# NHS England

# Evidence review: Hyperbaric Oxygen Therapy for Carbon Monoxide Poisoning



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## Contents

## 1. Introduction

**Indication and epidemiology**

- Carbon monoxide (CO) is a colourless, odourless, tasteless gas generated during incomplete combustion of carbon-based compounds. It binds to haemoglobin (Hb) with an affinity 210 times that of oxygen, forming carboxyhaemoglobin (COHb), and also increases[1] the affinity of the remaining Hb sites for oxygen, thus reducing the oxygen carrying and oxygen delivery capacity of blood. It has also been shown to lead to harm by other mechanisms including disruption of cellular oxidative processes resulting in marked oxidative stress and inflammatory responses (Buckley et al 2011).
- CO poisoning is the most common cause of fatal poisoning in the USA and Europe (Ritchie et al 2008). In 2000, CO was recorded as the cause of 521 deaths in England and Wales, of which 148 were accidental and 373 the result of suicide or self-inflicted injury (Smollin and Olson 2010). It usually results from incomplete combustion of carbon fuels, including inadequately ventilated heating systems and car exhausts, as well as from chemicals such as methylene chloride paint stripper (Smollin and Olson 2010).
- Poisoning is considered to have occurred at COHb levels of over 10%, and severe poisoning is associated with levels over 20-25% plus symptoms of severe cerebral or cardiac ischemia (Smollin and Olson 2010), although there is variation in these definitions. Severe poisoning can be fatal and up to a third of survivors have delayed neurological sequelae. People with comorbidity, the elderly, very young and pregnant women are most susceptible (Smollin and Olson 2010).
- The main symptoms of CO poisoning are non-specific and varied and relate to effects on the brain and heart, which are most sensitive to hypoxia, including headache, fatigue, malaise, “trouble thinking”, confusion, nausea, dizziness, visual disturbance, chest pain, shortness of breath, loss of consciousness and seizures (Smollin and Olson 2010).
- Two neurological syndromes are recognised to occur: persistent neurologic sequelae (PNS) which is characterised by symptoms and signs of CO poisoning which are evident immediately following poisoning, and delayed neurologic sequelae (DNS) which is characterised by the reappearance of or development of new symptoms and signs after days to weeks. This may be abrupt and dramatic and may be non-specific, ranging from subtle personality changes, mood disorders and memory loss, to (much less commonly) focal neurological injuries and severely disabling manifestations of hypoxic brain injury such as cortical blindness and epilepsy (Buckley et al 2011, Pepe et al 2011). The reported incidence of DNS varies widely from 3% to 40% because of a lack of established diagnostic criteria (Pepe et al 2011).
- Standard treatment for CO poisoning includes removal from the site of exposure, administration of supplemental oxygen and general supportive care. The elimination half-life of COHb (approximately 320 minutes in room air) is shortened approximately five-fold by administration of 100% oxygen at atmospheric pressure (normobaric oxygen, NBO) (Buckley et al 2011).

**The intervention**

- Hyperbaric oxygen treatment (HBOT) refers to administration of 100% oxygen at pressures higher than atmospheric pressure. This is achieved in a hyperbaric chamber. A wide range of protocols have been used involving different pressures, duration and frequency of treatments (Buckley et al 2011).

[1] This means that the oxygen that is able to bind to Hb is not easily released in the tissues.

- HBOT hastens the elimination of COHb. For example, HBOT at three atmospheres absolute pressure (ATA) reduces the half-life of COHb in blood to 15-30 minutes, and this is one of the theoretical bases for use of HBOT in promoting the supply of oxygen to tissues following CO poisoning (NHS QIS 2008). In addition, there are several other theories as to why HBOT might be effective in treating CO poisoning, such as through cerebral vasoconstriction and reduction in cerebral oedema, prevention of CO-induced lipid peroxidation and blocking of leukocyte adhesion (Neubauer et al 2006).
- HBOT has been used mainly to treat acute CO poisoning of varying levels of severity within hours of exposure (Smollin and Olson 2010), although it has occasionally been used to treat DNS days to weeks after CO exposure (Coric et al 2017).
- HBOT is available at only a few hospitals, thus often necessitating transfer of patients. It is occasionally complicated by barotrauma, seizures, pulmonary oedema and claustrophobia (Buckley et al 2011).

**Existing national policies and guidance**

- The NHS Commissioning Board (now known as NHS England) published its clinical commissioning policy for HBOT in April 2013. Its technical report states that:

  *"No robust evidence was found for the treatment of carbon monoxide poisoning with HBO either soon after acute poisoning, or for delayed effects of acute poisoning. HBO treatment for acute carbon monoxide poisoning is not currently recommended by the UK National Poisons Information Service (on Toxbase) or NHS Direct; these bodies recommend the use of normobaric 100% oxygen. However, the national position was confused by a statement issued by the Department of Health in November 2010 that the use of HBO therapy should be considered for patients with CO poisoning who met specific criteria, but that advice from Toxbase should be considered."* (NHS Commissioning Board 2013)

- The NHS Commissioning Board clinical commissioning policy states the following:

  *"The use of hyperbaric oxygen as standard care for decompression illness, gas embolism and carbon monoxide poisoning is not supported by RCT level data but, given the good theoretical basis, long-standing use and clinical consensus it would be hard to justify further trials in these treatment areas.*

  *Criteria for selecting HBOT versus normobaric oxygen for CO intoxication have been published which identify neurological deficit; loss of consciousness; cognitive impairment as key indicators for emergency treatment.*

  *Thus, based on the quality of evidence available, HBOT will only be commissioned for the following indications:*

  - *Decompression illness*
  - *Gas embolism*
  - *Acute CO poisoning*

  *No other indications are commissioned as there is currently insufficient evidence….."* (NHS Commissioning Board 2013).

- The commissioning policy provides guidance regarding governance arrangements required of all facilities using HBOT (NHS Commissioning Board 2013).

## 2. Summary of results

- This evidence review is based on two randomised controlled trials (RCTs) of the use of hyperbaric oxygen therapy (HBOT) following CO poisoning in non-pregnant adults, and one Cochrane systematic review which included these two studies (and which also included four further RCTs which do not meet the criteria for inclusion in this current review).
- The most commonly reported outcomes were neurological sequelae at four to six weeks following CO poisoning, including persistent neurological sequelae (PNS) and delayed neurological sequelae (DNS). DNS are new neurological CO poisoning-associated symptoms and signs that appear or reappear after a period of days to weeks. They may be non-specific, ranging from subtle personality changes, mood disorders and memory loss, to (much less commonly) focal neurological injuries and severely disabling manifestations of hypoxic brain injury such as cortical blindness and epilepsy, and may appear abruptly (Buckley et al 2011, Pepe et al 2011, Thom et al 1995).
- The presence of neurological symptoms and signs at four to six weeks following CO poisoning in non-pregnant adults was not found to be affected by HBOT administered in the hours after CO exposure in the Cochrane systematic review meta-analysis of six studies (odds ratio (OR) 0.78; 95% confidence interval (CI) 0.54-1.12; n=1361; Buckley et al 2011).
- Because four of the six studies included in the Cochrane systematic review do not meet the requirements of this review due to differences in population, treatment protocol or only being published in abstract form, we assessed the two RCTs that do meet the PICO requirements in more detail. These compared HBOT with 100% normobaric oxygen (NBOT) (Weaver et al 2002 and Thom et al 1995).
- Delayed neurological sequelae: one RCT found that DNS developed in 0% of the HBOT group and 23% of the control NBOT group (95% CI for the difference in proportions 8.2% to 38.4%; $p<0.05$; n=65; Thom et al 1995). However, by 77 days post CO poisoning, DNS symptoms had resolved in all patients in this study.
- Cognitive sequelae: one RCT found significantly fewer cognitive sequelae at six weeks, six months and one year after CO poisoning in the HBOT group compared to the control NBOT group (25.0% vs 46.1%, OR=0.39, p=0.007 at six weeks; 21.1% vs 38.2%, OR=0.43, p=0.02 at six months; 18.4% vs 32.9%, OR=0.46, p=0.04 at one year; n=152; Weaver et al 2002). The HBOT group also had significantly fewer patients reporting difficulties with memory at six weeks compared to the group that received NBOT (28.0% vs 51.4%; p=0.004).
- No significant benefit of HBOT was found at six weeks for most of the other outcomes measured by Weaver et al (2002), including neuropsychological test scores, apart from one subset test (Trail Making Test Part A[2], p=0.03), Geriatric Depression Scale, Katz index of activities of daily living scores and SF 36 scores for quality of life. In this study, neurological abnormalities on examination after the third chamber session were also not significantly different between HBOT and NBOT groups apart from more nystagmus[3] in the HBOT group (12% vs 2.7%; p=0.05).
- No studies of cost effectiveness were identified.
- Adverse events: although major adverse events have been reported following HBOT in other studies, they were not seen in these studies for which the most common adverse events reported were anxiety (seven patients), cough (one patient), tympanic membrane rupture (one

[2] The Trail Making Test Part A requires subjects to draw a line as quickly as possible connecting a series of numbers in sequence.
[3] Nystagmus refers to repetitive involuntary eye movements

patient) and difficulty equalising middle ear pressure (four patients).

