

## Carbon monoxide poisoning (acute)

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### ABSTRACT

**INTRODUCTION:** Carbon monoxide is an odourless, colourless gas, and poisoning causes hypoxia, cell damage, and death. Exposure to carbon monoxide is measured either directly from blood samples and expressed as a percentage of carboxyhaemoglobin, or indirectly using the carbon monoxide in expired breath. Carboxyhaemoglobin percentage is the most frequently used biomarker of carbon monoxide exposure. Although the diagnosis of carbon monoxide poisoning can be confirmed by detecting elevated levels of carboxyhaemoglobin in the blood, the presence of clinical signs and symptoms after known exposure to carbon monoxide should not be ignored. **METHODS AND OUTCOMES:** We conducted a systematic review and aimed to answer the following clinical question: What are the effects of oxygen treatments for acute carbon monoxide poisoning? We searched: Medline, Embase, The Cochrane Library, and other important databases up to June 2010 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). **RESULTS:** We found 12 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. **CONCLUSIONS:** In this systematic review, we present information relating to the effectiveness and safety of the following interventions: 100% hyperbaric oxygen, oxygen 28%, and oxygen 100% by non-re-breather mask.

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### Key points

- The main symptoms of carbon monoxide poisoning are non-specific in nature and relate to effects on the brain and heart. The symptoms correlate poorly with serum carboxyhaemoglobin levels.
  - People with comorbidity, elderly or very young people, and pregnant women are most susceptible.
  - Carbon monoxide is produced by the incomplete combustion of carbon fuels, including inadequately ventilated heaters and car exhausts, or from chemicals such as methylene chloride paint stripper.
  - Poisoning is considered to have occurred at carboxyhaemoglobin levels of over 10%, and severe poisoning is associated with levels over 20–25%, plus symptoms of severe cerebral or cardiac ischaemia. However, people living in areas of pollution may have levels of 5%, and heavy smokers can tolerate levels up to 15%.
  - Severe poisoning can be fatal, and up to a third of survivors have delayed neurological sequelae.
- Immediate care requires removal of the person from the source of carbon monoxide and giving oxygen through a non-re-breather mask.
  - **Normobaric 100% oxygen** reduces the half-life of carboxyhaemoglobin and is considered to be effective, but studies confirming benefit compared with air or lower concentrations of oxygen have not been identified, and would be unethical.
  - Paramedics use **28% oxygen**, which is thought to be beneficial compared with air but may be less effective than higher concentrations of oxygen.
  - We don't know what is the optimum duration of oxygen treatment, but it is usually continued for at least 6 hours, or until carboxyhaemoglobin levels fall below 5%.
- We don't know whether hyperbaric oxygen is more effective than normobaric 100% oxygen at preventing neurological complications in people with **mild to moderate** or **moderate to severe** carbon monoxide poisoning.
  - Clinical benefit of hyperbaric 100% oxygen may depend on the treatment regimen used.
  - The possible benefits of hyperbaric oxygen for an individual need to be weighed against the hazards of a long journey by ambulance.

**DEFINITION**

Carbon monoxide is an odourless, colourless gas, and poisoning causes hypoxia, cell damage, and death.<sup>[1] [2]</sup> **Diagnosis of carbon monoxide poisoning:** Exposure to carbon monoxide is measured either directly from blood samples and expressed as a percentage of carboxyhaemoglobin, or indirectly using the carbon monoxide in expired breath. Carboxyhaemoglobin percentage is the most frequently used biomarker of carbon monoxide exposure. Although the diagnosis of carbon monoxide poisoning can be confirmed by detecting elevated levels of carboxyhaemoglobin in the blood, the presence of clinical signs and symptoms after known exposure to carbon monoxide should not be ignored. The signs and symptoms of carbon monoxide poisoning are mainly associated with the brain and heart, which are most sensitive to hypoxia. The symptoms of carbon monoxide poisoning are non-specific and varied, and include headache, fatigue,<sup>[3]</sup> malaise, “trouble thinking”, confusion, nausea, dizziness, visual disturbances, chest pain, shortness of breath, loss of consciousness, and seizures.<sup>[4] [5] [6]</sup> In people suffering from co-morbidities, symptoms such as shortness of breath or chest pain may be more evident. The classical signs of carbon monoxide poisoning — described as cherry-red lips, peripheral cyanosis, and retinal haemorrhages — are rarely seen.<sup>[7]</sup> **Interpretation of carboxyhaemoglobin levels:** Non-smokers living away from urban areas have carboxyhaemoglobin levels of 0.4–1.0%, reflecting endogenous carbon monoxide production, whereas levels of up to 5% may be considered normal in a busy urban or industrial setting.<sup>[8]</sup> Smokers are exposed to increased levels of carbon monoxide in cigarettes, and otherwise healthy heavy smokers can tolerate levels of carboxyhaemoglobin of up to 15%.<sup>[9]</sup> The use of carboxyhaemoglobin percentage as a measure of severity of carbon monoxide poisoning, or to predict treatment options, is limited because carboxyhaemoglobin levels are affected by removal from the source of carbon monoxide and any oxygen treatment given before measurement of percentage carboxyhaemoglobin. Additionally, people with co-morbidities that make them more sensitive to the hypoxia associated with carbon monoxide can present with symptoms of poisoning at carboxyhaemoglobin levels that are either low or within the normal range.<sup>[10]</sup> Attempts have been made in the literature to equate symptoms and signs to different carboxyhaemoglobin levels,<sup>[11]</sup> but it is accepted that carboxyhaemoglobin levels in an acutely poisoned person only roughly correlate with clinical signs and symptoms, especially those relating to neurological function.<sup>[12]</sup> Earlier studies attempted to differentiate between smokers and non-smokers. Attempts have also been made in the literature to divide carbon monoxide poisoning into mild, moderate, and severe based on carboxyhaemoglobin percentage levels and clinical symptoms,<sup>[13]</sup> but there is no clear clinical consensus or agreement on this issue. The degrees of poisoning have been described as *mild carbon monoxide poisoning*: a carboxyhaemoglobin level of over 10% without clinical signs or symptoms of carbon monoxide poisoning; *moderate carbon monoxide poisoning*: a carboxyhaemoglobin level of over 10%, but under 20–25%, with minor clinical signs and symptoms of poisoning, such as headache, lethargy, or fatigue; and *severe carbon monoxide poisoning*: a carboxyhaemoglobin level of over 20–25%, loss of consciousness, and confusion or signs of cardiac ischaemia, or both. **Population:** For the purpose of this review, we have included adults presenting to healthcare professionals with suspected carbon monoxide poisoning. Although there is no clear consensus on this issue, most studies examining carbon monoxide poisoning and its management use a carboxyhaemoglobin level of 10% or more, or the presence of clinical signs and symptoms after known exposure to carbon monoxide, to be indicative of acute carbon monoxide poisoning. Unless otherwise stated, this definition of acute carbon monoxide poisoning has been used throughout this review. Where appropriate, the terms mild, moderate, or severe have been used to reflect the descriptions of populations in individual studies.

