UHMS POSITION PAPER
THE TREATMENT OF AUTISM SPECTRUM DISORDER WITH HYPERBARIC OXYGEN THERAPY

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Summary

It has been proposed that low pressure/ low oxygen concentration hyperbaric treatment can improve the clinical manifestations of autism. Several case series and a randomized trial have all supported this position despite little physiological or biological evidence of a likely mechanism.
The available comparative data suggest widespread improvements in physician assessed Clinical Global Impression (CGI) score, parental Aberrant Behavior Checklist (ABC) score and parental Autism Treatment Evaluation Checklist (ATEC) scores in several dimensions. There has been considerable controversy about the validity and interpretation of these scores as reported in the randomized trial.
Given the nature and epidemiology of this group of conditions, there is a strong case for further trials to be done in this area. Any future trials would need to be well planned, appropriately powered and include several relevant treatment arms. The UHMS highly recommends the inclusion of functional neuroimaging in any future investigations. These clinical efforts should be combined with efforts to elucidate the basic mechanisms by which mild hyperbaric therapy might exert a therapeutic effect.
At this time, however, we cannot recommend the routine treatment of ASD with HBO_2T.

Overview and burden of disease

Autism spectrum disorders (ASDs) are a range of life-long neurodevelopmental disorders chiefly characterised by a lack of flexibility in thought and behaviour, along with deficits in communication and social interaction.[1] ASD is one of several related disorders covered by the more general term 'pervasive developmental disorders' (PDD), such as Asberger syndrome and childhood disintegrative syndrome. The true prevalence of ASD is very difficult to determine because of definitional difficulties and widely differing methods of case identification across studies. A recent review of the epidemiology suggests a current prevalence around 20/10,000 and this estimate been rising, perhaps in large part due to broadening diagnostic criteria and improved awareness of the diagnosis.[2] Others put the incidence much higher at 1:150-1:200.[3] There is substantial controversy in this area, with some authors suggesting a real and dramatic rise in the incidence of ASD due to a range of potential triggers such as environmental toxins.[4] ASD is four times more likely to be found in boys than girls, although the reason for this is not yet clear. There can be a regressive loss of attained developmental skills in 30% of cases – mostly over the age of 18 to 24 months.[5]

Currently, ASDs are thought to involve a complex interaction between susceptibility genes, epigenetic effects and environmental factors. The current most likely hypothesis is that a genetically susceptible child develops autism when exposed to an as yet unidentified environmental trigger. The pathophysiology of these disorders remain an active area of investigation.[6] Whilst a central mechanism has yet to be identified, neuropoathological studies have identified a substantial loss of Purkinje cells in the cerebellum and structural abnormalities in the cortex and subcortical areas.[7] The clear cerebellar neuropathology has proved difficult to reconcile with the clinical findings in ASD.

ASD is a difficult diagnosis to make. There is considerable overlap in the clinical picture of ASD, Asperger's syndrome and other disorders within the PDD group. Diagnosis is best made by an experienced clinician using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and may involve the use of the Autism Diagnostic Observation Schedule and the Autism Diagnostic Interview. Using these tools requires significant training and is beyond the scope of this position statement. Several other diagnostic tools have been described.[8]

Diagnosis is often made following recognition of impairment in the areas of social interaction and communication, combined with repetitive behaviours. Generally, ASD can be diagnosed reliably

around the age of 2 years, but is often delayed to the third or fourth year. The most typical presentation is delayed or abnormal speech development, but often impairments in social interaction may be evident prior to clear delay in speech.[8]

Hyperbaric oxygen therapy (HBO_2T) has only recently been formally proposed as a potentially useful therapeutic measure in ASD. Rossignol hypothesised in 2006 that because ASD was a neurodevelopmental condition sometimes characterised by cerebral hypoperfusion and neuroinflammation, HBO_2T would improve the symptoms of autism.[9] This hypothesis was based on the assertion that HBO_2T has potent anti-inflammatory effects, reduces oxidative stress, can help overcome hypoperfusion, and has been used with clinical success in other cerebral conditions including cerebral palsy, foetal alcohol syndrome, closed head injury and stroke. The extent of this clinical success has been challenged, including in UHMS position papers and Cochrane reviews.[10-12]

Currently, a group of highly committed physicians advocate strongly for the therapeutic benefits of HBO_2T in ASD. Many of these physicians work in the USA and references to this practice can be found on a number of internet sites. The treatment does not, however, appear to have gained widespread acceptance outside this group.

