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Evolution and Preliminary Testing of a Hyperoxic Therapy for Autism Spectrum Disorders

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Abstract

The diagnosis of autism spectrum disorders (ASD) comprises a range of developmental disabilities, the established prevalence of which has been increasing globally. Despite decades of research, however, ASD is still not well understood and a generally accepted intervention or group of interventions which consistently and comprehensively address the spectrum of needs has not yet been identified or developed. Thus, in seeking a solution to their children's conditions, some parents have felt compelled to try complementary and alternative medical treatments.

One such intervention that has attracted some advocates is off-label hyperbaric oxygen therapy. In examining the data for this application, we were struck by the wide range of oxygen partial pressures reported to have benefit and the fact that many could be easily provided at normobaric pressure. As we knew of no reason for the use of increased pressure in treating ASD with hyperoxic therapy, we determined to find out if benefits could be obtained from such treatments at normal atmospheric pressure.

A pilot study with five cases involving preteens and teenagers with autism was conducted using a normobaric form of hyperoxic treatment we have called Microbaric® Oxygen Therapy (MBO_2). All five cases benefitted, three remarkably so. Improvements were across the full range of symptoms of autism, and no regression was reported on cessation of treatment or during follow up for as long as six years. Thus, it appears that the outcomes of MBO_2 for autism are permanent. As a consequence of this pilot study, it would seem imperative to conduct controlled research to confirm our findings. Should similar outcomes be obtained, then MBO_2 would offer a new, cost-effective, and time efficient way forward as a stand-alone therapy or as an adjunct to other therapies in the treatment of autism.

Keywords: Normobaric; Hyperbaric; Microbaric; Oxygen; Hyperoxic; Autism

Abbreviations: ATA: Atmosphere Absolute (atmospheric pressure at sea level); PiO_2: Pressure of Inspired Oxygen; PEEP: Positive End Expired Pressure; FRC: Functional Residual Capacity.

Introduction

The diagnosis of autism spectrum disorders (ASD) comprises a range of developmental disabilities, the established prevalence of which has been increasing globally. In 2017, the World Health Organization (WHO) estimated the worldwide prevalence of autism to be 1 in 160 but advised this was an average figure and varied widely between studies [1]. This WHO estimate is consistent with the median global prevalence of 62 in 10,000 (i.e., 1 in 161.3) provided by Elsabbagh and colleagues in 2012 [2]. In the US, the 2018 report from the CDC Autism and Developmental Disabilities Monitoring (ADDM) Network indicates the estimated prevalence of ASD among 8 year old children increased from 1 in 150 (0.67%) during 2000-2002 to 16.8 per 1,000 (1 in 59/1.69%) in 2014 with prevalence reaching nearly 3% in some communities [3]. This increase, it seems, is the result of several contributing factors including diagnostic consolidation and improved diagnostic recognition as well as a very real growth in the incidence of this condition [4-6].

The etiology of ASD is not well understood, and it is considered incurable. It is recognized to be a neurodevelopmental condition, however, characterized by difficulties in communication, social interaction, stereotypical and repetitive behaviours, and cognitive delays usually affecting more than one region of the brain [7,8]. The existence of underlying morphological and physiological abnormalities in the autism brain was first recognized about 60 years ago, and it is now generally acknowledged to be a biological disorder that impacts not only the brain but also the immune system, gastrointestinal tract, and other organ systems [9-23].

Some of those afflicted with autism may overcome it and lead relatively normal lives, perhaps as few as 5%, though this figure may have increased with the more recent advances in diagnosis bringing about the identification of less severe cases. Others with autism, however, are incapable of supporting and even caring for themselves over their lifetimes. As ASD does not affect lifespan directly, it can place a great burden on the families of those afflicted, and eventually on governments [24]. In the United States, for example, when those with autism who are incapable of supporting themselves reach the age of majority, they are entitled to Supplemental Security Income (SSI) with Medicaid health benefits [25]. Consequently, autism can be an increasing burden on society as a whole.

In 2014, British economists Buescher, Cidav, Knapp, and Mandell estimated that the overall cost of autism in the United States could be as high as US$262 billion annually [26]. This amount was equivalent to 1.56% of the entire gross domestic product (GDP) of the U.S. in 2013 (i.e., $16.69 trillion), the approximate time frame the economic analysis applied to, and equivalent to almost 34% of the total U.S. Government outlay for CMS (Medicare and Medicaid) for FY 2013 [27,28].

As the recent wave of children diagnosed with autism gets older,

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costs will continue to increase even if prevalence does not. Thus, without improvements in prevention and/or case management, it is not inconceivable that the annual cost of ASD in the U.S. could grow significantly beyond the estimate of Buescher and associates. The worst-case estimate of American economists Leigh and Du, for instance, exceeds an annual cost of one trillion dollars for as early as 2025 [29]. To put this amount into perspective, it is equivalent to 3.8% of the entire U.S. gross domestic product projected for the year 2025 (i.e., $26.595 trillion) [30]. Despite the rapid growth in the prevalence of ASD and its huge financial impact, a generally accepted intervention or group of interventions which consistently and comprehensively address the spectrum of needs of most individuals with autism in a cost-effective and time-efficient manner has not yet been identified or developed. This includes behavioural interventions such as applied behaviour analysis (ABA) which at present seems the most recognized and common form of treatment [31].

As a consequence, when parents first discover that their child has an autism spectrum disorder, they encounter a variety of interventions [32]. Which of these they choose is undoubtedly influenced by the biases of the professionals they consult, what is provided by their local government or covered by their health insurance, and/or what they can afford to pay privately. In reality, however, no particular intervention comes with any assurance that it will be successful. When the interventions tried do not achieve the desired objectives, parents ultimately may be faced with a decision as to whether or not to employ psychotropic drugs to suppress specific undesirable behaviours developing in a difficult-to-control child [33]. Many opt for this "solution" as the child ages. A review of psychotropic drug use (i.e., one or more such pharmaceuticals) found that for 47 studies conducted from 1976 to 2012 including more than 300,000 individuals with autism, the median for the overall group was 45.7%; the median for children was 41.9%; the median for adults was 61.5% [34]. Other parents, at least some of whom are concerned about the potential side effects of psychotropic drugs, may have interest in one or more complementary and alternative medicines (CAM). One such intervention that has attracted some advocates among professionals, support groups, and parents of children with autism is off-label hyperbaric oxygen therapy (HBO_2).

Treatment of Autism with Hyperbaric Oxygen Therapy

HBO_2 is a process in which the patient breathes oxygen or a gas mixture with an increased concentration of oxygen while inside a whole body chamber at a pressure greater than that of the normal atmosphere. It is a well-established clinical modality employed around the world to treat medical conditions involving gas phase pathology and conditions where impaired oxygen availability, uptake, and/or utilization, are recognized as factors affecting the response to treatment. Primary indications for use include decompression sickness, arterial gas embolism, and acute carbon monoxide poisoning. Adjunctive indications range from use in combination with surgery and antibiotics in the acute phase of clostridial myonecrosis (gas gangrene) to chronic, refractory arterial insufficiencies such as delayed effects of radiation injury (soft tissue and bony necrosis) and diabetic wounds of the lower extremity.

Conventional clinical hyperbaric oxygen therapy is administered in hard-shelled monoplace (single occupant) or multiplace (multiple occupants) chambers at pressures up to 3 ATA (303.975 kPa) (Figures 1 and 2). Another form which is only used for off-label applications is called mild hyperbaric oxygen therapy ($mHBO_2$). This involves the breathing of a hyperoxic gas, a gas having a partial pressure of oxygen greater than that of air at normal atmospheric pressure (i.e., 0.2095 atm). For $mHBO_2$, the oxygen concentration is usually 24% produced by the output of a small oxygen concentrator mixed with air in an inflatable, zippered bag which encompasses the whole body at a pressure of 1.3 ATA (131.723 kPa) (Figure 3).

