Hyperbaric oxygen therapy for multiple sclerosis (Review)

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[Intervention Review]

Hyperbaric oxygen therapy for multiple sclerosis

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ABSTRACT

Background

Multiple Sclerosis (MS) is a chronic, recurrent and progressive illness with no cure. On the basis of speculative pathophysiology, it has been suggested that Hyperbaric Oxygen Therapy (HBOT) may slow or reverse the progress of the disease.

Objectives

The object of this review was to evaluate the efficacy and safety of HBOT in the treatment of MS.

Search methods

We searched the Cochrane Multiple Sclerosis Group's Trials Register (25 February 2011).

Selection criteria

All randomised, controlled trials involving a comparison between HBOT and a sham therapy in MS were evaluated.

Data collection and analysis

Two reviewers independently appraised all comparative trials identified, extracted data and scored them for methodological quality.

Main results

We identified ten reports of nine trials that satisfied selection criteria (504 participants in total). Two trials produced generally positive results, while the remaining seven reported generally no evidence of a treatment effect. None of our three a priori subgroup analyses placed these two trials in the same group and were therefore unable to account for this difference. Three analyses (of 21) did indicate some benefit. For example, the mean Expanded Disability Status Scale (EDSS) at 12 months was improved in the HBOT group (group mean reduction in EDSS compared to sham -0.85 of a point, 95% confidence interval -1.28 to -0.42, P = 0.0001). Only the two generally positive trials reported on this outcome at this time (16% of the total participants in this review).

Authors' conclusions

We found no consistent evidence to confirm a beneficial effect of hyperbaric oxygen therapy for the treatment of multiple sclerosis and do not believe routine use is justified. The small number of analyses suggestive of benefit are isolated, difficult to ascribe with biological plausibility and would need to be confirmed in future well-designed trials. Such trials are not, in our view, justified by this review.

PLAIN LANGUAGE SUMMARY

Hyperbaric oxygen therapy, which involves people breathing pure oxygen in a specially designed chamber, for the treatment of multiple sclerosis

Multiple sclerosis (MS) is a chronic disease of the nervous system which affects young and middle-aged adults. Repeated damage to parts of the nerves leads to progressive weakness and disability. Hyperbaric oxygen therapy (HBOT) involves people breathing pure oxygen in a specially designed chamber (such as used for deep sea divers suffering pressure problems after resurfacing). HBOT is sometimes used for MS in case a lack of oxygen to the affected nerves may be making MS worse, but this theory is unproven. The review of nine trials found no consistent evidence that HOBT can improve disability or modify the progression of MS. There is little need for further research.

BACKGROUND

Multiple sclerosis (MS) is a chronic neurological disease in which there is patchy inflammation, demyelination and gliosis in the central nervous system (CNS). Although it exhibits marked racial and geographic variability in its prevalence, MS occurs most widely in Northern European races (prevalence 30 to 150 per 100,000) (Compston 1998) and is the commonest cause of chronic neurological disability in these groups. While there is considerable variability in clinical features and rate of progression, the histological changes are remarkably constant (Prineas 1993). Discrete areas of inflammation appear and evolve within the CNS, showing a marked perivenular distribution. Perivascular cuffing with lymphocytes, breakdown of the blood-brain barrier (BBB) and egress of inflammatory cells from the intravascular compartment are followed by cascading inflammatory activation. Damage is seen in myelin sheaths and oligodendrocytes, and eventually degeneration of axons causes the neurological deficits by which the disease becomes apparent. A degree of recovery is possible, at least in the early stages (Prineas 1979), but with successive episodes of inflammation, remyelination becomes less efficient, axonal loss accumulates and neurological disability progresses.

Magnetic resonance imaging (MRI) data have shown that breakdown of the BBB is an extremely early event in the evolution of an inflammatory lesion in MS (Silver 1998). It is widely held that this process, and subsequent stages in the development of a plaque, are immunologically mediated (Bar-Or 1999). Despite the current wide adoption and success of immunosuppressive therapy in MS (corticosteroids, beta interferons, glatiramer acetate) the evidence for this remains circumstantial.

Several features of the disease suggest there may be a vascular association, including the observation of peri-venular lesions (Scheinker 1943), and both abnormal permeability (Aita 1978) and vasoconstriction (Brickner 1950) of vessels near MS lesions. A summary paper (James 1982) suggested that small fat emboli may be responsible for the typical lesions. James postulated that a subacute form of fat embolisation similar to that following trauma may be responsible and that such emboli were triggered by a number of stimuli. The reduced vascularity of the cortex in comparison to the white matter was postulated to explain the anatomical distribution of lesions.

James went on to suggest the use of hyperbaric oxygen therapy (HBOT) as a treatment for MS based on the demonstrated ability of HBOT to produce vasoconstriction with increased oxygen delivery and some anecdotal evidence of efficacy (James 1982). In the subsequent ten years a flurry of activity produced a number of randomised studies in the UK, USA and Europe, despite widespread scepticism concerning the postulated pathophysiology. Results were mixed and, while some have embraced the therapy with enthusiasm, most neurologists used these results to abandon the concept. The largest professional body in hyperbaric medicine does not list MS as one of its accepted indications (UHMS 2001).

Today, however, many patients in the UK continue to be treated on a permanent recurrent basis (Perrins 1996). At some centres, physicians are not directly involved in therapeutic decisions or outcome evaluation. Elsewhere, support groups are developing to provide this service to their own communities or to provide the necessary funds to allow MS patients to access treatment (e.g. the MUMS Network- www.netnet.net/mums - last accessed September 2003).

HBOT is associated with some risk of adverse effects including damage to the ears, sinuses and lungs from the effects of pressure, temporary worsening of short-sightedness, claustrophobia and oxygen poisoning. Although serious adverse events are rare, HBOT cannot be regarded as an entirely benign intervention.

If there is an appreciable therapeutic effect of HBOT on MS and this can be generated at reasonable cost, the use of this treatment modality should be encouraged. If there is little possibility of an important treatment effect, then physicians should be made aware of evidence that will discourage the use of resources in this area.

OBJECTIVES

The objectives of this review were to determine the efficacy and safety of hyperbaric oxygen therapy in the treatment of patients with MS.

Specifically we wish to address the following questions:

- Is a course of HBOT more efficacious than placebo or no treatment in improving disability for patients with MS?
- Is a course of HBOT more efficacious than placebo or no treatment in slowing the progress of disease in progressive MS?
- Is a course of HBOT more efficacious than placebo or no treatment in preventing or delaying relapse in relapsing/remitting MS?
- Is HBOT administration safe?

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials, regardless of allocation concealment and blinding, were included. Trials were considered where HBOT versus placebo or no therapy were part of the randomised methodology.

Types of participants

Trials enrolling any MS patients irrespective of the disease state or course were considered for inclusion. Patient selection based on clinical criteria alone was accepted (McDonald 1977).

Types of interventions

HBOT was the active intervention of interest and any trial employing a regimen of HBOT versus placebo or no treatment was evaluated.

Types of outcome measures

Trials that considered at least one of the following outcome measures were included.

Primary outcomes

(Objective assessments by neurologist/hyperbaric physician).
(1) Kurtzke Expanded Disability Status Scale (EDSS) at completion of the intervention, six months and/or one year (Kurtzke 1983). Data acceptable were group means with standard deviation where possible and dichotomous - number of participants improved versus those not improved. Improvement was a reduction in EDSS of at least one point .
(2) Numbers of participants suffering at least one exacerbation at six months and one year. Data was dichotomous- number of participants with at least one exacerbation versus the number of participants free of exacerbation. Exacerbation was defined as newly developed or recently worsened symptoms of neurological dysfunction, with or without objective confirmation, lasting more than 24 hours (Schumacher 1965).
(3) Numbers of participants suffering side-effects or adverse events associated with treatment, including those who dropped out. Data was dichotomous for each side-effect or adverse event-number of participants with side effects or adverse events versus number of participants without them.

Secondary outcomes

(Functional scores assessed by neurologist and those patient-reported).
(1) Kurtzke Functional Status Scores (FSS) at completion of the intervention, six months and/or one year (Kurtzke 1983). Both global estimates and those estimated for each system were considered. Data acceptable were group means with standard deviation where possible and dichotomous - number of participants improved versus those not improved. Improvement was a reduction in FSS of at least one point.
(2) Number of individuals with a change in individual elements of FSS. Dichotomous outcome with number improved versus those unchanged or deteriorated and/or numbers deteriorated versus those unchanged or improved.
The Kurtzke Expanded Disability Status Scale (EDSS) and Functional Status Scale (FSS) are summarised in Table 1.

Search methods for identification of studies

No language restrictions were applied to the search.

Electronic searches

The Trials Search Co-ordinator searched the Cochrane Multiple Sclerosis Group's Specialised Register (25 February 2011)
The Cochrane Multiple Sclerosis Trials Register is updated regularly and contains trials identified from:

1. The Cochrane Central Register of Controlled Trials (CENTRAL) (recent issue);
2. MEDLINE (PubMed) (1966 to date);

3. EMBASE (Embase.com) (1974 to date);
4. CINAHL (Ebsco host) (1981 to Feb 2011);
5. LILACS (Bireme) (1982 to date);
6. PEDro;
7. Clinical trials registries.

Information on the Cochrane Multiple Sclerosis Group's Trials Register and details of search strategies used to identify trials can be found in the 'Specialised Register' section within the Cochrane Multiple Sclerosis Group's module.

The keywords used to search for this review are listed in (Appendix 1).

For search methods used in the previous version please see (Appendix 2) and (Appendix 3).

Searching other resources

(7) hand searched all hyperbaric journals, proceedings and texts from 1970 to January 2010.

(8) examined the reference lists from relevant publications identified above.

(9) contacted the authors of all relevant trials published and requesting references for any further studies not identified by the search above.

Data collection and analysis

One reviewer (MB) examined the search results and identified comparative studies that may have been relevant. All comparative clinical trials identified were retrieved in full and reviewed independently by two reviewers (MB and RH), one with context expertise in the treatment of MS, one with context expertise in hyperbaric medicine and clinical epidemiology. Using a data extraction form developed for this review, each reviewer extracted relevant data, graded for methodological quality using the method of Jadad (Jadad 1996), and made a recommendation for inclusion or exclusion from the review. The method of Jadad scores trials on three criteria (randomisation, double-blinding and description of withdrawals), each of which, if present, is given a score of 1. Further points are available for description of a reliable randomisation method and use of a placebo. The scores are totalled as an estimate of overall quality. An independent clinical epidemiologist was available to settle differences, but was not required.

All data extracted reflected original allocation group to allow an intention to treat analysis. Drop-outs were identified where this information was given. We employed a priori sensitivity analyses using different approaches to imputing missing data. The best case scenario assumed that none of the originally enrolled participants missing from the primary analysis in the treatment group had the poor outcome of interest whilst all those missing from the control group did. The worst case scenario was the reverse.

For some outcomes, several studies reported no individuals with the outcome of interest in either group. As this review deals for the most part with outcomes that are uncommon, the inclusion of such data is of clinical relevance. Such data does not, however, contribute to the meta-analysis using RevMan 4.1, and this is noted in the results section where relevant. The list of studies and outcomes affected is given in Table 2 .

Data analysis

Separate analyses were made using RevMan 4.1 software of all primary outcomes identified above. Failure to improve EDSS was examined using comparison of group means and SD (difference between means across trials). As this data was not available from a number of trials, the number of participants failing to improve one point on the EDSS was also compared as a dichotomous variable and the results presented as an odds ratio of failure to improve. Other outcomes were similarly treated as dichotomous rather than continuous variables with estimations of odds ratios for the failure to improve in FSS, prevention of exacerbation and the incidence of side-effects of therapy.

All dichotomous variable data were analysed using the DerSimonian and Laird random-effects method and presented with 95% confidence intervals. Heterogeneity between trials was tested for using a standard chi squared test and we accepted there was significant heterogeneity when P was < 0.05. Where meaningful, the number needed to treat to achieve one extra favourable outcome was calculated and presented with 95% confidence intervals. Subgroup analysis was considered by individual treatment session nitrogen dose (nature of sham treatment), individual treatment oxygen dose (treatment pressure) and length of therapy - (one month (20 treatment sessions) versus six months or one year). In view of the paucity of data presented on patient entry severity, disease classification and comparator therapies (see table : 'Characteristics of included studies'), we did not consider subgroup analysis to be appropriate on the basis of these factors.

To assess possible effect of dropouts who did not enter analysis in these studies, a sensitivity analysis was performed where appropriate as a best case (all dropouts in the active groups assumed successes, all dropouts in the sham group assumed failures) and worst case (all dropouts in the active group assumed failures, all in the sham group assumed successes).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

This review search update yielded only four results, of which none were RCTs. The initial searches were performed in 2001 and repeated in June 2006, July 2009, January 2010 and February 2011. No new randomised trials have been identified since the initial

search and we have found very few relevant reports of any kind in the literature since then.

In total, we identified 36 publications dealing with the treatment of MS with HBOT (MEDLINE 16, DORCTIHM 4, HANDSEARCHING 8, REFERENCES 6, UNPUBLISHED 2). Initial examination suggested 19 possible comparative trials. After appraisal of the full report we excluded nine publications: two were reviews (one semi-quantitative, one qualitative) containing no new data (Gottlieb 1988; Kleijnen 1995), one was the results of a prospective registry (Kindwall 1991), two were comparative, but non-randomised (Pallotta 1986; Worthington 1987) and four were abstracts of randomised studies containing no appropriate clinical outcome data (Erwin 1985; Massey 1985; Murthy 1985; Slater 1985). None of these abstracts have been published as full accounts and an approach to the authors did not produce further data. (*See* 'Table of excluded studies'). A search in June 2006 found six further publications, none of which were reports of comparative trials.

In total, nine trials contributed to this review. One trial was the subject of two publications, one dealing with short-term results following treatment (Barnes 1985), the other with longer-term results at six months and two years (Barnes 1987). All included trials were published between 1983 (Fischer 1983) and 1990 (Oriani 1990) and the reviewers are unaware of any on-going RCTs in the area. In total, these trials include data on 504 participants, 260 receiving HBOT and 244 placebo, and the largest (Barnes 1985; Barnes 1987) accounts for 29.7% of cases. (*See* 'Table of included studies').

The dose of oxygen per treatment session varied between studies. The lowest dose administered (Harpur 1986) was 1.75 ATA for 90 minutes, while the highest dose was 2.5 ATA for 90 minutes {Confavreux 1986; Oriani 1990}. All others used 2.0 ATA for 90 minutes. All trials used an initial course of 20 treatment sessions over four weeks, while two (Harpur 1986; Oriani 1990) continued to administer 'top-up' treatments (*see* 'Table of included studies'). Subgroup analyses for the primary outcomes were performed with respect to oxygen dose and the use of top-up therapy where data were available.

The method of sham treatment also varied across the studies. Four studies (five reports) used air administered at a trivial pressure presumed sufficient to convince the participants of compression, an inspired partial pressure of oxygen (PIO_2) of approximately 167mmHg and nitrogen (PIN_2) of approximately 608mmHg (Barnes 1985; Neiman 1985; Confavreux 1986; Wiles 1986), four used nitrogen enriched air to achieve a PIO_2 equal to air at 1 ATA (152mmHg) at the same pressure as the active treatment group and consequently high PIN_2 varying from approximately 1100 to 1345 mmHg (Fischer 1983; Wood 1985; Harpur 1986; L'Hermitte 1986), while Oriani (Oriani 1990) used air at the same pressure as the treatment group (PIO_2 380mmHg, PIN_2 1520mmHg). Subgroup analysis for the main outcomes was performed with respect to sham PIN_2 where data were available.

All trials included participants with a clinical assessment of definite MS. Four trials used the clinical criteria of Poser (Neiman 1985; Harpur 1986; L'Hermitte 1986; Oriani 1990), two the clinical criteria of Schumacher (Fischer 1983; Barnes 1985) and one the clinical criteria of McDonald (Wood 1985) (Schumacher 1965; McDonald 1977; Poser 1983). For the remaining two trials the clinical criteria were unclear (Confavreux 1986; Wiles 1986). Specific exclusion criteria varied between trials, but in general included a period of between three months and 12 months free of an exacerbation (Fischer 1983; Barnes 1985; Wood 1985; Confavreux 1986; Harpur 1986; Wiles 1986; Oriani 1990), no recent administration of a new immunosuppressive drug (Fischer 1983; Confavreux 1986; L'Hermitte 1986; Wiles 1986) and no specific contraindication to HBOT (all trials). Several studies required EDSS scores between specified values, or less than a specified value (Oriani 1990 $\leq$ 5; L'Hermitte 1986 $\leq$ 6; Barnes 1985 $\leq$ 7; Wood 1985 3 to 8). Individual trial exclusions identified were Barnes (Barnes 1985) (aged over 60 years), Oriani (Oriani 1990) (definite disease for longer than 10 years), Fischer (Fischer 1983) (definite disease for longer than five years) and Wiles (Wiles 1986) (able to walk assisted or unassisted for 50 metres). All but one trial gave a mean and SD for entry EDSS scores in each group, the exception being Wood (Wood 1985), that gave a mean and range of entry EDSS.