- Overall, the findings of this evidence review suggest that HBOT is more effective than 100% normobaric oxygen therapy in preventing DNS and cognitive sequelae at 6 weeks, 6 months and 12 months post CO poisoning. The findings do not suggest an effect on DNS in the longer term (symptoms in both groups resolved), nor on activities of daily living, quality of life, depression or various neuropsychological tests.
- This review includes only two studies, both of which had a number of methodological issues which may have biased the results. The study by Thom et al (1995) was relatively small (n=65), was unblinded and was stopped early due to observed benefit, which tends to bias results in favour of the intervention. The study by Weaver et al (2002) was of higher quality in that it was double blind and larger (n=152). However, changes were made to the outcomes measured over the course of the study to rely increasingly on self-reported measures (Buckley et al 2011), control patients had more cerebellar dysfunction and longer average exposure to CO, assumptions were made about missing data, and the trial was stopped early due to observed benefit. These may have biased results in favour of HBOT.
- Although the evidence suggests a benefit of HBOT, most of the evidence is based on one RCT with several methodological issues. Replication of the results in at least one further good quality RCT would provide more certainty regarding whether HBOT should be routinely used for people with CO poisoning.

## 3. Methodology

- The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).
- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 9 for PICO).
- The PICO was used to search for relevant publications in the following sources: PubMed, Embase, Cochrane, TRIP and NHS Evidence (see section 10 for search strategy).
- The search dates for publications were between 1st January 2007 and 19th April 2017.
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion. Papers which matched the PICO were selected for inclusion in this review.
- Evidence from all papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using National Service Framework for Long Term Conditions (NSF-LTC) evidence assessment framework (see section 7 below).
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8 below).

## 4. Results

A total of three papers are included in this rapid evidence review (RER), consisting of one Cochrane systematic review and meta-analysis and two randomised controlled trials (RCTs).

The systematic review and meta-analysis (Buckley et al 2011) included six RCTs. Four of the six RCTs did not match the PICO inclusion criteria: one because it was only published as an abstract

(Mathieu et al 1996, n=575); two because the HBOT regime administered falls outside the scope of the PICO (maximum inspired partial pressure of oxygen of 2 ATA / 202 kPa as opposed to 250 to 304 kPa) (Annane et al 2011, n=179 and Raphael et al 1989, n=629); and one because patients were treated with high flow 100% oxygen for two to three days between HBOT treatments (Scheinkestel et al 1999, n=230). Both of the two remaining studies included within the systematic review were published prior to the earliest search date of 2007 but it was decided, given the heterogeneity of the studies included in the systematic review, to also include these two RCTs separately (Weaver et al 2002, n=152 and Thom et al 1995, n=65). The exact HBOT regime varied but included between one and three HBOT treatments of between 2.5 and 3.0 ATAs, with the first treatment beginning within 24 hours after the end of exposure to CO. Controls received 100% oxygen at normobaric pressure (NBOT) via a non-rebreather face mask.

No studies of cost-effectiveness were found.

**In the patient populations of interest, what is the effect of HBOT on the specified outcomes?**
The outcomes measured included persistence of neurological sequelae, incidence of delayed neurological sequelae, mortality, complete recovery, quality of life and adverse events.

***Neurological symptoms and signs at 4-6 weeks***
Most studies investigated the effects of HBOT administered within hours of CO poisoning on neurological symptoms and signs that persisted for four weeks or more. These included both neurological sequelae which started at the time of the CO poisoning and persisted (PNS), and sequelae that appeared days or weeks after poisoning (DNS).

Prevention of neurological sequelae at four to six weeks:. The Cochrane systematic review and meta-analysis (SRMA) of six RCTs (Buckley et al 2011) did not find a statistically significant effect of HBOT in preventing neurological symptoms and signs in non-pregnant adults at four to six weeks post treatment (combined odds ratio (OR) = 0.78; 95% confidence interval (CI) 0.54-1.12).

Cognitive sequelae at six weeks: Weaver et al (2002) reported cognitive sequelae at six weeks post CO poisoning. They found significantly fewer cognitive sequelae in the HBOT group compared to controls receiving NBOT, measured via a combination of self-report and neuropsychological testing (25.0% of HBOT patients vs 46.1% of controls; OR=0.39; p=0.007), and significantly fewer in the HBOT group reported difficulties with memory at six weeks compared to controls (28.0% versus 51.4%; p=0.004; n=152). However, for most other cognitive outcome symptoms and signs assessed at six weeks, Weaver et al (2002) observed no significant benefit of HBOT compared to NBOT, including for self-reports of difficulties with attention or concentration (32.0% versus 43.1%; p=0.17); and for neuropsychological test scores, where only one subset test (Trail Making Test Part A ) suggested a significant benefit from HBOT (p=0.03) (12 statistical significance tests were carried out).

***Delayed neurological sequelae***
Delayed neurological sequelae (DNS) are new neurological symptoms and signs that appear or reappear after a period of days to weeks following CO poisoning. Thom et al (1995) found no patients with DNS in the HBOT group and seven with DNS in the NBOT control group (0% vs 23%, 95% CI for the difference in proportions 8.2% to 38.4%; p<0.05; n=65). However, by 77 days after CO poisoning all DNS symptoms in the control group had resolved.

DNS was not specifically reported in the trial by Weaver et al (2002).

***Mortality***
Although not explicitly stated, no deaths were reported in either group in the studies by Weaver et al (2002) and Thom et al (1995). More severely poisoned patients may have died, however, without being enrolled in the study, as moribund patients were excluded by Weaver et al and patients with a history of unconsciousness or cardiac compromise were excluded by Thom et al.

***Quality of life***
No significant difference was found by Weaver et al (2002) between HBOT and NBOT groups at six weeks in three quality of life measures:

- Geriatric Depression Scale[4] scores (no significant difference; p=0.17)
- Katz index[5] of activities of daily living scores (normal for most patients in both groups)
- SF-36[6] scores for quality of life (no differences in scores were found between the groups, p values not stated).

Quality of life was not reported by Thom et al (1995).

***Neurological abnormalities immediately after the last treatment sessions***
No significant benefit of HBOT was observed compared to NBOT with respect to neurological abnormalities on examination after the third chamber session, and one sign, nystagmus (involuntary repetitive eye movements), was more common in the HBOT group at this point: 12% versus 2.7%; p=0.05 (Weaver et al 2002).

***Adverse events***
Major adverse effects of HBOT were relatively uncommon in these studies. None were reported by Thom et al (1995) (n=65) and of the 76 patients receiving HBOT in the study by Weaver et al (2002), anxiety was reported in seven, cough in one, tympanic membrane (ear drum) rupture in one and four patients had treatment sessions stopped because of difficulty in equalising middle ear pressure.

**Is there evidence that the effect of HBOT on the specified outcomes is different for pregnant women?**
No. No information was provided specifically relating to pregnant women and all studies except Thom et al (1995) specifically excluded pregnant women.