It is the aim of this document to define the position of the UHMS on the treatment of ASD with HBO_2T and to outline the evidence basis for this position.

Current Treatment Approaches

Although the prognosis for ASD children is variable, most of those with an early diagnosis are not ultimately able to function as completely independent adults.[13] Nevertheless, most authorities agree that early educational planning and the initiation of intervention as early as possible allows the best opportunity for limiting the impact of the disorder.[14] Better outcomes are achieved with higher IQ, language ability and the ability to perform cognitive shifts – all of which tend to be associated with later diagnosis.[15] The most commonly advocated treatment options are summarised in Table 1.

Treatment Type	Examples and indications
Early educational programs	Treatment and Education of Autistic and Related Communication Handicapped Children (TEACCH) Social skills training Facilitated communication
Behavioural intervention programs	Applied Behavior Analysis (ABA) The Denver approach
Occupational Therapy	
Speech therapy	
Antipsychotic	Risperidone* (aggression, self-injury) Aripiprazole,Quetiapine
Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine (repetitive, compulsive behaviours)
Amphetamines, alpha-agonists	Hyperactivity, inattention
Mood stabilisers	Divalproex sodium[#]
Anti-inflammatories	HBO_2T[#], omega-3 fatty acids
Anti-oxidants	Vit B12, GSH
Chelation	
Nutritional	Gluten-free, casein-free diets Antifungals, probiotics

Table 1. Some therapeutic measures used in ASDs.[8] *Approved by the FDA. [#]Subjected to randomised trialling in ASD

For the most part, several of these strategies are implemented simultaneously or serially and each individual receives those therapies that carers and parents feel are most efficacious for their particular sub-type of ASD. Few have been subject to good clinical trails and indeed, the condition is variable enough to make reliable clinical studies difficult to perform and interpret. A review of 30 individual systematic reviews concluded that although the majority suggested a positive outcome from both

behavioural and educational interventions, the methodological quality of the reviews was generally poor and no reliable assessment could be made of the relative effectiveness of different therapies.[16] The development of targeted therapies based on pathologically or aetiologically defined subtypes of ASD has been identified as an important goal of current research.[3]

The evidence concerning HBO_2T and ASD

A formal search was undertaken and the evidence is summarised in Table 3. There is very little published research in this area to date. Of note however, is the recently completed randomised trial of Rossignol et al, and this will be discussed in detail below.[17]

1. MEDLINE (from January 1966), EMBASE (from 1974), CENTRAL (issue 2).
2. The Database of Randomised Controlled Trials in Hyperbaric Medicine (DORCTHIM, Bennett 1999).
3. Hand search of all hyperbaric journals, proceedings and texts since 1980.
4. References from papers identified above.

Table 2. The resources consulted in the search for clinical evidence

The published literature is the work of two groups, and all but a single paper are from the Rossignol group in Florida. In 2006 and 2007, Rossignol published two papers setting out his hypothesis that HBO_2T might have some efficacy in reducing both pathophysiological changes and the symptoms of ASD.[18, 19] In these detailed reviews of both ASD and HBO_2 biochemistry and physiology, Rossignol suggests that the recently described pathophysiological changes, including cerebral hypoperfusion, neuroinflammation and gastrointestinal inflammation , may all be favourably affected by HBO_2T – a therapy with myriad biological effects. In particular, Rossignol focuses on the demonstrated ability of HBO_2 to modulate immune function, quench oxidative stress and induce angiogenesis while increasing the supply of oxygen to the brain. The 2006 paper included some data on a case series of six children who showed improvements in several scores of symptoms and abilities.

In these papers, Rossignol suggests that there may be a 'hyperbaric effect' as well as a 'hyperbaric oxygen effect' – that is, pressure itself might play a therapeutic role through an unidentified mechanism. Indeed, the children in the 2006 case series received hourly treatments at 1.3ATA on 30% oxygen – an equivalent oxygen dose of 39.5% oxygen at 1ATA. This dose of oxygen can be safely delivered without using a compression vessel and implies at least part of the therapeutic effect is due to compression itself rather than oxygen breathing. Experimental reports of the effects of pressure alone are few, but both a suppression of interferon-gamma and changes to cytokine production have been shown in cell cultures[20, 21] and a clinically important pressure effect cannot be completely discounted. This is of importance when attempting to interpret the available clinical data, and in particular it should be noted that none of the comparative trials using this 'low pressure hyperbaric approach' have included an analysis of outcomes on high inspired oxygen fractions at 1ATA.