There was no detail on the recruitment time period in any of the studies. The follow-up periods varied between immediate to one month (all trials), six months (Fischer 1983; Neiman 1985; Confavreux 1986; Harpur 1986; L'Hermitte 1986; Barnes 1987; Oriani 1990) and one year (Fischer 1983; Confavreux 1986; Barnes 1987; Oriani 1990). All included studies reported at least one clinical outcome of interest. Outcomes considered for this review were: group mean differences in EDSS pre-treatment to immediately post -treatment, six months post-treatment and one year post-treatment; improvement as defined as a decrease of at least one point on the EDSS at end of treatment, six months and one year; improvement in FSS on similar criteria at these assessment times; subjective ratings of improvement in individual systems of the FSS; relapse during treatment and at six months and one year; and the incidence of adverse events during therapy, specifically aural barotrauma and visual disturbances. The details of clinical outcomes evaluated at each time period for each trial can be seen in the table of included studies.

Non-clinical outcomes reported included Visual Evoked Potentials (Neiman 1985; Wood 1985; Harpur 1986; L'Hermitte 1986; Wiles 1986; Oriani 1990), Somatosensory Evoked Potentials (Wood 1985; L'Hermitte 1986; Oriani 1990), Auditory Evoked Potentials (L'Hermitte 1986; Oriani 1990), Magnetic Resonance Imaging (Harpur 1986; Wiles 1986), Micturating Cystometrography (Wiles 1986) and cortisol production (Wiles 1986).

Risk of bias in included studies

Jadad score

Study quality was generally assessed as high. Three of the nine included studies were assigned a score of 5 (Fischer 1983, Neiman 1985, Wood 1985), while the remaining six studies were assigned a score of 4. The significance of this small variation is unclear and it was not used as a basis for sensitivity analysis by study quality.

Randomisation

Allocation concealment was adequately described in two studies (Fischer 1983; Oriani 1990), while the issue remained unclear in the remaining studies. Randomisation procedures were loosely described, if at all, in these studies and there is no clear indication that the investigators were unable to predict the prospective group to which a participant would be allocated. In one study, (Harpur 1986), the participants were matched in pairs and then randomised to HBOT or sham.

Patient baseline characteristics

All participants were in a clinically stable state in all studies with the exception of L'Hermitte, where no specific mention was made concerning recent exacerbation (L'Hermitte 1986). There were differences in the mean and range of entry EDSS. The mildest cases on admission were those in Oriani (Oriani 1990), where the entry criteria was EDSS of less than 5 and the mean scores were 3.39 (SD 1.16) in the active group and 2.97 (SD 0.84) in the control group, whilst the most severely affected were the participants enrolled by Confavreux (Confavreux 1986) (mean EDSS 6.2, SD 0.7 active, mean 6.9, SD 1.4 control). The majority of studies enrolled participants with scores between 3 and 8. There were no obvious differences between groups in the same study, although no author made a specific statement to confirm this.

Blinding

The participants were blinded in all studies, although only Harpur attempted to test the success of patient blinding by questionnaire (no numerical result reported) (Harpur 1986). This author described blinding as "preserved, although most participants felt they had received placebo due to the lack of anticipated effect." All studies similarly reported blinding of outcome assessors to allocation. In all trials, assessment for primary clinical outcomes were made by the treating neurologist remote to the treatment facility. Although not clearly stated, it is probable that many of the treating physicians in the trials would have been aware of treatment allocation. The hyperbaric facility staff administering the gases would be required to know the mixture they were administering. Four trials, (Fischer 1983; Confavreux 1986; Barnes 1987; Oriani 1990), specifically defined who in their facility was blind to allocation.

Patients lost to follow-up

The numbers of participants lost to follow-up are summarised in Table 3. There were no participants withdrawn or lost to follow-up who appeared in the analysis in any of the studies. Sensitivity analysis in this review has made best and worse case analyses to examine potentially important effects on outcome. Overall, there were 31 participants lost to final follow-up (7.7% of the total number enrolled).

Intention to treat analysis

This was not mentioned as a strategy in any of the trials. While participants lost to follow-up or withdrawn were excluded from analysis, there was no re-allocation to placebo in participants who failed to complete active therapy. No information is available on these participants.

Effects of interventions

Primary Outcomes

Improvement in disability

(1) Improvement of mean EDSS at completion of 20 treatments.

Five trials contributed data to this outcome (Fischer 1983; Neiman 1985; Harpur 1986; Wiles 1986; Oriani 1990), involving 271 participants (54% of the total included in this review), 134 randomised to receive HBOT and 137 to a sham treatment. The Neiman trial contributed most weight to the analysis (58%). There was no significant reduction in the mean EDSS in the active treatment group compared to sham (P = 0.4, mean change in active group compared to sham of -0.07, 95%CI -0.23 to 0.09). The test for heterogeneity was marginal (Chi^2 9.48, P = 0.05). Subgroup analysis by PIN_2 during treatment and oxygen dose did not explain this possible heterogeneity.

(2) Improvement of mean EDSS at six months.

Three trials contributed data to this outcome (Fischer 1983; Harpur 1986; Oriani 1990), involving 163 participants (32% of the total), 80 randomised to HBOT, 83 to sham. The Harpur trial contributed most weight to the analysis (44.2%). There was no significant reduction in the mean EDSS in the HBOT group compared to the sham, (mean change in the active group compared to sham -0.22, 95%CI -0.54 to 0.09, P = 0.17). There was significant heterogeneity in this analysis (Chi^2 7.55, df2, P = 0.023). Subgroup analysis by length of treatment suggested there was a significant benefit of HBOT for those having a shorter course of therapy (20 treatments) compared to 20 treatments plus five months of boosters. This reflected the results of a single trial (Fischer 1983) using the shorter course (short course mean change in active group compared to sham, -0.84, 95%CI -1.43 to -0.25, P = 0.006, long course mean change -0.29, 95%CI -0.91 to 0.33, P = 0.4).

(3) Improvement of mean EDSS at 12 months.

Only two trials contributed data to this outcome (Fischer 1983; Oriani 1990), involving 81 participants (16% of the total), 39 randomised to HBOT and 42 to sham. There was a significant reduction in EDSS in the active group compared to sham, (mean change in the active group compared to sham -0.85, 95%CI -1.28 to -0.42, P = 0.0001). There was no significant heterogeneity in this analysis. It should be noted that the two trials contributing to this result were the only two of the nine trials to report generally positive results. One of the trials (Fischer 1983), gave 20 treatments

only, while the other (Oriani 1990) gave an initial course of 20 treatments plus a 'top-up' regimen to one year.

(4) The number of participants not improved by at least one point on EDSS at completion of 20 treatments.

Eight trials contributed data to this outcome (Wiles 1986 the exception), involving 411 participants (82% of the total), 215 randomised to HBOT and 196 to sham. In three trials, no participants were improved in either arm (Barnes 1985; Neiman 1985; L'Hermitte 1986) and these trials therefore do not contribute to the meta-analysis. Few participants improved in either group, 11 (5%) in the HBOT group and 3 (1.5%) in the sham group. There was no significant reduction in the odds of remaining unimproved following the administration of HBOT (OR 0.33, 95% CI 0.09 to 1.18, P = 0.09). There was no significant heterogeneity in this analysis. A pre-planned sensitivity analysis examining the effect of allocation of dropouts using a best case (all dropouts in active group deemed successes, all dropouts in sham group deemed failures) and worse case (all dropouts in the active group deemed failures, all in the sham group deemed successes) did not alter the result. (Best case odds of failing to improve with HBOT OR 0.36, 95%CI 0.09 to 1.49, P = 0.16, worst case OR 0.84, 95%CI 0.19 to 3.67, P = 0.82).

(5) The number of participants not improved by at least one point on EDSS at six months.

Seven trials contributed data to the outcome (Wood 1985, Wiles 1986 the exceptions), involving 363 participants (72% of the total), 192 randomised to HBOT and 171 to sham. In three trials, (L'Hermitte 1986, Confavreux 1986, Neiman 1985), no participants were improved in either arm, and these trials therefore did not contribute to the meta-analysis. 16 participants (8.3%) improved in the HBOT group and 8 participants (4.7%) in the sham group. The Oriani trial contributed 53% of the weight in this analysis. There was no significant reduction in the odds of remaining unimproved following the administration of HBOT (OR 0.42, 95%CI 0.16 to 1.08, P = 0.07). There was no significant heterogeneity in this analysis. The analysis was sensitive to the allocation of dropouts. With the best case assumptions, there was a significant reduction in the odds of failing to improve with HBOT (OR 0.35, 95%CI 0.15 to 0.83, P = 0.02), while with the worst case assumptions, the result remain non-significant (OR 1.58, 95% CI 0.47 to 5.29, P = 0.45).

(6) The number of participants not improved by at least one point on EDSS at 12 months.

Only three trials contributed data to this outcome (Barnes 1985; Confavreux 1986; Barnes 1987; Oriani 1990), involving 176 participants (35% of the total), 90 randomised to HBOT and 86 to sham. In one trial, (Confavreux 1986), no participants were improved in either arm, and this trial therefore did not contribute to the meta-analysis. Thirteen participants (14.3%) improved in the HBOT group and four participants (4.5%) in the sham group. This analysis largely reflects the Oriani study, to which it contributes 84.7% of the weight. There was a significant reduction in the odds of being unimproved following the administration of HBOT (OR 0.2, 95%CI 0.06 to 0.72, P = 0.01). There was no significant heterogeneity in this analysis. Subgroup analysis according to treatment length (20 treatments versus more than 20 treatments) was hampered by having only one study in each subgroup, but suggests benefit for the HBOT group for the longer course given by Oriani (OR 0.19, 95%CI 0.05 to 0.73, P = 0.02), but no benefit from the shorter course given by Barnes and Confavreux (OR 0.34, 95%CI 0.01 to 8.64, P = 0.52). The result was sensitive to the allocation of dropouts with a loss of any significant advantage from the administration of HBOT with worst case assumptions (OR 1.34, 95% CI 0.08 to 21.75, P = 0.21). The analysis suggests we would need to treat 10 participants with HBOT to achieve one extra patient with an improvement in EDSS of one point at one year, but we may have to treat as many as 71 (NNT = 10, 95%CI 5 to 71).

Prevention of deterioration

(1) Prevention of exacerbation during one month of treatment.

Only one trial (Barnes 1985) reported the incidence of exacerbation during the initial 20 treatment period of one month. This trial included 117 participants (23% of the total). Only one participant experienced an exacerbation during this period and that participant was in the sham group. There was no significant difference in the odds of exacerbation in either group (OR 0.31, 95%CI 0.01 to 7.80, P = 0.5).

(2) Prevention of exacerbation within six months.

Only two trials reported on this outcome (Harpur 1986; L'Hermitte 1986), involving 122 participants (24% of the total), 73 randomised to HBOT and 49 to sham. 10 participants (13.7%) in the active group suffered an exacerbation, while seven participants (14.3%) did so in the sham group. There was no significant reduction in the incidence of exacerbation following the administration of HBOT (OR 0.74, 95%CI 0.25 to 2.22, P=0.6). This result was, however, sensitive to the allocation of dropouts using the best case assumptions (best case OR 0.36, 95%CI 0.14 to 0.94, P = 0.04). There was no alteration using worst case assumptions (worst case OR 1.22, 95%CI 0.42 to 3.55).

(3) Prevention of exacerbation within 12 months.

Only two trials reported on this outcome (Fischer 1983; Barnes 1987) involving 153 participants (30% of the total), 77 randomised to HBOT and 76 to sham. 20 participants (25.9%) suffered an exacerbation within 12 months after receiving HBOT, while 28 participants (36.9%) did so in the sham group. There was no significant reduction in the odds of exacerbation following the administration of HBOT (OR 0.38, 95%CI 0.04 to 3.22, P = 0.4). The result was not sensitive to allocation of dropouts (best case OR 0.31, 95%CI 0.04 to 2.57, P = 0.3, worst case OR 0.61, 95% CI 0.16 to 3.22).

Secondary Outcomes

Improvement in functional status scale

(1) The number of participants not improved by at least one point on

FSS at completion of one month of therapy.

Four trials contributed data to the outcome (Neiman 1985; Harpur 1986; L'Hermitte 1986; Oriani 1990), involving 194 participants (39% of the total), 107 randomised to HBOT and 87 to sham. 31 participants (29%) improved in the HBOT group and 24 participants (28%) in the sham group. There was no significant increase in the odds of improving following the administration of HBOT (OR 1.17, 95%CI 0.59 to 2.33). There was no significant heterogeneity in this analysis. The result was not sensitive to the allocation of dropouts (best case OR 1.02, 95%CI 0.52 to 1.99, P = 1, worst case OR 1.43, 95%CI 0.58 to 3.50, P = 0.4).

(2) The number of participants not improved by at least one point on FSS at six months.

Four trials contributed data to the outcome (Neiman 1985; Harpur 1986; L'Hermitte 1986; Oriani 1990), involving 185 participants (37% of the total), 105 randomised to HBOT and 80 to sham. 24 participants (23%) improved in the HBOT group and 22 participants (28%) in the sham group. One study (Harpur) contributed 50.3% of the weight to this analysis. There was no significant increase in the odds of being unimproved following the administration of HBOT (OR 1.09, 95% CI 0.55 to 2.18, P = 0.8). There was no significant heterogeneity in this analysis. The result was not sensitive to the allocation of dropouts (best case OR 0.74, 95% CI 0.38 to 1.45, P = 0.4, worst case OR 2.07, 95% CI 0.69 to 6.18, P = 0.19).

(3) The number of participants not improved by at least one point on FSS at 12 months.

Only one trial measured this outcome (Oriani 1990). There were nine participants (41%) in each group who improved.

(4) Failure to improve bladder and/or bowel sphincter function after 20 treatments.

Eight trials contributed data to this outcome (L'Hermitte 1986 the exception), involving 408 participants (81% of the total), 203 randomised to HBOT and 205 to sham. 43 participants (21.2%) were improved in the HBOT group and 32 participants (15.6%) in the sham group. There was no significant reduction in the odds of remaining unimproved following the administration of HBOT (OR 0.72, 95%CI 0.33 to 1.60, P = 0.4). There was no significant heterogeneity between trials on testing. Sensitivity analysis for the effect of dropouts was not feasible as a number of trials did not report the sphincter function status at entry of all dropouts.

(5) Failure to improve bladder and/or bowel sphincter function at six months.

Four trials contributed data to this outcome (Confavreux 1986; Harpur 1986; Barnes 1987; Oriani 1990), involving 247 participants (49% of the total), 124 randomised to HBOT and 123 to sham. 27 participants (21.7%) improved following HBOT and 21 participants (17.1%) following sham. There was no significant reduction in the odds of remaining unimproved after the administration of HBOT (OR 0.50, 95% CI 0.08 to 2.94, P = 0.4). There was significant heterogeneity between trials in this analysis (Chi^2 11.94, df3, P = 0.008). Subgroup analysis by length of treatment (20 treatments versus 20 treatments plus boosters for six months) suggested there was a significant benefit from HBOT for those receiving only a short course (OR 0.24, 95%CI 0.07 to 0.80, P = 0.02), while there was no such benefit for those participants receiving more than 20 treatments (OR 0.65, 95%CI 0.02 to 19.07, P = 0.8). The latter analysis continued to display significant heterogeneity (Chi^2 4.74, df1, P = 0.03). This subgroup analysis should, therefore, be interpreted with great caution. No sensitivity analysis was attempted as a number of trials did not report the bladder function state on entry of all dropouts.

(6) Failure to improve bladder and/or bowel sphincter function at 12 months.

Only three trials contributed data to this outcome (Confavreux 1986; Barnes 1987; Oriani 1990), involving 174 participants (35% of the total), 87 randomised to both HBOT and sham. 15 participants (17.2%) improved in the HBOT group and 5 (5.7%) in the sham group. There was no significant reduction in the odds of remaining unimproved after the administration of HBOT (OR 0.36, 95% CI 0.11 to 1.19, P = 0.09). There was no significant heterogeneity between trials. No sensitivity analysis for allocation of dropouts was feasible as not all authors reported the bladder function entry status of all dropouts.

(7) Failure to improve pyramidal function after 20 treatments.

Five trials contributed data to this outcome (Fischer 1983; Barnes 1985; Wood 1985; Confavreux 1986; Oriani 1990) involving 250 participants (50% of the total), 125 randomised to both HBOT and sham. In one trial (Wood 1985) no participants improved in either arm, therefore this trial does not contribute to the meta-analysis. Seven participants (5.6%) improved in the HBOT group and one participant (0.8%) in the sham group. There was no significant reduction in the odds of failing to improve following the administration of HBOT (OR 0.30, 95%CI 0.06 to 1.47, P = 0.14). There was no significant heterogeneity between trials in this analysis. No sensitivity analysis for allocation of dropouts was feasible as not all authors reported the pyramidal function at entry for dropouts.

(8) Failure to improve pyramidal function at six months.