**Is there evidence that the effect of HBOT on the specified outcomes is different for patients who receive treatment most closely aligned to that administered in hyperbaric facilities in England?**
No. The two RCTs that met the PICO criteria and were therefore included in this review used different HBOT regimes. However, they reported different outcome measures and both showed some benefits of HBOT compared to NBOT. They therefore do not provide evidence to suggest that one of the regimes is more effective than the other.

Weaver et al (2002) used the HBOT regime described in the PICO. They used 100% oxygen at 3.0 ATA for 50 minutes followed by 2.0 ATA for 55 minutes in the first session and then two further HBOT sessions with 100% oxygen at 2.0 ATA for 90 minutes at six to twelve hour intervals

[4] The Geriatric Depression Scale is a 30-item self-report assessment used to identify depression in the elderly.
[5] The Katz index is an instrument used to assess functional status as a measurement of the client's ability to perform activities of daily living independently. It ranks adequacy of performance in the six functions of bathing, dressing, toileting, transferring, continence, and feeding.
[6] The SF-36 is an indicator of patient reported overall health status with questions in the eight areas of vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health.

(plus ten to fifteen minutes for compression/decompression, plus five minute air sessions every 30 to 40 minutes); HBOT starting within 24 hours after the end of CO exposure. Supplemental oxygen was only used between sessions if required to maintain oxygen saturation above 90%. They reported benefits in terms of fewer patients suffering from cognitive sequelae at six weeks, six months and 12 months.

Thom et al (1995) used 100% oxygen until HBOT started (2.0 +/- 2 hours), followed by HBOT at 2.8 ATA for 30 minutes followed by 2.0 ATA for 90 minutes; HBOT starting within six hours of exposure. They reported benefits in terms of fewer patients suffering from DNS.

**What is the cost effectiveness of HBOT for people with recent exposure to toxic doses of carbon monoxide?**
No studies were found that evaluated the cost effectiveness of HBOT for the treatment of CO poisoning.

**Is it possible to describe the characteristics of the patient group who are most likely to derive benefit and the intervention that was used?**
No. Neither of the two individual RCTs included analysed the effectiveness of HBOT in subgroups of patients and the small number of studies means that it is not possible to draw any conclusions regarding the different characteristics of patients included in the different studies or the intervention that was used and the effectiveness of HBOT. Additionally, both the studies were relatively small and were not designed to have the power to allow subgroup analysis.

**What evidence is there that any effects are sustained in the medium and longer term?**
Weaver et al (2002), assessed the presence of cognitive sequelae at six and twelve months. They found cognitive sequelae present at six months in 21.1% of HBOT patients versus 38.2% of NBOT controls (OR=0.43; p=0.02) and at twelve months they were present in 18.4% of HBOT patients versus 32.9% of control patients (OR=0.46; p=0.04). Other outcomes were not reported beyond six weeks in this study. This suggests that the effect of HBOT on cognitive sequelae persists for at least 12 months.

Thom et al (1995) reported outcomes beyond one month for DNS. In their study, seven patients in the control group and none in the HBOT group developed DNS. They telephoned patients at three months to “confirm that [further] new symptoms had not occurred” and they assessed four of the seven patients with DNS every two to three weeks until scores returned to baseline (the remaining three patients refused follow-up neuropsychologic examinations after they felt well). No specific treatment of patients with DNS was undertaken and normalisation of scores coincided with patients becoming clinically asymptomatic. All seven patients’ symptoms resolved between 25 and 77 days post CO poisoning, so that by 77 days no patients in either group continued to suffer from DNS. This suggests that HBOT does not affect the presence of longer term DNS.

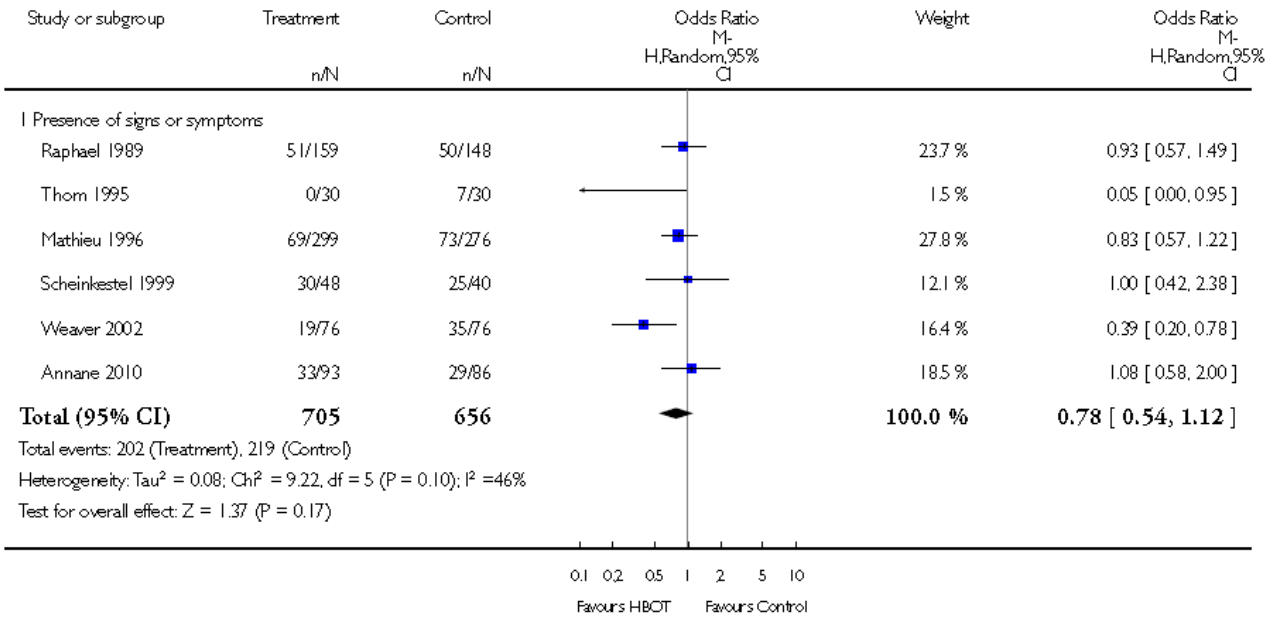
## 5. Discussion

The three studies found for this evidence review included one systematic review and meta-analysis and two RCTs that included non-pregnant adults.

The systematic review and meta-analysis of all six RCTs included by Buckley et al (2011) showed no evidence that HBOT administered soon after CO poisoning is effective in preventing neurological symptoms and signs at four to six weeks after CO poisoning in non-pregnant adults (Figure 1). The six studies were heterogeneous and only two match the requirements of the PICO

for this evidence review (Weaver et al 2002 and Thom et al 1995). The four RCTs which do not match the PICO were a large study that was only ever published in abstract form (Mathieu et al 1996; n=575); two studies which administered an HBOT regime that is outside the scope of that described in the PICO (maximum inspired partial pressure of oxygen of 2 ATA / 202 kPa as opposed to 250 to 304 kPa) (Annane et al 2011, n=179 and Raphael et al 1989, n=629); and a study which treated patients with 100% oxygen continuously for two to three days, which is contrary to standard practice due to the risk of oxygen toxicity (Scheinkestel et al 1999; n=230).

Figure 1: Result of Cochrane systematic review and meta-analysis: Comparison of hyperbaric oxygen vs normobaric oxygen for treatment of carbon monoxide poisoning.
Outcome measure: presence of symptoms or signs at time of primary analysis (4-6 weeks).




Source: Buckley et al 2011

The results of this systematic review should be interpreted cautiously as it combines results into a single figure from studies that covered different patient groups and different HBOT treatment regimes. Additionally, it does not provide detail on the type or severity of neurological symptoms and signs that were assessed, which can vary greatly following CO poisoning.

Two RCTs do meet the PICO requirements. The most recent of these, by Weaver et al (2002), found significantly fewer patients with cognitive sequelae at six weeks, six months and twelve months post CO poisoning, and significantly fewer self-reporting difficulties with memory at six weeks in the HBOT group compared to controls treated with NBOT.

