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Is Hyperbaric Oxygen Therapy an Effective Treatment for Autism? A Review

Daniel Dunleavy
Florida State University, Bthyer@mailer.fsu.edu

Bruce A. Thyer
Florida State University, Bthyer@fsu.edu

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Abstract

Objectives: We review outcome studies regarding the effectiveness of hyperbaric oxygen therapy (HBOT) for Autism Spectrum Disorders (ASD). **Method:** Studies were identified through electronic bibliographic databases and manual searches of article reference lists. **Results:** A total of 8 studies met eligibility criteria, consisting of three randomized controlled trials (RCTs), one quasi-experimental study involving a comparison group, two pre-experimental one-group pretest–posttest studies, and two single-system designs. Studies reviewed did not offer credible evidence to suggest that HBOT is an effective treatment for autism. **Conclusion:** It is premature to call HBOT an effective treatment for Autism and ASD. Individuals clinically treated with HBOT outside the context of a RCT should have the effects of the therapy evaluated using rigorous single-subject designs.

Keywords: Autism, Autism Spectrum Disorders, Autism Treatment, Hyperbaric Oxygen Therapy, HBOT

Is Hyperbaric Oxygen Therapy an Effective Treatment for Autism? A Review

Autism Spectrum Disorder (ASD) is a diagnostic label used to categorize individuals with persistent deficits in social communication and interaction and also with various forms of restricted and repetitive behavior (APA, American Psychiatric Association, 2013, pp. 50-59). Specific examples of these behaviors include the failure of back and forth communication, abnormal eye contact, a lack of facial expression, and an absence of interest in peers, among others. The prevalence of ASD remains constant and may even be rising, effecting an estimated 1% of the population (APA, 2013, p. 55). Males have been shown to be diagnosed with ASD more frequently than females, at a rate of 4.2:1 (Fombonne, 2009).

The etiology of autism remains unclear. Some have suggested a strong genetic component exists (Trottier, Srivastava, & Walker, 1999), but a definitive link to the disorder's development has not been established clinically or etiologically (Miles, 2011). Proponents of this view have relied primarily on research utilizing twin and family studies and/or molecular genetics, but these methods have been plagued by problematic assumptions (e.g. the equal-environment assumption) and a lack of replication (of autism-candidate genes) [For critiques of research utilizing twin and family studies, and on the genetic basis of psychiatric disorders, including autism, see Joseph, 2006, Ch. 7. on Autism]. Other etiological theories that are common yet remain unsupported, refuted, or unsettled include exposure to childhood vaccinations and mercury poisoning (Gerber & Offit, 2009; Wright, Pearce, Allgar, Miles, Whitton, Leon, Jardine, McCaffrey, Smith, Holbrook, Lewis, Goodall, & Alderson-Day, 2012; Geirer et al., 2008; Mrozek-Budzyn, Kieltyka, & Majewska, 2010; Roehr, 2013). Given the disorder's unknown etiology, the road towards treating it remains equally varied and unclear.

Treatments have ranged across the spectrum, from applied behavior analysis (ABA) (Rosenwasser & Axelrod, 2001) to dietary interventions such as a gluten-free/casein-free regimen (Elder, Shankar, Shuster, Theriaque, Burns, & Sherrill 2006), and the use of antipsychotics such as risperidone (Purdon, Lit, LaBelle, & Jones, 1994). New and novel treatments are continuously proposed, including hyperbaric oxygen therapy (HBOT).

Hyperbaric oxygen therapy is a treatment in which the patient breathes up to 100% oxygen in a pressurized environment. It is theorized that HBOT works by increasing atmospheric pressure, promoting the oxygenation of the blood via breathing this oxygen-enriched air, and thus blood flow and oxygenation in the brain is enhanced (Sharkey, 2000). Typically, treatments involve pressurization between 1.5 and 3.0 atmospheres absolute (ATA) for periods between 60 and 120 minutes, once or twice daily. However, there have been no clear HBOT treatment guidelines for autism.

Since finding success in treating decompression illness (Yarbough & Behnke, 1939), clinicians have proposed that HBOT could be a viable treatment for a wide variety of issues, including burns (Bilic et al., 2005), spinal cord injury (Asamoto, Suigiyama, Doi, Iida, Nagao, & Matsumoto, 2000), and other medical disorders (Gill & Bell, 2004). Rossignol and Rossignol (2006), two of the most active promoters of HBOT as a treatment for ASD, have suggested that autism is a neurodegenerative disorder, characterized by a lack of cerebral blood flow, neuroinflammation, and increased oxidative stress. They offered the following hypothesis on how hyperbaric therapy may alleviate some of the symptoms of autism:

> "HBOT helps overcome hypoperfusion, has potent anti-inflammatory effects and reduces oxidative stress. Furthermore, HBOT mobilizes stem cells from human bone marrow. Therefore, HBOT will improve symptoms of autism" (p. 217).