Only three trials contributed data to this outcome (Confavreux 1986; Barnes 1987; Oriani 1990), involving 176 participants (35% of the total), 89 randomised to HBOT and 87 to sham. In one trial, (Confavreux 1986), no participants were improved in either arm, and therefore this trial does not contribute to the meta-analysis. Ten participants (11%) improved in the HBOT group and two participants (2.3%) in the sham group. One trial (Oriani 1990) contributed greatly to the weight of this analysis (78.5%). There was a significant reduction in the odds of remaining unimproved after the administration of HBOT (OR 0.17, 95%CI 0.07 to 0.78, P = 0.02). There was no significant heterogeneity between the trials on testing. The analysis suggests we would need to treat 11 patients with HBOT to achieve one extra patient with improved pyramidal function at six months (NNT = 11, 95% CI 6 to 63).

(9) Failure to improve pyramidal function at 12 months.
Only three trials contributed data to this outcome (Confavreux 1986; Barnes 1987; Oriani 1990) involving 176 participants (35% of the total), 89 randomised to HBOT and 87 to sham. In two trials, (Confavreux 1986; Barnes 1987), no participants were improved in either arm, and therefore these trials would not contribute to the meta-analysis. Twelve participants (13.2%) improved in the HBOT group and four participants (4.5%) in the sham group. One trial (Oriani 1990) contributed 46.9% of the participants and is the only trial able to contribute to analysis (100% weight). Analysed in isolation, this trial suggests a significant reduction in the odds of failing to improve when HBOT is used, (OR 0.13, 95%CI 0.03 to 0.58, P = 0.007). This analysis suggests we would need to treat 11 patients with HBOT to achieve one extra patient with improved pyramidal function at 12 months (NNT = 11, 95%CI 6 to 197).

Prevention of functional deterioration

(1) Prevention of deterioration in bladder or bowel sphincter function at 20 treatments.
Five trials reported on this outcome (Neiman 1985; Confavreux 1986; Harpur 1986; Barnes 1987; Oriani 1990), involving 279 participants (55% of the total), 141 randomised to HBOT and 138 to sham. In two trials, (Oriani 1990; Neiman 1985), there were no participants who improved in either arm, and therefore these trials could not contribute to the meta-analysis. Ten participants (7%) suffered a deterioration in sphincter function in the active group, while eight participants (5.7%) did so in the sham group. One trial (Harpur 1986) contributed largely to the weight in this analysis (83.3%). There was no significant increase in the odds of deteriorated sphincter function with the application of HBOT (OR 1.26, 95%CI 0.50 to 3.19, P = 0.62). There was no significant heterogeneity between trials on testing. The result was not sensitive to the allocation of dropouts (best case OR 0.72, 95%CI 0.25 to 2.09, P = 0.55, worst case OR 1.36, 95% CI 0.54 to 3.43, P = 0.52). Sphincter function was often self-reported and therefore cannot be viewed as a hard outcome.
(2) Prevention of deterioration in bladder or bowel sphincter function at six months.
Four trials reported on this outcome (Confavreux 1986; Harpur 1986; Barnes 1987; Oriani 1990) involving 255 participants (51% of the total), 131 randomised to HBOT and 124 to sham. Eighteen (13.7%) participants suffered deterioration in the active group, while 22 (17.8%) participants did so in the sham group. One trial (Harpur) contributed 44.8% of the weight to this analysis. There was no significant reduction in the odds of deteriorated sphincter function with the application of HBOT (OR 0.70, 95% CI 0.30 to 1.63, P = 0.4). The result was not sensitive to the allocation of dropouts (best case OR 0.54, 95% CI 0.26 to 1.12, P = 0.1, worst case OR 0.74, 95% CI 0.30 to 1.83, P = 0.5).
(3) Prevention of deterioration in bladder or bowel sphincter function at 12 months.
Only three trials reported on this outcome (Confavreux 1986; Barnes 1987; Oriani 1990), involving 177 participants (35% of the total), 90 randomised to HBOT and 87 to sham. Twelve participants (13.3%) suffered deterioration in the HBO group, while 17 participants (19.5%) did so in the sham group. One trial (Barnes 1987) contributed largely to the weight of this analysis (57.7%). There was no significant reduction in the odds of suffering a deterioration following the administration of HBOT (OR 0.49, 95% CI 0.13 to 1.86, P = 0.3). The result was not sensitive to the allocation of dropouts (best case OR 0.52, 95% CI 0.22 to 1.21, worst case OR 0.49, 0.12 to 2.02).

Adverse effects

(1) The incidence of visual disturbance during therapy.
Four trials contributed data to this outcome (Fischer 1983; Barnes 1985; Confavreux 1986; Wiles 1986), involving 259 participants (51% of the total). 129 randomised to HBOT and 130 to sham. 71 participants (55%) suffered deterioration in visual acuity in the HBOT group and three participants (2.3%) in the sham group. There were significantly increased odds of deteriorating vision following the administration of HBOT (OR 24.87, 95% CI 1.44 to 428.50, P = 0.03). Although the effect was common to all studies, there was evidence of considerable heterogeneity between studies on testing (Chi^2 15.33, df3, P = 0.002). This was due to a very high rate of visual deterioration in the HBOT group in the Barnes study (92%). No author reported on resolution of visual changes following cessation of therapy. The analysis suggests the number need to treat with HBOT to get one further complaint of visual disturbance is very low (NNT = 1; 95%CI 1 to 2).
(2) The incidence of barotrauma.
Six trials contributed data to this outcome (Fischer 1983; Barnes 1985, Wood 1985; Confavreux 1986; L'Hermitte 1986; Wiles 1986), involving 349 participants (69% of the total), 184 randomised to HBOT and 165 to sham. Forty five participants (24.5%) in the HBOT group suffered an episode of barotrauma and 15 participants (9.3%) in the sham group. There were not significantly increased odds of barotrauma following the administration of HBOT (OR 2.94,95% CI 0.62 to 13.91, P = 0.17). There was significant heterogeneity between the trials on testing (Chi^2 12.3, df5, P = 0.031), however this was not explained by subgroup analysis of those trials employing a sham at the treatment pressure and those employing a sham at low pressure (High pressure OR 1.74, 95%CI 0.57 to 5.29, P = 0.3, low pressure OR 4.26, 95%CI 0.13 to 142.15, P = 0.4).
(3) The incidence of oxygen toxicity.
No data was available for this outcome.

DISCUSSION

We found little evidence of a significant effect for the administration of HBOT in this review. There were no clear and clinically

important benefits evident from HBOT administration with respect to the primary outcomes. While there was a modest benefit demonstrated in mean EDSS at 12 months, this result is uncertain given that only two trials reported on this outcome at this time (16% of the total participants in this review) and they were the only trials of the nine in this review to suggest benefit. Similarly, the modest benefit suggested at the same time in the proportion of participants with improved EDSS reflected a single trial (Oriani 1990), which contributed 84.7% of the weight to that analysis and was sensitive to the allocation of drop-outs. All other trials reporting this outcome at six months suggested no clinically useful benefit. There was similarly little consistent evidence for benefit with respect to the secondary outcomes relating to improvements in FSS. No analysis indicated benefit in global FSS or the bladder/bowel sphincter function element of this scale. The benefit in the pyramidal function element at six months and 12 months reflected one single positive trial (Oriani 1990). Of the 20 separate outcome factors where meta-analysis was possible, significant benefit was only suggested in three. Where appropriate we made three previously planned subgroup analyses with respect to treatment length (20 versus 20 plus 'top-ups'), nature of the sham therapy (high inspired nitrogen versus low inspired nitrogen) and oxygen dose per treatment session (high dose > 2.0 ATA versus low dose). None of these subgroup analyses could explain the heterogeneity between the results of Fischer and Oriani on the one hand, and the other seven trials, as those two trials were separated on analysis in all three subgroups.

This review has involved data from nine randomised controlled trials and we believe includes all such studies published in full. A further three studies presented in abstract only did not contain any useful outcome data and have not reached full publication, despite completion prior to 1985. We are not aware of any other unpublished studies. We note with interest that no significant investigations have been reported in this area since the original publication of our review and it is probable there is little ongoing interest in the application of HBOT to MS.

Using the Jadad criteria for study quality, these studies generally rated highly (Jadad 1996), however only two studies clearly defined allocation concealment and we therefore cannot be sure there has not been an element of selection bias at enrolment in some studies. This review is limited not only by the modest total number of participants enrolled (504), but the fact that all these studies are small (the largest enrolling 120 participants (Barnes 1985, 29.7% of the total), and there is considerable variation in entry criteria and treatment length. A further limitation for meta-analysis is that for some outcomes in some trials there were no individuals with the outcome of interest in either arm of the study. Data where this occurs cannot contribute to the meta-analysis using RevMan 4.1, and this has the effect of magnifying any differences between groups that exist in the remaining trials. Outcomes where no patient in either arm experienced the outcome of interest are listed in Table 13.

These studies were published between 12 and 19 years prior to this review and clinical diagnostic criteria were used for all these studies to determine eligibility (Schumacher 1965, McDonald 1977, Poser 1983). Entry criteria for disease severity and classification in many of these trials was incompletely defined and varied considerably between trials. While some specified a minimum and maximum entry EDSS, others specified only a maximum or some less well-defined physical criterion such as ability to enter the chamber environment unaided. Others appear to have recruited on an opportunistic basis. In general, the entry EDSS scores indicated the majority of participants had mild or moderate disabilities. While it may have been preferable to use individual patient data as the basis of this review, this was not possible given the period of time that has elapsed since these trials were reported. We have therefore been unable to perform analyses based on disease severity or classification at entry as originally planned.

The included studies used a variety of outcome measures, the most common being the EDSS and FSS developed by Kurtzke (Kurtzke 1965, Kurtzke 1983). These scales are summarised in Table 1. The original study (Fischer 1983) defined a reduction of one point on the EDSS as a 'major improvement', and a similar reduction of one point on the FSS as a 'minor improvement'. Most subsequent authors followed this example. Where the data were available we chose relative reductions in the mean EDSS between groups as our primary outcome measure. In order to include the maximum information from the studies where mean EDSS was not reported, we also compared the numbers of participants in each group who improved at least one point on this scale. As secondary outcome measures we considered reductions or increases of at least one point in the FSS.

For the primary outcome of mean reductions in EDSS, there were no significant benefits in the HBOT group compared to the sham group at the completion of 20 treatments or at six months. While there was a trend to a modest improvement in the HBOT group, this is unlikely to be clinically important. At the completion of 20 treatments there was a relative mean change in EDSS of -0.07 (95%CI -0.23 to 0.09), while at six months the change was -0.22 (95%CI -0.54 to 0.09). Neither of these changes would be clinically detectable in an individual patient. While there was a significant reduction in mean EDSS in the HBOT group at 12 months (-0.84, 95%CI -1.28 to -0.42), this result remains barely detectable on clinical examination and of unclear clinical benefit. Furthermore, this result should be interpreted with great caution for a number of reasons. Primarily, as discussed above, the only two studies that contributed to this outcome were also the only two studies in the review to report generally favourable outcomes and it is possible there was bias towards later reporting in those trials showing successful outcomes compared to those in which the initial findings were unpromising. It is also biologically implausible that a benefit be absent at six months after treatment and

present at 12 months. Proponents of HBOT suggest that a long course of treatment may be required to demonstrate benefit (James 1985) and that those trials giving only 20 treatments are flawed in this regard. Others also maintain that treatments over 2 ATA are toxic and unhelpful (Neubauer 1983). Both these assertions are difficult to sustain however, in that of the two trials contributing to this significant result, one gave a short course at only 2 ATA (Fischer 1983), while the other continued with top-up treatments to 12 months and used 2.5 ATA (Oriani 1990), and both showed benefits after 20 treatments and six months. Furthermore, the only other trial to administer a longer course of treatments (Harpur 1986) failed to suggest any benefit in EDSS at 20 treatment or six months (no data at 12 months). There is no reason to extrapolate that data from other trials, including Harpur, would have confirmed a benefit after 12 months, having failed to do so at earlier analyses.

Unsurprisingly, the related primary analyses comparing the numbers of participants with improvement in EDSS scores of at least one point mirror those above relating to mean scores. Only a small proportion of participants benefited in either group (at 20 treatments 6.8% HBOT group, 3% sham). There were no significant benefits following HBOT administration at the completion of 20 treatments or at six months, while the result at 12 months was again statistically significant. The odds of remaining unimproved in the HBOT group at 12 months were lower, (OR 0.2, 95%CI 0.06 to 0.72, P = 0.01) and we might expect to treat 10 participants in order produce one extra patient with an improvement in EDSS at 12 months, although perhaps as many as 71 (NNT = 10, 95%CI 5 to 71). This result suffers with many of the same problems as those discussed above for the mean EDSS analysis at 12 months. Here, the results reflect closely the Oriani study, to which it lends 84.7% of the weight. Furthermore, this result is sensitive to the allocation of a small number of dropouts who were not analysed in the original trials (12 participants, 4.2%). If these participants are allocated according to worst case assumptions, the benefit of HBOT is no longer significant (OR 1.34, 95%CI 0.08 to 21.75, P = 0.21).

Only four trials reported on the occurrence of exacerbation at any time and there were no significant differences in the number of participants suffering an exacerbation at any analysis. For example, at 12 months roughly one third of participants entered in the two studies that reported this outcome (Barnes 1987; Oriani 1990) had suffered an exacerbation (25.9% in the HBOT group and 36.9% in the sham).

With regard to the secondary outcomes, there was no evidence of a benefit from the administration of HBOT in the proportion of participants with improvements on estimation of global FSS. At the completion of 20 treatments, 29% of those who had received HBOT had improved, while 28% in the sham group had improved. Only Oriani (Oriani 1990) reported on global improvements in FSS after 12 months and found no difference between the groups (41% in each arm of the study).

It may be that certain elements of the FSS are more amenable to improvement during treatment. Anecdotally, most improvements reported have been in sphincter function and pyramidal system function, and these trials focus particularly on these areas. No other elements of the FSS were reported separately by more than one trial. There was no evidence from this review to support the improvement of bladder/bowel function following HBOT when compared to a sham. A significant proportion of participants in both groups did report improvement, however. At the completion of 20 treatments, for example, 21.1% of the participants receiving HBOT reported an improvement, while 16.5% did so in the sham group. Interestingly, the analysis at six months suffered significant heterogeneity and subgroup analysis by length of treatment (20 treatments in one month versus 20 treatments in one month plus five months of top-up treatments) suggested there was a significant benefit for those participants having the shorter course (OR 0.24, 95% CI 0.07 to 0.80, P = 0.02). It is difficult to find any plausible explanation for this and runs counter to the supporters of HBOT in MS (who advocate continuing therapy). This result should be interpreted with extreme caution.

Improvement in pyramidal function was also examined in this review. While there was no evidence to support the use of HBOT on assessment at 20 treatments, there was a statistically significant effect evident at six months in favour of those participants receiving HBOT. The odds of failing to improve following HBOT were reduced (OR 0.24, 95%CI 0.06 to 0.92, P = 0.04), and this analysis suggests we would need to treat 11 patients in order for one extra patient to improve at six months. Again, this analysis largely reflects the results of one trial (Oriani 1990) which contributes much of the weight toward the final estimate (78.5%) and we should interpret this result with some caution. Oriani 1990 was also the only trial to report any benefit in pyramidal function at 12 months.

While many of those who use HBOT do so on the basis of prevention of deterioration in function or disability, few outcomes were measured in these trials from that point of view. Five trials did however, report the number of participants in whom bladder/bowel function deteriorated and this review could find no evidence for a significant effect of HBOT administration. After 20 treatments, 9% of participants receiving HBOT had deteriorated, versus 8% of those allocated to sham. At 12 months these proportions had risen to 13.3% and 19.5% respectively.

HBOT is regarded as a relatively benign intervention. There are few major adverse effects (pulmonary barotrauma, drug reactions, injuries or death related to chamber fire) and while these are all rare enough not to expect to see them in the trials included in this review, they should be included in consideration of the benefit of this therapy. In practice it is likely than a beneficial effect strong enough to be clearly identified in clinical trials would overwhelm

the consideration of such rare events. There are however, a number of more minor complications that may occur commonly and several authors reported on these. Visual disturbance, usually reduction in visual acuity secondary to conformational changes in the lens, is very commonly reported. In this review participants receiving HBOT were significantly more likely to have reduced acuity compared to the participants receiving sham (55% versus 2.3%). While the great majority of patients recover spontaneously over a period of days to weeks, there is a small proportion that continue to require correction to restore sight to pre-treatment levels. No trial attempted to examine recovery. The second most common adverse effect associated with HBOT is aural barotrauma. Barotrauma can affect any air-filled cavity in the body (including the middle ear, lungs and respiratory sinuses) and occurs as a direct result of compression. Aural barotrauma is by far the most common as the middle ear air space is small, largely surrounded by bone and the sensitive tympanic membrane, and usually requires active effort by the patient in order to inflate the middle ear through the eustachian tube on each side. Barotrauma is thus not a consequence of HBOT directly, but rather of the physical conditions required to administer it. Not surprisingly, therefore, in trials utilising a sham treatment involving compression, we have not demonstrated any significant differences between those receiving HBOT and those receiving sham. The pooled figures from those trials that reported instances of aural barotrauma suggest we might expect 23.9% of patients to have an episode of aural barotrauma sufficiently serious to interrupt their treatment. This broadly reflects clinical practice. Problems may be resolved with education or one of a number of devices and techniques to improve or replace eustachian tube function, so an episode of barotrauma usually does not preclude continuing therapy.