These results need to be interpreted with caution for a number of reasons:

- The control group had more patients with cerebellar dysfunction and had longer average exposure to CO.
- 14 of the 76 HBOT patients and four of 76 control patients failed to complete all three sessions of treatment. Reasons for this are not known.
- Patients with missing data for neuropsychological tests at six weeks were assumed to have cognitive sequelae (one HBOT and four control patients). This may have introduced bias due to differing numbers with incomplete data in the two groups. When only patients

with complete data were included, p values were slightly higher (p=0.01 for cognitive sequelae at six weeks; p=0.03 for cognitive sequelae at six months; and p=0.08 (which is not statistically significant) for cognitive sequelae at 12 months).

- The severity of the cognitive sequelae and to what extent they impaired activities of daily living and quality of life are not reported.
- For all the other outcome measures tested in this trial, including neuropsychological test scores at six weeks (apart from one of the 12 tests carried out), self-reports of difficulties with attention or concentration, Geriatric Depression Scale scores, Katz index of activities of daily living scores, SF 36 scores for quality of life and neurological abnormalities on examination after the third chamber session (apart from more with nystagmus in the HBOT group), no significant differences were found between HBOT and control groups. The significance of finding more nystagmus in the HBOT group is difficult to interpret because we do not know whether or not it was present before treatment and whether or not it persisted.
- The number of different neuropsychological tests and comparisons made was such that some differences are likely to be found by chance alone rather than representing a true difference between the groups.

All these features could have biased the result in favour of HBOT. The fact that other outcome measures were not affected by HBOT in this trial, including quality of life, activities of daily living, depression and most neuropsychological tests scores at six weeks, suggests, for example, that the avoidance of cognitive sequelae did not translate into better quality of life or ability to perform activities of daily living.

Additionally, the authors of the Cochrane SRMA (Buckley et al 2011) described a number of concerns relating to the Weaver et al (2002) RCT methodology and outcomes:

- The pre-specified primary outcome changed from DNS at the start of the study to total cognitive sequelae. This change was not explained by the authors and the trial would not have stopped early if DNS was the outcome analysed.
- The thresholds for abnormal results changed as the trial progressed and self-reported difficulties with memory, attention and concentration were added to the definition between 1995 and 2001/02. The reported difference in neurological sequelae between the groups is likely to be the result of a difference in self-reported symptoms in the 2002 report (whereas in 1995 self-reported symptoms were not part of the outcome measure).
- The trial was stopped early due to observed benefit, and premature stopping of small trials "for benefit" tends to exaggerate the observed effect for statistical reasons.

Thus the findings of this RCT by Weaver et al (2002) need to be interpreted cautiously.

The second RCT that met the PICO requirements assessed the effect of HBOT on DNS (Thom et al 1995, n=65). It suggested that HBOT has a positive effect: no patients in the HBOT group developed DNS and 23% developed DNS in the control group ($p<0.05$). DNS had resolved in all patients by 77 days post CO poisoning, suggesting no longer term effect of HBOT on DNS. The unblinded nature of this study could have led to bias in favour of HBOT. Additionally, it was a small study, no power calculations were reported, no sensitivity analyses were carried out with respect to missing data and DNS symptoms tended to be non-specific such as headache and difficulty concentrating. In their systematic review, Buckley et al (2011) state that it seems likely that the trial was stopped early based on a positive result and that this practice "greatly exaggerates the observed effect for statistical reasons." The results should therefore be interpreted with caution.

Overall, there is some evidence suggesting that HBOT, compared to NBOT, reduces the likelihood of experiencing cognitive sequelae following CO poisoning and that this effect might persist for at least one year (Weaver et al 2002). There is also some evidence that HBOT reduces DNS following CO poisoning, although this effect was not seen to last beyond 77 days (Thom et al 1995). Several other outcome measures, such as those relating to quality of life, activities of daily living, depression and most neuropsychological test scores at six weeks, were not found to be affected by HBOT (Weaver et al 2002).

The findings from these studies should be treated with caution for a number of reasons:

- there are only two RCTs
- one was relatively small and only assessed DNS
- the other was larger but focused on different outcomes, which prevents confirmation of outcomes between studies
- both studies had significant methodological limitations, such as lack of blinding in one and changes to the original study protocol in the other
- both studies were stopped early due to observed benefit which introduces bias in favour of HBOT
- a number of key outcome measures were not seen to be affected by HBOT, with DNS not being affected in the longer term.

The small number of studies, one of which was relatively small and only assessed DNS, and the facts that both studies were stopped early due to observed benefit, both had other significant methodological limitations and a number of key outcome measures were not seen to be affected by HBOT, with DNS not being affected in the longer term, mean that the positive findings should be treated with caution. Replication of the results in at least one further good quality RCT would provide more certainty regarding whether HBOT should be routinely used for people with CO poisoning.

## 6. Conclusion

CO poisoning is a relatively common cause of poisoning in the UK and there are a number of plausible theories as to why HBOT might reduce the incidence and severity of neurological sequelae. This has led to ambiguous national guidance and to HBOT often being used to treat CO poisoning despite a lack of clarity regarding the evidence for its use.

This evidence review found two RCTs which matched the PICO requirements in terms of population group and specific HBOT regime used. These studies suggest a benefit of HBOT following CO poisoning with respect to DNS, although this effect was not sustained, and a benefit with respect to cognitive sequelae at six weeks, six months and possibly one year. However, other measures such as quality of life and activities of daily living were not found to be affected and both studies had a number of significant methodological limitations. This means that the results should be interpreted with caution. Replication of the results in at least one further good quality RCT would provide more certainty regarding whether HBOT should be routinely used for people with CO poisoning.

## 7. Evidence Summary Tables

| Use of hyperbaric oxygen therapy (HBOT) vs. normobaric 100% oxygen (NBOT) to treat carbon monoxide poisoning | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| **Systematic review** | | | | | | | | | |
| Buckley et al 2011<br><br>Cochrane | S1<br><br>Systematic review and meta-analysis of 6 RCTs, of which 3 meet the PICO criteria.<br><br>Those that are in line with PICO are also detailed below.<br><br>Annane et al 2011 RCT unblinded<br><br>Mathieu et al 1996 RCT unblinded<br><br>Raphael et al 1989 RCT unblinded | n=1361 (6 studies)<br><br>Annane et a, 2011 n=179, presenting in Oct 1989 to Jan 2000; within 12 hours of CO exposure; COHb>5% if non-smoker and >10-% if smoker; age≥15 years; history of transient (not sustained) loss of consciousness (LOC).<br><br>Mathieu et al 1996 n=575, recruited over 3 years; COHb>10% ; non- | Annane et al 2011: mask oxygen for 4 hours and HBOT at 2.0 atmospheres absolute pressure (ATA) for 90 minutes plus 60 minutes compression/decompression, plus diazepam 10mg i/m. (Control group received 6 hours NBO via mask).<br><br>Mathieu et al 1996: HBOT at 2.5 ATA for 90 minutes plus 15 minutes compression/decompression. (Control group received 12 hours NBO).<br><br>Raphael et al 1989: HBOT at 2.0 ATA for 1 hour plus 1 | Primary<br><br>Clinical effectiveness | Presence of neurological symptoms or signs at 4-6 weeks post treatment | Odds ratio (OR) for HBOT vs control 0.78 (95% CI 0.54 – 1.12) | 8 | Indirect<br><br>(some of the studies included patients with lower severity of CO poisoning than specified in PICO; lower COHb levels (all except Weaver et al 2002 had an average COHb of <25%); and one study (Scheinkestel et al 1999) provided 100% oxygen between treatments (for >2 days), which is excluded in PICO | The meta-analysis does not suggest a significant benefit from HBOT. However, 3 out of 6 of the studies are out of scope of the PICO criteria, either because they included patients with less severe CO poisoning or included HBOT protocols that involved providing 100% oxygen between HBOT treatments.<br><br>The result should be interpreted with caution as these six studies are markedly heterogeneous with respect to population and intervention HBOT protocol used (duration, frequency and oxygen pressure). Statistical measures also indicated a high degree of heterogeneity.<br><br>Additionally all studies were assessed as having design and analysis flaws and a high risk of bias for various reasons: most were unblinded and used self-reported outcomes, follow-up was sometimes poor and most were terminated prematurely which may inflate the observed effect.<br><br>Four studies did not meet the inclusion criteria specified for this review:<br>• Mathieu et al (1996), the second largest RCT, was published as an abstract of an interim analysis only and Buckley et al 2011 were not able to obtain any further information.<br><br>• Scheinkestel et al (1999), protocol of continuous 100% oxygen for more than 2 days is excluded from the PICO (due to the risk of oxygen toxicity this entails).<br><br>• Raphael et al (1989) and Annane et al (2011), the HBOT regime administered falls outside the scope of the PICO (maximum inspired partial |