**INCIDENCE/  
PREVALENCE**

Carbon monoxide poisoning is considered to be one of the leading causes of death and injury worldwide, and is a major public health problem.<sup>[14]</sup> In 2000, carbon monoxide was the recorded cause of 521 deaths (ICD 9–E986) in England and Wales<sup>[15]</sup> compared with 1363 deaths recorded in 1985;<sup>[16]</sup> a trend that has also been observed in the USA.<sup>[17]</sup> Of the 521 deaths attributed to carbon monoxide poisoning, 148 were accidental and the remaining 373 the result of suicide or self-inflicted injury. Poisoning by carbon monoxide is almost certainly underdiagnosed because of the varied ways in which it can present, and it has been estimated that, in the USA, there are over 40,000 emergency department visits a year; many presenting with a flu-like illness.<sup>[18]</sup> In 2003, 534 recorded medical episodes in English hospitals involved people suffering from the toxic effects of carbon monoxide.<sup>[19]</sup> This may be a substantial underestimate if the US experience reflects the true morbidity associated with carbon monoxide poisoning. Studies in the USA have shown that the incidence of accidental carbon monoxide poisoning peaks during the winter months,<sup>[20] [21]</sup> and is associated with increased use of indoor heating and petrol powered generators, and reduced external ventilation. This seasonal rise in numbers coincides with the annual increase in influenza notifications, and given the similarity in symptoms, many cases of mild carbon monoxide poisoning are probably misdiagnosed.

**AETIOLOGY/  
RISK FACTORS**

**People at high risk:** People who are most at risk from carbon monoxide poisoning include those with CHD, CVD, or anaemia; pregnant women and their fetus; infants; and elderly people. In people with CHD, experimentally induced blood carboxyhaemoglobin levels of 4.5% shorten the period of

exercise before the onset of anginal pain, and the duration of pain is prolonged.<sup>[22]</sup> <sup>[23]</sup> <sup>[24]</sup> In people with anaemia, the oxygen-carrying capacity of the blood is already compromised and therefore they will be more sensitive to carbon monoxide.<sup>[25]</sup> Elderly people are at risk because of existing co-morbidities, such as heart disease or respiratory disease, and because of a reduced compensatory response to hypoxic situations. During pregnancy, a woman's oxygen-carrying capacity is reduced because of an increased endogenous carbon monoxide production and additional endogenous carbon monoxide from the developing fetus, leading to an increased carboxyhaemoglobin concentration.<sup>[26]</sup> A higher ventilation rate during pregnancy will lead to increased uptake of carbon monoxide at any given carbon monoxide concentration.<sup>[27]</sup> The fetus is also at risk, and there have been occasional fetal deaths in non-fatal maternal exposures.<sup>[26]</sup> <sup>[28]</sup> <sup>[29]</sup> In the developing fetus, oxygen is released at a lower oxygen partial pressure, and fetal haemoglobin binds with carbon monoxide more quickly compared with adults. Carbon monoxide may be a teratogen where there is a significant increase in maternal carboxyhaemoglobin or where there is moderate to severe maternal toxicity.<sup>[30]</sup> Infants may be more susceptible to the effects of carbon monoxide because of their greater oxygen consumption in relation to adults, and their response and symptoms are more variable. There are recorded instances of children travelling in the same car and having varying symptoms with similar carboxyhaemoglobin levels, or widely varying carboxyhaemoglobin levels with similar carbon monoxide exposure.<sup>[31]</sup> **Sources of carbon monoxide:** Carbon monoxide is produced by the incomplete combustion of carbon-containing fuel, such as gas (domestic or bottled), charcoal, coke, oil, and wood. Potential sources include: gas stoves, fires, and boilers; gas-powered water heaters; car exhaust fumes; charcoal barbecues; paraffin heaters; solid fuel-powered stoves; boilers; and room heaters that are faulty or inadequately ventilated. An overlooked source of carbon monoxide is methylene chloride in some paint strippers and sprays. Methylene chloride is readily absorbed through the skin and lungs and, once in the liver, is converted to carbon monoxide. Methylene chloride is stored in body tissues and released gradually; the carbon monoxide elimination half-life in people exposed to methylene chloride is more than twice that of inhaled carbon monoxide. Natural background levels of carbon monoxide in the outdoor environment range from 0.01 to 0.23 mg/m<sup>3</sup> (0.009–0.2 ppm),<sup>[32]</sup> but, in urban traffic in the UK, the 8 hour mean concentrations are higher at about 20 mg/m<sup>3</sup> (17.5 ppm);<sup>[33]</sup> exposure to this level for prolonged periods could result in a carboxyhaemoglobin level of about 3%.

