CPAG Summary Report for Clinical Panel – Hyperbaric Oxygen Therapy for Carbon Monoxide Poisoning

The Benefits of the Proposition			
No	*Metric*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	Not measured	
2.	Progression free survival	Not measured	
3.	Mobility	Not measured	
4.	Self-care	Not measured	
5.	Usual activities	Not measured	Activities of daily living were measured – see “Katz index of activities of daily living scores” below.
6.	Pain	Not measured	
7.	Anxiety / Depression	Not measured	Depression was measured – see “Geriatric Depression Scale scores” below. Anxiety was reported as side effect (an adverse) reaction to treatment – see “Safety” below.
8.	Replacement of more toxic treatment	Not measured	
9.	Dependency on care giver / supporting independence	Not measured	
10.	Safety	Adverse events identified [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. 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. This suggests that major adverse effects of HBOT are relatively infrequent. HBOT is occasionally complicated by more serious adverse reactions such as convulsions and pulmonary oedema (collection of fluid in the lungs) (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.
11.	Delivery of intervention	Not measured	

Other health metrics determined by the evidence review			
No	Metric	Grade of evidence	Summary from evidence review
1.	Presence of neurological symptoms or signs at 4-6 weeks post treatment	Grade C	This outcome measure is derived from six different studies which used different methods for assessing the presence of neurological symptoms (disorder of the nervous system) and signs at 4-6 weeks post carbon monoxide (CO) poisoning. The combined odds ratio (OR) (a measure of effect, which allows the comparison of the intervention group of a study relative to the comparison or placebo group) 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).

			This means that these studies do not provide evidence of a positive effect of HBOT on reducing neurological sequelae (pathological condition resulting from a prior disease or injury) at 4-6 weeks. The studies included were heterogeneous (patients with varied characteristics) in the patients they included, the pressure of oxygen provided, the number and frequency of HBOT sessions and the treatment of the control group (sham treatment group). Only two of the studies met the requirements of the PICO (Weaver et al 2002 and Thom et al 1995). In only two studies was there an attempt to blind patients and staff to which treatment patients were receiving. Unblinded studies are more 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.
2.	Delayed neurological sequelae (DNS)	Grade 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).

			Thom et al defined DNS as a recurrence of original symptoms or development of new symptoms plus 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. 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. 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.
3.	Incidence of cognitive sequelae at 6 weeks	Grade 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. 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).

			This suggests that HBOT, compared to NBOT, reduces the risk of cognitive sequelae that persist to six weeks post CO poisoning. This result should be interpreted with caution for a number of reasons: the control group had more patients with cerebellar dysfunction (brain 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.
4.	Cognitive sequelae at 6 months	Grade 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. 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). This suggests that HBOT, compared to NBOT, reduces the risk of cognitive sequelae persisting to six months post CO poisoning.

			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.
5.	Cognitive sequelae at 12 months	Grade 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. 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). This suggests that HBOT, compared to NBOT, reduces the risk of cognitive sequelae persisting to 12 months post CO poisoning. 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.
6.	Neuropsychological test scores at 6 weeks	Grade 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. 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 numbers and letters in order). Neuropsychological testing overall therefore did not suggest that HBOT is more effective than NBOT in preventing neuropsychological sequelae at six weeks. 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.
7.	Self-reports of difficulties with memory and attention or concentration at 6 weeks.	Grade 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.) 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). This suggests that HBOT may be more effective than NBOT in reducing the effects of CO poisoning on memory. 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.
8.	Geriatric Depression Scale scores at 6 weeks	Grade 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. 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. This suggests that HBOT does not reduce the risk of depression at six weeks following CO poisoning compared to NBOT. 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.
9.	Katz index of activities of daily living scores at 6 weeks	Grade 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 independently. It ranks adequacy of performance in the six functions of bathing, dressing, toileting, transferring, continence, and feeding. 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. 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. 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.
10.	SF 36 scores at 6 weeks (quality of life)	Grade 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. 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. This suggests that HBOT does not improve quality of life at six weeks following CO poisoning compared to NBOT. 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.
11.	Neurologic abnormalities on examination after third chamber session	Grade 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. 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). There was therefore little difference between the groups in terms of objective neurological abnormalities at the end of the third treatment session. 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.