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| | Scheinke-stel et al 1999 double-blind RCT, cluster randomisation<br><br>Thom et al 1995 RCT unblinded<br><br>Weaver et al 2002 double-blind RCT | comatose, non-pregnant, with no evidence of mixed poisoning.<br><br>Raphael et al 1989 n=629, admitted within 12 hours of exposure; COHb>10% (smoker) or 5% (non-smoker); age>15 years; no other intoxication, not pregnant and no cardiovascular collapse or pulmonary oedema.<br><br>Scheinkestel et al 1999 n=230, single centre in Australia, average COHb 21%; coma in 50.6%; excluded if children, burns, pregnant.<br><br>Thom et al 1995 n=65, within 6 hours of | hour compression/decompression followed by 100% oxygen for 4 hours. (Controls received 100% NBO by mask for 6 hours).<br><br>Scheinkestel et al 1999: HBOT for 1 hour at 2.8 ATA plus 40 minutes compression/decompression daily for 3 days with 100% oxygen via mask continuously between sessions plus for those with deficits, 3 additional courses of HBOT with high-flow oxygen in between. (Controls received NBO 100 minutes at 1 TA as a sham dive and 100% oxygen via mask continuously between sessions plus 3 further sessions if deficits remained, with high flow oxygen in between). | | | | | | pressure of oxygen of 2 ATA / 202 kPa as opposed to 250 to 304 kPa).<br><br>For some studies the minimum COHb level for inclusion in the study is given and for other studies the mean COHb level of participants is given. These are not directly comparable as the mean may be very different from the minimum. In all studies patients were included with a COHb <25%. In Weaver et al (2002) the mean COHb was 25% whereas in other studies, where stated, it was lower than this.<br><br>Annane et al (2011) and Raphael et al (1989) each performed a second trial comparing one versus two HBOT sessions for patients with “initial coma” (Annane et al 2011) and those with a history of LOC (Raphael et al 1989) and these groups were not included by Buckley et al 2011 in their meta-analysis. The analysis therefore does not include all patients with severe CO poisoning. |

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| | | exposure; mean COHb 20 to 25%; excluded if history of LOC or active ischaemia.<br><br>Weaver et al 2002 n=152 within 24 hours of exposure; COHb>10% and symptomatic or unequivocal symptoms and signs of CO exposure; excluded if pregnant, age<16, moribund. | Thom et al 1995: 100% oxygen until HBOT given at 2.8 ATA for 30 minutes then 2.0 ATA for 90 minutes. (Controls received NBO 100% until all symptoms resolved (mean 4.2 +/- 0.3 hours).<br><br>Weaver et al 2002: one session of HBOT at 3 ATA for 1 hour and 2 ATA for 1 hour followed by 2 sessions at 2 ATA for 2 hours at 6-12 hour intervals. Oxygen not routinely use after first session. (Control NBO patients received sham treatment at 1 ATA). | | | | | | |
| **Randomised controlled trials (RCTs)** | | | | | | | | | |
| Weaver et al 2002 | P1<br><br>RCT, double blind<br><br>US, single centre, Nov 1992 to Feb | n=152: 76 in each group.<br><br>Within 24 hours of exposure; COHb>10% and symptomatic or unequivocal | 100% oxygen at 3 ATA for 50 minutes followed by 2 ATA for 55 minutes in first session. Two further HBOT sessions at 2 ATA 100% oxygen for 90 | Primary<br><br>Clinical effectiveness | Incidence of cognitive sequelae at 6 weeks.<br><br>This was defined by a combination of neuropsychological tests and self-reports, for example a self- | 25.0% in HBOT group versus 46.1% in controls, OR 0.39 (95% CI 0.20-0.78), p=0.007.<br><br>Significant difference was also observed when only patients with complete data were included (24.0% | 7 | Direct | A double blind trial. However randomisation was in blocks and side effects of HBOT may have made the HBOT arm apparent during analysis.<br><br>Buckley et al (2011) describe how the outcome measures changed during the course of the trial and there was no difference in the originally intended end point of DNS. Additionally, Buckley et al report that the threshold for definition of neurological sequelae changed over the course of the trial and in the final analysis non-specific symptoms were the primary |

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| | 1999. | symptoms and signs of CO exposure.<br><br>Excluded if pregnant, age<16, moribund.<br><br>Mean age 35 and 36 years in the HBOT and control groups respectively.<br><br>Average initial COHb 25% for both groups; 7 had COHb<10%. | minutes at 6-12 hour intervals. Plus 10 to 15 minutes compression/ decompressio n and 5 minute air sessions every 30-40 minutes; and all non-intubated patients received oxygen at 15 litres per minute using a reservoir and face mask that prevented rebreathing. Supplemental oxygen was only used between sessions if required to maintain oxygen saturation >90%.<br><br>(Comparator group: for the first treatment session, received oxygen at 15 litres per minute using a reservoir and face mask that prevented rebreathing, and for 2nd and | | reported difficulty plus any neurological subset T score >1 standard deviation (SD) below the mean; or one score >2 SDs below the mean; or two scores >1 SD below the mean. | vs 43.1%, OR 0.42 (0.21-0.85), p=0.01) and when only patients without cerebellar abnormalities were analysed (23.2% vs 39.0%, OR 0.47 (0.22-1.02), p=0.05). | | | determinant of the statistical difference.<br><br>1 HBOT and 3 control patients failed to return for 2nd or 3rd sessions.<br><br>14 of 76 HBOT patients and 3 of 76 control patients failed to complete all 3 sessions, p=0.005.<br><br>Results for the primary outcome (cognitive sequelae at 6 weeks) assume that patients with missing data for neuropsychological tests at six weeks all had cognitive sequelae (1 in HBOT group and 4 in control group), which may have slightly biased the result in favour of HBOT. Without this assumption the trial may not have been stopped early.<br><br>Patients who had missing data at 6 or 12 months were assumed to have cognitive sequelae at those time points if they had had cognitive sequelae at 6 weeks. New cognitive sequelae at 6 or 12 months were assumed not to be due to CO poisoning. For other secondary outcomes only patients with complete data were included in the analysis. This could have resulted in bias.<br><br>According to Buckley et al (2011), analyses at 6 and 12 months were not included in the study design, and if the analyses had been based on actual data rather than the assumptions used, there would have been little difference between the groups in cognitive sequelae at these time points (24 HBOT vs 29 NBOT abnormal rather than 14 vs 25 at 12 months).<br><br>The trial was stopped after the 3rd of 4 planned interim analyses due to observed benefit. Premature stopping of small trials “for benefit” tends to exaggerate the observed effect for statistical reasons (Buckley et al 2011).<br><br>The control group had more patients with cerebellar dysfunction than the HBOT group (15 versus 4, p=0.03) and had longer average exposure to CO (22+/-64 hours versus 13+/-41 hours). These may have biased results in favour of HBOT, although analysis that excluded those with cerebellar dysfunction remained statistically significant |
| | | | | Secondary<br><br>Clinical effectiveness | Cognitive sequelae at 6 months | 21.1% in HBOT group versus 38.2% in control group, OR 0.43 (95% CI 0.21-0.89), p=0.02 (for missing data this assumed result same as previous data point).<br><br>Analysis which only included those with complete data: OR 0.38, p=0.03. | | | |
| | | | | Secondary<br><br>Clinical effectiveness | Cognitive sequelae at 12 months | 18.4% in HBOT group versus 32.9% in control group, OR 0.46 (95% CI 0.22-0.98), p=0.04 (for missing data this assumed result same as previous data point).<br><br>Analysis which only included those with complete data: OR 0.45, p=0.08. | | | |
| | | | | Secondary outcome<br><br>Clinical effectiveness | Neuropsychologic al test scores at 6 weeks | T scores[7] did not differ significantly between groups (p=0.31), with similar rates of improvement in both groups (p=0.62).<br><br>Of 12 comparisons | | | |

[7] T scores are a statistical measure of the extremeness of the results and are used to test for the likelihood that a difference between the groups may have occurred by chance.