Oxygen is toxic to the tissues in high doses and this manifests acutely as a wide variety of pre-seizure symptoms, or as frank seizures, in the chamber. These events are self-terminating as the brain oxygen tension falls and rarely result in any permanent sequelae. The incidence varies with oxygen dose and is thus more likely at higher treatment pressures. The incidence at 2.5 ATA for 90 minutes oxygen breathing is approximately 1:1,500. Many patients continue therapy after such events, but the episode can be traumatic and may result in withdrawal from further treatment. No data regarding oxygen toxicity was presented in any of the trials in this review.

AUTHORS' CONCLUSIONS

Implications for practice

We found no consistent evidence to confirm a beneficial effect of hyperbaric oxygen therapy for the treatment of multiple sclerosis and do not believe routine use is justified. The small number of analyses suggestive of benefit were isolated, difficult to ascribe with biological plausibility and would need to be confirmed in future well-designed trials. Such trials are not, in our view, justified by this review.

Implications for research

Although the trials included in this review are somewhat dated and difficult to interpret compared to contemporary investigations, we do not believe there is a strong case for further research in this area as there is little indication of strong treatment effects. It is possible, however, that modest treatment benefits may be present in a subset of disease severity or classification. One of the two trials indicating some benefit (Oriani 1990), for example, enrolled patients with relatively mild disabilities, and it may be that HBOT has a role in mild disease. Any future trials would need to consider in particular:

- Appropriate sample sizes with power to detect expected differences
- Careful definition and selection of target patients
- Appropriate oxygen dose per treatment session (pressure and time)
- Demonstration of any differential treatment effect between single intensive treatment courses and ongoing regular treatments
- Appropriate outcome measures including quantitative serial MRI data and quality of life measures
- Careful elucidation of any adverse effects
- The cost-utility of the therapy

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Barnes 1985

Methods	Randomised, controlled trial. Participants and observers blinded
Participants	120 MS patients with EDSS less than 8. Allocation 60 sham, 60 HBOT.
Interventions	Active: HBOT 20 daily sessions at 2.0ATA for 90 minutes. Control: Air 20 daily sessions at 1.1ATA for 90 minutes.
Outcomes	EDSS improved at end of therapy. Bladder and bowel sphincter function improved at end of therapy. Pyramidal function improved at end of therapy. Bladder and bowel function deteriorated at end of therapy. Relapse at end of therapy. Adverse effects during therapy.
Notes	Jadad score 4. Includes two separate reports, one of immediate and 6 month findings, the other at 12 months. See Barnes2.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Barnes 1987

Methods	Randomised, controlled trial. Participants and observers blinded
Participants	120 MS patients with EDSS less than 8. Allocation 60 sham, 60 HBOT.
Interventions	Active: HBOT 20 daily sessions at 2.0 ATA for 90 minutes. Control: Air 20 daily sessions at 1.1 ATA for 90 minutes.
Outcomes	EDSS improved at 6 months and 12 months. Bladder and bowel sphincter function improved at 6 months and 12 months. Pyramidal function improved at 6 months and 12 months. Bladder and bowel function deteriorated at 6 months and 12 months. Relapse at 6 months and 12 months.

Barnes 1987 (*Continued*)

Notes	Jadad score 4. Includes two separate reports, one of immediate and 6 month findings, the other at 12 months. See Barnes1.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Confavreux 1986

Methods	Randomised, controlled trial. Participants and observers.
Participants	17 MS patients with EDSS 3 to 8. Allocation 9 sham, 8 HBOT.
Interventions	Active: HBOT 20 daily sessions at 2.5 ATA for 90 minutes. Control: Air 20 daily sessions at 1.1 or 1.2 ATA for 90 minutes
Outcomes	EDSS improved at end of therapy, 6 months and 12 months. Bladder and bowel sphincter function improved at end of therapy, 6 months and 12 months. Pyramidal function improved at end of therapy, 6 months and 12 months. Bladder and bowel function deteriorated at end of therapy, 6 months and 12 months. Adverse effects during therapy.
Notes	Jadad score 4. Short course steroids given as indicated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Fischer 1983

Methods	Randomised, controlled trial. Participants and observers blinded
Participants	40 MS patients with EDSS less than 6. Allocation 20 sham, 20 HBOT.
Interventions	Active: HBOT 20 daily sessions at 2.0 ATA for 90 minutes. Control: 10% oxygen 20 daily sessions at 2.0 ATA for 90 minutes

Fischer 1983 (*Continued*)

Outcomes	EDSS improved at end of therapy and 6 months. Bladder sphincter function improved at end of therapy. Pyramidal function improved at end of therapy. Relapse at 12 months. Adverse effects during therapy.	
Notes	Jadad score 5.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Harpur 1986

Methods	Randomised, controlled trial. Participants and observers blinded	
Participants	82 MS patients with EDSS 3 to 7.5. Allocation 41 sham, 41 HBOT.	
Interventions	Active: HBOT 20 daily sessions at 1.75 ATA for 90 minutes. 7 similar 'booster' sessions over 6 months. Control: 12.5% oxygen 20 daily sessions at 1.75 ATA for 90 minutes, plus 7 'booster' sessions over 6 months	
Outcomes	EDSS improved at end of therapy and 6 months. Bladder sphincter function improved at end of therapy and 6 months. Bladder function deteriorated at end of therapy and 6 months. Relapse at 6 months. KFSS improved at end of therapy and 6 months.	
Notes	Jadad score 4.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

L'Hermitte 1986

Methods	Randomised, controlled trial. Participants and observers blinded
Participants	49 MS patients with group EDSS mean approx 5.25. Allocation 15 sham, 34 HBOT.
Interventions	Active: (1) HBOT 20 daily sessions at 2.3 ATA plus diazepam 5mg for 90 minutes. (2) HBOT 20 daily sessions at 2.0ATA for 90 minutes. Control: 10.5% oxygen 20 daily sessions at 2.0 or 2.3 ATA for 90 minutes
Outcomes	EDSS improved at end of therapy and 6 months. Relapse at 6 months. KFSS improved at end of therapy and six months. Adverse effects during therapy.
Notes	Jadad score 4. Two active groups versus one control.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Neiman 1985

Methods	Randomised, controlled trial. Participants and observers blinded
Participants	24 MS patients with mean EDSS 6 (active)and 6.1(control). Allocation 12 sham, 12 HBOT.
Interventions	Active: HBOT 20 daily sessions at 2.0 ATA for 90 minutes. Control: Air 20 daily sessions at 1.2 ATA for 5 minutes, then 1.0ATA for 85 minutes
Outcomes	EDSS improved at end of therapy and 6 months. Bladder sphincter function improved at end of therapy and 6 months. Bladder function deteriorated at end of therapy. KFSS improved at end of therapy and 6 months.
Notes	Jadad score 5.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Oriani 1990

Methods	Randomised, controlled trial. Participants and observers blinded
Participants	44 MS patients with EDSS less than 5. Mean EDSS 3.39 (active) and 2.97 (control). Allocation 22 sham, 22 HBOT.
Interventions	Active: HBOT 20 daily sessions at 2.5ATA for 90 minutes. 5 similar 'booster' sessions each month to 1 year. Control: Air 20 daily sessions at 2.5ATA for 90 minutes, plus 5 'booster' sessions each month to 1 year
Outcomes	EDSS improved at end of therapy, 6 months and 12 months. Bladder and bowel sphincter function improved at end of therapy, 6 months and 12 months. Pyramidal function improved at end of therapy, 6 months and 12 months. Bladder and bowel function deteriorated at end of therapy, 6 months and 12 months. KFSS improved at end of therapy, 6 months and 12 months.
Notes	Jadad score 4.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Wiles 1986

Methods	Randomised, controlled trial. Participants and observers blinded
Participants	84 MS patients with mean EDSS 5.4 (active) and 5.9 (control). Allocation 42 sham, 42 HBOT.
Interventions	Active: HBOT 20 daily sessions at 2.0ATA for 90 minutes. Control: Air 20 daily sessions at 1.1ATA for 90 minutes.
Outcomes	Bladder sphincter function improved at end of therapy. Adverse effects during therapy.
Notes	Jadad score 4.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Wood 1985

Methods	Randomised, controlled trial. Participants and observers blinded
Participants	44 MS patients with EDSS less than 3 to 8. Allocation 23 sham, 21 HBOT.
Interventions	Active: HBOT 20 daily sessions at 2.0ATA for 90 minutes. Control: 10% oxygen 20 daily sessions at 2.0ATA for 90 minutes
Outcomes	EDSS improved at end of therapy. Bladder sphincter function improved at end of therapy. Pyramidal function improved at end of therapy. Adverse effects during therapy.
Notes	Jadad score 5.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

ATA: Atmospheres Absolute
EDSS: Extended Disability Status Score
FSS: Functional Status Score
HBOT: Hyperbaric Oxygen Therapy
MS: Multiple Sclerosis

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Erwin 1985	Abstract only. No clinical outcome data for analysis. Same trial as Massey 1985
Gottlieb 1988	Not a randomised comparative study.
Kindwall 1991	Not a randomised comparative study.
Kleijnen 1995	A semi-quantitative review.
Massey 1985	Abstract only. Crossover trial with no clincial data after first phase. same study as Erwin 1985
Murthy 1985	Abstract only. No data supplied.
Pallotta 1986	Not a randomised comparative study.

(*Continued*)

Slater 1985	Abstract only. No data supplied.
Worthington 1987	Not randomised and selection method unclear. No useful clinical data for analysis

DATA AND ANALYSES

Comparison 1. Hyperbaric Oxygen Therapy versus Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in mean EDSS after 20 treatments	5	271	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.23, 0.09]
2 Cange in mean EDSS at 20 treatments. Subgroup analysis by oxygen dose	5	271	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.43, 0.13]
2.1 High oxygen dose	4	227	Mean Difference (IV, Random, 95% CI)	-0.17 [-0.52, 0.18]
2.2 Low oxygen dose	1	44	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.63, 0.41]
3 Change in mean EDSS at 20 treatments. Subgroup analysis by nitrogen dose during therapy.	5	271	Mean Difference (IV, Random, 95% CI)	-0.22 [-0.65, 0.20]
3.1 Low PIN2	1	24	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 High PIN2	4	247	Mean Difference (IV, Random, 95% CI)	-0.22 [-0.65, 0.20]
4 Changes in mean EDSS at 6 months	3	163	Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.54, 0.09]
5 Change in mean EDSS at 6 months. Subgroup analysis by treatment length	3	163	Mean Difference (IV, Random, 95% CI)	-0.29 [-0.91, 0.33]
5.1 20 treatments only	1	37	Mean Difference (IV, Random, 95% CI)	-0.84 [-1.43, -0.25]
5.2 20 treatments plus	2	126	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.51, 0.50]
6 Change in mean EDSS at 12 months	2	81	Mean Difference (IV, Fixed, 95% CI)	-0.85 [-1.28, -0.42]
7 Failure to improve EDSS by at least 1 point after 20 treatments	8	411	Odds Ratio (M-H, Random, 95% CI)	0.33 [0.09, 1.18]
8 Sensitivity analysis: Failure to improve EDSS at 20 treatments. Best case.	8	420	Odds Ratio (M-H, Random, 95% CI)	0.36 [0.09, 1.49]
9 Sensitivity analysis: Failure to improve EDSS at 20 treatments. Worst case.	8	420	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.19, 3.67]
10 Failure to improve EDSS by at least 1 point at 6 months	7	363	Odds Ratio (M-H, Random, 95% CI)	0.42 [0.16, 1.08]
11 Sensitivity analysis: Failure to improve EDSS at 6 months. Best case.	7	376	Odds Ratio (M-H, Random, 95% CI)	0.35 [0.15, 0.83]
12 Sensitivity analysis: Failure to improve EDSS at 6 months. Worst case.	7	375	Odds Ratio (M-H, Random, 95% CI)	1.58 [0.47, 5.29]
13 Failure to improve EDSS by at least 1 point at 12 months	3	176	Odds Ratio (M-H, Random, 95% CI)	0.20 [0.06, 0.72]

14 Failure to improve EDSS at least 1 point at 12 months (subgroup analysis by treatment length)	3	177	Odds Ratio (M-H, Random, 95% CI)	0.20 [0.06, 0.72]
14.1 Studies with 20 treatment sessions only	2	133	Odds Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.64]
14.2 Studies with treatment continuing beyond 20 sessions	1	44	Odds Ratio (M-H, Random, 95% CI)	0.19 [0.05, 0.73]
15 Sensitivity analysis: Failure to improve in EDSS at 12 months. Best case.	3	181	Odds Ratio (M-H, Random, 95% CI)	0.20 [0.06, 0.71]
16 Sensitivity analysis: Failure to improve EDSS at 12 months. Worst case.	3	181	Odds Ratio (M-H, Random, 95% CI)	1.34 [0.08, 21.75]
17 Exacerbation during treatment course.	1	117	Odds Ratio (M-H, Fixed, 95% CI)	0.31 [0.01, 7.80]
18 Patients experiencing exacerbation within 6 months	2	122	Odds Ratio (M-H, Random, 95% CI)	0.74 [0.25, 2.23]
19 Sensitivity analysis: Exacerbation within 6 months. Best case.	2	131	Odds Ratio (M-H, Random, 95% CI)	0.36 [0.14, 0.94]
20 Sensitivity analysis: Exacerbation within 6 months. Worst case.	2	131	Odds Ratio (M-H, Random, 95% CI)	1.22 [0.42, 3.55]
21 Patients experiencing exacerbation within 12 months	2	153	Odds Ratio (M-H, Random, 95% CI)	0.38 [0.04, 3.22]
22 Sensitivity analysis: Exacerbation within 12 months. Best case.	2	160	Odds Ratio (M-H, Random, 95% CI)	0.31 [0.04, 2.57]
23 Sensitivity analysis: Exacerbation within 12 months. Worst case.	2	160	Odds Ratio (M-H, Random, 95% CI)	0.61 [0.16, 2.31]
24 Failure to improve at least 1 point in FSS after 20 treatments	4	194	Odds Ratio (M-H, Random, 95% CI)	1.17 [0.59, 2.33]
25 Sensitivity analysis: failure to improve FSS at 20 treatments. Best case.	4	199	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.52, 1.99]
26 Sensitivity analysis: Failure to improve FSS at 20 treatments. Worst case.	4	199	Odds Ratio (M-H, Random, 95% CI)	1.43 [0.58, 3.50]
27 Failure to improve at least 1 point on FSS at 6 months	4	185	Odds Ratio (M-H, Random, 95% CI)	1.09 [0.55, 2.18]
28 Sensitivity analysis: Failure to improve FSS at 6 months. Best case.	4	195	Odds Ratio (M-H, Random, 95% CI)	0.74 [0.38, 1.44]
29 Sensitivity analysis: Failure to improve FSS at 6 months. Worst case.	4	195	Odds Ratio (M-H, Random, 95% CI)	2.07 [0.69, 6.18]

30 Failure to improve bladder and/or bowel sphincter function after 20 treatments	8	408	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.33, 1.60]
31 Failure to improve bladder and/or bowel sphincter function at 6 months.	4	247	Odds Ratio (M-H, Random, 95% CI)	0.50 [0.08, 2.94]
32 Failure to improve bladder and/or bowel sphincter function at 6 months (by treatment length)	4	247	Odds Ratio (M-H, Random, 95% CI)	0.50 [0.08, 2.94]
32.1 Studies with 20 treatment sessions only	2	129	Odds Ratio (M-H, Random, 95% CI)	0.24 [0.07, 0.80]
32.2 Studies with treatment continuing beyond 20 sessions	2	118	Odds Ratio (M-H, Random, 95% CI)	0.65 [0.02, 19.07]
33 Failure to improve bladder and/or bowel sphincter function at 12 months	3	174	Odds Ratio (M-H, Random, 95% CI)	0.36 [0.11, 1.19]
34 Failure to Improve pyramidal function after 20 treatments.	5	250	Odds Ratio (M-H, Random, 95% CI)	0.30 [0.06, 1.47]
35 Failure to improve pyramidal function at 6 months	3	176	Odds Ratio (M-H, Random, 95% CI)	0.17 [0.04, 0.78]
36 Failure to improve pyramidal function at 12 months	3	176	Odds Ratio (M-H, Random, 95% CI)	0.13 [0.03, 0.58]
37 Deterioration in bladder and/or bowel function after 20 treatments	5	279	Odds Ratio (M-H, Fixed, 95% CI)	1.26 [0.50, 3.19]
38 Sensitivity analysis: Deterioration in sphincter function at 20 treatments. Best case.	5	287	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.25, 2.09]
39 Sensitivity analysis: Deterioration in sphincter function at 20 treatments. Worst case.	5	286	Odds Ratio (M-H, Random, 95% CI)	1.36 [0.54, 3.43]
40 Deterioration in bladder and/or bowel sphincter function at 6 months	4	255	Odds Ratio (M-H, Random, 95% CI)	0.70 [0.30, 1.63]
41 Sensitivity analysis: deterioration in sphincter function at 6 months. Best case.	4	263	Odds Ratio (M-H, Random, 95% CI)	0.54 [0.26, 1.12]
42 Sensitivity analysis: deterioration of sphincter function at 6 months. Worst case.	4	263	Odds Ratio (M-H, Random, 95% CI)	0.74 [0.30, 1.83]
43 Deterioration in bladder and/or bowel function at 12 months	3	177	Odds Ratio (M-H, Random, 95% CI)	0.49 [0.13, 1.86]
44 Sensitivity analysis: Deterioration in sphincter function at 12 months. Best case.	3	181	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.22, 1.21]

45 Sensitivity analysis: Deterioration in sphincter function at 12 months. Worst case.	4	183	Odds Ratio (M-H, Random, 95% CI)	0.49 [0.12, 2.02]
46 Incidence of visual disturbance after 20 treatments	4	259	Odds Ratio (M-H, Random, 95% CI)	24.87 [1.44, 428.50]
47 Incidence of barotrauma during therapy. Subgroup analysis by sham pressure.	6	349	Odds Ratio (M-H, Random, 95% CI)	2.94 [0.62, 13.91]
47.1 Low pressure sham	3	222	Odds Ratio (M-H, Random, 95% CI)	4.26 [0.13, 142.15]
47.2 High pressure sham	3	127	Odds Ratio (M-H, Random, 95% CI)	1.74 [0.57, 5.29]

Analysis 1.1. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 1 Change in mean EDSS after 20 treatments.

