PCS) and mental component summary (MCS) scale scores (31).

Safety parameters
All of the adverse events spontaneously reported by the patients or observed by physicians were recorded.

Treatment
HBOT was administered in accordance with the guidelines defined by the Undersea and Hyperbaric Medical Society (UHMS). The patients intermittently breathed 100% oxygen through a face mask while sitting in a multi-place chamber pressurised with air at 1 ata (32). The protocol involved twenty 90-minute sessions (one session on three days per week) during which they breathed 100% oxygen at 2.5 ata with air breaks. Each session actually lasted 120 minutes as it consisted of a period of compression in air for 20 minutes, followed by treatment at 2.5 ata for three periods of 25 minutes separated by two 5-minute air breaks (mask off), and ending with a decompression period of 15 minutes.

Statistical analysis
The continuous data are expressed as mean values ± standard deviation (SD), and the categorical data as absolute numbers and percentages. A two-sided paired t-test was used to compare the values before and after HBOT. The normal distribution of all of the variables was tested by means of the Kolmogorov-Smirnov test. The analyses were made using SPSS 19.0 software, and a two-tailed p-value of <0.05 was considered statistically significant. Power analysis initially suggested recruiting a sample of 34 subjects Assuming an effect size of minimum interest of 0.5 (moderate magnitude according to Cohen (33)), a power of 0.8, and an α value of 0.05.

Results
Patients
Between May 2010 and December 2012, 53 FM patients were screened: 14 did not fulfil the inclusion criteria and seven were excluded because of contraindia-
## Table II. Clinical outcomes after 10 and 20 HBOT sessions.

<table>
<thead>
<tr>
<th>Table II</th>
<th>Clinical outcomes after 10 and 20 HBOT sessions.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain VAS</strong></td>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td>Arithmetic mean ± SD</td>
<td>8.11 ± 1.82</td>
</tr>
<tr>
<td>Mean difference ± SD</td>
<td>-1.27 ± 16</td>
</tr>
</tbody>
</table>

| **FACIT** | **Baseline** | **After 10 sessions** | **After 20 sessions** |
| Arithmetic mean ± SD | 20.43 ± 7.07 | 23.77 ± 6.82 | 26.36 ± 8.25 |
| Mean difference ± SD | 3.34 ± 1.89 | 5.93 ± 2.10 | 8.59 ± 2.10 |

| **PSQI** | **Baseline** | **After 10 sessions** | **After 20 sessions** |
| Arithmetic mean ± SD | 9.81 ± 3.55 | 9.50 ± 3.70 | 9.12 ± 3.83 |
| Mean difference ± SD | 0.31 ± 1.80 | -0.48 ± 2.26 | -0.29 ± 2.26 |

| **ZSDS** | **Baseline** | **After 10 sessions** | **After 20 sessions** |
| Arithmetic mean ± SD | 51.83 ± 10.12 | 49.37 ± 11.10 | 50.48 ± 11.49 |
| Mean difference ± SD | -2.46 ± 5.90 | -2.13 ± 6.84 | -2.33 ± 6.84 |

| **ZSAS** | **Baseline** | **After 10 sessions** | **After 20 sessions** |
| Arithmetic mean ± SD | 59.33 ± 10.82 | 55.71 ± 10.28 | 54.54 ± 11.96 |
| Mean difference ± SD | -3.62 ± 4.96 | -4.21 ± 7.29 | -4.73 ± 7.29 |

| **FIQ-R total score** | **Baseline** | **After 10 sessions** | **After 20 sessions** |
| Arithmetic mean ± SD | 68.04 ± 3.90 | 59.84 ± 4.42 | 55.56 ± 5.19 |
| Mean difference ± SD | 8.20 ± 14.08 | 12.89 ± 17.04 | 17.69 ± 17.04 |

| **FAS total score** | **Baseline** | **After 10 sessions** | **After 20 sessions** |
| Arithmetic mean ± SD | 8.14 ± 0.47 | 7.08 ± 0.51 | 5.99 ± 0.50 |
| Mean difference ± SD | -1.07 ± 3.24 | -2.02 ± 3.14 | -3.03 ± 3.14 |