This view was supported by James Neubrander in his 2007 speech (Neubrander, 2007a) at the conference of the United States Autism and Asperger Association (USAAA), stating that "the following…*irrefutably demonstrates* from collective observations of over 250,000 treatment hours by my colleagues and me that hyperbaric oxygen therapy is a valuable treatment option for children with autism" (p. 1, emphasis added). He has also stated that in his clinic, "two of the most *powerful treatments* now commonly used for children on the autistic spectrum were discovered by accident - methylcobalamin (methyl-B12) and hyperbaric oxygen therapy. My presentation focuses on the use of oxygen under pressure as *a powerful treatment* modality for children on the spectrum...In my practice*, approximately 80% of children respond* to HBOT to some degree, especially if they continue their treatments....I have found that HBOT is a treatment, not a cure and continued treatment sets of sessions actually build upon any previous treatment sets of sessions therefore providing a cumulative beneficial effect..." (Neubrander, 2007b, p. 2).

Here is how one father of a boy treated with HBOT described the treatment, in a newspaper article:

> "HBOT's success is not only the ability to deliver more oxygen, but also to do so under pressure. More oxygen without the pressure, the body simply can't absorb it. That's because red blood cells, which transport oxygen throughout the body, are already doing so at capacity. Pressurization enables the blood plasma, which makes up more than half of blood, to deliver additional oxygen. For an autistic child, HBOT reactivates blood vessels in the brain that have ceased functioning and reduces brain inflammation. ...The Vitaeris 320...allows parent and child to enter the chamber together. Since it is a mild oxygen-enriched environment, a parent and child can go into the chamber for 1.5 to 2

> hours. Once under pressure they are stuck there until someone else turns off the machine and the pressure inside the HBOT is reduced to the pressure outside. Exiting the chamber prematurely puts the person at risk of rupturing his or her eardrums. It takes oxygen from the surrounding air, compresses it, and pumps it into the chamber where a mask can direct the oxygen to the child. There is a wireless alarm bell inside that allows a parent to signal to end the dive session. The user can bring toys and water inside. A viewing port allows a two-way visual communication (Grundvig, 2007, p. 1).

Each treatment session is said to cost between $250 and $1000. The claims that the brains of autistic youth suffer from a lack of oxygen is merely a hypothesis and thus far there is no evidence to support it. The optimistic view of HBOT as a treatment for ASD is not shared by all hyperbarists. Some researchers (Yildiz, Aktas, & Uzun, 2008; Kot & Mathieu, 2011) are calling for more empirical evidence of HBOTs effectiveness, before establishing it as a viable treatment for ASDs. This is a necessary step before professional healthcare workers can ethically recommend HBOT as a treatment option for ASD. Fortunately, over the past decade, research on HBOT as a treatment for autism has grown, with some researchers calling for its widespread use. We conducted the following review evaluating and synthesizing the results of all the available outcome studies published in English, in peer-reviewed journals, in order to help answer the question: is hyperbaric oxygen therapy an effective treatment for autism?