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

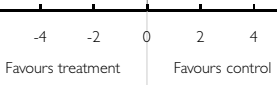
Outcome: 1 Change in mean EDSS after 20 treatments

Study or subgroup	HBOT N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Fischer 1983	17	-1 (1)	20	0 (1)		5.9 %	-1.00 [-1.65, -0.35]
Harpur 1986	41	0 (1.06)	41	-0.16 (1.13)		10.9 %	0.16 [-0.31, 0.63]
Neiman 1985	12	0 (0.2)	12	0 (0.3)		58.8 %	0.0 [-0.20, 0.20]
Oriani 1990	22	0.05 (1.16)	22	0.1 (0.84)		6.8 %	-0.05 [-0.65, 0.55]
Wiles 1986	42	0.01 (1.16)	42	0.16 (0.42)		17.6 %	-0.15 [-0.52, 0.22]
Total (95% CI)	**134**		**137**			**100.0 %**	**-0.07 [-0.23, 0.09]**

Heterogeneity: Chi^2 = 9.48, df = 4 (P = 0.05); I^2 =58%

Test for overall effect: Z = 0.89 (P = 0.37)

Test for subgroup differences: Not applicable



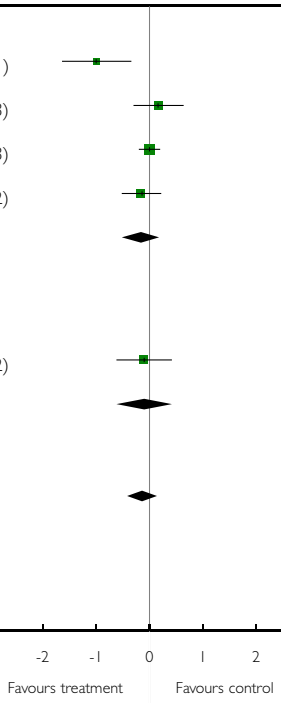
Analysis 1.2. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 2 Cange in mean EDSS at 20 treatments. Subgroup analysis by oxygen dose.

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 2 Cange in mean EDSS at 20 treatments. Subgroup analysis by oxygen dose

Study or subgroup	HBOT N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High oxygen dose							
Fischer 1983	17	-1 (1)	20	0 (1)		12.5 %	-1.00 [-1.65, -0.35]
Harpur 1986	41	0 (1.06)	41	-0.16 (1.13)		17.9 %	0.16 [-0.31, 0.63]
Neiman 1985	12	0 (0.2)	12	0 (0.3)		30.9 %	0.0 [-0.20, 0.20]
Wiles 1986	42	0.01 (1.16)	42	0.16 (0.42)		22.3 %	-0.15 [-0.52, 0.22]
Subtotal (95% CI)	**112**		**115**			**83.6 %**	**-0.17 [-0.52, 0.18]**
Heterogeneity: Tau^2 = 0.08; Chi^2 = 9.48, df = 3 (P = 0.02); I^2 =68%							
Test for overall effect: Z = 0.96 (P = 0.34)							
2 Low oxygen dose							
Oriani 1990	22	0.05 (1.16)	22	0.16 (0.42)		16.4 %	-0.11 [-0.63, 0.41]
Subtotal (95% CI)	**22**		**22**			**16.4 %**	**-0.11 [-0.63, 0.41]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.42 (P = 0.68)							
Total (95% CI)	**134**		**137**			**100.0 %**	**-0.15 [-0.43, 0.13]**
Heterogeneity: Tau^2 = 0.06; Chi^2 = 9.50, df = 4 (P = 0.05); I^2 =58%							
Test for overall effect: Z = 1.03 (P = 0.30)							
Test for subgroup differences: Chi^2 = 0.04, df = 1 (P = 0.85), I^2 =0.0%							



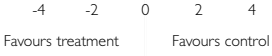
Analysis 1.3. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 3 Change in mean EDSS at 20 treatments. Subgroup analysis by nitrogen dose during therapy..

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 3 Change in mean EDSS at 20 treatments. Subgroup analysis by nitrogen dose during therapy.

Study or subgroup	HBOT N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Low PIN2						
Neiman 1985	12	0 (0)	12	0.3 (0)		0.0 [0.0, 0.0]
Subtotal (95% CI)	**12**		**12**			**0.0 [0.0, 0.0]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.0 (P < 0.00001)						
2 High PIN2						
Fischer 1983	17	-1 (1)	20	0 (1)		-1.00 [-1.65, -0.35]
Harpur 1986	41	0 (1.06)	41	-0.16 (1.13)		0.16 [-0.31, 0.63]
Oriani 1990	22	0.05 (1.16)	22	0.1 (0.84)		-0.05 [-0.65, 0.55]
Wiles 1986	42	0.01 (1.16)	42	0.16 (0.42)		-0.15 [-0.52, 0.22]
Subtotal (95% CI)	**122**		**125**			**-0.22 [-0.65, 0.20]**
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 8.36$, df = 3 (P = 0.04); $I^2 = 64\%$						
Test for overall effect: Z = 1.02 (P = 0.31)						
Total (95% CI)	**134**		**137**			**-0.22 [-0.65, 0.20]**
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 8.36$, df = 3 (P = 0.04); $I^2 = 64\%$						
Test for overall effect: Z = 1.02 (P = 0.31)						
Test for subgroup differences: Not applicable						



Analysis 1.4. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 4 Changes in mean EDSS at 6 months.

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 4 Changes in mean EDSS at 6 months

Study or subgroup	HBOT N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Fischer 1983	17	-0.59 (1.06)	20	0.25 (0.72)		28.1 %	-0.84 [-1.43, -0.25]
Harpur 1986	41	-0.08 (1.06)	41	-0.3 (1.13)		44.2 %	0.22 [-0.25, 0.69]
Oriani 1990	22	-0.38 (1.16)	22	-0.08 (0.84)		27.7 %	-0.30 [-0.90, 0.30]
Total (95% CI)	**80**		**83**			**100.0 %**	**-0.22 [-0.54, 0.09]**

Heterogeneity: $Chi^2 = 7.55$, df = 2 (P = 0.02); $I^2 = 74\%$

Test for overall effect: Z = 1.38 (P = 0.17)

Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 5 Change in mean EDSS at 6 months. Subgroup analysis by treatment length.

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 5 Change in mean EDSS at 6 months. Subgroup analysis by treatment length

Study or subgroup	HBOT N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 20 treatments only							
Fischer 1983	17	-0.59 (1.06)	20	0.25 (0.72)		32.1 %	-0.84 [-1.43, -0.25]
Subtotal (95% CI)	**17**		**20**			**32.1 %**	**-0.84 [-1.43, -0.25]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.77 (P = 0.0056)							
2 20 treatments plus							
Harpur 1986	41	-0.08 (1.06)	41	-0.3 (1.13)		35.9 %	0.22 [-0.25, 0.69]
Oriani 1990	22	-0.38 (1.16)	22	-0.08 (0.84)		32.0 %	-0.30 [-0.90, 0.30]
Subtotal (95% CI)	**63**		**63**			**67.9 %**	**-0.01 [-0.51, 0.50]**
Heterogeneity: Tau^2 = 0.06; Chi^2 = 1.78, df = 1 (P = 0.18); I^2 =44%							
Test for overall effect: Z = 0.03 (P = 0.98)							
Total (95% CI)	**80**		**83**			**100.0 %**	**-0.29 [-0.91, 0.33]**
Heterogeneity: Tau^2 = 0.22; Chi^2 = 7.55, df = 2 (P = 0.02); I^2 =74%							
Test for overall effect: Z = 0.90 (P = 0.37)							
Test for subgroup differences: Chi^2 = 4.38, df = 1 (P = 0.04), I^2 =77%							

Analysis 1.6. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 6 Change in mean EDSS at 12 months.

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 6 Change in mean EDSS at 12 months

Study or subgroup	HBOT N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Fischer 1983	17	-0.59 (1.06)	20	0.35 (0.81)		48.5 %	-0.94 [-1.56, -0.32]
Oriani 1990	22	-0.98 (1.16)	22	-0.21 (0.84)		51.5 %	-0.77 [-1.37, -0.17]
Total (95% CI)	**39**		**42**			**100.0 %**	**-0.85 [-1.28, -0.42]**

Heterogeneity: $Chi^2 = 0.15$, df = 1 (P = 0.70); $I^2 = 0.0\%$

Test for overall effect: Z = 3.89 (P = 0.00010)

Test for subgroup differences: Not applicable

Analysis 1.7. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 7 Failure to improve EDSS by at least 1 point after 20 treatments.

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 7 Failure to improve EDSS by at least 1 point after 20 treatments

Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
Barnes 1985	60/60	57/57		0.0 [0.0, 0.0]
Confavreux 1986	7/8	8/9		0.88 [0.05, 16.74]
Fischer 1983	12/17	19/20		0.13 [0.01, 1.22]
Harpur 1986	40/41	41/41		0.33 [0.01, 8.22]
L'Hermitte 1986	34/34	15/15		0.0 [0.0, 0.0]
Neiman 1985	12/12	12/12		0.0 [0.0, 0.0]
Oriani 1990	18/22	22/22		0.09 [0.00, 1.81]
Wood 1985	21/21	19/20		3.31 [0.13, 86.06]
Total (95% CI)	**215**	**196**		**0.33 [0.09, 1.18]**

Total events: 204 (HBOT), 193 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.75$, df = 4 (P = 0.44); $I^2 = 0.0\%$

Test for overall effect: Z = 1.71 (P = 0.088)

Test for subgroup differences: Not applicable

Analysis 1.8. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 8 Sensitivity analysis: Failure to improve EDSS at 20 treatments. Best case..

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 8 Sensitivity analysis: Failure to improve EDSS at 20 treatments. Best case.

Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
Barnes 1985	60/60	60/60		0.0 [0.0, 0.0]
Confavreux 1986	7/8	8/9		0.88 [0.05, 16.74]
Fischer 1983	12/20	19/20		0.08 [0.01, 0.71]
Harpur 1986	40/41	40/41		1.00 [0.06, 16.55]
L'Hermitte 1986	34/34	15/15		0.0 [0.0, 0.0]
Neiman 1985	12/12	12/12		0.0 [0.0, 0.0]
Oriani 1990	18/22	22/22		0.09 [0.00, 1.81]
Wood 1985	21/21	22/23		2.87 [0.11, 74.28]
Total (95% CI)	**218**	**202**		**0.36 [0.09, 1.49]**

Total events: 204 (HBOT), 198 (Placebo)

Heterogeneity: $Tau^2 = 0.56$; $Chi^2 = 5.10$, df = 4 (P = 0.28); $I^2 = 22\%$

Test for overall effect: Z = 1.41 (P = 0.16)

Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 9 Sensitivity analysis: Failure to improve EDSS at 20 treatments. Worst case..

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 9 Sensitivity analysis: Failure to improve EDSS at 20 treatments. Worst case.

Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
Barnes 1985	60/60	57/60		7.37 [0.37, 145.75]
Confavreux 1986	7/8	8/9		0.88 [0.05, 16.74]
Fischer 1983	15/20	19/20		0.16 [0.02, 1.50]
Harpur 1986	40/41	40/41		1.00 [0.06, 16.55]
L'Hermitte 1986	15/15	34/34		0.0 [0.0, 0.0]
Neiman 1985	12/12	12/12		0.0 [0.0, 0.0]
Oriani 1990	18/22	22/22		0.09 [0.00, 1.81]
Wood 1985	21/21	20/23		7.34 [0.36, 151.09]
Total (95% CI)	**199**	**221**		**0.84 [0.19, 3.67]**

Total events: 188 (HBOT), 212 (Placebo)

Heterogeneity: $Tau^2 = 1.33$; $Chi^2 = 8.24$, df = 5 (P = 0.14); $I^2 = 39\%$

Test for overall effect: Z = 0.23 (P = 0.82)

Test for subgroup differences: Not applicable

Analysis 1.10. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 10 Failure to improve EDSS by at least 1 point at 6 months.

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 10 Failure to improve EDSS by at least 1 point at 6 months

Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
Barnes 1987	59/60	56/56		0.35 [0.01, 8.80]
Confavreux 1986	8/8	8/8		0.0 [0.0, 0.0]
Fischer 1983	14/17	19/20		0.25 [0.02, 2.62]
Harpur 1986	39/41	39/41		1.00 [0.13, 7.46]
L'Hermitte 1986	32/32	12/12		0.0 [0.0, 0.0]
Neiman 1985	12/12	12/12		0.0 [0.0, 0.0]
Oriani 1990	12/22	17/22		0.35 [0.10, 1.30]
Total (95% CI)	**192**	**171**		**0.42 [0.16, 1.08]**

Total events: 176 (HBOT), 163 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.99$, df = 3 (P = 0.80); $I^2 = 0.0\%$

Test for overall effect: Z = 1.79 (P = 0.073)

Test for subgroup differences: Not applicable

Analysis 1.11. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 11 Sensitivity analysis: Failure to improve EDSS at 6 months. Best case..

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 11 Sensitivity analysis: Failure to improve EDSS at 6 months. Best case.

Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
Barnes 1987	59/60	60/60		0.33 [0.01, 8.21]
Confavreux 1986	8/8	9/9		0.0 [0.0, 0.0]
Fischer 1983	14/20	19/20		0.12 [0.01, 1.14]
Harpur 1986	39/41	39/41		1.00 [0.13, 7.46]
L'Hermitte 1986	32/34	15/15		0.42 [0.02, 9.27]
Neiman 1985	10/12	12/12		0.17 [0.01, 3.90]
Oriani 1990	12/22	17/22		0.35 [0.10, 1.30]
Total (95% CI)	**197**	**179**		**0.35 [0.15, 0.83]**

Total events: 174 (HBOT), 171 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.14$, df = 5 (P = 0.83); $I^2 = 0.0\%$

Test for overall effect: Z = 2.40 (P = 0.017)

Test for subgroup differences: Not applicable

Analysis 1.12. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 12 Sensitivity analysis: Failure to improve EDSS at 6 months. Worst case..

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 12 Sensitivity analysis: Failure to improve EDSS at 6 months. Worst case.

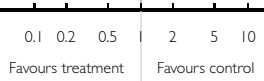
Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Barnes 1987	59/60	56/60		15.3 %	4.21 [0.46, 38.86]
Confavreux 1986	8/8	7/8		9.2 %	3.40 [0.12, 96.70]
Fischer 1983	17/20	19/20		14.4 %	0.30 [0.03, 3.15]
Harpur 1986	39/41	39/41		16.9 %	1.00 [0.13, 7.46]
L'Hermitte 1986	34/34	12/15		10.6 %	19.32 [0.93, 401.08]
Neiman 1985	12/12	9/12		10.4 %	9.21 [0.42, 200.59]
Oriani 1990	12/22	17/22		23.2 %	0.35 [0.10, 1.30]
Total (95% CI)	**197**	**178**		**100.0 %**	**1.58 [0.47, 5.29]**

Total events: 181 (HBOT), 159 (Placebo)

Heterogeneity: $Tau^2 = 1.19$; $Chi^2 = 11.41$, df = 6 (P = 0.08); $I^2 = 47\%$

Test for overall effect: Z = 0.75 (P = 0.45)

Test for subgroup differences: Not applicable



Analysis 1.13. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 13 Failure to improve EDSS by at least 1 point at 12 months.