This small case series and two others published in 2007 and 2008, all suggest that children with ASD improve on a regimen of modest hyperbaric exposure ranging from 1.5ATA on 100% oxygen down to 1.3ATA on 28% oxygen.[19, 22, 23] The total number of children reported is only is only 31 individuals – (the original six children reported by Rossignol in 2006 are not included in the group reported in 2007 – personal communication). Interestingly, the degree of improvement in both clinical picture and biochemistry (reductions in mean serum C-reactive protein) do not seem to be oxygen or pressure dose-related. In the 2007 report for example, Rossignol combined the results of both a 1.5ATA 100% oxygen exposure group and a 1.3ATA 28-30% oxygen group in order to find a significant reduction in CRP over the treatment course.

The only other clinical evidence published is the recent randomised trial by Rossignol et al.[17] This trial has generated significant interest since publication because it is one of the few trials of 'low pressure' HBO_2T to use a research design with a low propensity for bias.

The randomised evidence

Trial summary
Rossignol et al[17] enrolled 66 children aged 2 to 7 years and with a diagnosis of ASD into a multi-centered, randomised and blinded trial of a hyperbaric exposure compared to a control exposure. Randomisation was in blocks of eight and stratified by enrolling center, while only the hyperbaric technician responsible for the chamber was aware of the treatment allocation.

Nature of Evidence	Author	Study Characteristics	Subjects	Conclusion
Randomised, controlled trial	Rossignol et al 2009[17]	Multi-centered. 62 children. 40 treatments, 1 hour each. Active: 1.3ATA 24% oxygen (n=33) Control: 1.03ATA air Children and assessors blind to allocation	Aged 2-7 years meeting DSMV-IV criteria for AD, no prior HBO_2T.	Improvements in active group were significantly greater than controls in clinical impression, receptive language, social intyeraction and eye contact (see text)
Case series	Rossignol et al 2007[22]	18 children, 40 treatments, 45 minutes each at 1.5ATA on 100% oxygen or 1.3ATA at 24% oxygen.	Aged 3-16 yrs	Improvements in both groups in parental assessment of speech, motivation and cognitive awareness.
Case series	Chungpa ibulpatana et al[23]	7 children, 10 treatments at 1.3ATA on 100% oxygen.		75% of subjects improved.
Case series and hypothesis	Rossignol et al 2006[19]	6 children, 40 treatments, 1 hour each at 1.3ATA 28-30% oxygen.	ASD diagnosis by DSMV-IV	Improvement in several scores of symptoms and abilities.
Letter	Yildiz et al[24]	Response to Rossignol 2007.	N/A	Point out that one arm of this study was hyperbaric treatment rather than HBO_2T. Question the conclusions.
Hypothesis	Rossignol 2007[18]	Hypothetical paper concerning the potential for HBO_2T	N/A	N/A

Table 3. Evidence hierarchy for treatment of ASD with HBO_2T.

Four children did not have the diagnosis confirmed by independent psychological examination, leaving 62 children in the trial. Seven others subsequently withdrew for a variety of reasons (four in the treatment group, three in the control), of whom only one was included in the analysis. The analysis was otherwise by intention to treat. Prior to treatment, all children were assessed on two commonly used assessment tools by parents or primary caretaker – the Aberrant Behavior Checklist (ABC) and the Autism Treatment Evaluation Checklist (ATEC). Following the treatment these were repeated, plus parents and physicians both assessed the Clinical Global Impression (CGI).

The children were allocated to 40 one hour sessions in the chamber over a four week period. The 'active treatment' group received 24% oxygen at 131.7kPa (1.3 ATA), while the 'control treatment' received 21% oxygen at 104.3kPa (1.03 ATA). All measures were repeated immediately following the 40 sessions.

The principle outcomes were changes in the scores using the assessment tools described above and summarised in Table 4. The range of scores for each of these tools has been located at a variety of sources.[25-27] It is not clear what degree of improvement would be widely accepted as of clinical significance and some of these figures are given only in the appendix files on-line. The authors also

documented any adverse effects of therapy in order to establish the safety of the procedure. There were few problems in this group: one child had worsening symptoms of asthma and was withdrawn after nine treatments and a second child was anxious and removed during the first treatment. There were no episodes of barotrauma or seizures.

The authors concluded that this therapy was safe and 'may improve certain autistic behaviours', but recommended that further studies be conducted to confirm these findings.