With respect to the treatment of ASD with any form of hyperbaric oxygen therapy, research is inconclusive [35,36]. This would seem to be, at least in part, because effective control data are lacking. This latter deficiency is the result of practical issues related to the conduct of sham treatments which must be done in whole body chambers at increased atmospheric pressure in order to blind the subjects effectively. Because of this and safety considerations for the control subjects, such sham treatments end up providing a hyperoxic gas to breathe, though not to the same oxygen pressure as the hyperbaric oxygen treatments. When control subjects breathe air at 1.3 ATA (131.723 kPa), for example, which is a common sham condition for hyperbaric oxygen research, the inspired oxygen would be slightly greater than 27% sea level equivalent. Such hyperoxic sham treatments increase plasma oxygen by at least 50% and have produced results as good as or better

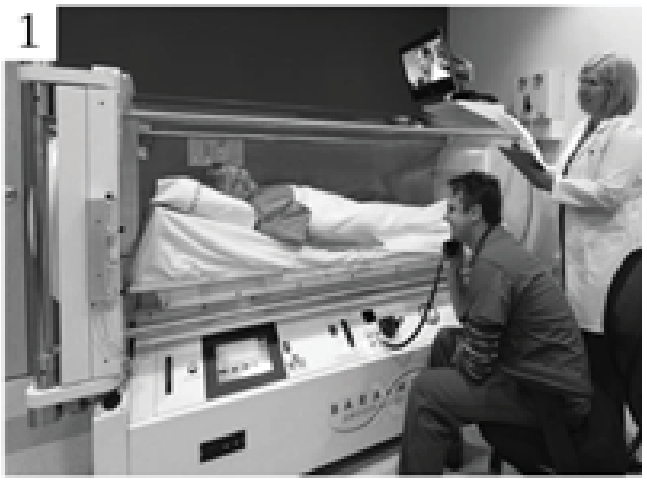

Figure 1: Clinical monoplace hyperbaric oxygen chamber (Courtesy of ETC, Southampton, PA, USA)

Figure 2: Clinical multiplace hyperbaric oxygen chamber (Courtesy of Fink Engineering, Warana, Queensland, Australia).

Figure 3: "Mild" hyperbaric oxygen chamber (Courtesy of Atlanta Hyperbaric Center, Smyrna, GA, USA).

than those achieved with hyperbaric oxygen therapy in the conduct of research on several neurological applications including stroke, cerebral palsy, autism spectrum disorder, and traumatic brain injury [37-44]. Invariably in such situations, the investigators have judged that hyperbaric oxygen is not effective since it was no better than their intended sham treatments. In view of the known sensitivity of the brain and central nervous system to even small changes in oxygenation, with such results, it can be difficult to determine whether or not the control condition is an effective placebo or, in fact, a treatment in its own right.

An alternative to such hyperoxic sham treatments from the research design standpoint would be to use a breathing gas with an inspired oxygen pressure (PiO2) at the sham treatment pressure which would be the same as breathing air (20.95% O_2) at normobaric pressure (i.e., sea level). At 1.3 ATA (131.723 kPa), this would require the use of a gas with an oxygen concentration just over 16%. Such a gas would be notably hypoxic if it had to be breathed at normobaric pressure. Consequently, its use would present unacceptable risks for subjects and is considered unethical.

Thus, so far as we are aware, no government healthcare regulatory authority such as the FDA or Health Canada has recognized hyperbaric oxygen therapy as an efficacious and safe treatment for autism spectrum disorders. The FDA, in fact, has issued guidance notices advising consumers that the FDA has not recognized HBO_2 for a number of off-label conditions for which it is widely promoted by free-standing (i.e., not hospital-based) clinics and purveyors of mild hyperbaric oxygen chambers [45,46]. The conditions listed include ASD. Despite this, there is considerable encouraging research data concerning the application of HBO_2 and $mHBO_2$ to ASD. Consequently, we wanted to reexamine the data for HBO_2 treatments of ASD, but from a different perspective than had been done previously. This was to take the contrarian view by assuming that all hyperbaric treatments producing better results than no treatments at all, whether test or sham, are effective. This has led to some interesting possibilities.

Analysis of Experience

Since the first case reports of treating autism with hyperbaric oxygen therapy in the mid to late 1990s, ten studies of this modality for autism that we are aware of have been reported with a total of 294 treated subjects (Table 1) [47,48]. These have involved both conventional hyperbaric oxygen therapy and mild hyperbaric oxygen therapy. Two of the studies included in Table 1 utilized both HBO_2 and $mHBO_2$. A total of 12 results are, therefore, included in the table. Hyperbaric oxygen therapy has been utilized in five studies where 100% oxygen was breathed in clinical whole-body chambers at a pressure 1.5 times that of normal atmospheric pressure (i.e., 1.5 ATA (151.988 kPa)) and in one study where 100% oxygen was breathed in a whole-body clinical chamber at a pressure 1.3 times that of normal atmospheric pressure (i.e., 1.3 ATA (131.723 kPa)) [43,49-53]. All six of these studies, involving 180 subject children, reported that HBO_2 provided benefits in comparison to no HBO_2.

Mild hyperbaric oxygen therapy has been utilized in six studies. Four of these, involving 80 subject children, have reported outcomes superior to no mild hyperbaric oxygen treatments [43,50-55]. The remaining two studies involving 34 subject children reported no benefit from $mHBO_2$ [56,57]. In one study, air was administered at 1.15 ATA (116.524 kPa) as a sham treatment for oxygen administered at 1.5 ATA (151.988 kPa). These two groups have been included with the $mHBO_2$ and HBO_2 studies listed in Table 1 and discussed above, respectively. Because the hyperbaric oxygen treatment, though producing results significantly better than no treatments at all, was no more effective than the supposed sham treatment, it was concluded by the investigators that the benefits achieved were not due to the hyperoxic therapy. Since both these outcomes were significantly better than no treatments at all, however, they are considered to be positive in our analysis of these data.

In examining the results of these hyperbaric oxygen therapy studies for ASD, we were struck by the fact that the PiO_2s of the $mHBO_2$ treatments and one sham treatment at increased pressure were very much lower than the PiO_2s of the HBO_2 treatments, but still seemed to produce largely comparable benefits when administered to children with ASD. These lower oxygen pressures, and even considerably higher ones, can be administered at normal atmospheric (i.e., normobaric) pressure without the use of a whole-body chamber. Since we could neither think of nor find any rationale in the scientific literature for the necessity of increased pressure to treat ASD with hyperoxic therapy, we decided to find out if benefits could be obtained without any increase in pressure. If this were to be the case, hyperoxic treatments could be delivered without the inherent cost, complexity, and safety concerns that are associated with the use of increased treatment pressures and whole-body chambers of any sort.

Test Cases of Microbaric® Oxygen Therapy for ASD

To determine if hyperoxic therapy administered at normobaric pressure without a whole-body chamber has potential for the treatment of autism and therefore warrants further, more rigorous investigation, we conducted a pilot study with five male preteens and teenagers recruited through personal contacts. Upon determination that these individuals met our criteria for participation in the study and their parents formally agreed to it, the subjects received courses of what we have called "Microbaric® Oxygen Therapy" (MBO_2) (The term, microbaric, is derived from the very small positive pressure in the gas delivery system against which the patient exhales).

The qualifications for participation in this pilot study were minimal. They consisted of diagnosis of ASD by a healthcare professional; an age from 6 to 18 years, inclusive; not taking any drug that might reduce oxygen tolerance or interact with oxygen to produce a potentially harmful effect; not taking any psychotropic agent that might mask changes resulting from the therapy. Information for determining subject qualification was obtained during a meeting with the children's parents and/or from a detailed case history, also provided by the

Published studies of hyperoxic therapy for autism spectrum disorders. Treatments include hyperbaric oxygen therapy (HBO_2), mild hyperbaric oxygen therapy ($mHBO_2$), and untreated control subjects (CONT). Treatment results (Tx RESULT) reflect the overall outcome of treatments with respect to producing change in the ASD, either positive (+) or negative (-). The specified result does not necessarily apply to all results in the study. Control subjects are not included in the result total.