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 13 Failure to improve EDSS by at least 1 point at 12 months

Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
Barnes 1987	59/60	56/56		0.35 [0.01, 8.80]
Confavreux 1986	8/8	8/8		0.0 [0.0, 0.0]
Oriani 1990	10/22	18/22		0.19 [0.05, 0.73]
Total (95% CI)	**90**	**86**		**0.20 [0.06, 0.72]**

Total events: 77 (HBOT), 82 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.13$, df = 1 (P = 0.72); $I^2 = 0.0\%$

Test for overall effect: Z = 2.47 (P = 0.014)

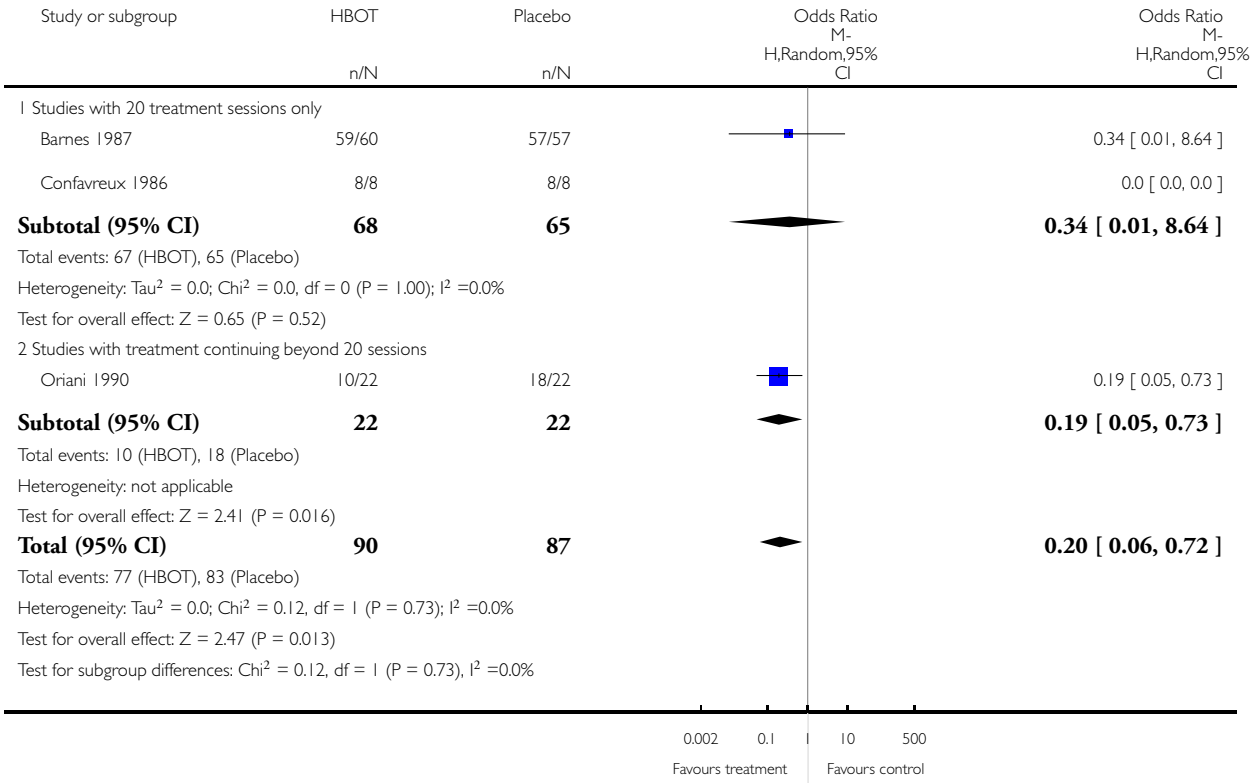
Test for subgroup differences: Not applicable

Analysis 1.14. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 14 Failure to improve EDSS at least 1 point at 12 months (subgroup analysis by treatment length).

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 14 Failure to improve EDSS at least 1 point at 12 months (subgroup analysis by treatment length)



Analysis 1.15. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 15 Sensitivity analysis: Failure to improve in EDSS at 12 months. Best case..

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 15 Sensitivity analysis: Failure to improve in EDSS at 12 months. Best case.

Study or subgroup	HBOT n/N	Sham n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
Barnes 1987	59/60	60/60		0.33 [0.01, 8.21]
Confavreux 1986	8/8	9/9		0.0 [0.0, 0.0]
Oriani 1990	10/22	18/22		0.19 [0.05, 0.73]
Total (95% CI)	**90**	**91**		**0.20 [0.06, 0.71]**

Total events: 77 (HBOT), 87 (Sham)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.10$, df = 1 (P = 0.75); $I^2 = 0.0\%$

Test for overall effect: Z = 2.49 (P = 0.013)

Test for subgroup differences: Not applicable

Analysis 1.16. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 16 Sensitivity analysis: Failure to improve EDSS at 12 months. Worst case..

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 16 Sensitivity analysis: Failure to improve EDSS at 12 months. Worst case.

Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Barnes 1987	60/60	56/60		30.5 %	9.64 [0.51, 183.05]
Confavreux 1986	8/8	8/9		27.8 %	3.00 [0.11, 84.56]
Oriani 1990	10/22	18/22		41.7 %	0.19 [0.05, 0.73]
Total (95% CI)	**90**	**91**		**100.0 %**	**1.34 [0.08, 21.75]**

Total events: 78 (HBOT), 82 (Placebo)

Heterogeneity: $Tau^2 = 4.36$; $Chi^2 = 7.43$, df = 2 (P = 0.02); $I^2 = 73\%$

Test for overall effect: Z = 0.21 (P = 0.84)

Test for subgroup differences: Not applicable

Analysis 1.17. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 17 Exacerbation during treatment course..

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 17 Exacerbation during treatment course.

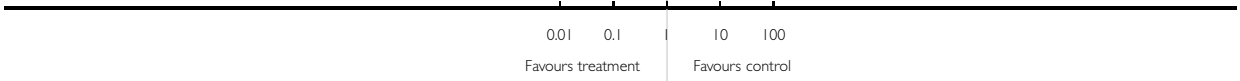
Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Barnes 1985	0/60	1/57		100.0 %	0.31 [0.01, 7.80]
Total (95% CI)	**60**	**57**		**100.0 %**	**0.31 [0.01, 7.80]**

Total events: 0 (HBOT), 1 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.71 (P = 0.48)

Test for subgroup differences: Not applicable



Analysis 1.18. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 18 Patients experiencing exacerbation within 6 months.

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 18 Patients experiencing exacerbation within 6 months

Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Harpur 1986	3/41	4/37		49.5 %	0.65 [0.14, 3.12]
L'Hermitte 1986	7/32	3/12		50.5 %	0.84 [0.18, 3.97]
Total (95% CI)	**73**	**49**		**100.0 %**	**0.74 [0.25, 2.23]**

Total events: 10 (HBOT), 7 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.05$, df = 1 (P = 0.82); $I^2 = 0.0\%$

Test for overall effect: Z = 0.53 (P = 0.59)

Test for subgroup differences: Not applicable

Analysis 1.19. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 19 Sensitivity analysis: Exacerbation within 6 months. Best case..

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 19 Sensitivity analysis: Exacerbation within 6 months. Best case.

Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Harpur 1986	3/41	8/41		47.1 %	0.33 [0.08, 1.33]
L'Hermitte 1986	7/34	6/15		52.9 %	0.39 [0.10, 1.46]
Total (95% CI)	**75**	**56**		**100.0 %**	**0.36 [0.14, 0.94]**

Total events: 10 (HBOT), 14 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.03$, df = 1 (P = 0.86); $I^2 = 0.0\%$

Test for overall effect: Z = 2.09 (P = 0.037)

Test for subgroup differences: Not applicable

Analysis 1.20. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 20 Sensitivity analysis: Exacerbation within 6 months. Worst case..

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 20 Sensitivity analysis: Exacerbation within 6 months. Worst case.

Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Harpur 1986	3/41	4/41		46.4 %	0.73 [0.15, 3.49]
L'Hermitte 1986	11/34	3/15		53.6 %	1.91 [0.45, 8.20]
Total (95% CI)	**75**	**56**		**100.0 %**	**1.22 [0.42, 3.55]**

Total events: 14 (HBOT), 7 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.78$, df = 1 (P = 0.38); $I^2 = 0.0\%$

Test for overall effect: Z = 0.37 (P = 0.71)

Test for subgroup differences: Not applicable

Analysis 1.21. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 21 Patients experiencing exacerbation within 12 months.

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 21 Patients experiencing exacerbation within 12 months

Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Barnes 1987	18/60	17/56		56.2 %	0.98 [0.44, 2.17]
Fischer 1983	2/17	11/20		43.8 %	0.11 [0.02, 0.61]
Total (95% CI)	**77**	**76**		**100.0 %**	**0.38 [0.04, 3.22]**

Total events: 20 (HBOT), 28 (Placebo)

Heterogeneity: $Tau^2 = 1.97$; $Chi^2 = 5.23$, df = 1 (P = 0.02); $I^2 = 81\%$

Test for overall effect: Z = 0.89 (P = 0.37)

Test for subgroup differences: Not applicable

Analysis 1.22. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 22 Sensitivity analysis: Exacerbation within 12 months. Best case..

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 22 Sensitivity analysis: Exacerbation within 12 months. Best case.

Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Barnes 1987	18/60	21/60		56.4 %	0.80 [0.37, 1.71]
Fischer 1983	2/20	11/20		43.6 %	0.09 [0.02, 0.50]
Total (95% CI)	**80**	**80**		**100.0 %**	**0.31 [0.04, 2.57]**

Total events: 20 (HBOT), 32 (Placebo)

Heterogeneity: $Tau^2 = 1.92$; $Chi^2 = 5.22$, df = 1 (P = 0.02); $I^2 = 81\%$

Test for overall effect: Z = 1.09 (P = 0.28)

Test for subgroup differences: Not applicable

Analysis 1.23. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 23 Sensitivity analysis: Exacerbation within 12 months. Worst case..

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 23 Sensitivity analysis: Exacerbation within 12 months. Worst case.

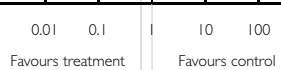
Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Barnes 1987	18/60	17/60		58.1 %	1.08 [0.49, 2.38]
Fischer 1983	5/20	11/20		41.9 %	0.27 [0.07, 1.04]
Total (95% CI)	**80**	**80**		**100.0 %**	**0.61 [0.16, 2.31]**

Total events: 23 (Treatment), 28 (Control)

Heterogeneity: $Tau^2 = 0.64$; $Chi^2 = 3.02$, df = 1 (P = 0.08); $I^2 = 67\%$

Test for overall effect: Z = 0.73 (P = 0.46)

Test for subgroup differences: Not applicable

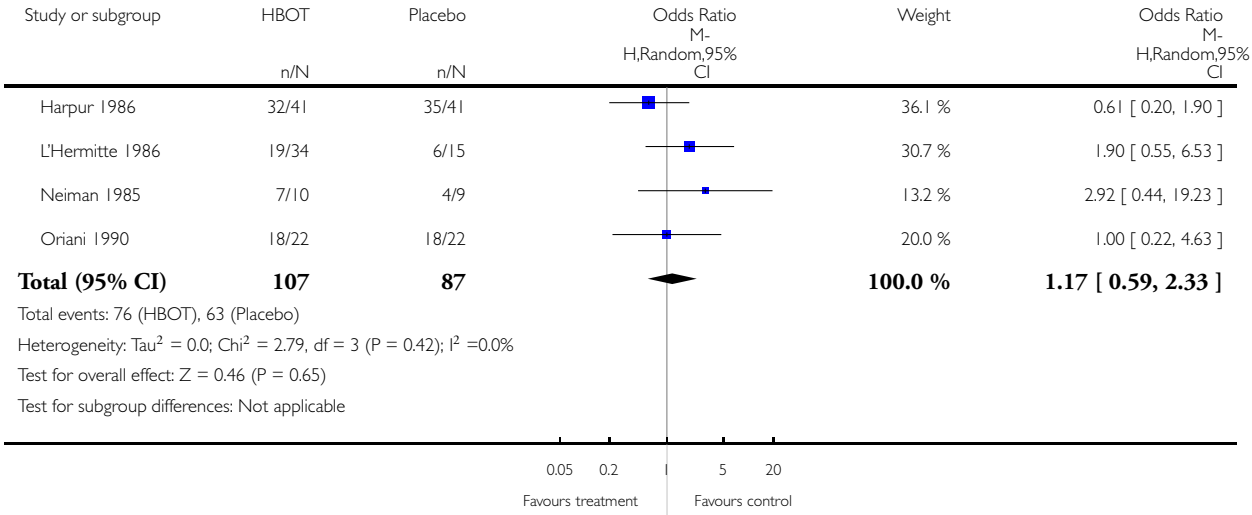


Analysis 1.24. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 24 Failure to improve at least 1 point in FSS after 20 treatments.

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 24 Failure to improve at least 1 point in FSS after 20 treatments

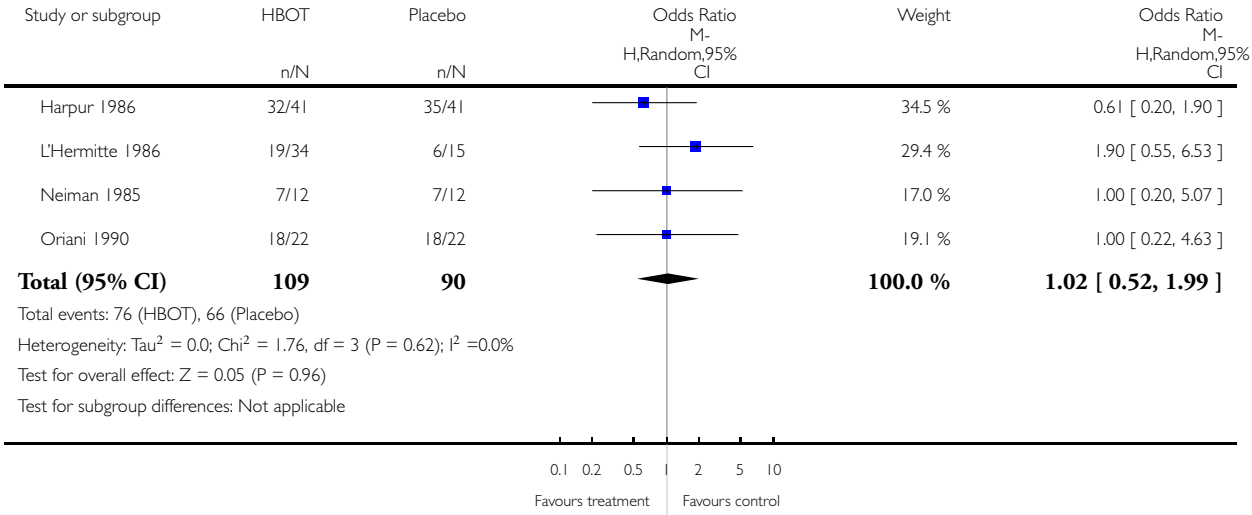


Analysis 1.25. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 25 Sensitivity analysis: failure to improve FSS at 20 treatments. Best case..

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 25 Sensitivity analysis: failure to improve FSS at 20 treatments. Best case.



Analysis 1.26. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 26 Sensitivity analysis: Failure to improve FSS at 20 treatments. Worst case..

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 26 Sensitivity analysis: Failure to improve FSS at 20 treatments. Worst case.

Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Harpur 1986	32/41	35/41		31.1 %	0.61 [0.20, 1.90]
L'Hermitte 1986	19/34	6/15		28.6 %	1.90 [0.55, 6.53]
Neiman 1985	9/12	4/12		18.1 %	6.00 [1.02, 35.37]
Oriani 1990	18/22	18/22		22.1 %	1.00 [0.22, 4.63]
Total (95% CI)	**109**	**90**		**100.0 %**	**1.43 [0.58, 3.50]**

Total events: 78 (HBOT), 63 (Placebo)

Heterogeneity: $Tau^2 = 0.34$; $Chi^2 = 5.03$, df = 3 (P = 0.17); $I^2 = 40\%$

Test for overall effect: Z = 0.77 (P = 0.44)

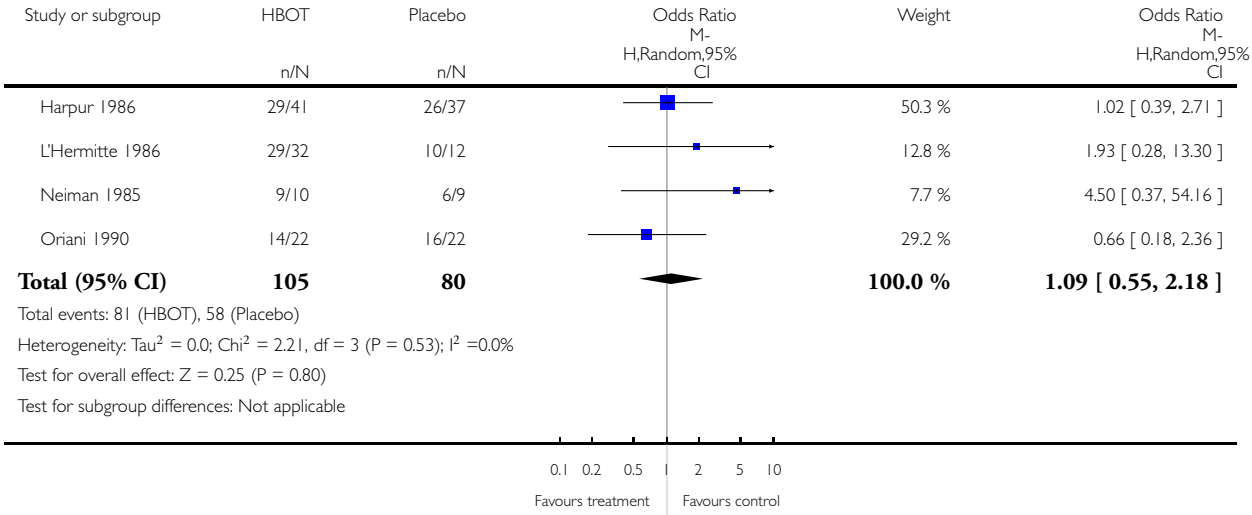
Test for subgroup differences: Not applicable

Analysis 1.27. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 27 Failure to improve at least 1 point on FSS at 6 months.