Method

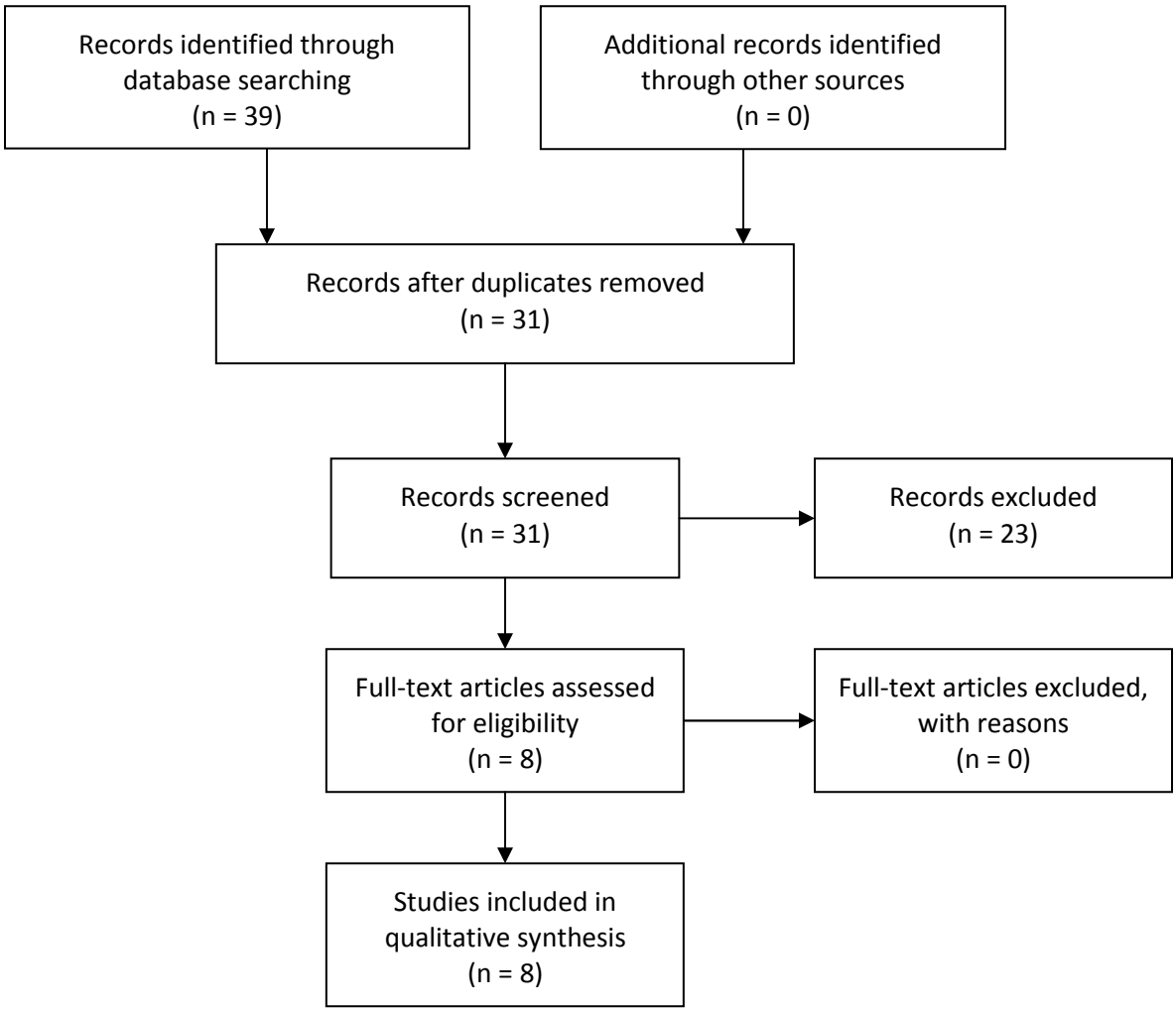
Electronic searches were used to identify relevant studies. Searches were made using the following bibliographic databases: *PubMed, ASSIA: Applied Social Sciences Index and Abstracts, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane*

Database of Systematic Reviews, PsycINFO, Social Services Abstracts, Database of Randomized Controlled Trials in Hyperbaric Medicine. Key words used in searching were: *Hyperbaric Oxygen Therapy, Oxygen Therapy, HBOT, Hyperbaric Oxygenation*, or *Atmospheric Pressure* AND *Autism* or *Autism Spectrum Disorder*. Located studies were initially screened based on their title and abstract. Studies were included if they met all of the following criteria: (a) a single-system, pre-experimental, quasi-experimental, or experimental design was used to evaluate outcomes, (b) the study arrived at an autism or ASD diagnosis based on the DSM-III, DSM-IV. DSM-IV-TR, Autism Diagnostic Observation Scale (ADOS), Autism Diagnosis Interview (ADI), Autism Diagnostic Interview-Revised (ADI-R), or other standardized instrument that assess Autism or ASD symptomology, and have no other severe clinical disorder (e.g. Fragile X syndrome, cerebral palsy) or have suffered traumatic brain injury, (c) the study used hyperbaric oxygen therapy as a treatment for symptoms of autism or ASDs, (d) the study reported empirical outcome measures on any of three behavioral domains (social interaction, communication, behavior), (e) the study was published in English, and (f) the study was published in a peer-reviewed journal. Studies were excluded if they did not report outcomes of treatment or provided only narrative or case reports. A search of the grey literature (conference papers, unpublished works, etc.) was not conducted. Hand searches were not performed, nor were attempts made to contact subject experts. Reference lists were searched for additional studies, but no studies meeting criteria were identified that had not been previously revealed through electronic searches. There were no year filters used during searches.

Based on this approach, 39 studies were initially identified. After removing 8 duplicates, 31 records were screened, applying the previously specified inclusion criteria. This resulted in the exclusion of 23 studies because they reported case reports or were not empirical studies. The

full-text of the 8 remaining articles was closely examined. All 8 studies are included in this review, consisting of three randomized-controlled trials (RCTs), one quasi-experimental study, two pre-experimental evaluations, and two single-system designs. A flow chart depicting the literature search process is displayed in Figure 1.