STUDY	PUB.	Tx	TREATMENT CONDITIONS			NUMBER OF SUBJECTS		
AUTHORS	YEAR	RESULT	PiO_2 (ATM)	P (ATA)	FiO_2 (%)	$mHBO_2$	HBO_2	CONT
Rossignol, Rossignol [54]	2006	+	0.364-0.390	1.3	28.0-30.0	6		
Rossignol, Rossignol [50]	2007	+	0.312	1.3	24	12		
Rossignol, Rossignol [55]	2009	+	0.312	1.3	24	33		29
Granpeesheh, Tarbox, et al. [56]	2010	-	0.312	1.3	24	18		26
Jepson, Granpeesheh, et al. [57]	2011	-	0.312	1.3	24	16		16
Sampanthavivat, et al. [43]	2012	+	0.241	1.15	21	29		
Rossignol, Rossignol, et al. [50]	2007	+	1.5	1.5	100		6	
Chungpaibulpatana, et al. [53]	2008	+	1.3	1.3	100		7	
Kinaci, Kinaci, Alan, Elbuken [49]	2009	+	1.5	1.5	100		108	
Bent, Bertoglio, Ashwood, et al. [51]	2012	+	1.5	1.5	100		10	
Sampanthavivat, et al. [43]	2012	+	1.5	1.5	100		29	
El-Baz, Elhossiny, Azeem, Girgis [52]	2014	+	1.5	1.5	100		20	
TOTALS		260/-34				114	180	71

Table 1: Results of studies of hyperbaric hyperoxic therapy for autism spectrum disorders.

parents. During the first meeting with the parents, we also reviewed an informed consent document which included a release to use data gathered on an anonymous basis. On receipt of the signed informed consent and a physician's prescription for the therapy gas, a supply of oxygen was arranged with a licensed home respiratory care company.

The agreement made with families who participated in the trial was that Microbaric® Oxygen Systems would provide and maintain the equipment free of charge while the family would pay for the oxygen (i.e., monthly cylinder rental and periodic oxygen refills) at a cost of approximately $400 per month. As the cost of oxygen was not reimbursable in any way, this approach provided us with a high level of confidence that the family would terminate the program if MBO_2 showed no benefit.

In order to monitor what changes might occur in our subjects over the course of treatment and subsequent follow-up period; we selected the Autism Treatment Evaluation Checklist (ATEC). The ATEC was developed by Bernard Rimland and Stephen M. Edelson of the Autism Research Institute to provide a valid monitoring tool specific to autism spectrum disorders that is sensitive-to-change and easy-to-complete by parents, caregivers, and other non-professionals [58]. It has been in use as a measure of changes in autism severity since 1999 and is freely available with scoring on the Internet.

The ATEC is divided into four categories or subscales and together, these produce a total score. The subscales are:

(a) Speech, language, and communication

(b) Sociability

(c) Sensory and cognitive awareness

(d) Health, physical, and behaviour

For all scores, the higher the value, the more severe the autism. The highest total score possible is 179. A total score over 104 is considered to be severely autistic, and a total score of 30 or less is considered to be mildly autistic.

Validity of the ATEC is considered to be high, and its results consistently match subjective reports and the results of other measures that evaluate specific characteristics. Several studies provide valuable insight for assessing the accuracy of data obtained with the ATEC [59-63]. In brief, though not without issues, the ATEC seems to provide what its developers intended, an easy-to-administer, sensitive-to-change, and valid monitoring tool specific to autism spectrum disorders [64].

Before the oxygen and therapy equipment were delivered and set up, parent-rated baseline ATEC assessments were conducted on each subject in order to establish severity level and any trend for change over time. Following commencement of treatment, ATEC assessments were conducted, by the same parent, which in each case was the mother, and submitted every 2-3 weeks to monitor progress. In addition to submitting regular ATEC reports, the mothers were requested to provide a brief review of the period between reports. On occasion, these reviews gave us valuable insight into how the family dynamic, and the mothers themselves, were affected as the treatments brought about change in their children. Monitoring continued periodically during the follow-up period for Subjects 1, 2, 3, and 4. Subject 5 was lost to follow up.

The breathing systems provided for MBO_2 were assembled with FDA 510(k) cleared equipment used in accordance with the indications for use statements mandated by the 510(k) process. The system comprised three main elements, a Sea-Long Medical Systems breathing hood, liquid oxygen storage cylinders approved for home use, and an interface panel. The liquid oxygen storage cylinders were joined by a manifold connected to the inlet side of the interface panel. A breathing circuit was formed using large bore anaesthesia tubing that delivered a continuous flow of fresh oxygen from the interface panel to the breathing hood and returned exhaust gas to the interface panel. The flow of breathing gas through the hood was monitored and regulated on the interface panel with an adjustable rotameter, and an analog gauge indicated pressure in the breathing hood in real time. This ensured that:

(a) The hood remained inflated throughout the respiratory cycle;

(b) A continuous supply of fresh breathing gas was flowing into the hood;

(c) Carbon dioxide (CO_2) and moisture in the expired gas was continuously carried away, thus limiting any build-up in the hood.

In order to prevent build-up of oxygen in the treatment area, the exhaust gas from the interface panel was routed into a hose and vented to the outside of the building as shown in Figure 7. The equipment was set up to allow the child free range of movement within an area defined by the mother (eg: the family room). As the hood readily transmitted sound and provided good visibility, the children could continue with their normal activities while taking daily treatments (Figures 4-6).

Treatments were typically conducted once a day, five days a week, for sixty minutes. These treatments were easily incorporated into the families' homes and daily schedules, and readily adapted to within several days by the children with autism. All five cases treated produced some degree of positive outcome, and three outcomes (i.e., those for Subjects 1, 2, and 4) were particularly noteworthy. A summary of all of these results is given below.

Subjects 1 and 2

Subjects 1 and 2 were brothers in a family with four children, all boys, and their parents. Subject 2 was the oldest child and Subject 1 was the second oldest.

Subject 1

Subject 1 was formally diagnosed as having an autism spectrum disorder at three years of age. At seven, he was given a course of 20, one-hour hyperbaric oxygen treatments administered twice daily over a two week period in a typical clinical hyperbaric chamber. These treatments were considered beneficial by his parents, they "woke him up." No formal assessment of Subject 1's status was made in conjunction with the hyperbaric oxygen therapy, however.

Over the six-month period before MBO_2 was commenced in November 2010 when he was 12½ years old, Subject 1's mother reported that he was in a declining state. He was depressed and defiant about everything. He would not go outside and had no tolerance of the sun. He had become pale, gray, and skinny. His appetite was non-existent. He kept the blinds in his room closed and answered, "No" to everything. Subject 1's average baseline total ATEC score at the outset of MBO_2 was approximately 101, just short of severely autistic (i.e., >104).

During MBO_2, Subject 1's total ATEC score and subscale ATEC scores declined dramatically, and he continued to improve following cessation of routine therapy after about 1½ years (i.e., 550 days).

Figure 4: Home schooling with mother during MBO_2.

Figure 5: Working with therapist during MBO_2.

Figure 6: Watching TV during MBO_2.

His lowest total ATEC score was 7 achieved on two occasions, both around the end of therapy. In terms of standard deviations of his own baseline ATEC scores, Subject 1's total score improved by a factor of almost 10 (i.e., 9.94). In practical terms, Subject 1's mother reported that he became a totally different child and part of a totally different family dynamic than had been the case previously. He is now much more communicative and social; seeks out interaction with his siblings, which he did not do at all before; enjoys being outdoors, and is grasping more mature concepts such as money.

Subject 2

Subject 2's mother reported that he first exhibited developmental abnormalities at the age of four. At that time, he was diagnosed as having attention deficit disorder. Further regression with the onset of irrational fears and demands occurred, however, and development of mental and social maturity slowed dramatically. He was diagnosed as having Asperger's syndrome when he was eight.

Figure 7: Liquid cylinder oxygen supply and interface panel with exhaust line to outside the house.

In the period leading up to the commencement of MBO_2, Subject 2 is reported to have had a very rough time through puberty and was "wired" constantly, staying awake easily for 36 hours at a time. Like his younger brother with autism, he was depressed and defiant about everything. In addition, when he did not get his way, Subject 2 would go into a rage, lose control, and physically strike out at his parents, siblings, and even his grandmother. A psychiatrist was consulted and prescribed an antidepressant drug.