### SF-36 PHYSICAL COMPONENT SCORES

| **SF-36 General health status** | **Baseline** | **After 10 sessions** | **After 20 sessions** |
| Arithmetic mean ± SD | 26.00 ± 15.78 | 32.44 ± 14.14 | 34.60 ± 14.3 |
| Mean difference ± SD | 6.04 ± 11.01 | 7.80 ± 13.01 | 8.76 ± 13.01 |

| **SF-36 Bodily pain** | **Baseline** | **After 10 sessions** | **After 20 sessions** |
| Arithmetic mean ± SD | 21.04 ± 11.29 | 24.96 ± 10.15 | 30.52 ± 13.89 |
| Mean difference ± SD | 3.92 ± 12.13 | 6.00 ± 15.84 | 9.00 ± 15.84 |

| **SF-36 Physical functioning** | **Baseline** | **After 10 sessions** | **After 20 sessions** |
| Arithmetic mean ± SD | 41.20 ± 19.11 | 47.60 ± 17.74 | 48.20 ± 19.89 |
| Mean difference ± SD | 6.40 ± 15.84 | 8.60 ± 14.11 | 11.00 ± 14.11 |

| **SF-36 Role function - physical aspect** | **Baseline** | **After 10 sessions** | **After 20 sessions** |
| Arithmetic mean ± SD | 3.00 ± 8.29 | 6.00 ± 20.77 | 18.00 ± 28.43 |
| Mean difference ± SD | 3 ± 22.03 | 16.00 ± 29.65 | 24.00 ± 29.65 |

| **SF-36 Physical component summary score** | **Baseline** | **After 10 sessions** | **After 20 sessions** |
| Arithmetic mean ± SD | 25.88 ± 5.49 | 28.48 ± 4.40 | 30.20 ± 4.87 |
| Mean difference ± SD | 2.60 ± 5.32 | 4.60 ± 5.83 | 6.00 ± 5.83 |

### SF-36 MENTAL COMPONENT SCORES

| **SF-36 Mental health** | **Baseline** | **After 10 sessions** | **After 20 sessions** |
| Arithmetic mean ± SD | 57.28 ± 16.03 | 53.24 ± 15.73 | 58.64 ± 18.86 |
| Mean difference ± SD | -4.04 ± 12.15 | 20 ± 15.14 | 24 ± 15.14 |

| **SF-36 Vitality** | **Baseline** | **After 10 sessions** | **After 20 sessions** |
| Arithmetic mean ± SD | 32.20 ± 14.65 | 33.72 ± 13.65 | 34.20 ± 16.87 |
| Mean difference ± SD | 1.72 ± 16.27 | 1.00 ± 18.87 | 1.50 ± 18.87 |

| **SF-36 Role function - emotional aspect** | **Baseline** | **After 10 sessions** | **After 20 sessions** |
| Arithmetic mean ± SD | 30.48 ± 37.03 | 34.52 ± 41.28 | 43.88 ± 44.81 |
| Mean difference ± SD | 4.04 ± 36.19 | 12.08 ± 38.26 | 14.08 ± 38.26 |

| **SF-36 Social functioning** | **Baseline** | **After 10 sessions** | **After 20 sessions** |
| Arithmetic mean ± SD | 38.80 ± 20.21 | 39.32 ± 17.44 | 42.24 ± 23.07 |
| Mean difference ± SD | 0.52 ± 13.87 | 4.44 ± 20.71 | 7.34 ± 20.71 |

| **SF-36 Mental component summary score** | **Baseline** | **After 10 sessions** | **After 20 sessions** |
| Arithmetic mean ± SD | 37.56 ± 8.72 | 37.76 ± 9.66 | 58.64 ± 18.85 |
| Mean difference ± SD | 0.20 ± 8.45 | 21.04 ± 15.81 | 22.04 ± 15.81 |
Clinical outcomes
Table II shows the clinical outcomes after 10 and 20 HBOT sessions. There was a significant improvement in pain VAS scores after both 10 (p=0.0062) and 20 sessions (p=0.0032), a significant improvement in fatigue after 20 sessions (p=0.006), but no significant change in the quality of sleep scores. Psychologically, the patients experienced a significant improvement from baseline in anxiety symptom severity after both 10 (p=0.001) and 20 sessions (p=0.009), but not in depressive symptom scores.
FM symptom severity scores showed the greatest improvement from baseline after 20 sessions (total FIQ score p=0.001; total FAS score p=0.006).