Assessment tool	Range	Pre-treatment (+/-sd)^		Post-treatment (+/-sd)	
		Active	Control	Active	Control
ABC*	0 – 174 (5 subscales, 58 total items)	55.2 (28.7)	53.3 (24.0)	46.4 (24.7)	45.5 (17.3)
ATEC[#]	0 -180 (5 subscales, weighted)	75.3 (19.5)	75.6 (21.0)	65.9 (16.4)	70.1 (21.9)
CGI (parent)[&] for overall functioning	1 – 7 Descriptive scale 'very much improved' to 'very much worse'	N/A		2.70 (0.81)	3.17 (0.73)
CGI (doctor)[&] for overall functioning	1 – 7 Descriptive scale 'very much improved' to 'very much worse'	N/A		2.87 (0.78)	3.62 (0.75)

Table 4. Main outcome measures used in the RCT. The figures refer to total scores rather than subscale scores. *Aman et al[25], [#]http://www.autism.com/ari/atec/atec_report.htm[26], [&]Guy[27]. ^The authors reported mean +/- SEM in error – the figures in the paper are standard deviations (see comments to the original report).

Commentary

This trial has generated some controversy since publication. Despite the use of a double-blind and randomised methodology, several features of the report have reduced the confidence some experts place in the results. The majority of these are discussed below. Despite these potential shortcomings, this trial remains clearly the most reliable published clinical evidence available. Indeed, this study constitutes a serious effort to respond to general criticisms about the delivery of 'mild' HBO_2T for 'off-label' indications in general. The successful conduct of a randomised trial with blinding and sham therapy is no small achievement, and Rossignol et al are to be congratulated for this. Furthermore, they have made limited and cautious conclusions regarding the implications of their findings.

There are, however a few relevant concerns revealed by a detailed appraisal of the report. First, the trial has been undertaken by a group of physicians who are committed to this therapy and currently treating children with ASD on a regular basis. Further, the study was fully funded by a group active in this area, and for whom the first author is a medical advisor (the International Hyperbarics Association). Combined with the high probability that the subject group are likely to represent a highly motivated and pro-hyperbaric group (they were referred to one of these clinics), these associations are an argument for independent confirmation of the findings – as suggested by Rossignol et al. themselves.

It is of interest that both groups showed improvements in many of the reported outcomes – suggesting that an underlying Hawthorn or Placebo effect may be operating in addition to any actual treatment effect. Indeed, whatever underlying efficacy may operating, the mechanism has not yet been clearly identified. In the discussion in this paper (and elsewhere) Rossignol et al cite a body of experimental evidence in order to establish the pathophysiology and biological plausibility of benefit using 24% oxygen at 1.3 ATA. However, the great majority of this work used much higher (and conventional) hyperbaric oxygen doses (100% oxygen above 2.0ATA) and in general cannot be convincing as an explanation of such low dose therapy as that employed in this report.

In fact, closer consideration of the two treatment regimens used suggests that this study has not utilized HBO_2T at all. The active arm is equivalent to using 31% oxygen at one atmosphere – that is, one does

not require a chamber to deliver this dose. Oxygen therapy alone may be responsible for the reported findings, there may be an effect of pressure itself, or there may be a participation effect of some kind rather than a true therapeutic benefit. Without further research – including an arm with around 31% of oxygen at 1ATA, we cannot be sure which is primarily responsible. Indeed, some of the participating sites were well above sea level - implying that the treatment effect may have been obtained with even lower absolute pressures than is being suggested.

Outcome analysis is a further area of concern for several reasons. First, a significant number of participants were not included in the ATEC scores 'due to an administrative error' at one centre. In fact, only 43 participants were included in this analysis – a loss of approximately 30%. Considering this represents one of six enrolling centers, some doubt must be cast on the integrity of the remaining data from that center.