After about three months when this drug was at its ultimate effectiveness, Subject 2's rages were even more severe. His parents abruptly terminated the antidepressant drug against the psychiatrist's advice and also rejected the latter's recommendation that they begin giving Subject 2 risperidone, an antipsychotic agent primarily used to treat schizophrenia and bipolar disorder as well as irritability in people with autism. After this, Subject 2's rages subsided to their former, unsatisfactory state. As he was still prone to uncontrolled rage and violence, his parents were seriously considering institutionalizing him.

Subject 2 was within several weeks of 14 years old when MBO_2 was commenced. His average baseline total ATEC score at that point was approximately 82. As with his younger brother, Subject 2's total ATEC score and subscale ATEC scores declined significantly during the approximately 1½-year course of therapy (Figure 9). His lowest total ATEC score was 2 achieved once during the follow-up period. His mother also reported total ATEC scores of 4 on five occasions, the first at the end of therapy. In terms of standard deviations of his own baseline ATEC scores, Subject 2's total score improved by a factor of almost 12 (i.e., 11.99). In practical terms, Subject 2 is reported to have calmed dramatically, having no further attacks of rage after about six months of MBO_2. He also started to mature. Spontaneously and unbidden, he threw out his juvenile toys and, for the first time, did not request a toy for his birthday geared to a child of a younger chronological age.

Subjects 1 and 2

In summary, both Subjects 1 and 2 made dramatic progress in all ATEC subcategories during their course of MBO_2. This was not only to their benefit, but as noted by their mother, took an incredible burden off her as the primary caregiver and created a totally different and much happier family environment. This change was brought about when the only interventions were MBO_2 and longstanding dietary control and supplementation. With regard to the latter, their mother said, "*vitamins and fish oil would have worked a decade ago if that were the magic bullet*."

After ceasing regular MBO_2, their mother also reported that Subjects 1 and 2 continued to progress. The younger, more severely autistic brother (Subject 1) is shown in Figure 10 having spontaneously outfitted himself as a circus ringmaster. His mother's caption to this picture was, "*autistic kids have no imaginative play*." Among other things, Subject 1 now tunes into and participates in family discussions, routinely plays interactive games with his brothers, and has overcome a number of phobias. The older, initially violent brother (i.e., Subject 2) went from facing institutionalization to helping his father with projects around the house and taking responsibility for lawn care (Figure 11). Encouraged by this, the parents purchased a working farm so their autistic sons will have a safe place to live and work in the future while contributing to their own support. On this farm, the oldest brother (Subject 2) plows the fields on a tractor and performs other chores (Figure 12). His parents hope that he will be able to get an automobile driver's license in due course. Also, Subject 2 has become so reliable and caring for all of his siblings that his parents consider it a possibility that he will become the guardian for Subject 1 when they can no longer be responsible for him. Such post-therapy progress makes it seem as if their courses of MBO_2 had, in effect, enabled the two boys to restart the behavioral and cognitive development that autism had interrupted when they were much younger.

Subject 3

Subject 3 was 17 months old when it was determined that he had an autism spectrum disorder. When 7 years old, he was given a course of mild hyperbaric oxygen therapy which involved being sealed in a soft "chamber," a pressure-resistant, reinforced-fabric bag, and breathing oxygen-enriched gas at increased pressure (i.e., 1.3 atmospheres absolute). These treatments were started in a physician's office and then continued with an $mHBO_2$ chamber located in the family home. The treatments were given for two hours a day, five or six days per week for three months. Then, two months were taken off, and the same cycle repeated. Over the course of about two-and-one-half years, some 900 hours of treatments were administered. Though no rating scale or other formal measure was utilized to assess Subject 3's progress during this course of therapy, his mother noted improved sleep, eating habits, and eye contact which did not regress following cessation of this therapy. As time went on, however, his mother states that Subject 3 "seemed to hit a standstill on progress in all areas, socialization, academics, and language." Thus, she sought a new therapy and was brought into contact with us. Subject 3 was 10 years old when MBO_2 was initiated. At that point, his average baseline total ATEC score was approximately 62.

As shown in Figure 13, Subject 3's total ATEC score declined to a low of 37 during the course of MBO_2 and subjective reports on Subject 3's health and behaviour correlated with this. In terms of standard deviations of his own baseline ATEC scores, Subject 3's total score improved by a factor of over 1 (i.e., 1.21). Relative to the other subjects, this is not a large value, and its size is significantly influenced by a large standard deviation for the pre-therapy mean ATEC score. As Subject 3's mother had a very heavy business travel schedule, only two pre-treatment sets of ATEC scores were obtained.

After approximately five months, however, Subject 3's improvement seemed to plateau, and after about six months (i.e., 185 days), MBO_2 was halted by his mother. About four and one-half months following cessation of MBO_2, his mother noted that Subject 3 had not regressed

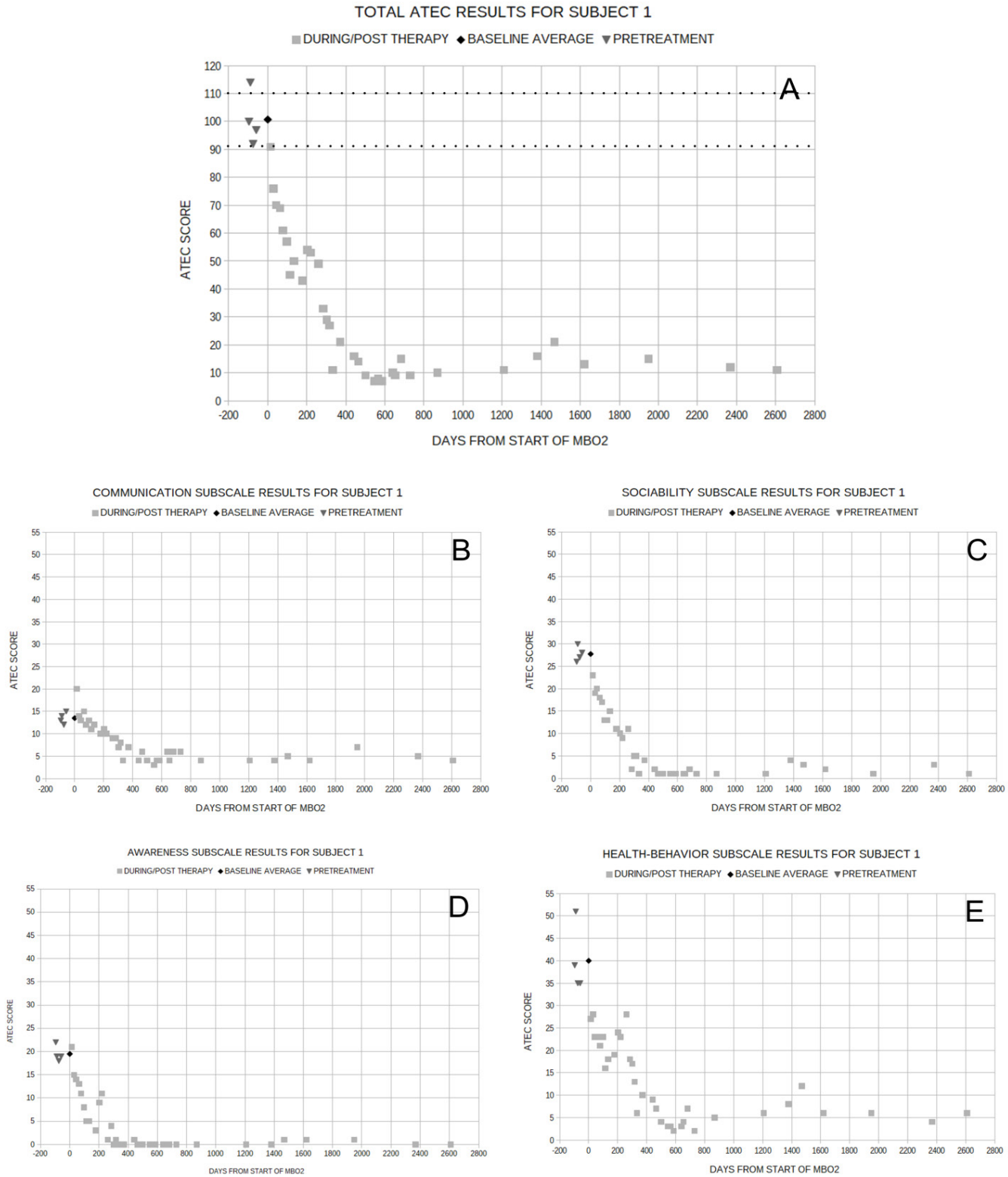

Figure 8: ATEC results for Subject 1 during baseline, treatment, and follow-up periods. A-Total score; B-Communication subscale score; C-Sociability subscale score; D-Awareness subscale score; E-Health Behavior subscale score. Horizontal dotted lines on Graph A are plus and minus one standard deviation from average baseline total ATEC score.