Figure 1. Flow Chart Depicting the Literature Search Process.



Results

Study Characteristics:

The studies reviewed included Rossignol et al. (2007), Chungpaibulpatana, Sumpatanarax, Thadakul, Chantharatreerat, Konkaew and Aroonlimsa (2008), Lerman, Sansbury, Hovanetz, Wolever, Garcia, O'Brien and Adedipe (2008), Granpeesheh, Tarbox, Dixon, Wilke, Allen and Bradstreet (2010), Rossignol et al. (2009), Bent, Bertoglio, Ashwood,, Nemeth, and Hendren (2012), Jepson et al. (2011) and Sampanthavivat, Singkhwa, Chaiyakul, Karoonyawanich and Ajpru, (2012). An overview of study characteristics is presented in Table 1.

Table 1: Features of Reviewed Studies

Experimental and Quasi-Experimental Designs

Study	Intervention	Study Population	Study Design	Outcomes	Results
Sampanthav -ivat et al. (2012)	Real (n = 28) versus Sham (n = 28) HBOT	Children aged 3-9 years, diagnosed with Autism	R O-X-O R O-X-O	ATEC, CGI. CGIS	Both groups improved equally, leading to the conclusion that HBOT is a placebo-based treatment.
Granpeesheh et al. (2008)	$HBOT_a$ (n=16) vs. sham placebo (n=18)	Children ages 2-14 w/Autistic Disorder.	R O-X-O R O-X-O	ABC, BRIEF, CGI, PSI, PPVT-III, RBS, SRS, VABS-II, VMI-5, & direct observation.	Nine participants saw improvement on ADOS classifications in both groups. No significant differences in scores were reported on any other outcome measures. Both groups improved the same degree over time.

Study	Intervention	Study Population	Study Design	Outcomes	Results
Rossignol et al. (2009)	$HBOT_a$ (n=33) vs. sham placebo (n=29)	Children ages 2-7 w/Autistic Disorder.	R O-X-O R O-X-O	ABC, ATEC, CGI	Significant improvement within the hyperbaric group was observed across the domains of overall functioning, receptive language, social interaction, eye contact, and sensory/cognitive awareness, compared to participants in the control condition.
Rossignol et al. (2007)	$HBOT_a$ (n=12) vs. $HBOT_b$ (n=6)	Children ages 3-16 w/Autistic Disorder.	O-X-O-O-O-O-O O-X-O-O-O-O-O	ABC-C, SRS, and ATEC	Improvements seen in both groups, across measures for irritability, social withdrawal, hyperactivity, motivation, speech, and sensory/cognitive awareness

a-24% oxygen at 1.3 ATA b-100% oxygen at 1.5ATA c-100% oxygen at 1.3 ATA d-88% oxygen at 1.3 ATA

Pre-Experimental Designs

Study	Intervention	Study Population	Study Design	Outcomes	Results
Bent et al. (2011)	$HBOT_b$ (n=10)	Children ages 3-8 w/ASD.	O-X-O-X-O	ABC, PDD-BI, PIA-CV, PPVT, SB-V, and SB-NW	Symptom improvement was seen in areas of the CGI-I, ABC, PDDBI, PIA-CV, PPVT. The Stanford-Binet however, did not corroborate these findings, showing no changes in non-verbal or verbal intelligence.

Study	Intervention	Study Population	Study Design	Outcomes	Results
Chungpaibulpatana et al. (2008)	$HBOT_c$ (n=7)	Children ages 5-9 w/ASD or Autistic Disorder.	O-X-O	*Social development, Fine motor and hand-eye coordination, Language development, Gross-motor development, Self-help skills	Improvements reported in 75% of participants. 25% of participants showed no improvement. 33.34% of children showed improved sleeping habits, improvement in cognitive abilities, improved social skills, and increased flexibility in terms of problem solving. Parents corroborated these gains.

a-24% oxygen at 1.3 ATA b-100% oxygen at 1.5ATA c-100% oxygen at 1.3 ATA d-88% oxygen at 1.3 ATA

*- did not disclose instruments used in assessing behavioral domains.