**PROGNOSIS** Prognosis data in carbon monoxide poisoning are inconclusive and contradictory. However, there is general agreement that outcome and prognosis are related to the level of carbon monoxide that a person is exposed to, the duration of exposure, and the presence of underlying risk factors.<sup>[33]</sup> A poor outcome is predicted by lengthy carbon monoxide exposure, loss of consciousness, and advancing age. In addition, hypotension and cardiac arrest independently predict permanent disability and death. After acute carbon monoxide poisoning the organs most sensitive to hypoxia (the brain and heart) will be most affected. Pre-existing co-morbidities that affect these organs will, to an extent, influence the clinical presentation and the prognosis; an individual with pre-existing heart disease may present with myocardial ischaemia that could lead to infarction and death. The prognosis for people resuscitated after experiencing cardiac arrest with carbon monoxide poisoning is poor. In a small retrospective study,<sup>[34]</sup> 18 people with carboxyhaemoglobin levels of 31.7 ± 11.0% given hyperbaric oxygen after resuscitation post-cardiac arrest all died. The effects on the brain are more subtle, given that different sections of the brain are more sensitive to hypoxic insults, either as a consequence of reduced oxygen delivery, or by direct effects on intracellular metabolism.<sup>[35]</sup> Therefore, in addition to the acute neurological sequelae leading to loss of consciousness, coma, and death, neurological sequelae, such as poor concentration and memory problems, may be apparent in people recovering from carbon monoxide poisoning (persistent neurological sequelae) or develop after a period of apparent normality (delayed neurological sequelae). Delayed neurological sequelae develop between 2 and 240 days after exposure, and are reported to affect 10–32% of people recovering from carbon monoxide poisoning.<sup>[36]</sup> <sup>[37]</sup> Symptoms include cognitive changes, personality changes, incontinence, psychosis, and Parkinsonism.<sup>[38]</sup> Fortunately, 50–75% of people recover within 1 year.<sup>[39]</sup>

**AIMS OF INTERVENTION** To reduce mortality, normalise carboxyhaemoglobin levels, alleviate symptoms, reduce the incidence of delayed neuropsychological sequelae, and reduce cardiovascular morbidity, with minimal adverse effects of treatment.

**OUTCOMES** Mortality, levels of consciousness, cardiovascular parameters, hyperoxic seizures, serum carboxyhaemoglobin levels, neurological sequelae, adverse effects, including barotrauma associated with hyperbaric oxygen.

**METHODS** *Clinical Evidence* search and appraisal June 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to June 2010, Embase 1980 to June 2010, and The Cochrane Database of Systematic Reviews, May 2010 [online] (1966 to date of issue). When

editing this review, we used the Cochrane Database of Systematic Reviews 2010, Issue 2. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: for hyperbaric oxygen, only published systematic reviews and RCTs in any language, and containing any number of individuals; for interventions other than hyperbaric oxygen, published systematic reviews and RCTs and observational studies in any language, and containing any number of individuals. There was no minimum length or follow-up loss required to include studies. We included studies described as "blinded", "open", or "open label". We also did a search for cohort studies on specific harms of named interventions. Studies where the population consisted wholly of children or adolescents have been excluded. Studies and trials were considered in a hierarchical manner with systematic reviews of RCTs being considered as most robust evidence and anecdote the least robust. In the event of no systematic reviews or RCTs being available, observational study data were considered, but only included where it was considered unethical or impractical to conduct an RCT. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 12 ). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website ([www.clinicalevidence.com](http://www.clinicalevidence.com)).

**QUESTION** What are the effects of oxygen treatments for acute carbon monoxide poisoning?

**OPTION** OXYGEN 28%

We found no clinically important results from RCTs about 28% normobaric oxygen compared with air in people with carbon monoxide poisoning. There is consensus that normobaric oxygen 28% is likely to be beneficial compared with air. Oxygen 28% will affect carboxyhaemoglobin levels, but may not be as effective as higher concentrations of oxygen for reducing carboxyhaemoglobin half-life. UK paramedics routinely use oxygen 28% so that individuals who may be dependent on their hypoxic drive are not adversely affected.

For GRADE evaluation of interventions for carbon monoxide poisoning (acute), see table, p 12 .

**Benefits:** **Oxygen 28% versus air:**  
We found no systematic review, RCTs, or analytical observational studies comparing normobaric oxygen 28% versus air that assessed clinically relevant outcomes of interest. An RCT comparing normobaric oxygen 28% versus air in people with suspected acute carbon monoxide poisoning may be considered unethical. There is consensus that there will be an increased benefit with normobaric oxygen 28% compared with air.

**Harms:** **Oxygen 28% versus air:**  
We found no systematic review, RCTs, or analytical observational studies comparing normobaric oxygen 28% versus air in people with acute carbon monoxide poisoning for clinically relevant outcomes of interest.

**Comment:** Based on physiological studies, UK paramedics use normobaric oxygen 28% so that individuals who may be dependent on their hypoxic drive are not adversely affected. Normobaric oxygen 28% will affect carboxyhaemoglobin levels, but may not be as effective as higher concentrations of oxygen for reducing carboxyhaemoglobin half-life.