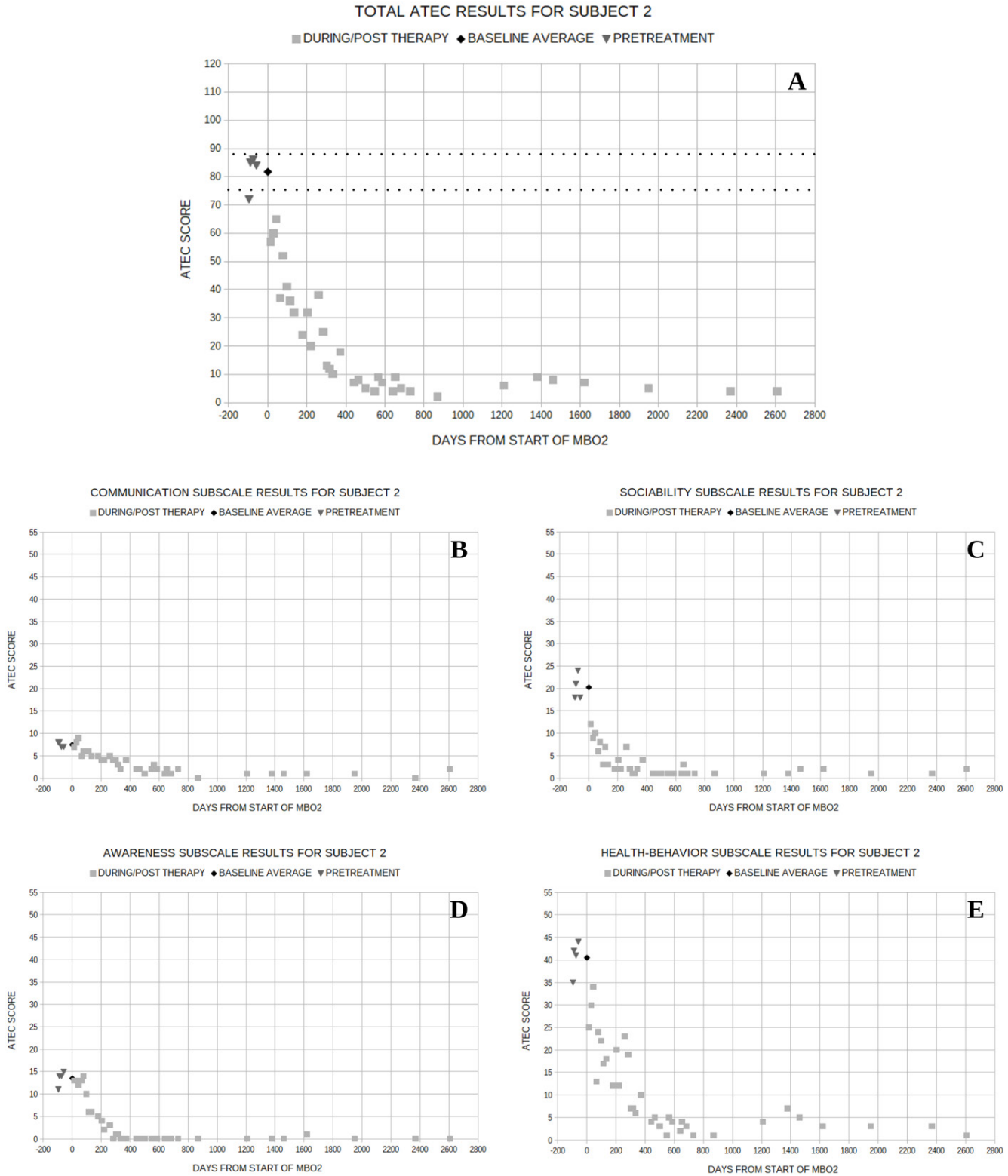

Figure 9: ATEC results for Subject 2 during baseline, treatment, and follow-up periods. A-Total score; B-Communication subscale score; C-Sociability subscale score; D-Awareness subscale score; E-Health Behavior subscale score. Horizontal dotted lines on Graph A are plus and minus one standard deviation from average baseline total ATEC score.

Figure 10: Subject 1 dressed as ringmaster.

Figure 11: Subject 2 mows family lawn at 16½.

Figure 12: Subject 2 driving tractor to plow field of family farm at 19½.

subjectively from the improvements made in focus, concentration during academic tasks, and reduction in aggressive behavior, and eye contact during the course of MBO_2. Additional follow-up reports given at about nine months and eighteen months following cessation of MBO_2 indicated that the advances made during Subject 3's course of MBO_2 had been retained and that at the time of the last report, no new intervention had been started.

Subject 4

Subject 4 was 2½ years old when he was diagnosed as having autism. Over the course of time, he had a number of interventions. These included applied behavior analysis (ABA) for thirty hours per week when he was four years old; a variation of ABA, verbal behavior, when he was 5 to 6; relationship development intervention (RDI); speech therapy from 4 to 10 years old; food supplements and vitamins. His mother felt that ABA and verbal behavior benefited Subject 4's academic efforts, but bored him; that the RDI was beneficial in Subject 4's relating to others and involvement in "real life." From a communication standpoint, prior to MBO_2, Subject 4 could sign about ten requests; had a very small vocabulary of basic words which he used in a slurred, quiet voice; shook his head, yes or no, in response to questions; looked at something he wanted, raised his eyebrows to request it, and then looked at his mother for her response.

When he started MBO_2, Subject 4 was 12 years old, and his average total ATEC score was approximately 113, a severely autistic and disabled child, not only in terms of ATEC classification but also practical terms. The only other interventions Subject 4 was getting at that time were vitamins and food supplements. Over his course of MBO_2, however, he made dramatic strides as evidenced by his ATEC results and the subjective reports of his mother. He had a total ATEC score of 60 near the end of therapy and then again during the follow-up period. His lowest total score was 58 reported about 1½ years into the follow-up period (Figure 14). In terms of standard deviations of his baseline ATEC scores, Subject 4's total score improved by a factor of almost 16 (i.e., 15.96).

At the outset of treatment with MBO_2, Subject 4's parents were uncertain if the initial significant drop in his total ATEC score and the changes in his behavior were the result of the treatment or simply imagined because of their own intense desire for him to improve. This doubt continued through about 40 treatments. At that point, the changes in Subject 4 were so marked that a woman in their church and a neighbor both commented spontaneously on his improved behavior. Together with their own observations, this led his parents to finally conclude the changes must be real.

Among firsts that ensued following commencement of MBO_2, Subject 4 gave his mother a spontaneous kiss which he had never done before; in one week, cooperated completely in getting a haircut, a medical examination, and a dental checkup with his teeth cleaned. In no case had Subject 4 cooperated during any such visits before, and in regards to the dental appointment, this was the first time he had not needed to be sedated or restrained by several adults in order for the dentist to complete his work.

After the initiation of MBO_2, Subject 4 showed awareness of conversations between his parents and acted on what was being said without direction to do so. He also sought to play with other children whom he did not know. Needless to say, the life of Subject 4's family changed dramatically over his course of MBO_2.