Single-System Designs

Study	Intervention	Study Population	Study Design	Outcomes	Results
Lerman et al. (2008)	$HBOT_d$ (n=3)	3 children, ages 6-7 w/ Autism.	A-B-A	Task engagement, spontaneous communication, problematic behavior	HBOT did not improve task engagement or decrease problematic behavior. Data on spontaneous communication showed improvement for one participant, but overall, no robust changes were found.
Jepson (2011)	$HBOT_a$ (n=16)	Children ages 3-10 w/ Autistic Disorder, PDD NOS, Asperger syndrome.	A-B-A-A-A	ABC-C, SRS, ATEC, ADOS, BRIEF, CGI, PSI, PPVT-III, RBS, VABS-II, VMI-5, the Expressive Vocabulary Test, PDDBI, and SB-5	No consistent effect across any class of behavior was seen, nor was there a clear change seen for any individual behavior.

a-24% oxygen at 1.3 ATA b-100% oxygen at 1.5ATA c-100% oxygen at 1.3 ATA d-88% oxygen at 1.3 ATA

Various assessment measures were used to measure both patient functioning and outcomes across several domains. While some studies reported biological measures, only behavioral instruments and measurements will be presented in this review, given that the diagnosis of autism is arrived at solely by reviewing behavioral indicators. Behavioral measures included the Aberrant Behavior Checklist-Community (ABC-C), the Social Responsiveness Scale (SRS), the Autism Treatment Evaluation Checklist (ATEC), the Autism Diagnostic Observation Schedule (ADOS), the Behavior Rating Inventory of Executive Functioning (BRIEF), the Clinical Global Impression Scale (CGI), the Parent Stress Index (PSI), Peabody Picture Vocabulary Rest (PPVT-III), the Repetitive Behavior Scale (RBS), the Vineland Adaptive Behavior Scales-Second Edition (VABS-II), the Beery-Buktenica Developmental Test of Visual-Motor Integration-5th Edition (VMI-5), the Expressive Vocabulary Test, the Pervasive Developmental Disorder Behavior Inventory (PDDBI), and the Stanford-Benet-IV IQ test.

One study (Lerman et al., 2008) directly observed and recorded behaviour across three primary domains: task engagement, spontaneous communication, and problem behavior. These domains were operationally defined before assessment of the intervention's possible effects. Chungpaibulpatana, Sumpatanarax, Thadakul, Chantharatreerat, Konkaew, & Aroonlimsa (2008) also reported pre- and post-test measures of social development, fine motor and eye-hand coordination, language development, gross motor development, and self-help skills, but did not report the measures used.

Study Outcomes:

Randomized-Controlled Trials

Granpeesheh et al. (2010). The Granpeesheh et al. (2010) study included 34 youth (ages 2-14) diagnosed with Autistic Disorder using DSM-IV criteria and corroborated with the ADOS.

These participants were recruited from a large community-based agency, which provided behavioral intervention services for children with ASDs. Originally, 46 children were recruited, but 12 were subsequently withdrawn from the study by their caregivers. The main reason for withdrawal was due to travel requirements for treatment. One of the 12 participants withdrew from the placebo group after having a seizure.

The 34 remaining participants were initially matched in pairs based on the amount of hours of behaviour-analytic treatment they had received up to the beginning of the study. These pairs were also matched based on age. Through use of a coin toss, pairs were randomly assigned to one of two groups, genuine hyperbaric oxygen therapy (n = 18) or placebo HBOT (n = 16). Both the hyperbaric therapy and the placebo consisted of 80 1-hour sessions in a HBOT chamber. Participants were to complete the 80 sessions within 15 weeks or less, with a range of 6-10 sessions in the hyperbaric chamber per week. The difference between the two conditions was that the HBOT group received 24% oxygen at 1.3 ATA, while the placebo group received free airflow through the chamber at ambient pressure. Investigators, assessors, and the patients' caregivers were blind to the clients' treatment condition.

Outcome measures included the ABC, BRIEF, CGI, PSI, PPVT-III, RBS, SRS, VABS-II, and VMI-5. The ASOD, BRIEF, PPVT-III, SRS, VABS, and VMI-5 were administered pre and post-treatment, while the ABC, CGI, and RBS were administered weekly. The PSI was administered four times, once at baseline, twice during the treatment phase, and once at the completion of the study. The authors also utilized direct observation, twice weekly, using standard functional analysis of "Toy Play." Trained observers collected data on toy play, hyperactivity, appropriate vocalizations, vocal stereotypy, physical stereotypy, and challenging behaviors. Observers were blind to assignment, and observational assessments were subject to

interobserver agreement (IOA) in at least 30% of observations for each participant. Mean agreement among observers was 80% or higher for each participant.

Both groups improved over time, but there were no differences in the degree of improvement between conditions, leading the authors to conclude that HBOT had no genuine therapeutic effect. This study strongly illustrates the need to compare the results obtained via real HBOT to a credible placebo treatment, preferably a blinded sham HBOT condition. Solely examining the results of patients treated with real HBOT may give the appearance of improvement attributable to the treatment, and give both clinicians and family members observing these "improvements" a false sense of therapeutic benefit. Thus uncontrolled studies may be virtually useless in determining the real effects of HBOT above and beyond placebo factors.