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| | | | 3rd treatment sessions received air; the chamber was pressurised to sea-level pressure (1ATA) with air for all 3 sessions; all intubated patients (8 of 76 patients) received 100% oxygen at 1 ATA for all 3 sessions; supplemental oxygen was only used between sessions if required to maintain oxygen saturation >90%.) | | | made, only the Trail Making Test Parts A[8] showed a significant difference between groups (p=0.03). | | | (p=0.05).<br><br>Note that the average COHb level estimated at initial entry into the chamber was in the normal range (4.3% +/- 2.9% for HBOT and 4.6% +/- 3.1% in the control group).<br><br>It is not clear why the Geriatric Depression Scale was used, as this is a scale developed to identify depression in the elderly, whereas the mean age of patients was less than 40 years. |
| | | | | Secondary outcome<br><br>Clinical effectiveness | Self-reports of symptoms at 6 weeks including difficulties with memory and with attention or concentration | Difficulties with memory reported in 28.0% in HBOT group versus 51.4% in control group, OR 0.37 (95% CI 0.19-0.73), p=0.004.<br><br>Difficulties with attention or concentration reported in 32.0% in HBOT group versus 43.1% in control group, OR 0.62 (95% CI 0.32-1.22), p=0.17. | | | |
| | | | | Secondary outcome<br><br>Clinical effectiveness | Geriatric Depression Scale[9] scores at 6 weeks | Mean score +/- standard error was 8.0 +/- 0.9 for HBOT group and 9.7 +/- 0.9 for control patients, p=0.17. | | | |
| | | | | Secondary outcome<br><br>Clinical effectiveness | Katz index[10] of activities of daily living scores at 6 weeks | This was normal for most patients in both groups, with only 4 patients reporting minor problems which they deemed unrelated to CO poisoning. | | | |
| | | | | Secondary outcome<br><br>Clinical effectiveness | SF36[11] scores at 6 weeks | No treatment-related differences in scores were found on the subscales of the SF-36 scores including social function, physical role, mental | | | |

[8] The Trail Making Test Part A requires subjects to draw a line as quickly as possible connecting a series of numbers in sequence.
[9] The Geriatric Depression Scale is a 30-item self-report assessment used to identify depression in the elderly.
[10] The Katz index is an instrument used to assess functional status as a measurement of the client's ability to perform activities of daily living independently. It ranks adequacy of performance in the six functions of bathing, dressing, toileting, transferring, continence, and feeding.
[11] The SF-36 is an indicator of patient reported overall health status with questions in the eight areas of vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health.

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| | | | | | | health and energy; details of comparisons were not provided. | | | |
| | | | | Secondary outcome<br><br>Clinical effectiveness | Neurologic abnormalities on examination after third chamber session | No significant differences between treatment groups found except for nystagmus: 12.0% in HBOT group vs 2.7% in control group; OR 4.84 (95% CI 1.01-23.22); p=0.05. | | | |
| | | | | Secondary outcome<br><br>Adverse events | Adverse effects of hyperbaric treatment | First HBOT session stopped prematurely due to anxiety (7 patients), tympanic membrane rupture (1 patient), cough (1 patient). Subsequent HBOT sessions stopped due to difficulty of equalisation of middle ear pressure (4 patients). | | | |
| Thom et al 1995 | P1<br><br>RCT, unblinded<br><br>US, single centre, Sept 1989 to Dec 1993. | n=65: 33 HBOT; 32 NBO.<br><br>History of acute exposure, increased COHb and symptoms consistent with CO poisoning.<br><br>Excluded if history of LOC or cardiac compromise (chest pain or ischaemic changes on ECG).<br><br>Patients in the 2 groups | 100% oxygen until HBOT started (2.0 +/- 2 hours), followed by HBOT at 2.8 ATA for 30 minutes followed by 2.0 ATA for 90 minutes; HBOT starting within 6 hours of exposure.<br><br>(Comparator group received 100% oxygen through non-rebreather face mask until all symptoms resolved (4.2 +/- 3 hours). | Primary<br><br>Clinical effectiveness | DNS | No DNS symptoms occurred in HBOT group; 7 NBO patients (23%) had symptoms consistent with DNS plus deterioration in at least one subtest category of neuropsychological tests: 95% CI for the difference in proportions 8.2% to 38.4%, p<0.05. All patients' DNS symptoms resolved by 77 days post CO poisoning. | 7 | Indirect<br><br>(excluded most severely poisoned patients) | DNS were defined as a recurrence of original symptoms or development of new symptoms plus a deterioration in one or more subtest scores on neuropsychometric testing.<br><br>No specific treatment of patients with DNS was undertaken and normalisation of scores coincided with patients becoming clinically asymptomatic.<br><br>Most severely poisoned patients were not included (eg if LOC or cardiac compromise), and the aim was to include patients with "mild to moderate CO poisoning".<br><br>3 patients in the HBOT group and 2 in the NBO group were lost to follow up.<br><br>After treatment "baseline" neuropsychological test scores were not significantly different between the two groups and "neurologic status was not discernibly different".<br><br>No apparent difference reported in clinical histories of those who did and did not develop DNS.<br><br>Bias in favour of HBOT is possible due to the lack of |
| | | | | Secondary<br><br>Adverse events | Adverse effects of hyperbaric treatment | None | | | |

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| | | were similar. Age was 35.0 +/- 2.9 years in HBOT group versus 39.0 +/- 3.4 years in NOB group; and mean COHb was 24.6% +/- 1.4% in HBOT group versus 20.0% +/- 1.6% in NBO group. | Patients were followed up by interview at 1 week, testing of symptomatic patients at 3-4 weeks and telephone interview of all patients at 3 months. Those with abnormalities had further testing at 2-3 week intervals until scores returned to baseline. | | | | | | blinding.<br><br>No sensitivity analysis was carried out with respect to missing data.<br><br>This was a small study without power / sample size calculations provided and, according to Buckley et al (2011), it seems likely that the trial was stopped early based on a positive result and this practice "greatly exaggerates the observed effect for statistical reasons".<br><br>Deterioration in the patients who developed DNS occurred in 3 subtests: Trial Making, Digit Symbol and Block Design.<br><br>All seven patients' DNS symptoms resolved between 25 and 77 days post CO poisoning, so that by 77 days no patients in either group suffered from DNS. This suggests that HBOT did not affect the presence of longer term DNS. |

## 8. Grade of evidence tables

| Use of Hyperbaric Oxygen vs. Normobaric 100% Oxygen to treat Carbon Monoxide Poisoning | | | | | |
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| **Outcome Measure** | **Reference** | **Quality of Evidence Score** | **Applicability** | **Grade of Evidence** | **Interpretation of Evidence** |
| Presence of neurological symptoms or signs at 4-6 weeks post treatment | Buckley et al 2011 | 8 | Indirect | C | This outcome measure is derived from six different studies which used different methods for assessing the presence of neurological symptoms and signs at 4-6 weeks post carbon monoxide (CO) poisoning.<br><br>The combined odds ratio (OR) for the 6 studies did not show a statistically significant effect of hyperbaric oxygen treatment (HBOT) compared to normobaric oxygen (oxygen provided at atmospheric pressure (NBOT)); OR=0.78 (95% CI 0.54-1.12).<br><br>This means that these studies do not provide evidence of a positive effect of HBOT on reducing neurological sequelae at 4-6 weeks.<br><br>The studies included were heterogeneous in the patients they included, the pressure of oxygen provided, the number and frequency of HBOT sessions and the treatment of the control group. Only two of the studies met the requirements of the PICO (Weaver et al 2002 and Thom et al 1995).<br><br>In only two studies was there an attempt to blind patients and staff to which treatment patients were receiving.. Unblinded studies are more |