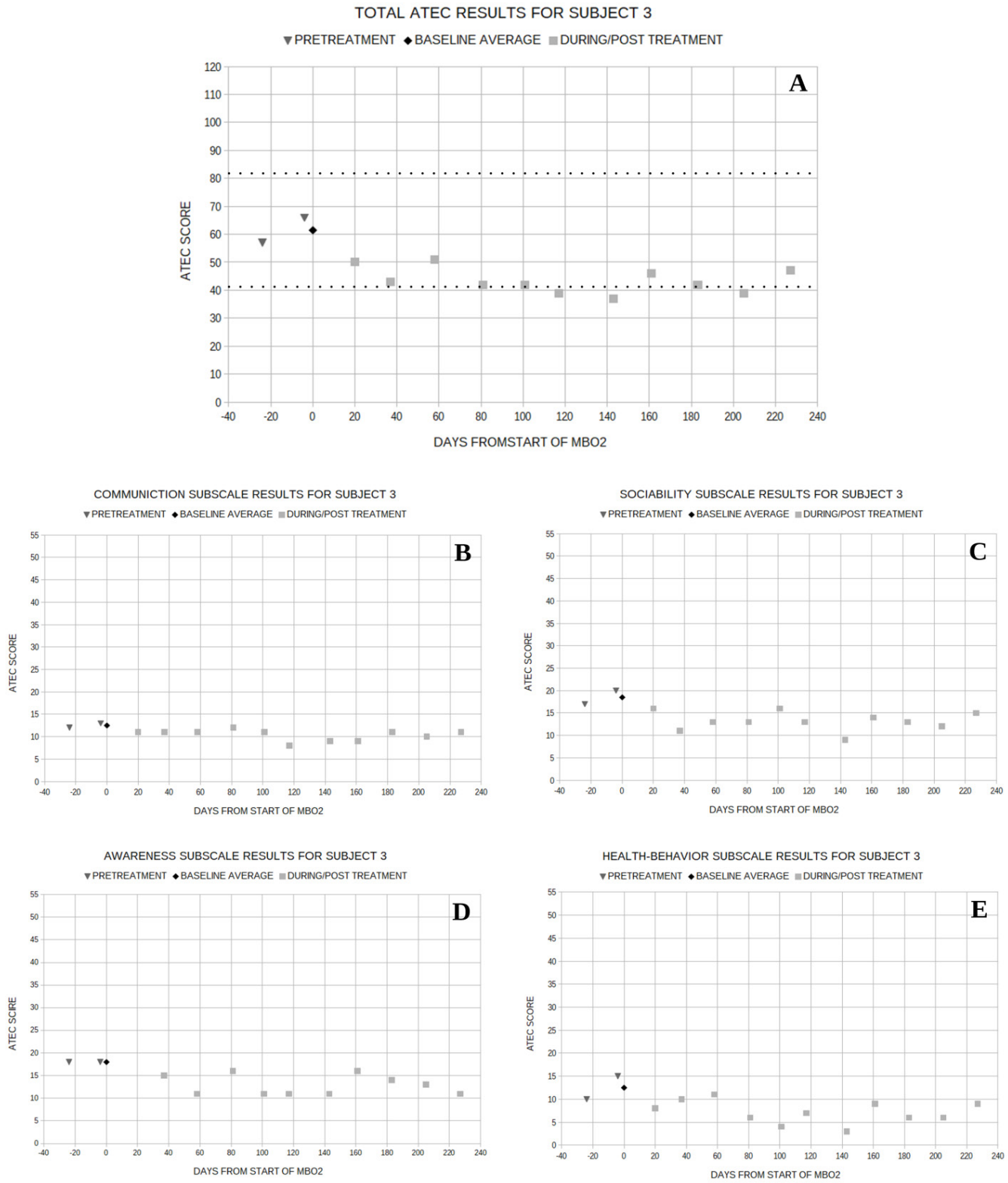

Figure 13: ATEC results for Subject 3 during baseline and treatment periods. A-Total score; B-Communication subscale score; C-Sociability subscale score; D-Awareness subscale score; E-Health-Behavior subscale score. Horizontal dotted lines on Graph A are plus and minus one standard deviation from average baseline total ATEC score.

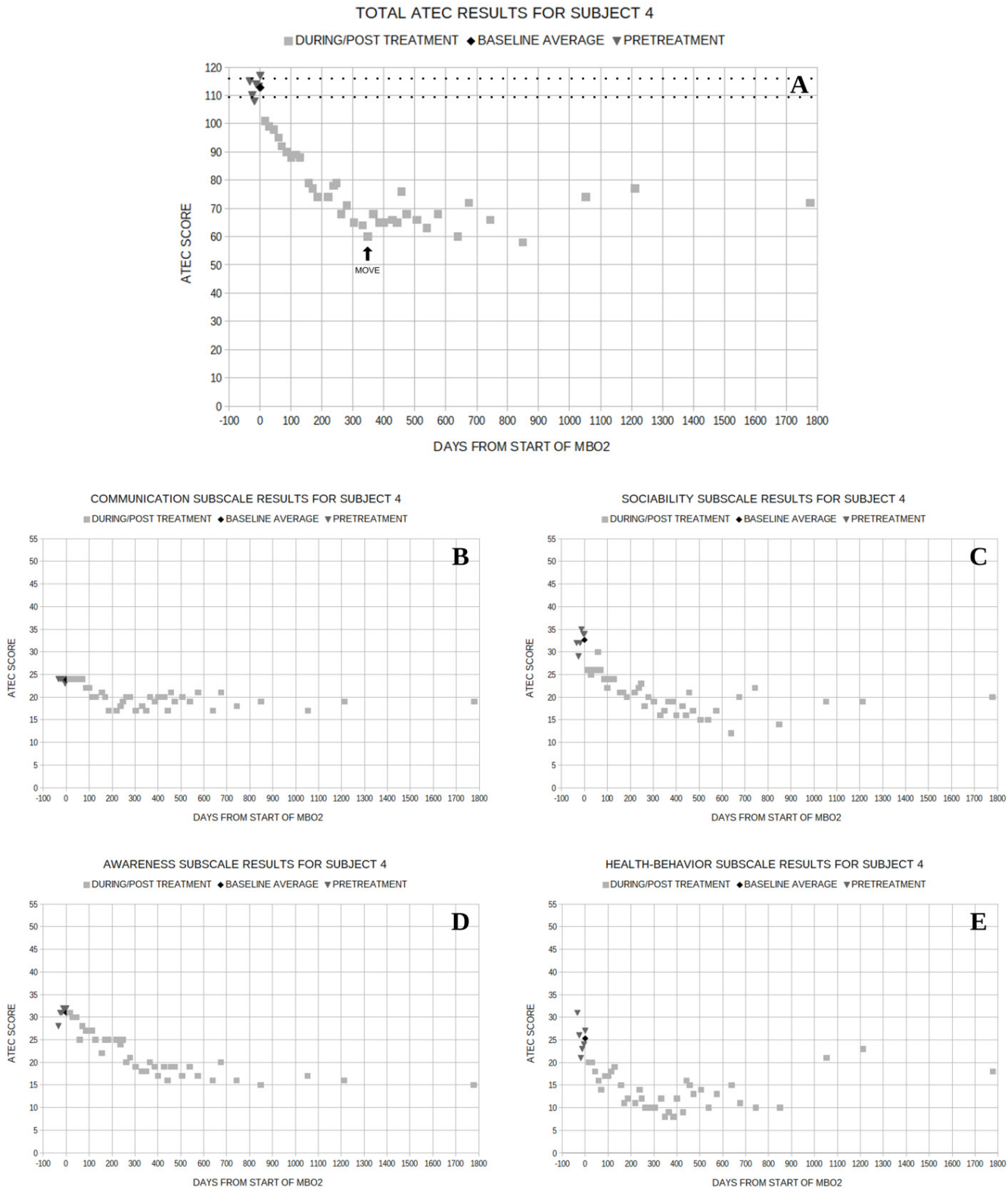

Figure 14: ATEC results for Subject 4 during baseline, treatment, and follow-up periods. A-Total score; B-Communication subscale score; C-Sociability subscale score; D-Awareness subscale score; E-Health-Behavior subscale score. Treatment was terminated at the time of the move at approximately 350 days. Horizontal dotted lines on Graph A are plus and minus one standard deviation from average baseline total ATEC score.