**OPTION** OXYGEN 100% BY NON-RE-BREATHING MASK

We found no clinically important results from RCTs about oxygen 100% by non-re-breathing mask compared with air in people with acute carbon monoxide poisoning. Based on physiological studies, the benefits of oxygen 100% by non-re-breathing mask in the emergency situation are universally accepted, but there is still considerable debate about the optimum duration of treatment in secondary- or tertiary-care settings.

For GRADE evaluation of interventions for carbon monoxide poisoning (acute), see [table, p 12](#) .

#### Benefits:

##### Oxygen 100% by non-re-breather mask versus air:

We found no systematic review, RCTs, or analytical observational studies comparing 100% [normobaric oxygen](#) by tight-fitting [non-re-breather mask](#) versus air in people with suspected acute carbon monoxide poisoning for clinically relevant outcomes of interest. Such an RCT would be considered unethical. We found one retrospective chart review of 93 people, with various levels of severity of acute carbon monoxide poisoning, receiving normobaric oxygen 100% either by non-re-breather mask or by ventilation, if intubated in a tertiary teaching hospital setting. <sup>[40]</sup> The study found that oxygen 100% delivered by non-re-breather mask, or endotracheal tube, reduced carboxyhaemoglobin half-life to 74 minutes (mean half-life) with a range of 26–148 minutes. Another retrospective chart review found similar results for reduction in carboxyhaemoglobin half-life. <sup>[41]</sup> The review included 43 people with carbon monoxide poisoning (first carboxyhaemoglobin measured at greater than 10%) resulting from suicidal attempt (specifically, from burning charcoal) who were receiving normobaric oxygen 100% by non-re-breather mask. It found that oxygen 100% by non-re-breather mask reduced carboxyhaemoglobin half-life to 78 minutes (mean half-life) with a range of 21–154 minutes. In young, healthy volunteers breathing air at sea level, the half-life of carboxyhaemoglobin is 320 minutes (range: 128–409 minutes). Administration of oxygen 100% at 1 atmosphere reduces the half-life to 80 minutes. <sup>[42]</sup>

##### Duration of treatment:

We found no systematic review, RCTs, or cohort studies that indicated the optimal duration of treatment.

##### Oxygen 100% by non-re-breather mask versus hyperbaric oxygen in mild to moderate poisoning:

[See option on hyperbaric oxygen in mild to moderate poisoning, p 5](#) .

##### Normobaric oxygen 100% versus hyperbaric oxygen in moderate to severe poisoning:

[See option on hyperbaric oxygen in moderate to severe poisoning, p 7](#) .

#### Harms:

##### Oxygen 100% by non-re-breather mask versus air:

Oxygen toxicity is not usually seen with use of oxygen in concentrations of less than 50%; the maximum concentration that the commonly used re-breather masks on maximum flow can achieve. The first signs of toxicity can appear after 10 hours of exposure to oxygen at concentrations greater than 50%, with increasing incidence of signs and symptoms with increasing duration of exposure. Oxygen toxicity can present as either central nervous system toxicity (the Bert Effect) or pulmonary toxicity (the Smith Effect). Pulmonary toxicity can include a progressive decrease in vital capacity, tightness in the chest, discomfort, coughing, congestion, increased depth of respiration, rapid panting or asthma-like attacks, and cogwheel-like breathing. Central nervous system toxicity, such as hyperoxic seizures, is usually only seen when high concentrations of [hyperbaric oxygen](#) are used. Cardiovascular effects may include bradycardia and peripheral vasoconstriction. Bilateral progressive constriction of visual acuity has been found after breathing pure oxygen for 4.5 hours at normal atmospheric pressures. <sup>[43]</sup> <sup>[44]</sup>

##### Duration of treatment:

We found no systematic review, RCTs, or cohort studies that indicated the optimal duration of treatment.

#### Comment:

The maximum concentration of oxygen that can be delivered with a re-breather mask, regardless of the oxygen flow, is just under 50%. To achieve as high an inspired oxygen concentration as possible, a non-re-breather mask is needed. Non-re-breather masks can provide 60–80% oxygen, depending on the seal quality of the mask against the face. Based on physiological studies, the benefits of normobaric oxygen 100% by non-re-breather mask in the emergency situation and in the field are universally accepted, but there is still considerable debate about the optimum duration of treatment in secondary- or tertiary-care settings. Further clinical research on the optimum duration of exposure to oxygen 100% is needed. In the absence of such studies, it has been suggested <sup>[45]</sup> that people with mild carbon monoxide poisoning (see definition) should receive normobaric oxygen 100% for no less than 6 hours' duration. In moderate to severe carbon monoxide poisoning (see definition), oxygen 100% is usually given until the carboxyhaemoglobin is within normal parameters (i.e., less than 5%).

#### OPTION

#### HYPERBARIC OXYGEN 100% (MILD TO MODERATE POISONING)

##### Neurological sequelae

*Compared with oxygen 100% given by non-re-breather mask* We don't know how hyperbaric oxygen 100% given at 2–2.8 atmospheric pressure and oxygen 100% given by non-re-breather mask compare at preventing the development

of delayed neurological symptoms in people with mild to moderate carbon monoxide poisoning ([very low-quality evidence](#)).

#### Note

We found no direct information from RCTs about hyperbaric oxygen 100% in people with mild carbon monoxide poisoning.