Rossignol et al. (2009). This Rossignol et al. study initially consisted of 62 participants (ages 2-7) who met DSM-IV criteria for autism, which was corroborated by the ADI-R and ADOS. Potential participants were excluded if they had met the criteria for Pervasive Developmental Disorder - Not Otherwise Specified (PDD-NOS), asperger syndrome, seizure disorder, current ear infection, uncontrolled asthma, Fragile X syndrome, had trouble equalizing ear pressure, or were receiving ongoing treatment using chelation therapy.

The 62 children were randomly assigned to one of two groups, HBOT (33 children) or "near-placebo" hyperbaric conditions (29 children). Both conditions provided 40 1-hour treatment sessions, twice daily, with a minimum of 4 hours between treatments. This was done for 5 days a week, for 4 consecutive weeks, totalling 40 treatments per participant. Hyperbaric treatment involved breathing 24% oxygen at 1.3 ATA. The placebo control condition involved breathing 21% oxygen at 1.03 ATA (e.g. near normal air). Four children in the HBOT group

dropped out of treatment, whereas three children dropped out of the control group. Of the HBOT dropouts, two were due to illness, one due to parental and child anxiety, and one due to worsening asthma symptoms. In the control condition, one child dropped out due to a family death, another due to travel commitments, and one due to parental claustrophobia. 29 children completed the study in the hyperbaric condition and 26 in the sham HBOT condition. Allocation was concealed to everyone involved (investigators, participants, parents, clinic staff, nursing staff, etc.), with the exception of the hyperbaric technician.

Outcome measures assessed change from baseline to post-treatment. The ABC, ATEC, and CGI scales were rated by parents or guardians and separately by the treating physician. Significant improvement within the hyperbaric group was observed across the domains of overall functioning, receptive language, social interaction, eye contact, and sensory/cognitive awareness, compared to participants in the placebo control condition. These positive results have been criticized by other researchers in the field. Bent et al. (2012) noted that while this study reported improvement on the CGI-I for participants in the hyperbaric condition, improvements in other outcome measures, such as the ABC scale, were not reported. Jepson et al. (2010) point out that statistically significant outcomes were found in the sensory/cognitive subscale of the ATEC, but not others. Likewise, it is pointed out that the ATEC has not been validated by the scientific community for use in this type of study. The Rossignol et al. (2009) study was also criticized for not collecting pre-treatment reports of the CGI, which prohibits pre-post effect ratings. Also, physicians did not complete the entire CGI, instead focusing on only one item of the instrument

Sampanthavivat et al. (2012) randomly assigned 60 Thai children with a diagnosis of Autism to 20 one-hour sessions of HBOT. The children were aged 3-9 years. The experimental group received 1.5 ATA with 100% oxygen for 20 one-hour sessions conducted over weekdays.

The placebo control group received sham HBOT, experiencing exactly the same procedures as did the experimental group, except they breathed a normal air mixture maintained at 1.15 ATA, a level of air pressure needed to keep the door to the chamber tightly closed and to convey sensations of increased pressure. Children were accompanied by a parent or other caregiver during their HBOT sessions. The primary outcome measures were the Autism Treatment Evaluation Checklist, and the Clinical Global Impression scale, given one-time pre and post-HBOT. Patients and their families did not know which treatment they were receiving, real HBOT or sham HBOT, and neither did the assessors. Thus the study was a double-blind trial. Initial outcome measure scores did not differ between the two groups pre-treatment. Post-treatment, the real HBOT group demonstrated statistically significant improvements on the outcome measures, but these were matched by similar improvements among the parents whose children received sham HBOT. The authors concluded that "HBOT conferred no benefit above that owing to a participation (or placebo) effect...Considerably more evidence is needed before accepting there is a true rationale to support the routine use of low-pressure hyperbaric treatment in order to improve behavior in children with autism...we cannot recommend the routine use of HBOT in this regard" (Sampanthavivat et al. 2013, p. 131, 131, 132).

Quasi-Experimental Designs

Rossignol et al. (2007). This study consisted of 18 participants (ages 3-16) diagnosed with autism by an independent mental health professional. Two groups of children were formed from the four girls and fourteen boys, using nonrandomized methods. One group (N = 12), 1 girl) received HBOT at 1.3 ATA and 24% oxygen, while the other group (N = 6, 3 girls) received HBOT at 1.5 ATA and 100% oxygen (e.g., two different forms of 'real' HBOT). Both groups

were given HBOT for 45 minutes a session, for 40 treatments per child. The group receiving 24% oxygen averaged 4.6 sessions per week over a 9-week period and the group receiving 100% oxygen averaged 4.7 treatments over an 8.8-week period. All 18 children were able to complete the 40 hyperbaric sessions.