Self-reported health status
All of the scales in the physical component of the SF-36 significantly improved after 20 sessions (but not after 10), as did the PCS scale scores (p=0.006); four of the scales in the mental component did not change, whereas there was a highly significant improvement in the MCS scale scores after 20 sessions (p=0.0001).

Side effects
Two patients reported MEBT and one anxiety associated with agoraphobia. Four of the 32 patients discontinued the treatment: two with MEBT, one because of claustrophobia, and one because of dizziness. The MEBTs were mild and fully reversible in three days. The other reported side effect was somnolence (one patient).

Discussion
The results of this study show that ten (but mainly twenty) HBOT sessions not only improve patient-rated pain scores, but also functional impairment, anxiety and self-reported health status in patients with FM. These findings are in line with those of two randomised controlled studies evaluating the effect of HBOT on different clinical aspects of FM.

Yildiz et al. (18) randomised 50 patients to receive HBOT (26 patients) or normal air (24 patients, control group). The HBOT group underwent fifteen 90-min sessions at 2.4 ata on five days a week, and the control group underwent breathed air at 1 ata following the same schedule. The number of tender points and pain thresholds were assessed before treatment, and after the first and fifteenth sessions using an algometer and a VAS. There was a significant reduction in both the number of tender points and VAS scores, and a significant increase in pain thresholds of the HBO group after the first and fifteenth sessions, and significant differences in all of the measurements other than VAS scores between the HBOT group and the controls after the first session.

Efrati et al. (19) randomly assigned 60 female FM patients to treated and crossover groups. The treated group (n=30) underwent forty 90-minute HBOT sessions using 100% oxygen at 2 ata on five days a week over a period of two months, whereas the crossover control group (n=30) went without treatment during that time and then underwent the same HBOT protocol two months later. The study endpoints included tender point counts, pain thresholds, functional impairment (FIQ), psychological symptoms, and the QoL. In addition, brain activity was evaluated by means of single-photon emission computed tomography (SPECT). HBOT significantly improved all FMS symptoms and the QoL in both groups. SPECT revealed the rectification of abnormal brain activity, with a decrease in posterior hyperactivity and an increase in the reduced frontal activity. No improvement in any of the parameters was observed after the control period. Various assumptions can be made about why HBOT seems to be effective in treating FM. The analgesic effects of HBOT have been observed in pre-clinical models of nociceptive, inflammatory and neuropathic pain (13). Neuropathic pain, which is caused by nervous system injury or dysfunction, shares some of the characteristics of FM, including changes in central nervous system and peripheral nerve fibres (34, 35), and the clinical features of hyperalgasia and allodynia (36). It is thought that chronic nervous system inflammation involving sustained glia activation (37) is a key factor in the pathogenesis of both neuropathic pain and FM. Glial cells (particularly astrocytes) play a central role in pain-producing cytokines such as IL-1, IL-6, tumour necrosis factor (TNF)-α, and the neurotransmitters involved in pain signals.

Nitric oxide (NO) also induces chronic pain (38), and plays a dual role in modulating pain levels (39): it not only contributes to the development of central sensitisation (40), but also inhibits nociception in the spinal cord (41) and mediates the analgesic effect of opioids and other analgesic substances. NO synthesis is regulated by NO synthases (NOS), and neuronal NOS (nNOS), and inducible NOS (iNOS) are protein variants that participate in central pain modulation and sensitisation. NOS are also expressed in the presence of inflammation (42) and in activated microglia, which leads to the massive NO synthesis that increases pain generation. It has been demonstrated that HBOT inhibits the release of inflammatory cytokines (43) and glial cell activation (44), which further decreases cytokine release. In particular, the positive effect of HBOT on allodynia and hyperalgasia seems to be related to the inhibition of endoneuronal TNF-α production (45). It is also known that HBOT decreases the expression of spinal iNOS and nNOS in a rat model of neuropathic pain (46, 43).