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 27 Failure to improve at least 1 point on FSS at 6 months



Analysis 1.28. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 28 Sensitivity analysis: Failure to improve FSS at 6 months. Best case..

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 28 Sensitivity analysis: Failure to improve FSS at 6 months. Best case.

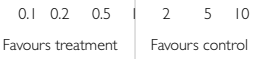
Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Harpur 1986	29/41	30/41		48.9 %	0.89 [0.34, 2.32]
L'Hermitte 1986	29/34	13/15		14.6 %	0.89 [0.15, 5.22]
Neiman 1985	7/12	9/12		15.0 %	0.47 [0.08, 2.66]
Oriani 1990	14/20	16/20		21.5 %	0.58 [0.14, 2.50]
Total (95% CI)	**107**	**88**		**100.0 %**	**0.74 [0.38, 1.44]**

Total events: 79 (HBOT), 68 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.55$, df = 3 (P = 0.91); $I^2 = 0.0\%$

Test for overall effect: Z = 0.89 (P = 0.37)

Test for subgroup differences: Not applicable



Analysis 1.29. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 29 Sensitivity analysis: Failure to improve FSS at 6 months. Worst case..

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 29 Sensitivity analysis: Failure to improve FSS at 6 months. Worst case.

Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Harpur 1986	29/41	26/41		35.5 %	1.39 [0.55, 3.52]
L'Hermitte 1986	31/34	10/15		23.6 %	5.17 [1.04, 25.57]
Neiman 1985	11/12	6/12		15.0 %	11.00 [1.06, 114.09]
Oriani 1990	14/20	16/20		25.9 %	0.58 [0.14, 2.50]
Total (95% CI)	**107**	**88**		**100.0 %**	**2.07 [0.69, 6.18]**

Total events: 85 (HBOT), 58 (Placebo)

Heterogeneity: $Tau^2 = 0.66$; $Chi^2 = 6.56$, df = 3 (P = 0.09); $I^2 = 54\%$

Test for overall effect: Z = 1.30 (P = 0.19)

Test for subgroup differences: Not applicable

Analysis 1.30. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 30 Failure to improve bladder and/or bowel sphincter function after 20 treatments.

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 30 Failure to improve bladder and/or bowel sphincter function after 20 treatments

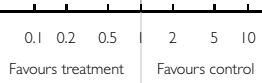
Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Barnes 1985	39/51	44/47		17.0 %	0.22 [0.06, 0.84]
Confavreux 1986	4/5	7/8		5.7 %	0.57 [0.03, 11.85]
Fischer 1983	8/13	16/17		8.7 %	0.10 [0.01, 1.01]
Harpur 1986	36/41	31/41		19.0 %	2.32 [0.72, 7.53]
Neiman 1985	8/10	6/9		10.1 %	2.00 [0.25, 15.99]
Oriani 1990	20/22	22/22		5.5 %	0.18 [0.01, 4.02]
Wiles 1986	26/40	28/41		22.6 %	0.86 [0.34, 2.17]
Wood 1985	19/21	17/20		11.4 %	1.68 [0.25, 11.27]
Total (95% CI)	**203**	**205**		**100.0 %**	**0.72 [0.33, 1.60]**

Total events: 160 (HBOT), 171 (Placebo)

Heterogeneity: $Tau^2 = 0.51$; $Chi^2 = 12.17$, df = 7 (P = 0.10); $I^2 = 42\%$

Test for overall effect: Z = 0.80 (P = 0.42)

Test for subgroup differences: Not applicable



Analysis 1.31. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 31 Failure to improve bladder and/or bowel sphincter function at 6 months..

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 31 Failure to improve bladder and/or bowel sphincter function at 6 months.

Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Barnes 1987	47/60	53/56		30.8 %	0.20 [0.05, 0.76]
Confavreux 1986	4/5	7/8		17.8 %	0.57 [0.03, 11.85]
Harpur 1986	28/37	20/37		33.2 %	2.64 [0.98, 7.12]
Oriani 1990	18/22	22/22		18.1 %	0.09 [0.00, 1.81]
Total (95% CI)	**124**	**123**		**100.0 %**	**0.50 [0.08, 2.94]**

Total events: 97 (HBOT), 102 (Placebo)

Heterogeneity: $Tau^2 = 2.22$; $Chi^2 = 11.94$, df = 3 (P = 0.01); $I^2 = 75\%$

Test for overall effect: Z = 0.77 (P = 0.44)

Test for subgroup differences: Not applicable

Analysis 1.32. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 32 Failure to improve bladder and/or bowel sphincter function at 6 months (by treatment length).

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 32 Failure to improve bladder and/or bowel sphincter function at 6 months (by treatment length)

Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Studies with 20 treatment sessions only					
Barnes 1987	47/60	53/56		30.8 %	0.20 [0.05, 0.76]
Confavreux 1986	4/5	7/8		17.8 %	0.57 [0.03, 11.85]
Subtotal (95% CI)	**65**	**64**		**48.6 %**	**0.24 [0.07, 0.80]**
Total events: 51 (HBOT), 60 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.37, df = 1 (P = 0.54); I^2 =0.0%					
Test for overall effect: Z = 2.31 (P = 0.021)					
2 Studies with treatment continuing beyond 20 sessions					
Harpur 1986	28/37	20/37		33.2 %	2.64 [0.98, 7.12]
Oriani 1990	18/22	22/22		18.1 %	0.09 [0.00, 1.81]
Subtotal (95% CI)	**59**	**59**		**51.4 %**	**0.65 [0.02, 19.07]**
Total events: 46 (HBOT), 42 (Placebo)					
Heterogeneity: Tau^2 = 4.81; Chi^2 = 4.74, df = 1 (P = 0.03); I^2 =79%					
Test for overall effect: Z = 0.25 (P = 0.80)					
Total (95% CI)	**124**	**123**		**100.0 %**	**0.50 [0.08, 2.94]**
Total events: 97 (HBOT), 102 (Placebo)					
Heterogeneity: Tau^2 = 2.22; Chi^2 = 11.94, df = 3 (P = 0.01); I^2 =75%					
Test for overall effect: Z = 0.77 (P = 0.44)					
Test for subgroup differences: Chi^2 = 0.30, df = 1 (P = 0.58), I^2 =0.0%					

Analysis 1.33. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 33 Failure to improve bladder and/or bowel sphincter function at 12 months.

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 33 Failure to improve bladder and/or bowel sphincter function at 12 months

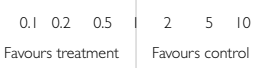
Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Barnes 1987	50/60	52/56		72.3 %	0.38 [0.11, 1.31]
Confavreux 1986	5/5	8/9		12.1 %	1.94 [0.07, 56.76]
Oriani 1990	17/22	22/22		15.5 %	0.07 [0.00, 1.37]
Total (95% CI)	**87**	**87**		**100.0 %**	**0.36 [0.11, 1.19]**

Total events: 72 (HBOT), 82 (Placebo)

Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 2.16$, df = 2 (P = 0.34); $I^2 = 8\%$

Test for overall effect: Z = 1.67 (P = 0.095)

Test for subgroup differences: Not applicable



Analysis 1.34. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 34 Failure to Improve pyramidal function after 20 treatments..

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 34 Failure to Improve pyramidal function after 20 treatments.

Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
Barnes 1985	57/58	54/54		0.35 [0.01, 8.82]
Confavreux 1986	7/7	8/9		2.65 [0.09, 75.29]
Fischer 1983	15/17	20/20		0.15 [0.01, 3.38]
Oriani 1990	18/22	22/22		0.09 [0.00, 1.81]
Wood 1985	21/21	20/20		0.0 [0.0, 0.0]
Total (95% CI)	**125**	**125**		**0.30 [0.06, 1.47]**

Total events: 118 (HBOT), 124 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.44$, df = 3 (P = 0.49); $I^2 = 0.0\%$

Test for overall effect: Z = 1.48 (P = 0.14)

Test for subgroup differences: Not applicable

Analysis 1.35. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 35 Failure to improve pyramidal function at 6 months.

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 35 Failure to improve pyramidal function at 6 months

Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
Barnes 1987	59/60	56/56		0.35 [0.01, 8.80]
Confavreux 1986	7/7	9/9		0.0 [0.0, 0.0]
Oriani 1990	13/22	20/22		0.14 [0.03, 0.78]
Total (95% CI)	**89**	**87**		**0.17 [0.04, 0.78]**

Total events: 79 (HBOT), 85 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.23$, df = 1 (P = 0.63); $I^2 = 0.0\%$

Test for overall effect: Z = 2.29 (P = 0.022)

Test for subgroup differences: Not applicable

Analysis 1.36. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 36 Failure to improve pyramidal function at 12 months.

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 36 Failure to improve pyramidal function at 12 months

Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
Barnes 1987	60/60	56/56		0.0 [0.0, 0.0]
Confavreux 1986	7/7	9/9		0.0 [0.0, 0.0]
Oriani 1990	10/22	19/22		0.13 [0.03, 0.58]
Total (95% CI)	**89**	**87**		**0.13 [0.03, 0.58]**

Total events: 77 (HBOT), 84 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 2.69 (P = 0.0072)

Test for subgroup differences: Not applicable

Analysis 1.37. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 37 Deterioration in bladder and/or bowel function after 20 treatments.

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 37 Deterioration in bladder and/or bowel function after 20 treatments

Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Barnes 1985	2/60	1/57		1.93 [0.17, 21.90]
Confavreux 1986	2/8	0/9		7.31 [0.30, 178.57]
Harpur 1986	7/41	8/41		0.85 [0.28, 2.61]
Neiman 1985	0/10	0/9		0.0 [0.0, 0.0]
Oriani 1990	0/22	0/22		0.0 [0.0, 0.0]
Total (95% CI)	**141**	**138**		**1.26 [0.50, 3.19]**

Total events: 11 (HBOT), 9 (Placebo)

Heterogeneity: $Chi^2 = 1.76$, df = 2 (P = 0.42); $I^2 = 0.0\%$

Test for overall effect: Z = 0.49 (P = 0.62)

Test for subgroup differences: Not applicable

Analysis 1.38. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 38 Sensitivity analysis: Deterioration in sphincter function at 20 treatments. Best case..

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 38 Sensitivity analysis: Deterioration in sphincter function at 20 treatments. Best case.

Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
Barnes 1985	2/60	4/60		0.48 [0.09, 2.74]
Confavreux 1986	2/8	0/9		7.31 [0.30, 178.57]
Harpur 1986	7/41	8/41		0.85 [0.28, 2.61]
Neiman 1985	0/12	3/12		0.11 [0.00, 2.36]
Oriani 1990	0/22	0/22		0.0 [0.0, 0.0]
Total (95% CI)	**143**	**144**		**0.72 [0.25, 2.09]**

Total events: 11 (HBOT), 15 (Placebo)

Heterogeneity: $Tau^2 = 0.26$; $Chi^2 = 3.75$, df = 3 (P = 0.29); $I^2 = 20\%$

Test for overall effect: Z = 0.60 (P = 0.55)

Test for subgroup differences: Not applicable

Analysis 1.39. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 39 Sensitivity analysis: Deterioration in sphincter function at 20 treatments. Worst case..

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 39 Sensitivity analysis: Deterioration in sphincter function at 20 treatments. Worst case.

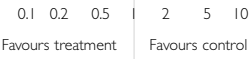
Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
Barnes 1985	2/60	1/60		2.03 [0.18, 23.06]
Confavreux 1986	2/8	0/8		6.54 [0.27, 160.97]
Harpur 1986	7/41	8/41		0.85 [0.28, 2.61]
Neiman 1985	2/12	0/12		5.95 [0.26, 138.25]
Oriani 1990	0/22	0/22		0.0 [0.0, 0.0]
Total (95% CI)	**143**	**143**		**1.36 [0.54, 3.43]**

Total events: 13 (HBOT), 9 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.59$, df = 3 (P = 0.46); $I^2 = 0.0\%$

Test for overall effect: Z = 0.64 (P = 0.52)

Test for subgroup differences: Not applicable



Analysis 1.40. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 40 Deterioration in bladder and/or bowel sphincter function at 6 months.

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 40 Deterioration in bladder and/or bowel sphincter function at 6 months

Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Barnes 1987	4/60	8/56		33.6 %	0.43 [0.12, 1.51]
Confavreux 1986	2/8	4/9		14.7 %	0.42 [0.05, 3.31]
Harpur 1986	12/41	8/37		44.8 %	1.50 [0.53, 4.21]
Oriani 1990	0/22	2/22		7.0 %	0.18 [0.01, 4.02]
Total (95% CI)	**131**	**124**		**100.0 %**	**0.70 [0.30, 1.63]**

Total events: 18 (HBOT), 22 (Placebo)

Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 3.61$, df = 3 (P = 0.31); $I^2 = 17\%$

Test for overall effect: Z = 0.82 (P = 0.41)

Test for subgroup differences: Not applicable

Analysis 1.41. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 41 Sensitivity analysis: deterioration in sphincter function at 6 months. Best case..

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 41 Sensitivity analysis: deterioration in sphincter function at 6 months. Best case.

Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Barnes 1987	4/60	12/60		33.3 %	0.29 [0.09, 0.94]
Confavreux 1986	2/8	4/9		12.0 %	0.42 [0.05, 3.31]
Harpur 1986	12/41	12/41		49.3 %	1.00 [0.39, 2.59]
Oriani 1990	0/22	2/22		5.5 %	0.18 [0.01, 4.02]
Total (95% CI)	**131**	**132**		**100.0 %**	**0.54 [0.26, 1.12]**

Total events: 18 (HBOT), 30 (Placebo)

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 3.24$, df = 3 (P = 0.36); $I^2 = 7\%$

Test for overall effect: Z = 1.65 (P = 0.10)

Test for subgroup differences: Not applicable

Analysis 1.42. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 42 Sensitivity analysis: deterioration of sphincter function at 6 months. Worst case..

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 42 Sensitivity analysis: deterioration of sphincter function at 6 months. Worst case.

Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Barnes 1987	4/60	8/60		33.5 %	0.46 [0.13, 1.63]
Confavreux 1986	2/8	4/9		16.0 %	0.42 [0.05, 3.31]
Harpur 1986	12/41	8/41		42.7 %	1.71 [0.61, 4.75]
Oriani 1990	0/22	2/22		7.9 %	0.18 [0.01, 4.02]
Total (95% CI)	**131**	**132**		**100.0 %**	**0.74 [0.30, 1.83]**

Total events: 18 (HBOT), 22 (Placebo)

Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 4.08$, df = 3 (P = 0.25); $I^2 = 26\%$

Test for overall effect: Z = 0.65 (P = 0.51)

Test for subgroup differences: Not applicable

Analysis 1.43. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 43 Deterioration in bladder and/or bowel function at 12 months.

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 43 Deterioration in bladder and/or bowel function at 12 months

Study or subgroup	HBOT n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Barnes 1987	10/60	9/56		57.7 %	1.04 [0.39, 2.80]
Confavreux 1986	2/8	6/9		27.1 %	0.17 [0.02, 1.38]
Oriani 1990	0/22	2/22		15.3 %	0.18 [0.01, 4.02]
Total (95% CI)	**90**	**87**		**100.0 %**	**0.49 [0.13, 1.86]**

Total events: 12 (HBOT), 17 (Placebo)

Heterogeneity: $Tau^2 = 0.56$; $Chi^2 = 3.13$, df = 2 (P = 0.21); $I^2 = 36\%$

Test for overall effect: Z = 1.05 (P = 0.29)

Test for subgroup differences: Not applicable

Analysis 1.44. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 44 Sensitivity analysis: Deterioration in sphincter function at 12 months. Best case..

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 44 Sensitivity analysis: Deterioration in sphincter function at 12 months. Best case.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Barnes 1987	10/60	13/60		76.9 %	0.72 [0.29, 1.81]
Confavreux 1986	2/8	6/9		15.7 %	0.17 [0.02, 1.38]
Oriani 1990	0/22	2/22		7.4 %	0.18 [0.01, 4.02]
Total (95% CI)	**90**	**91**		**100.0 %**	**0.52 [0.22, 1.21]**

Total events: 12 (Treatment), 21 (Control)

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 2.05$, df = 2 (P = 0.36); $I^2 = 3\%$

Test for overall effect: Z = 1.52 (P = 0.13)

Test for subgroup differences: Not applicable

Analysis 1.45. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 45 Sensitivity analysis: Deterioration in sphincter function at 12 months. Worst case..