Behavioral outcome measures included pre-treatment and post-treatment scores of the ABC-C, SRS, and ATEC. Parents or guardians, who were not blinded, filled out each scale prior to treatment, and after 10, 20, 30, and 40 treatment sessions. The authors reported improvements in both groups, across measures for irritability, social withdrawal, hyperactivity, motivation, speech, and sensory/cognitive awareness. The authors note, however, that this data is limited by a lack of assessor blinding, a lack of placebo or control group, non-random assignment to conditions, and the possibility that chance or natural development of the children influenced the outcomes.

Pre-Experimental Designs

Bent et al. (2012). This Bent et al. study examined the effects of HBOT on one group of 10 children, recruited from an outpatient autism clinic. The children ranged in age from 3 to 8 years, and had a DSM-IV diagnosis of ASD, corroborated by the ADOS and the SCW.

Treatment consisted of all participants receiving HBOT at 1.5 ATA and 100% oxygen. Participants received a total of 80 treatment sessions over the course of 20 weeks. 40 treatment sessions were given over the course of 8 weeks, followed by a 4-week break, followed by another 40 treatment sessions over an 8 week period. Children were assessed pre-treatment, after 40 days, and after 80 days of treatment. Outcome measures used included the ABC, PDD-BI, PIA-CV, PPVT, SB-V, and SB-NW. Guardians completed the ABC and PDDBI. Clinicians rated and scored the CGI-I, based on parent interviews and direct clinical observation. The

authors reported marked improvement in symptoms for parent-reported measures. Symptom improvement was seen in areas of the CGI-I related to imitation, eye contact, language, eczema, gastrointestinal problems, and severity/frequency of tantrums. Scores on the ABC showed improvement in irritability, lethargy, hyperactivity, and total score. The PDDBI showed statistically significant improvements across three of ten subscales. The PIA-CV showed improvement in terms of language, intelligence, while the PPVT showed improvement in receptive vocabulary. The Stanford-Binet however, did not corroborate these findings, showing no changes in non-verbal or verbal intelligence. The authors caution that these outcomes relied heavily on parent reported measures, and that reporting may be influenced by parental bias or the placebo effect. Due to the small sample size, weak methodology (being a one group, pre-test post-test design lacking any comparison groups), and reliance on parent reported outcomes, it is not possible to definitively say whether HBOT was responsible for any improvements reported at the conclusion of treatment.

Chungpaibulpatana et al. (2008). This study examined the effects of HBOT on seven Thai children (ages 5-9) who had a DSM diagnosis of ASD or Autistic Disorder. Treatment involved HBOT at 1.3ATA and 100% oxygen given once a week for 10 weeks. Assessment measures were taken pre and post-treatment.

The study measured changes across five domains: 1) Social development, 2) Fine motor and hand-eye coordination, 3) Language development, 4) Gross-motor development, and 5) Self-help skills. Scales used in assessment were not disclosed. The authors reported statistically significant improvements across all five domains with 75% of participants having positive outcomes and 25% not improving. 33.34% of children showed improved sleeping habits, improvement in cognitive abilities, improved social skills, and increased flexibility in terms of

problem solving. These gains were corroborated by parents, but the findings are limited in several ways. First, the study lacked a comparison or no-treatment group, which prevents the authors from concluding that HBOT was responsible for the changes witnessed in the children. Second, subjective responses from children and parents may have been influenced by the placebo effect or by reporting bias. Lastly, the clinical significance of the data cannot be determined due to the study's small sample size and the authors' limited description of outcome measures.

Single-System Designs

Lerman et al. (2008). This study examined the effects of HBOT given to three children diagnosed with Autism. The participants were two 6-year-old boys and one 7-year-old girl. HBOT was given in 60-minute sessions, for a total of 40 sessions, at 88% oxygen and 1.3 ATA. Ultimately, the two boys completed 40 sessions of treatment and the girl completed 27 sessions before stopping due to the development of an unrelated eye infection.

A non-concurrent multiple-baseline design across participants was utilized for the study. The first participant was measured at baseline for a minimum of 20 days before treatment. The second participant received treatment after 40 days of baseline and the third received treatment after 60 days.

Participants were videotaped three times a week, during 10-minute instructional session given at the center. Data software was utilized to score child and therapist responses, by observers who were blind to the study's purpose and to the timing of the intervention. Participant behavior was measured in terms of the frequency of unprompted task engagement and the frequency of spontaneous communication and problem behavior. The results suggest that HBOT did not improve task engagement or decrease problematic behavior. Data on spontaneous communication was inconclusive (with one participant showing improvement for this measure),

but overall, no clinically meaningful behavioral improvements were found. A strength of this study is that detailed and reliable measures of the children's functioning were repeatedly assessed before and after the use of HBOT. To the extent that HBOT is claimed to yield improvements in behavior among youth with autism, this hypothesis was falsified in this intensive study.