At the end of about one year (i.e., 350 days) of therapy, however, the family moved to a different state and an irregular living situation over the next year and then other constraints prevented them from restarting MBO_2. Despite this, Subject 4's ATEC scores and behavior did not deteriorate during the next two years and then, after he reached puberty, only in the health-behavior subscale results over the next 23 months.

Subject 5

Subject 5 was diagnosed with Asperger's syndrome and severe social anxiety in kindergarten. This diagnosis progressed over time to PDD-NOS and then high functioning autism. He developed GI symptoms in the eighth grade. A number of therapies were tried after his diagnoses with limited success. These included group social therapy, working with behavioral therapists, and a gluten free/casein free diet with no preservatives or additives. A six-month course of Lexapro prescribed by a psychiatrist eliminated panic attacks, and removing dairy products as part of a Vegan diet he personally desired to start also seemed to help. Subject 5 had also received occupational and physical therapy, and speech therapy, the latter for 12 years.

At the start of his course of MBO_2, Subject 5 was a high-functioning 18-year-old with good verbal communication skills. The only interventions he was receiving for autism at that time were vitamins and food supplements. He had significantly lower starting ATEC scores than any of the other subjects we worked with (i.e., average of approximately 43) and was attending a regular school. Despite there being relatively little room for improvement in comparison to our other cases, we had special interest in Subject 5 because of his relatively advanced age at the outset of therapy. His parents were advised before MBO_2 began that because of their son's low baseline scores, changes produced by MBO_2, if any, were likely to be subtle and, thus, difficult to recognize on a day-to-day basis.

Other than a number of ATEC results prior to and during therapy, there was little information forthcoming from the parents after we received Subject 5's case history, and treatments were terminated rather quickly by his mother (i.e., after about 3 months) because she felt no benefits were being achieved. Contrary to the mother's subjective view, however, the total ATEC scores she had rated and reported showed a steady decline following commencement of MBO_2 ending with a final total score of 28 (Figure 15A), a reduction of over 3 standard deviations from his average baseline score in a period of just 2½ months. As indicated by the ATEC subscale scores, this improvement came from the sociability and health-behavior subscales (Figure 15).

Summary of Results from this MBO_2 Study

Outcomes

In these five case studies, MBO_2 would appear to have been responsible for dramatically attenuating or eliminating challenging behaviors in three subjects (i.e., Subjects 1, 2, and 4), and improving symptoms in the other two (i.e., Subjects 3 and 5).

In the three most notable outcomes (i.e., Subjects 1, 2, and 4), quality of life for both the subjects and their families was markedly improved, and produced more positive long-term outlooks for the afflicted children. These improvements were across the full range of symptoms of ASD and have persisted with further gradual improvements and no deterioration, other than in Subject 4's behavior upon reaching puberty, for 6 years, 6 years, and 4 years, respectively.

In one case (i.e., Subject 2), the therapy outcome included elimination of extreme violence which was accomplished in approximately six months without the use of psychotropic drugs and their attendant side effects. Thus, Subject 2 progressed from facing institutionalization because of his uncontrollable violence to becoming a reliable and productive member of his family and capable of taking on responsibilities that will aid him in caring for not only himself, independently, but perhaps for others as well.

Of the two remaining cases, one (i.e., Subject 3) improved initially, but then reached a plateau after about 5 months and made no further advances. We believe that the prior lengthy course of $mHBO_2$ this subject completed about one year before commencing MBO_2 may have been a relevant factor in this outcome. Follow-up for approximately 18 months after cessation of therapy indicated that the advances made during MBO_2 were retained.

The final case (i.e., Subject 5) involved only about 3 months of MBO_2. Nevertheless, distinct though apparently subtle benefits appeared to be developing in those behaviors and conditions in which the subject was most affected.

Durations of courses of treatments in this study varied significantly, ranging from approximately 18 months for Subjects 1 and 2 to 3 months for Subject 5. Subject 4 received almost 12 months of MBO_2 before his family's move brought it to a close, and Subject 3 received about 6 months of therapy. Thus, the absolute changes in ATEC scores were directly related to treatment duration. While this relationship seems entirely logical, it is worth noting that the time frames involved in these cases were in keeping with those suggested by Efrati and associates for hyperoxia induced brain regeneration and angiogenesis in cerebral palsy [65]. In view of the apparent permanence of changes occurring with MBO_2 in ASD, it may be that the same sorts of biological processes are involved in these treatments.

As a final point, with the uncontrolled nature of this pilot study, the question of whether or not the outcomes achieved would have occurred without MBO_2 is a relevant one. In this study, however, it would seem highly unlikely that the consistent nature of changes reported in all five subjects would have occurred spontaneously without MBO_2.

Before the commencement of MBO_2, there was no indication of improvement in any of the five subjects. This was true for both their baseline ATEC scores which had no downward (i.e., improving) trend and the reports of their parents. When administration of MBO_2 was commenced, however, there was a distinct coincidental downward progression in the ATEC results for all of the subjects together with concomitant reports of improvement in the accompanying subjective observations received from the mothers of Subjects 1, 2, 3, and 4. While Subject 3 was receiving in-home ABA therapy before and during his course MBO_2, none of the other four subjects had concurrent interventions with MBO_2 other than the long-term taking of vitamins and food supplements. As indicated in the case summary above, this caused the mother of Subjects 1 and 2 to observe that if vitamins and fish oil were the solution to her son's autism; their outcomes would have been achieved a decade earlier. With Subject 4, not only did the onset of improvement coincide with the commencement of MBO_2, but when the hyperoxic therapy was terminated after about a year because of a family move, the distinct downward trend in his ATEC scores abruptly levelled out (Figure 14).

Safety, Practicality, and Follow-on Research

Safety of therapy

Before commencing this study, we considered four main elements related to the delivery of therapy in our effort to ensure the safety of