**For GRADE evaluation of interventions for carbon monoxide poisoning (acute), see [table, p 12](#) .**

#### Benefits:

We found four systematic reviews (search dates 1999, <sup>[46]</sup> 2002, <sup>[47]</sup> 2004, <sup>[48]</sup> and not reported <sup>[49]</sup>), which identified a total of eight RCTs (5 of which were identified by all the reviews) on the effects of [hyperbaric oxygen](#) in the treatment of carbon monoxide poisoning of varying severities. The reviews did not analyse data on the basis of severity of carbon monoxide poisoning, and came to different conclusions regarding the possible benefit and uses of hyperbaric oxygen in the treatment of carbon monoxide poisoning. Two of the reviews performed a meta-analysis. <sup>[48]</sup> <sup>[49]</sup> However, we have not reported these data because of the heterogeneity of the study populations and regimens of the RCTs included in the meta-analyses. Of the eight RCTs identified by the reviews, four RCTs did not meet our inclusion criteria and are not discussed further. Below, we report the two RCTs (identified by all 4 reviews) assessing the effects of hyperbaric oxygen in the treatment of mild carbon monoxide poisoning. <sup>[50]</sup> <sup>[51]</sup>

#### **Hyperbaric oxygen 100% versus oxygen 100% by non-re-breather mask in mild poisoning:**

We found no systematic review or RCTs in people with only mild carbon monoxide poisoning. We found two RCTs comparing hyperbaric oxygen 100% versus oxygen 100% by [non-re-breather mask](#) in people with mild to moderate carbon monoxide poisoning. <sup>[50]</sup> <sup>[51]</sup> The first RCT compared hyperbaric oxygen 100% at 2 ATA for 2 hours plus 4 hours of [normobaric oxygen](#) versus oxygen 100% by non-re-breather mask for 6 hours. <sup>[50]</sup> It found no significant difference between groups in the proportion of people with mild to moderate acute carbon monoxide poisoning who did not develop neurological symptoms at 4 weeks (1 RCT, 307 people fitting the definition of mild to moderate acute carbon monoxide poisoning; absence of neurological symptoms at 4 weeks: 108/159 [68%] with hyperbaric oxygen 100% v 98/148 [66%] with oxygen 100% by non-re-breather mask; OR and CI not reported; P = 0.75). <sup>[50]</sup> However, this RCT has important limitations which influence the conclusions that can be drawn from the results, because any neurophysiological changes would be subtle and slight in people with mild to moderate carbon monoxide poisoning. In this RCT, acute carbon monoxide poisoning was defined as carboxyhaemoglobin levels of 5% or more in non-smokers, 10% or more in smokers, and no impairment of consciousness. Recovery was defined as the absence of neurological signs and symptoms of carbon monoxide poisoning. However, the study was not blinded and no validated neurophysiological tests were used. Self-administered patient questionnaires were used without any apparent standardisation of the testing for neurological symptoms, such as "impaired vision" and "difficulty in concentrating", thus allowing an unknown degree of subjectivity and inter-observer variation. This RCT also included a group of more severely poisoned people in whom one session of hyperbaric oxygen was compared with two, but this aspect is not included in this review. The second RCT <sup>[51]</sup> found that, compared with oxygen 100% by non-re-breather mask given until all symptoms resolved, hyperbaric oxygen 100% at 2.8 ATA for 30 minutes followed by 2.0 ATA for 90 minutes significantly reduced the proportion of people developing neurological symptoms at 4 weeks (1 RCT, 60 people with mild to moderate carbon monoxide poisoning; neurological symptoms at 4 weeks: 0/30 [0%] with hyperbaric oxygen 100% v 7/30 [23%] with normobaric oxygen 100%; difference between groups 23.0%, 95% CI 8.2% to 38.4%; P <0.05). Treatment was given within 6 hours of the people being removed from the source of carbon monoxide. However, this RCT has important limitations which influence the conclusions that can be drawn from the results, because any neurophysiological changes would be subtle and slight in people with mild to moderate carbon monoxide poisoning. In this RCT, acute carbon monoxide poisoning was defined as a history of acute exposure to combustion products, an increased carboxyhaemoglobin level not explained by a smoking history, and the presence of symptoms consistent with carbon monoxide poisoning. People were excluded if there was a history of loss of consciousness, cardiac compromise, or if they declined to participate. However, the study was not blinded and the definition of delayed neurological symptoms was vague. Delayed neurological sequelae was defined as recurrence of original symptoms, or development of new symptoms considered to be typical of the delayed neurological syndrome, plus deterioration in one or more of six neuropsychological tests, at 4 weeks. A control group of eight people had neuropsychological testing to see if repeated screening improved scores. The value of including and comparing with a control group of eight people is questionable. We found no systematic review or RCTs for other clinical outcomes of interest.

#### Harms:

Two systematic reviews did not include the harms associated with hyperbaric oxygen treatment in their assessments of costs and benefits. <sup>[47]</sup> <sup>[48]</sup> The third systematic review included a list of the possible harms associated with hyperbaric treatment (similar to those listed below), but did not in-

clude these in an overall assessment of the costs and benefits.<sup>[46]</sup> The fourth review gave no information on adverse effects.<sup>[49]</sup>

**Hyperbaric oxygen 100% versus oxygen 100% by non-re-breather mask in mild poisoning:** One RCT reported that in the group considered in this review, 6/170 (4%) people receiving one session of hyperbaric treatment reported anxiety and 1/170 (1%) experienced barotrauma.<sup>[50]</sup> One RCT found no adverse effects associated with hyperbaric oxygen treatment.<sup>[51]</sup>