One further mechanism involved in the positive effect of HBOT on chronic pain is neuroplasticity. It has been demonstrated at cellular level that HBOT induces neuroplasticity by promoting cell proliferation and neurogenesis (47), axonal regeneration and growth (48), myelination (49), and brain angiogenesis (50). From a clinical point of view, the ability of HBOT to induce neuroplasticity is suggested by the findings of studies showing an improvement in chronic...
cally impaired brain function (even years after the brain insult) in post-stroke patients and in those who develop post-concussion syndrome after a mild traumatic brain injury (51, 52). The ability of HBOT to induce neuroplasticity in FM patients is suggested by the results of the study by Efrati et al. (19), who demonstrated that effective HBOT rectifies the abnormal brain activity related to pain processing by decreasing posterior hyperactivity and increasing pre-frontal cortical activity. 

In healthy subjects, a hyperbaric oxygen-enriched environment significantly improves both single and combined (multi-tasking) cognitive and motor performances in comparison with a normal environment (normal air at sea level) (53), and repeated exposure to HBOT improves memory performance (54). In patients with anoxic brain injury due to cardiac arrest, HBOT may improve cognitive functions even during the late chronic phase of brain anoxia. These findings suggest that HBOT may be useful in treating the cognitive dysfunction in the attentional and executive domains affecting some FM patients (55). Future adequately powered and methodologically sound studies should be carried out in order to determine whether HBOT is efficacious in treating FM-related cognitive dysfunction.

In terms of the optimal dose and duration of HBOT, the findings of this study support the hypothesis that 10-20 sessions may improve a number of the physical and psychological symptoms of FM. Symptoms such as pain and anxiety improved after ten sessions, whereas fatigue improved only after twenty, and the quality of sleep and depressive symptoms did not seem to be positively affected. These findings are in line with those coming from pre-clinical and clinical studies. One of these studies found that the anti-nociceptive effect of HBOT in a rodent model was apparent immediately after treatment and persisted for up to five hours (56), and another found that two weeks of HBOT in a rat neuropathic pain model significantly improved pain levels both during and after treatment (57). In mice, four daily 60-minute HBOT sessions at 3.5 ata induced an anti-nociceptive response consisting of an early phase lasting about six hours followed by a late phase that started 18 hours later and continued for up to three weeks (this late phase only developed after the fourth session) (58). In patients with idiopathic trigeminal neuralgia, one course of HBOT (10 consecutive days) led to rapid-onset, dose-dependent and long-lasting analgesic effects documented a decrease in the carbamazepine dose required to control pain and lower self-evaluated pain VAS scores (59).

However, it is challenging to establish the efficacy and optimal dose-response curve of HBOT in FM and other pain syndromes because patient blinding and a true placebo control group are difficult to obtain. One way of administering a HBOT “placebo” is to increase environmental pressure inside the hyperbaric chamber to at least 1.3 ata in order to make the patients feel the pressure, but this significantly increases plasma oxygen tension to a level that can lead to noticeable physiological effects (60).

In addition to its lack of a sound randomised controlled design, this study was limited by the relatively small number of recruited patients. Nevertheless, our findings are in line with and strengthen the similar findings of previous prospective controlled trials.

Acknowledgements
We would like to thank all the staff members of the HBOT Service of Habilita, Hospitals & Research, Zingonia. We would also like to offer our special thanks to Dr Ugo Pani, HBOT medical manager, and Ing. Roberto Scandella, HBOT technical supervisor.

References
Fibromyalgia and hyperbaric oxygen therapy / F. Atzeni et al.


35. ÜÇEYLER N, SOMMER C: Objective evidence that small-fiber polyneuropathy underlies some illnesses currently labeled as fibromyalgia. Pain 2013; 154: 2569.