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| | | | | | prone to bias in favour of the intervention. Several other factors, for example differences between the patients in the HBOT and control groups, could also have led to bias in the results. |
| Delayed neurological sequelae (DNS) | Thom et al 1995 | 7 | Indirect | C | Delayed neurological sequelae (DNS) are characterised by the development or reappearance of new CO poisoning-associated neurological symptoms and signs after a period of days to weeks. They may be non-specific, ranging from subtle personality changes, mood disorders and memory loss, to (much less commonly) focal neurological injuries and severely disabling manifestations of hypoxic brain injury such as cortical blindness and epilepsy, and may appear abruptly (Buckley et al 2011, Pepe et al 2011, Thom et al 1995).<br><br>Thom et al defined DNS as a recurrence of original symptoms or development of new symptoms plus a deterioration in one or more subtest scores on neuropsychometric testing. They found no DNS symptoms in the HBOT group, whereas seven control patients (23%) had symptoms consistent with DNS: 95% CI for the difference in proportions 8.2% to 38.4%, p<0.05. DNS symptoms resolved in all patients by 77 days post CO poisoning.<br><br>This suggests that HBOT benefits patients in terms of fewer DNS compared to NBOT, but that this benefit may not persist in the longer term.<br><br>This was a relatively small (n=65) unblinded study and so care should be taken when interpreting the results. The most severely poisoned patients (who were in a coma or had cardiac compromise) were not included, and hence the effect of HBOT in this group is not known. |
| Incidence of cognitive sequelae at 6 weeks | Weaver et al 2002 | 7 | Direct | B | Cognition relates to mental processes involving conscious intellectual activity such as thinking, reasoning, or remembering. The presence of cognitive sequelae was assessed using a combination of self-report and neuropsychological testing aimed at picking up a range of symptoms that are associated with acute CO poisoning.<br><br>Cognitive sequelae were present at six weeks in 25.0% of HBOT patients vs 46.1% of NBOT patients (OR=0.39; p=0.007).<br><br>This suggests that HBOT, compared to NBOT, reduces the risk of cognitive sequelae that persist to six weeks post CO poisoning.<br><br>This result should be interpreted with caution for a number of reasons: the control group had more patients with cerebellar dysfunction and had longer average exposure to CO; 14 of the 76 HBOT patients and 4 of 76 control patients failed to complete all 3 sessions of treatment; results assume that all those with missing data for neuropsychological tests at six weeks had cognitive sequelae (1 HBOT and 4 control patients) (when only patients with complete data are included, p=0.01); the trial was stopped early due to observed benefit (Buckley et al 2011). These features could bias the result in favour of HBOT. |
| Cognitive sequelae at 6 months | Weaver et al 2002 | 7 | Direct | B | Cognition relates to mental processes involving conscious intellectual activity such as thinking, reasoning, or remembering. The presence of |

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| | | | | | cognitive sequelae was assessed using a combination of self-report and neuropsychological testing aimed at picking up a range of symptoms that are associated with acute CO poisoning.<br><br>Cognitive sequelae were present at six months in 21.1% of HBOT patients vs 38.2% of NBOT patients (OR=0.43; p=0.02).<br><br>This suggests that HBOT, compared to NBOT, reduces the risk of cognitive sequelae persisting to six months post CO poisoning.<br><br>This result should be interpreted with caution for a number of reasons: the control group had more patients with cerebellar dysfunction and had longer average exposure to CO; 14 of the 76 HBOT patients and 4 of 76 control patients failed to complete all 3 sessions of treatment; assumptions were made regarding missing data; the trial was stopped early due to observed benefit (Buckley et al 2011). These features could bias the result in favour of HBOT. |
| Cognitive sequelae at 12 months | Weaver et al 2002 | 7 | Direct | B | Cognition relates to mental processes involving conscious intellectual activity such as thinking, reasoning, or remembering. The presence of cognitive sequelae was assessed using a combination of self-report and neuropsychological testing aimed at picking up a range of symptoms that are associated with acute CO poisoning.<br><br>Cognitive sequelae were present at 12 months in 18.4% of HBOT patients vs 32.9% of NBOT patients (OR=0.46; p=0.04).<br><br>This suggests that HBOT, compared to NBOT, reduces the risk of cognitive sequelae persisting to 12 months post CO poisoning.<br><br>This result should be interpreted with caution for a number of reasons: the control group had more patients with cerebellar dysfunction and had longer average exposure to CO; 14 of the 76 HBOT patients and 4 of 76 control patients failed to complete all 3 sessions of treatment; assumptions were made regarding missing data; the trial was stopped early due to observed benefit (Buckley et al 2011). These features could bias the result in favour of HBOT. |
| Neuropsychological test scores at 6 weeks | Weaver et al 2002 | 7 | Direct | B | T scores were used to compare neuropsychological test scores between the groups. Neuropsychological tests included tests of general orientation, digit span, block design (making designs from coloured blocks), trail making, and story recall. T scores are a statistical measure of the extremeness of the results and are used to test for the likelihood that a difference between the groups may have occurred by chance.<br><br>T scores for neuropsychological tests at six weeks did not differ significantly between the groups (p=0.31). Of the 12 comparisons made, scores for only one subset test (Trail Making Part A) showed a significant difference with slightly better scores in the HBOT group compared to the NBOT group (p=0.03). The Trail Making Test Part A requires subjects to draw a line as quickly as possible connecting a series of numbers in sequence (Part B involves connecting alternating |

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| | | | | | numbers and letters in order).<br><br>Neuropsychological testing overall therefore did not suggest that HBOT is more effective than NBOT in preventing neuropsychological sequelae at six weeks.<br><br>T scores suggest that the differences in neuropsychological tests between the groups may well have been due to chance. When multiple comparisons are made it is likely that one difference will appear significant due to chance. The one subset test score that was different therefore may or may not represent a true difference in outcomes between the groups treated with HBOT and NBOT. |
| Self-reports of difficulties with memory and attention or concentration at 6 weeks. | Weaver et al 2002 | 7 | Direct | B | Patients were given questionnaires that were developed for this study regarding symptoms of CO poisoning, including questions about difficulties with memory and with attention or concentration. (Details of other symptoms covered by the questionnaire were not reported.)<br><br>The HBOT group was found to have significantly fewer difficulties with memory compared to the control group at 6 weeks (28.0% in the HBOT group vs 51.4% in the control group; p=0.004). For attention and concentration no significant difference was found (p=0.17).<br><br>This suggests that HBOT may be more effective than NBOT in reducing the effects of CO poisoning on memory.<br><br>This result should be interpreted with caution because the questionnaire used was not validated (tests have not been carried out to ascertain whether the questionnaire reliably measures these symptoms). Additionally, the baseline differences between the two groups, missing data and the stopping of the trial early may have biased the result in favour of HBOT. |
| Geriatric Depression Scale scores at 6 weeks | Weaver et al 2002 | 7 | Direct | B | The Geriatric Depression Scale is a 30-item self-report assessment used to identify depression in the elderly. It is a validated tool that was used to compare levels of depression in the HBOT and control groups six weeks after CO poisoning. It is not clear why a tool developed for identification of depression in the elderly was used for the younger population in this study.<br><br>Mean scores for depression were not significantly different between the groups with mean scores and standard errors of 8.0 +/- 0.9 for the HBOT group and 9.7 +/- 0.9 for controls; p=0.17.<br><br>This suggests that HBOT does not reduce the risk of depression at six weeks following CO poisoning compared to NBOT.<br><br>This result occurred despite the risk that the analysis may have been biased in favour of HBOT because of the baseline differences between the two groups, missing data and the stopping of the trial early. |
| Katz index of activities of daily | Weaver et al 2002 | 7 | Direct | B | The Katz index is a validated tool that assesses functional status as a measurement of the client's ability to perform activities of daily living |