**Comment:**

**Clinical guide:**

From a purely physiological perspective, it has been demonstrated and is universally accepted that hyperbaric oxygen 100% significantly reduces the half-life of carboxyhaemoglobin.<sup>[52]</sup> Animal studies suggest that hyperbaric oxygen 100% has other beneficial effects on brain cells that have been traumatised by carbon monoxide, including a reduction in lipid peroxidation, endothelial leukocyte migration, and other post-hypoxic events.<sup>[53]</sup><sup>[54]</sup> The question is whether there is any worthwhile clinical effect in terms of prognosis or outcome. The evidence is unclear as to whether hyperbaric oxygen improves the prognosis or outcomes of people with persistent or delayed neurological sequelae. Furthermore, the size of the effect derived from hyperbaric oxygen treatment may be highly sensitive to the pressure at which the oxygen is delivered, the number of treatment sessions, and the oxygen content of control treatments. Further research is needed to address these and other important clinical questions. These include the optimal duration of treatment, the optimum pressure within the chamber, the duration after presentation when treatment may be effective, the types of people who may benefit from treatment, and whether hyperbaric treatment is indicated in mild carbon monoxide poisoning. Most people will need to be transported to a hyperbaric centre, and the number of centres available are limited. In making a decision about whether hyperbaric treatment is needed, the effects of a long ambulance trip and associated risks need to be considered. The possibility of using an inflatable portable hyperbaric chamber (a modified Gamow bag used to treat altitude sickness) to treat carbon monoxide poisoning has been explored in a small study (10 people).<sup>[55]</sup> The results suggested that the 1.58 ATA pressures used to treat experimentally induced elevated carboxyhaemoglobin levels in the study may increase the rate at which carbon monoxide dissociates from carboxyhaemoglobin, and field studies of a device capable of delivering higher pressures are currently being tested. If successful, this device may prove to be a possible treatment option for those centres situated some distance from a hyperbaric chamber.

**OPTION**

**HYPERBARIC OXYGEN 100% (MODERATE TO SEVERE POISONING)**

**Neurological sequelae**

*Compared with normobaric oxygen 100%* We don't know how hyperbaric oxygen 100% delivered within 24 hours of presentation at pressures of 2–3 atmospheres and normobaric oxygen 100% compare at preventing cognitive sequelae at 6 weeks or at delaying neurological sequelae in people with moderate to severe carbon monoxide poisoning (*very low-quality evidence*).

*Hyperbaric oxygen 100% interspersed with normobaric oxygen compared with normobaric oxygen 100% alone* We don't know how 3-day continuous normobaric oxygen 100% interspersed with sessions of hyperbaric oxygen compares with normobaric oxygen alone at preventing cognitive sequelae at 6 weeks or at delaying neurological sequelae in people with moderate to severe carbon monoxide poisoning (*very low-quality evidence*).

**Note**

High doses of oxygen can cause adverse effects.

**For GRADE evaluation of interventions for carbon monoxide poisoning (acute), see table, p 12 .**

**Benefits:**

We found four systematic reviews (search dates 1999,<sup>[46]</sup> 2002,<sup>[47]</sup> 2004,<sup>[48]</sup> and not reported<sup>[49]</sup>), which identified a total of eight RCTs (5 of which were identified by all the reviews) on the effects of **hyperbaric oxygen** in the treatment of carbon monoxide poisoning of varying severities. The reviews did not analyse data on the basis of severity of carbon monoxide poisoning, and came to different conclusions regarding the possible benefit and uses of hyperbaric oxygen in the treatment of carbon monoxide poisoning. Two of the reviews performed a meta-analysis.<sup>[48]</sup><sup>[49]</sup> However, we have not reported these data because of the heterogeneity of the study populations and regimens of the RCTs included in the meta-analyses. Of the eight RCTs identified by the reviews, four RCTs did not meet our inclusion criteria and are not discussed further. Below, we report the two RCTs (3 publications; identified by all 4 reviews) assessing the effects of hyperbaric oxygen in the treatment of moderate to severe carbon monoxide poisoning.<sup>[56]</sup><sup>[57]</sup><sup>[58]</sup>

**Hyperbaric oxygen 100% versus normobaric oxygen 100% in moderate to severe poisoning:**

We found one RCT (reported in 2 publications).<sup>[56]</sup><sup>[57]</sup> One RCT found that, compared with one 150-minute session of 100% **normobaric oxygen** followed by two 120-minute sessions of normobaric air, one 150-minute session of 100% oxygen at 3 ATA followed by two 120-minute sessions