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 45 Sensitivity analysis: Deterioration in sphincter function at 12 months. Worst case.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
Barnes 1985	0/1	0/1		0.0 [0.0, 0.0]
Barnes 1987	10/60	9/60		1.13 [0.42, 3.02]
Confavreux 1986	2/8	6/9		0.17 [0.02, 1.38]
Oriani 1990	0/22	2/22		0.18 [0.01, 4.02]
Total (95% CI)	**91**	**92**		**0.49 [0.12, 2.02]**

Total events: 12 (Treatment), 17 (Control)

Heterogeneity: $Tau^2 = 0.70$; $Chi^2 = 3.43$, df = 2 (P = 0.18); $I^2 = 42\%$

Test for overall effect: Z = 0.99 (P = 0.32)

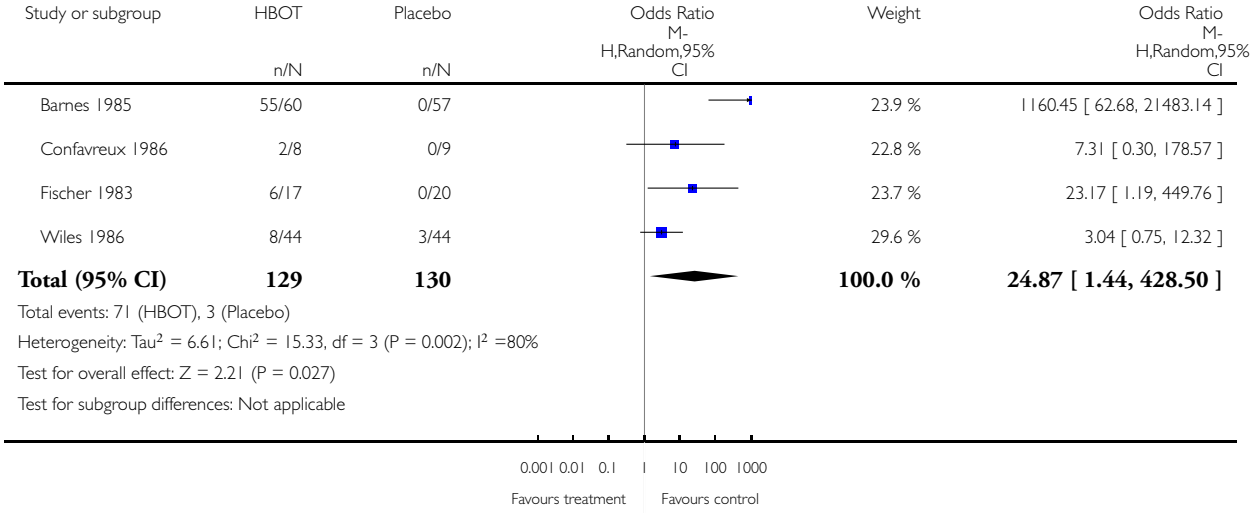
Test for subgroup differences: Not applicable

Analysis 1.46. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 46 Incidence of visual disturbance after 20 treatments.

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 46 Incidence of visual disturbance after 20 treatments

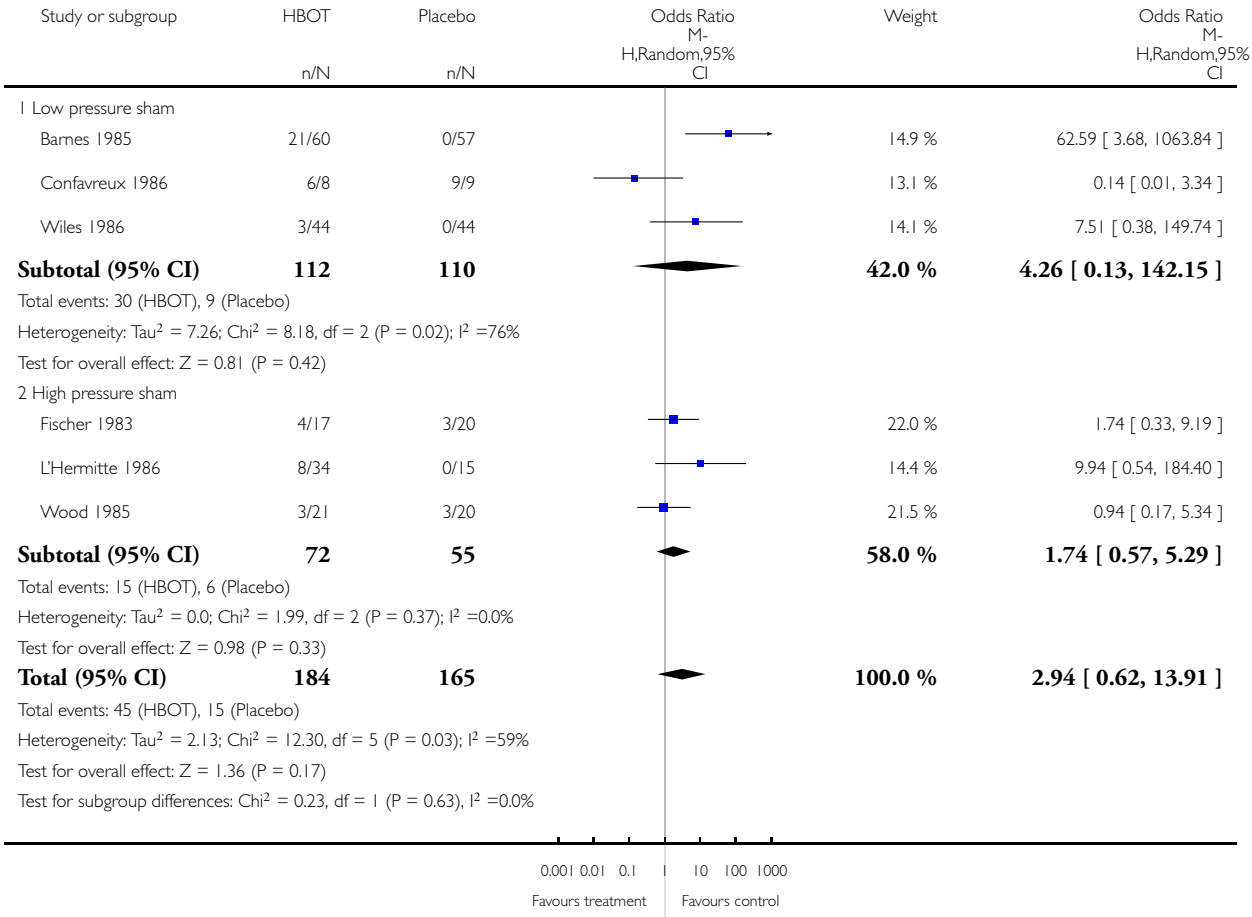


Analysis 1.47. Comparison 1 Hyperbaric Oxygen Therapy versus Placebo, Outcome 47 Incidence of barotrauma during therapy. Subgroup analysis by sham pressure..

Review: Hyperbaric oxygen therapy for multiple sclerosis

Comparison: 1 Hyperbaric Oxygen Therapy versus Placebo

Outcome: 47 Incidence of barotrauma during therapy. Subgroup analysis by sham pressure.



ADDITIONAL TABLES

Table 1. Summary of Kurtzke Scales for Disability and Functional Status

EDSS	FSS
0 - Normal neurological examination.	Pyramidal: 0 - Normal, 1 - Signs without disability, 2 - Mild disability, ... 6 - Quadriplegia, 9 - Unknown

Table 1. Summary of Kurtzke Scales for Disability and Functional Status (*Continued*)

1.0 - No disability. Minimal signs on one FS.	Cerebellar: 0 - Normal, 1 - Signs without disability, 2 - Mild ataxia .... 5 - Unable to perform co-ordinated movements because of ataxia, 9 - Unknown
1.5 - No disability. Minimal signs on >1 FS.	Brainstem: 0 - Normal, 1 - Signs only, 2 - moderate nystagmus .. .... 5 - Inability to swallow or speak, 9 - Unknown
2.0 - Minimal disability in 1 FS.	Sensory: 0 - Normal, 1 - Vibration or figure writing decreased in one or two limbs, 2 - Mild decrease in touch, pain or position sense..... 6 - sensation lost below head, 9 - Unknown
2.5 - Minimal disability in 2 FS.	Visual: 0 - Normal, 1 - Scotoma with corrected acuity >20/30, 2 - Scotoma with worse eye corrected acuity 20/30 to 20/59 ..... 6 - Worse eye corrected acuity < 20/200 and betetr eye <20/60, 9 - Normal
3.0 - Moderate disability in 1 FS, or mild disability in 3-4 FS. Fully ambulatory	Mental: 0 - Normal, 1 - Mood alteration, 2 - Mild decrease in mentation ..... 5 - Dementia severe or incompetent, 9 - Unknown
3.5 - Fully ambulatory. Moderate disability in 3-4 FS.	Bladder/bowel: 0- Normal, 1 - Mild urinary hesitance, urgency or retention, 2 - Moderate same or occasional incontinence ..... 6 - Loss of bladder and bowel function, 9 - Unknown
4.0 - Fully ambulatory, walk without aid 500m. Up and about 12 hours/day despite relatively severe disability	Other
4.5 - Fully ambulatory, walk 300m without aid. Up and about much of day, able to work a full day but may have some limitation of full activity or require minimal assistance	
5.0 - Ambulatory without aid for 200m. Disability impairs full daily activities	
5.5 - Ambulatory for about 100m. Disability precludes full daily activity	
6.0 - Intermittent or unilateral constant assistance required to walk 100m with or without resting	
6.5 - Constant bilateral support required to walk 20m without resting	
7.0 - Unable to walk beyond 5m with aid. essentially restricted to wheelchair. wheels self, transfers alone	
7.5 - A few steps only. restricted to wheelchair, needs aid to transfer. Wheels self but may need motorised chair for full days activities	

Table 1. Summary of Kurtzke Scales for Disability and Functional Status (*Continued*)

8.0 - Essentially restricted to bed, chair or wheeled. may be out of bed much of the day. Retains self-care functions. generally effective use of arms	
8.5 - Essentially restricted to bed much of the day. Some effective use of arms, some self-care functions	
9.0 - Helpless bed patient. can communicate and eat.	
9.5 - Unable to communicate effectively, eat or swallow.	
10 - Dead.	

Table 2. Outcomes where no patients in either arm experienced the outcome of interest

Study	Outcome
Barnes 1985, 1987	Improvement in EDSS at 20 treatments. Improvement in pyramidal function at 12 months
Confavreux 1986	Improvement in EDSS at 6 months and 12 months. Improvement in pyramidal function at 6 months and 12 months
L'Hermitte 1986	Improvement in EDSS at 20 treatments and 6 months.
Neiman 1895	Improvement in EDSS at 20 treatments and 6 months. Deterioration of bladder function at 20 treatments
Oriani 1990	Deterioration of bladder function at 20 treatments.
Wood 1985	Improvement in pyramidal function at 20 treatments.

Table 3. Patients lost to follow-up

Study	Lost but included	Lost to follow-up	% of patients
Barnes	0	4	3.3%
Confavreux	0	1	5.9%
Fischer	0	3	7.5%

Table 3. Patients lost to follow-up (*Continued*)

Harpur	0	0	0%
L'Hermitte	0	5	10.2%
Neiman	0	5	20.8%
Oriani	0	0	0%
Wiles	0	7	8.3%
Wood	0	3	12%

APPENDICES

Appendix 1. Keywords used to search the MS Group Specialised Register

{hyperbaric oxygenation} OR {hyperbaric} OR {oxygenation} OR {hyperbaric oxygenation*} OR {hyperbaric oxygen therapy} OR {hyperbaritc oxygen therapies}

Appendix 2. Search methods used in previous version

Search methods for identification of studies

A systematic search was conducted using the optimally sensitive strategy developed for the Cochrane Collaboration to identify all relevant published and unpublished randomised controlled trials. (Lefebvre 2009)
For additional information about the Group's search strategy please see: Cochrane Multiple Sclerosis Group

Electronic searches

We searched the following databases:
(1) The Cochrane Multiple Sclerosis Group trials register (January 2010)
(2) The Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 1, 2010)
(3) MEDLINE (PubMed) (January 1966 to January 2010)
(4) EMBASE (EMBASE.com) (1974 to January 2010)
(5) The Database of Randomised Controlled Trials in Hyperbaric Medicine (DORCTHIM)(Bennett 2001) using the search term 'Multiple Sclerosis'.
Non-English publications were considered and translated by professional service if required.

Appendix 3. Previous search strategies

1 CENTRAL search strategy

#1MeSH descriptor Multiple Sclerosis explode all trees
#2MeSH descriptor Demyelinating Diseases, this term only
#3MeSH descriptor Myelitis, Transverse, this term only
#4MeSH descriptor Optic Neuritis explode all trees
#5MeSH descriptor Encephalomyelitis, Acute Disseminated, this term only
#6"multiple sclerosis":ti,ab,kw
#7(demyelinating NEXT disease):ti,ab,kw
#8(transverse NEXT myelitis):ti,ab,kw
#9"neuromyelitis optica":ti,ab,kw
#10"optic neuritis":ti,ab,kw
#11(devic):ti,ab,kw
#12"acute disseminated encephalomyelitis":ti,ab,kw
#13(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)
#14MeSH descriptor Hyperbaric Oxygenation explode all trees
#15(hyperbaric AND oxygen):ti,ab,kw or "hyperbaric oxygen":ti,ab,kw
#16(#14 OR #15)
#17(#13 AND #16)

2 MEDLINE (PubMed) search strategy

((("Hyperbaric Oxygen Therapy "[Title/Abstract]) OR ("Hyperbaric Oxygen Therapies "[Title/Abstract])) OR ("hyperbaric oxygenation"[MeSH Terms] OR "Hyperbaric Oxygenation*"[Title/Abstract])) AND ((((("Multiple Sclerosis"[mh]) OR ("Myelitis, Transverse"[mh:noexp]) OR ("Demyelinating Diseases"[mh:noexp]) OR ("Encephalomyelitis, Acute Disseminated"[mh:noexp]) OR ("Optic Neuritis"[mh])) OR (("multiple sclerosis"[Title/Abstract]) OR ("neuromyelitis optica"[Title/Abstract]) OR ("transverse myelitis"[Title/Abstract]) OR ("encephalomyelitis"[Title/Abstract]) OR ("devic"[Title/Abstract]) OR ("optic neuritis"[Title/Abstract]) OR ("demyelinating disease*"[Title/Abstract]) OR ("acute disseminated encephalomyelitis"[Title/Abstract]))) AND (((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab]) OR (placebo[tiab]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT ((animals[mh]) NOT ((animals[mh]) AND (human[mh])))))

3 EMBASE (EMBASE.com)

((('encephalomyelitis'/exp) OR ('demyelinating disease'/exp) OR ('multiple sclerosis'/exp) OR ('myelooptic neuropathy'/exp) OR ('multiple sclerosis':ti,ab) OR ('neuromyelitis optica':ab,ti) OR (encephalomyelitis:ab,ti) OR (devic:ti,ab)) AND (('crossover procedure'/exp) OR ('double blind procedure'/exp) OR ('single blind procedure'/exp) OR ('randomized controlled trial'/exp) OR (random*:ab,ti) OR (factorial*:ab,ti) OR (crossover:ab,ti) OR (cross:ab,ti AND over:ab,ti) OR (placebo:ab,ti) OR ('double blind':ab,ti) OR ('single blind':ab,ti) OR (assign*:ab,ti) OR (allocat*:ab,ti) OR (volunteer*:ab,ti))) AND (('hyperbaric oxygen'/exp) OR ('hyperbaric oxygen':ab,ti) OR (hyperbaric:ab,ti AND oxygen:ab,ti)) AND [humans]/lim AND [embase]/lim

WHAT'S NEW

Last assessed as up-to-date: 29 May 2011.

Date	Event	Description
21 June 2011	Review declared as stable	There is no evidence of further research interest in this area
25 February 2011	New search has been performed	Search strategy run. No new evidence found.

HISTORY

Protocol first published: Issue 3, 2001

Review first published: Issue 1, 2004

Date	Event	Description
25 January 2010	New search has been performed	Search strategies repeated. No new evidence found.
25 August 2008	Amended	Converted to new review format.
23 June 2006	Amended	Minor updates: no new randomised trials published, therefore no new data
23 June 2006	New search has been performed	Searches re run.

CONTRIBUTIONS OF AUTHORS

Bennett: Conception, search strategy and execution, critical appraisal, Hyperbaric Medicine context expert, statistical analysis, writer.

Heard: Conception, critical appraisal, Multiple Sclerosis context expert, co-writer.

DECLARATIONS OF INTEREST

Dr. Bennett is medical director of a hyperbaric facility and does not routinely treat multiple sclerosis patients. He has not participated in any relevant sponsored trials.

Dr Heard is a consultant neurologist and director of a neuroimmunology unit where he routinely treats multiple sclerosis patients. He has not participated in any relevant sponsored trials.

SOURCES OF SUPPORT

Internal sources

- New Source of support, Not specified.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Hyperbaric Oxygenation [adverse effects; *methods]; Multiple Sclerosis [*therapy]; Randomized Controlled Trials as Topic; Treatment Outcome

MeSH check words

Humans