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| living scores at 6 weeks | | | | | independently. It ranks adequacy of performance in the six functions of bathing, dressing, toileting, transferring, continence, and feeding.<br><br>Scores were normal for most patients in both groups at six weeks, with only four patients reporting minor problems which they deemed unrelated to CO poisoning. Statistical details were not provided.<br><br>This tool did not show that HBOT, compared to NBOT, makes a significant difference to the ability to perform activities of daily living at six weeks following CO poisoning.<br><br>Very few patients in either group had problems with activities of daily living at six weeks, as measured by this tool, hence a difference was not likely to be found. |
| SF 36 scores at 6 weeks (quality of life) | Weaver et al 2002 | 7 | Direct | B | SF-36 is a validated tool used to measure quality of life. It measures patient reported overall health status with questions in the eight areas of vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health.<br><br>Six weeks after CO poisoning no differences in scores were found between patients receiving HBOT vs NBOT on the subscales of the SF-36 scores including social function, physical role, mental health and energy; details of comparisons and p values were not provided.<br><br>This suggests that HBOT does not improve quality of life at six weeks following CO poisoning compared to NBOT.<br><br>This result occurred despite the risk that the analysis may have been biased in favour of HBOT because of the baseline differences between the two groups, missing data and the stopping of the trial early. |
| Neurologic abnormalities on examination after third chamber session | Weaver et al 2002 | 7 | Direct | B | After the third session of HBOT or NBOT, patients were tested for a range of neurological signs such as problems with sensation, vision, balance and co-ordination.<br><br>No significant differences were found between those receiving HBOT vs NBOT except for nystagmus (involuntary eye movements) which was more common in the HBOT group (12% vs 2.7%; p=0.05).<br><br>There was therefore little difference between the groups in terms of objective neurological abnormalities at the end of the third treatment session.<br><br>The significance of the HBOT group being more likely to have nystagmus at this stage is difficult to assess because it is not clear whether this was also the case before treatment or happened as a result of treatment and we do not know whether it persisted. |

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| Adverse effects of hyperbaric treatment | Weaver et al 2002 | 7 | Direct | A | Subjecting a patient to high pressures of oxygen could potentially have side effects relating to the pressure and/or to the level of exposure to oxygen, which is known to be toxic at high concentrations over long periods of time.<br><br>Major adverse events were relatively uncommon and included anxiety (7 of 76 HBOT patients), cough (1 patient) and tympanic membrane (ear drum) rupture (1 patient), with four patients having treatment sessions stopped because of difficulty equalising middle ear pressure.<br><br>This suggests that major adverse effects of HBOT are relatively infrequent.<br><br>HBOT is occasionally complicated by more serious adverse reactions such as convulsions and pulmonary oedema (Buckley et al 2011) and although these were not seen in these studies, it is not clear whether this was because of the treatment regimes used (pressure, duration and frequency of oxygen treatment) or whether it is because these side effects are rare and would have been seen if larger numbers of patients had been included. |
| | Thom et al 1995 | 7 | Indirect | | |

## 9. Literature Search Terms

| Search strategy | |
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| **P – Patients / Population**<br>Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered? | Children and adults likely to have been exposed to toxic levels of carbon monoxide within the last 24 hours with one or more of the following features:<br>• COHb>25%<br>• recorded loss of consciousness at some stage<br>• persistent neurological symptoms or signs (other than a simple headache) in whom other causes of neurological impairment have been excluded<br>• pregnant<br><br>The following subgroups should also be considered:<br><br>1. The group that receives treatment most closely aligned to that administered in hyperbaric facilities in England. That is: a maximum inspired partial pressure of oxygen between 280 and 304 kPa during the first treatment (the initial inspired partial pressure of oxygen is maximised while avoiding central nervous system oxygen toxicity) and no additional administration of high fraction oxygen ( in excess of 50%) between HBOT treatments to prevent oxygen toxicity.<br><br>2. Pregnant women |
| **I – Intervention**<br>Which intervention, treatment or approach should be used? | Hyperbaric oxygen therapy, preferably following the Weaver protocol (http://www.nejm.org/doi/full/10.1056/NEJMoa013121#t=article) which uses an initial hyperbaric treatment within 24 hours of extraction from the incident that delivers a maximum inspired partial pressure of oxygen of 304 kPa and lasts 150 minutes followed by two more treatments each delivering a maximum inspired partial pressure of oxygen of 203 kPa and lasting 120 minutes, finishing within 24 hours of the start of the initial treatment.<br><br>Using the tables widely adopted in England, the schedule that most closely aligns to the Weaver protocol is a Royal Navy Table 61 (284 kPa lasting 2.25 hours) within 24 hrs of extraction; two Royal Navy Table 66 (243 kPa lasting 100 minutes), the second to finish within 24hrs of the start of the Royal Navy Table 61.<br><br>Acceptable regimes are those that administer a maximum partial pressure of oxygen of between 250 and 304 kPa in the initial treatment and no additional administration of high fraction oxygen ( in excess of 50%) between HBOT treatments to prevent oxygen toxicity |
| **C – Comparison**<br>What is/are the main alternative/s | Any, including treatment with normobaric, high flow oxygen |

| | |
|---|---|
| to compare with the intervention being considered? | |
| **O – Outcomes**<br>What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use. | <u>Critical to decision-making:</u><br><br>Clinical effectiveness:<br>- MMSE score or any other validated assessment of mental state;<br>- Restoration of normal cardiac rhythm;<br>- Short term memory<br>- Oxygenated haemoglobin levels;<br>- Neuropsychological tests<br>- Clinical signs (e.g. Romberg's test, finger-nose movement, gait including heel toe walking.)<br>- Job retention<br>- Activities of daily living<br>- Survival from effects of carbon monoxide poisoning<br>- Cardiovascular mortality<br>- Length of stay in critical care<br>- Overall in-patient LoS<br>- Pregnancy outcome for pregnant women<br>- Incidence of delayed neurological sequelae (appearance of neuropsychological problems up to 8 months post-exposure.)<br>- Safety,<br>- Adverse events<br>- Quality of life<br><br><u>Important to decision-making:</u><br>- Cost effectiveness |

**Assumptions / limits applied to search**

Inclusion criteria

Peer reviewed studies published in English in the last 10 years including:

- Systematic reviews with or without meta-analysis (including indexed HTAs)
- RCTs
- Prospective cohort studies with control

Exclusion criteria

- Non comparator studies
- Uncontrolled studies/case series and reports
- Conference reports, abstracts, letters. Grey literature
-

Unpublished evidence

## 10. Search Strategy

We searched PubMed, Embase, Cochrane Library, TRIP and NHS Evidence limiting the search to papers published in England from **1st January 2007 to 19th April 2017**. We excluded uncontrolled studies, conference abstracts, commentaries, letters, editorials and case reports.

Embase search:

| # ▲ | Searches |
|---|---|
| 1 | carbon monoxide intoxication/ |
| 2 | ((carbon monoxide or co) adj2 (poison* or toxic* or intoxic*)).ti,ab. |
| 3 | (carbon monoxide or co).ti. |
| 4 | 1 or 2 or 3 |
| 5 | hyperbaric oxygen/ |
| 6 | ((hyperbaric adj2 (oxygen* or therap* or treatment)) or hbot or oxygen chamber* or barochamber*).ti,ab. |
| 7 | 5 or 6 |
| 8 | 4 and 7 |
| 9 | (exp animals/ or nonhuman/) not human/ |
| 10 | conference*.pt. |
| 11 | 9 or 10 |
| 12 | 8 not 11 |
| 13 | limit 12 to (english language and yr="2007 -Current") |

## 11. Evidence Selection

- Total number of publications reviewed: 35
- Total number of publications considered potentially relevant: 11
- Total number of publications selected for inclusion in this briefing: 3

## 12. References


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