of 100% oxygen at 2 ATA significantly reduced cognitive sequelae at 6 weeks (cognitive sequelae at 6 weeks: 19/76 [25%] with hyperbaric oxygen *v* 35/76 [46%] with normobaric oxygen; unadjusted odds ratio 0.39, 95% CI 0.20 to 0.78; *P* = 0.007).<sup>[56]</sup> <sup>[57]</sup> The trial was stopped after the third of four interim analyses because hyperbaric oxygen was judged to be efficacious (*P* < 0.01). The results of the analysis of the incidence of cognitive sequelae at 6 and 12 months was presented, but neither the raw figures nor the follow-up rates were reported, and so are not included in this review. However, it has been noted that the clinical definition of neurological sequelae (the primary outcome measure) changed over the course of the trial, and that one arm of the RCT included a disproportionate number of people with cerebellar problems.<sup>[49]</sup> Another potential weakness of this RCT is that, although all participants received normobaric oxygen 100% for a mean duration of 4.5 hours ( $\pm$  2.2 hours in the normobaric group *v*  $\pm$  2.6 hours in the hyperbaric group) before entering the study and the levels of carboxyhaemoglobin were below 5% and not significantly different, only one session of normobaric oxygen 100% was given to people in the normobaric oxygen arm. Supplemental oxygen was given, if necessary, after treatment to maintain the arterial oxygen saturation at a level higher than 90%, but it was not reported how frequently this occurred. This information would have indicated the effectiveness of one session of normobaric oxygen. In this RCT, acute carbon monoxide poisoning was defined as a documented exposure to carbon monoxide (carboxyhaemoglobin >10% or elevated ambient carbon monoxide), or an obvious exposure to carbon monoxide, and symptoms consistent with carbon monoxide poisoning. People were excluded if 24 hours had elapsed since the exposure to carbon monoxide had ended; if they were moribund, pregnant, under 16 years of age, or if informed consent could not be obtained. The primary outcome was the incidence of neurological sequelae, as measured by six neuropsychological tests at 6 weeks. Neurological sequelae were considered present if any T score was more than two standard deviations below the mean, if two or more tests were one standard deviation below the mean, or if the patient reported difficulties with memory, attention, or concentration and one T score was more than one standard deviation below the mean. The results on neurological sequelae should be interpreted with caution, as the disparity between groups in proportion of people with abnormal cerebellar findings on arrival (greater in the control group compared with the hyperbaric group) might have affected the outcome: cerebellar findings were associated with a greater likelihood of central nervous system sequelae.

#### **Hyperbaric oxygen 100% plus normobaric oxygen 100% versus normobaric oxygen 100% alone in moderate to severe poisoning:**

We found one RCT, which was in people with all levels of carbon monoxide poisoning, but included a high proportion (73%) of people with severe carbon monoxide poisoning.<sup>[58]</sup> The RCT found no significant difference between 3-day continuous normobaric oxygen 100% and 3-day continuous normobaric oxygen 100% interspersed with sessions of hyperbaric oxygen in the incidence of persistent neurological sequelae in people with all levels of carbon monoxide poisoning (191 people, including 139 people with severe carbon monoxide poisoning; persistent neurological sequelae after treatment hyperbaric oxygen *v* normobaric oxygen: OR 1.7, 95% CI 0.8 to 4.0; *P* = 0.19). It found a significant increase in persistent neurological sequelae on completion of treatment in people with severe carbon monoxide poisoning who had received hyperbaric oxygen (139 people; persistent neurological sequelae after treatment hyperbaric oxygen *v* normobaric oxygen: OR 3.6, 95% CI 1.1 to 11.9; *P* = 0.03). However, the use of oxygen 100% for 3 days or more is not a widely used treatment for carbon monoxide poisoning, as high doses of oxygen can cause adverse effects.<sup>[59]</sup> Overall, the **Mini-Mental scores** were high and showed little change at the end of treatment. This is surprising given that 102 of the people were in coma, and 36 were being ventilated at initial assessment. There is a possibility that bias may have been introduced. The RCT used cluster randomisation for people presenting simultaneously, with the risk of introducing bias by assigning people with similar baseline characteristics to one type of treatment. Participants and assessors were double blinded to intervention received (by using sham hyperbaric sessions), but the hyperbaric technicians and nursing staff were not.

#### **Harms:**

Two systematic reviews did not include the harms associated with hyperbaric oxygen treatment in their assessments of costs and benefits.<sup>[47]</sup> <sup>[48]</sup> The third systematic review included a list of the possible harms associated with hyperbaric treatment (similar to those listed below), but did not include these in an overall assessment of the costs and benefits.<sup>[46]</sup> The fourth review gave no information on adverse effects.<sup>[49]</sup> The most common fatal complication of hyperbaric oxygen treatment is fire; from 1927 to 1996 there were 35 hyperbaric fires with 77 fatalities.<sup>[59]</sup> Since then there has been one fire in a chamber in Milan in 1997 which killed 10 patients and one nurse. Other problems include claustrophobia, barotraumas (including rupture of the tympanic membrane), sinus damage, pneumothorax, and gas emboli. The risk of pneumothorax is high in those people who receive external cardiac massage. Oxygen 100%, when used at greater than atmospheric pressure, can have toxic effects and produce a variety of symptoms that increase in severity with the duration of treatment. It is generally accepted that hyperbaric oxygen 100% delivered at 3 atmospheres for less than 120 minutes is safe. Respiratory effects are similar to those seen in oxygen toxicity at 1 ATA. The primary difference is that the duration of exposure before symptoms appear is shorter.



They include tightness in the chest, discomfort, coughing, congestion, oedema, atelectasis (partial or complete collapse of the lung), increased depth of respiration, rapid panting, asthma-like attacks, or apnoea on inspiration. Cardiovascular effects include bradycardia, hyperthermia or hypothermia, and peripheral vasoconstriction. Central nervous system toxicity is seen primarily in hyperbaric oxygen treatment where pressures of 3 ATA or more are used for periods in excess of 2 hours. Signs and symptoms include mood changes, dizziness, slowing of mental processes, paraesthesia, fasciculation of the lips and face, muscular twitching, visual and auditory hallucinations progressing to vertigo, nausea, and convulsions. The incidence of hyperoxic convulsions is estimated to be about 1.3/10,000.<sup>[60]</sup> At increased atmospheric pressures, vision may be affected with reversible myopia and mydriasis.

**Hyperbaric oxygen 100% versus normobaric oxygen 100% in moderate to severe poisoning:**

The RCT reported that at least one session of hyperbaric treatment was stopped prematurely in 7/76 (9%) people because of anxiety, 1/76 (1%) because of tympanic membrane rupture, 1/76 (1%) because of cough, and 4/76 (5%) because of difficulty in equalising middle-ear pressure.<sup>[56]</sup><sup>[57]</sup> It should be noted that there was no consistency in the pressures and durations of hyperbaric treatment used in the RCTs identified.