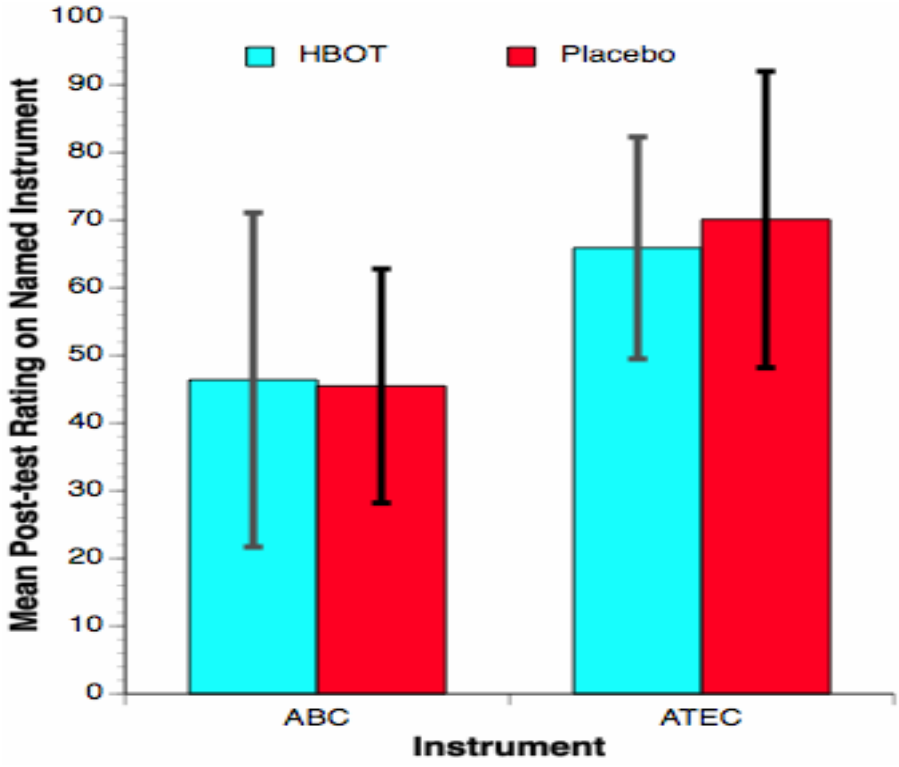

Figure 1. Comparison of actual score for ABC and ATEC after 40 treatment sessions. There are no significant differences. The authors quote the comparison between changes in each group instead. [Actual values for ABC: HBOT 46.4 ± 24.7 versus Control 45.5 ± 17.3 and for ATEC HBOT 65.9 ± 16.4 versus Control 70.1 ± 21.9]. (With thanks to John Lloyd).

Second, the authors have compared changes in scores between the groups over the treatment period as the main outcome, rather than a direct comparison between the groups after treatment. Any differences may therefore have more to do with a regression to the mean from a random difference in pre-therapy scores, rather than a treatment effect. This is illustrated when considering the outcomes in both ABC and ATEC if we compare the actual scores after therapy (Figure 1). The groups did not start in the same place, but are very similar at the post-therapy analysis. It is also true that the outcome is very short-term and we cannot know from this work how long any apparent improvements may persist.

Finally, we note that a great number of comparisons have been made on the data generated by this group of 62 patients, but there is no clear explanation of the approach made to adjusting the statistical significance levels to allow for multiple comparisons. For more detail on many of these points, we refer to an extensive series of comments and replies to the original report.

Cost of HBO_2T

The patient charge for providing HBO_2T is highly variable and in part dependent on the type of facility, presence or absence of physician supervision and the facility funding arrangements. The authors suggest each session is likely to be charged at between $40.00 and $60.00, giving a total for a 40 treatment course of $1,600.00 to $2,400.00. It is not clear how many treatments would be given over the long-term, and therefore the total cost to the family concerned is equally unclear. The authors report a greater proportion of participants receiving the active treatment improved 'very much' or 'much' on the physician-rated CGI (30% treatment versus 8% control). These proportions suggest we would need to treat 5 children in order to achieve one 'good outcome' than would be so without hyperbaric treatment. If we were to accept these figures, this suggest an initial expenditure of about $10,000 to achieve each extra positive outcome. Little data are available with which to compare this figure, and indeed, it is not clear that hyperbaric therapy would replace any other mode of therapy in ASD.

Conclusion

There are few data upon which to base firm conclusions regarding the use of HBO_2T for the treatment of ASD. Those data provided by the only RCT in the area (and most of the case series data) suggest there may be a benefit from the provision of low doses of oxygen – doses that do not require compression. Despite some speculation to the contrary, there is very little evidence to support an effect of pressure alone, or that oxygen has differing effects whether given by increasing the ambient pressure or increasing the inspired fraction.

While the RCT data are thought-provoking, some concerns remain about the methodology of this trial and the way in which the outcomes were analysed. As the authors themselves suggest, this work needs to be replicated by other groups before it could gain general acceptance. The UHMS recommends any further trials include an arm designed to deliver an increased fraction of oxygen at 1 ATA using a suitable sham protocol. Future trials should also incorporate outcomes that are not subjective in order to support the clinical findings as reported. This might include functional neuroimaging using SPECT or PET.

At this time, the UHMS cannot recommend the routine treatment of ASD with HBO_2T outside appropriate comparative research protocols. The UHMS is available to assist in the development and conduct of suitable studies of high methodological rigor in this area.

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