Jepson et al. (2011). This study directly observed the behaviors of 16 children (ages 3-10) diagnosed with Autistic Disorder, PDD NOS, or Asperger's syndrome. Participants were assessed prior to treatment using the ADOS, the Wechsler Preschool and Primary Intelligence-III or the Wechsler Abbreviated Scale of Intelligence, the Vineland Adaptive Behavior Scale-II, and the ABC.

This study used a non-concurrent multiple-baseline design, across participants. Treatment consisted of 40 sessions of HBOT at 24% oxygen and 1.3 ATA, for 60 minutes, conducted over an average of 8 weeks. Participants were followed up at 2 weeks after the last HBOT session and at the 3-month mark, for observational play sessions. These sessions were used to gather data across 11 operationally defined behaviors.

The behavioral observations results were recorded in three classes: 1) adaptive behavior (vocal initiations, physical initiations, vocal response, and physical response), 2) stereotypy (vocal and physical stereotypy), and 3) aberrant behavior (rate of aggression, self-injurious behavior, tantrums, and disruption). The authors concluded: "Multiple topographies of behavior were measured under carefully controlled conditions and no consistent effects (positive or negative) were observed. Based on these results, there is no compelling evidence to suggest that HBOT, delivered at 24% oxygen and 1.3 ATA, is an effective treatment modality for the core behavior symptoms of Autism" *(Jepson et al., 2011, p. 583).*

Discussion

Of the eight studies included in this review, four (Granpeesheh et al., 2010; Bent et al., 2012; Lerman et al., 2008; Jepson et al., 2011) suggested that HBOT might not be an effective treatment for the behavioral symptoms of Autism and ASDs. The remaining three studies (Rossignol et al., 2009; Rossignol et al., 2007; Chungpaibulpa et al., 2008) suggested that HBOT might help decrease some behavioral symptoms associated with Autism and ASDS. The data gathered from these eight studies is limited by small sample sizes (214 total participants), a lack of rigorous study designs, a reliance on parent-rated assessments, and a lack of comparison, placebo, and no-treatment groups. These limitations could be remedied through the use of a large, multi-armed, double-blinded randomized control trial that compares different types of hyperbaric treatment with placebo and no treatment conditions. While this has been attempted by Granpeesheh et al. and Rossignol et al. (2009), several issues have risen. Granpeesheh et al. were lacking a no-treatment group and relied heavily on parent-rated assessments, which left open the possibility of parental bias. The Rossignol study also relied heavily on these assessments and has been criticized by other hyperbaric researchers (Bent et al.; Jepson et al.) for faulty data interpretation and usage.

It remains to be seen if hyperbaric therapy can alleviate some of the symptoms of autism. The three strongest designs to date, Lerman et al., (2008), Jepson et al. (2011) and Sampanthavivat et al. (2013), suggest that it does not. The current evidence reviewed does not support hyperbaric oxygen therapy as an effective treatment for autism or Autism Spectrum Disorders. Clinicians have the responsibility to offer safe as well as empirically supported treatments. Currently, it is premature to call HBOT an efficacious treatment and the available evidence suggests that the limited positive changes following its application are most

parsimoniously explained as placebo effects. Support of more rigorous trials, especially large-scale RCTs, with valid control and comparison groups, and proper blinding and assessment tools, are required before HBOT can be recommended as an option for those with autism and ASD. Persons who receive HBOT as a clinical treatment, outside of the context of a well-designed RCT, should have the effects of their therapy carefully evaluated using an experimental single subject research design.

We note the principles enunciated in the American Medical Association's Code of Ethics, reading:

"The following general guidelines are offered to serve physicians when they are called upon to decide among treatments:

(1) Treatments which have no medical indication and offer no possible benefit to the patient *should not be used*.

(2) *Treatments which have been determined scientifically to be invalid should not be used*

(4) Among the various treatments that are scientifically valid, medically indicated, legal, and offer a reasonable chance of benefit for patients, the decision of which treatment to use should be made between the physician and patient." (American Medical Association's Code of Ethics, downloaded from http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics.page? on 27 March 2013, emphases added)

Individuals and families seeking accurate and up-to-date information about the scientific status of various therapies for autism may consult a summary of the evidence on these treatments to be found at http://www.asatonline.org/treatment/treatments_desc, a website maintained by the

Association for Science in Autism Treatment, as well as Offit (2010) and Thyer & Pignotti (2010). Until better evidence accrues through carefully controlled evaluations, individuals with Autistic Spectrum Disorders should not be subjected to expensive sessions of HBOT.

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*Refers to included studies