**Hyperbaric oxygen 100% plus normobaric oxygen 100% versus normobaric oxygen 100% alone in moderate to severe poisoning:**

The RCT reported that treatment was stopped early in 7/104 (7%) people because of ear barotraumas, 1/104 (1%) because of oxygen toxicity (convulsions), and 1/104 (1%) because of severe claustrophobia in people given hyperbaric treatment.<sup>[58]</sup> In addition, 1/87 (1%) people given sham hyperbaric treatment developed severe claustrophobia. It should be noted that there was no consistency in the pressures and durations of hyperbaric treatment used in the RCTs identified.

**Comment:**

**Clinical guide:**

From a purely physiological perspective, it has been demonstrated and is universally accepted that hyperbaric oxygen 100% significantly reduces the half-life of carboxyhaemoglobin.<sup>[52]</sup> Animal studies suggest that hyperbaric oxygen 100% has other beneficial effects on brain cells that have been traumatised by carbon monoxide, including a reduction in lipid peroxidation, endothelial leukocyte migration, and other post-hypoxic events.<sup>[53]</sup><sup>[54]</sup> The question is whether there is any worthwhile clinical effect in terms of prognosis or outcome. The evidence is unclear as to whether hyperbaric oxygen improves the prognosis or outcomes of people with persistent or delayed neurological sequelae. Furthermore, the size of the effect derived from hyperbaric oxygen treatment may be highly sensitive to the pressure at which the oxygen is delivered, the number of treatment sessions, and the oxygen content of control treatments. Further research is needed to address these and other important clinical questions. These include the optimal duration of treatment, the optimum pressure within the chamber, the duration after presentation when treatment may be effective, the types of people who may benefit from treatment, and whether hyperbaric treatment is indicated in mild carbon monoxide poisoning. Most people will need to be transported to a hyperbaric centre, and the number of centres available are limited. In making a decision about whether hyperbaric treatment is needed, the effects of a long ambulance trip and associated risks need to be considered. The possibility of using an inflatable portable hyperbaric chamber (a modified Gamow bag used to treat altitude sickness) to treat carbon monoxide poisoning has been explored in a small study (10 people).<sup>[55]</sup> The results suggested that the 1.58 ATA pressures used to treat experimentally induced elevated carboxyhaemoglobin levels in the study may increase the rate at which carbon monoxide dissociates from carboxyhaemoglobin, and field studies of a device capable of delivering higher pressures are currently being tested. If successful, this device may prove to be a possible treatment option for those centres situated some distance from a hyperbaric chamber.

## GLOSSARY

**ATA** An abbreviation of atmospheres absolute used to describe atmospheric pressure; one ATA is about roughly equivalent to sea level atmospheric pressure.

**Normobaric oxygen** Oxygen supplied at a barometric pressure equivalent to sea level pressure.

**Hyperbaric oxygen** Oxygen supplied at a barometric pressure greater than sea level; usually 2–3 atmospheres. This is delivered in single- or multiple-occupancy hyperbaric chambers.

**Mini-Mental score** A score derived from the Folstein Mini Mental State Examination. This examination is used to evaluate dementia, and consists of a series of questions and tasks to assess a patient's orientation, attention, calculation, language, visuospatial, executive, and short-term memory abilities. The cut off for dementia is a score of less than 24 out of a possible 30.

**Non-re-breather mask** Usually a tight-fitting mask with an oxygen reservoir bag and a one-way valve that remains open during inspiration. The mask will allow oxygen concentrations of 80–100% to be delivered in a situation where high levels of inspired oxygen are required.

**Very low-quality evidence** Any estimate of effect is very uncertain.

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# Carbon monoxide poisoning (acute)

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**TABLE** GRADE evaluation of interventions for carbon monoxide poisoning (acute)

Important outcomes	Carboxyhaemoglobin levels, neurological sequelae, mortality, adverse effects									
	Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of oxygen treatments for acute carbon monoxide poisoning?										
2 (367) <sup>[50]</sup> <sup>[51]</sup>	Neurological sequelae	Hyperbaric oxygen 100% v oxygen 100% given by non-re-breather mask in mild to moderate poisoning	4	-1	0	-2	0	Very low	Quality point deducted for lack of blinding. Directness points deducted for uncertainty about definition of outcome and inclusion of differing severities of CO poisoning	
1 (152) <sup>[56]</sup> <sup>[57]</sup>	Neurological sequelae	Hyperbaric oxygen 100% v normobaric oxygen 100% in moderate to severe poisoning	4	-2	0	-1	0	Very low	Quality points deducted for sparse data and methodological weaknesses (possible bias). Directness point deducted for disparity between groups at baseline in number of people with cerebellar abnormalities	
1 (139) <sup>[58]</sup>	Neurological sequelae	Hyperbaric oxygen 100% interspersed with normobaric oxygen v normobaric oxygen 100% in moderate to severe poisoning	4	-2	0	-2	0	Very low	Quality points deducted for sparse data and methodological weaknesses (change in definition of outcome during trial). Directness points deducted for disparity in high Mini-Mental scores at baseline and for unclear reporting of numbers of sessions of treatment given and pressures/durations of hyperbaric treatment	

Type of evidence: 4 = RCT; 2 = Observational  
 Consistency: similarity of results across studies  
 Directness: generalisability of population or outcomes  
 Effect size: based on relative risk or odds ratio