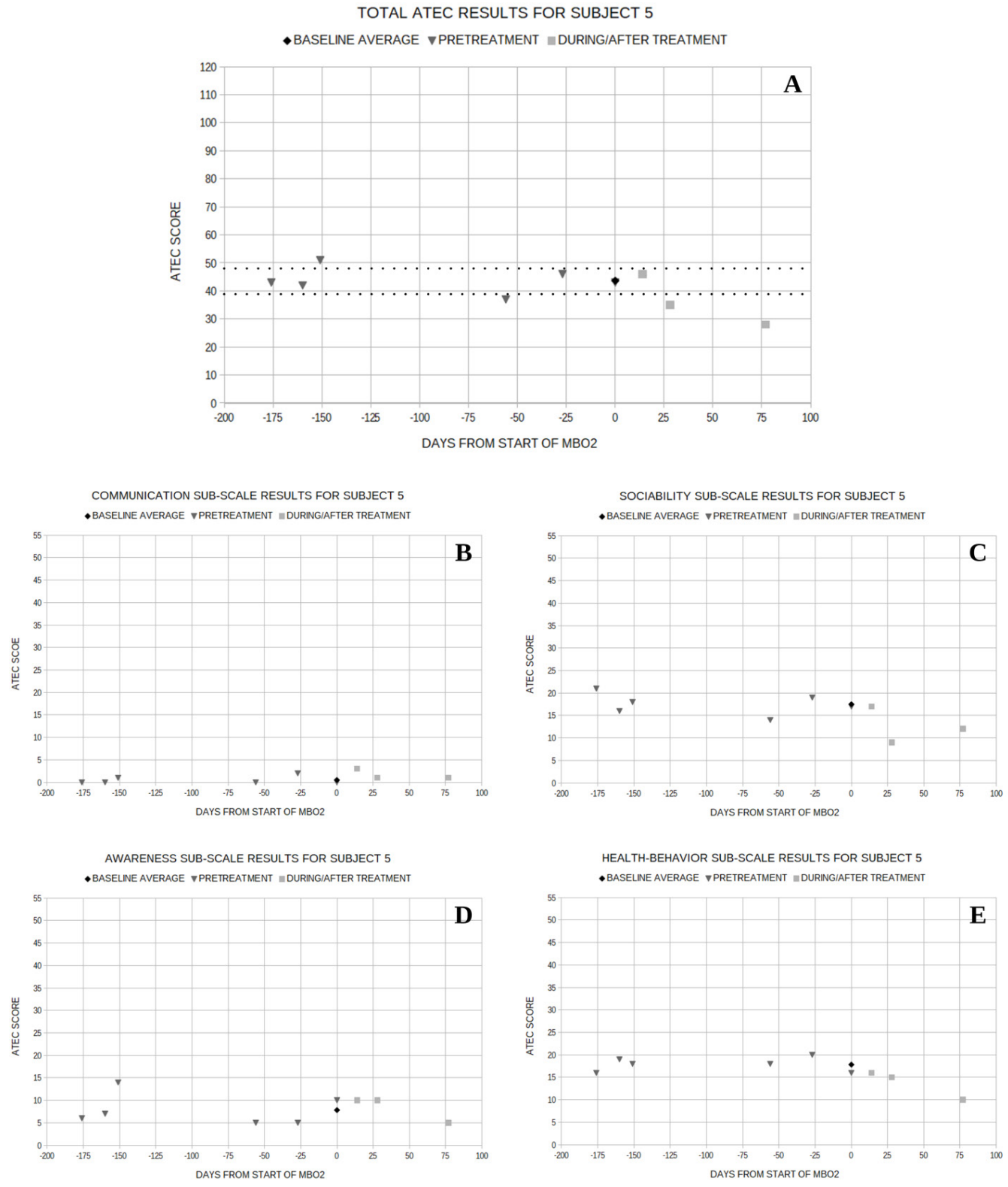

Figure 15: ATEC results for Subject 5 during baseline and treatment periods. A-Total score; B-Communication subscale score; C-Sociability subscale score; D-Awareness subscale score; E-Health-Behavior subscale score. Horizontal dotted lines on Graph A are plus and minus one standard deviation from average baseline total ATEC score.

MBO_2. These were atelectasis, middle ear barotrauma, fire safety, and issues related to breathing in enclosed spaces. During the course of this study, the five subjects received therapy using equipment located in their homes and delivered by their mothers totalling approximately 5 man-years. During this time, there were no significant technical problems or adverse events other than one report of dry eyes in the first week of Subject 4's therapy. For this, the family physician advised his mother to administer eye drops and no further problems were reported.

Atelectasis

From a general physiological safety standpoint, a known complication of oxygen breathing is absorption atelectasis. It occurs when a portion of the lung collapses as a result of absorption of oxygen, carbon dioxide, and water vapor from alveoli with obstructed or restricted gas flow [66]. While this is normally only seen as a complication during recovery from general anesthesia and thoracic and abdominal surgery, one case has been reported in hyperbaric oxygen therapy administered in a study of this modality for stroke [38]. Because absorption atelectasis has been so uncommon in HBO_2, no special measures are routinely taken to prevent its occurrence. While it is improbable that absorption atelectasis would occur in active children breathing hyperoxic gases in the course of MBO_2, we nonetheless mitigated this recognized risk of oxygen breathing by establishing a 7.5 cm H_2O backpressure in the hood with an FDA-cleared PEEP valve located in the interface panel on the exhaust side of the breathing circuit. Research has shown that exhaling against such a pressure increases the functional residual capacity (FRC) of the lungs sufficiently to prevent atelectasis in high-risk cases [67].

Middle ear barotrauma

With hyperbaric oxygen therapy, middle ear barotrauma caused by pressure increase in the chamber is the most common side effect [68-70]. This results from the patient's inability to equalize the pressure in one or both of his middle ears as the chamber is compressed. With respect to the magnitude of the pressure increase in the breathing hood during MBO_2 to mitigate absorption atelectasis, it is less than 1% of any of the pressure changes used in either standard clinical HBO_2 or off-label $mHBO_2$, and also less than 6% of the change in pressure experienced when a commercial airliner pressurizes its cabin in preparation for landing. Consequently, while the backpressure used in the hood is sufficient to change breathing mechanics and expand airways, thus reducing the likelihood of lung collapse associated with the oxygen breathing, it is not sufficient to produce middle ear barotrauma, even if equalization between ambient pressure and the middle ear does not occur. Further, a variety of routine actions such as talking, swallowing, yawning, or simply moving the head can produce spontaneous equalization of the small pressure differential involved through the Eustachian tube. Thus, middle ear barotrauma is not a complication seen in Microbaric® Oxygen Therapy.

Fire safety

Another safety consideration in any type of oxygen therapy is fire. Materials in elevated oxygen atmospheres ignite at lower temperatures and burn faster [71]. Reports from the U.S. Centers for Disease Control and Prevention and the U.S. National Fire Protection Association, however, indicate that there is less than one fire per 5,000 patients receiving long-term home oxygen therapy in the US (typically breathing oxygen for at least six hours per day and perhaps for as long as twenty-four hours per day) [72]. Thus, such fires are rare. The risk of fire should be even less for children with autism being given Microbaric® Oxygen Therapy for sixty minutes per day as, during these relatively short treatments, they should never be in the vicinity of such things as smoking materials, stoves or ovens, candles, matches or lighters, gas grills, grinding wheels, or incense which, together, are reported to account for 99% of the fires related to home oxygen therapy in the US [73]. In order to prevent any build-up of oxygen in the area while the equipment was in use, exhaust gas from the breathing system was routed into a hose and vented to the outside of the building (Figure 7).

Issues related to breathing in enclosed spaces

Prolonged interruption of gas exchange in any enclosed space will result in effects ranging from mild discomfort to severe hypoxia and/or hypercapnia. In the relatively small enclosed space formed by the soft-skinned breathing hood used in this study, the onset of these symptoms could occur relatively quickly. In practice, these flow-through breathing hoods have been routinely employed in multiplace hyperbaric chambers around the world for over 20 years without reported incident related to their use. In this study, the ability to exchange gas constantly and maintain proper hood inflation during normal operation was built into the breathing system described previously, and proper use was discussed at length with the parents during a period of orientation until at least one of them, invariably the mother, was comfortable and competent in administering the therapy. This never took longer than three treatments. In regards to managing a contingency situation, should one arise, the point most strongly emphasized was that the subject should never be left unattended when the hood was in use. To ensure proper procedures would be followed in the event of a failure in the gas supply to the hood, detailed instructions were given, and actions required in managing such an event were demonstrated and practiced. These involved removing the supply and exhaust hoses from the hood to allow fresh air to flow in and then removing the hood from the subject. In addition, a second, independent safety feature in the form of an inward-opening relief valve was added to the hood. This valve would open automatically during inspiration if positive pressure inside the hood were lost, thus allowing room air to be drawn in.

Practicality of therapy

MBO_2 was originally envisioned as a home-based treatment administered around the family's schedule and was delivered this way during the pilot study. This approach proved highly successful. By removing the need for travel, it ensured treatment could be delivered when convenient with minimal disruption to family life. This, we believe, reduced stress levels for both the subjects and their mothers, and improved compliance with the treatment regimen. With respect to cost, MBO_2 is projected as being one-half to one-fifth that of hyperbaric oxygen therapy administered in multiplace or monoplace chambers in freestanding clinics operating on an off-label, private-pay basis. Hospital-affiliated facilities do not commonly treat off-label cases, and health care insurers will not pay for off-label therapy in any type of facility.

A recent article addressing safety concerns about off-label hyperbaric oxygen therapy administered in freestanding clinics estimates that there are about 200 facilities providing such services in the US [74]. Even if this is an underestimate, it is clear that there are not many such facilities for a population and geographic area as large as the US. Consequently, a best-case scenario for treatments in a freestanding clinic might be for 4 hours of driving and treatment time five days a week with treatments restricted to business hours and scheduled at the convenience of the facility. A worst case scenario could require travel

to another city or even another country with a prolonged stay in order for the patient to receive a course of treatments.

In our case studies, it proved practical to conduct MBO_2 simultaneously with other forms of therapy or training (eg: home schooling, working with a therapist) or while the subjects simply relaxed and watched TV, played computer games, or just chilled out (Figures 4-6). Thus, among other advantages in comparison to hyperbaric oxygen therapies, MBO_2 is more convenient to administer, more cost-effective, and without the risks associated with compression to and decompression from increased atmospheric pressure. Because of such factors, longer courses of hyperoxic therapy are more practical with MBO_2 than they are with HBO_2. This latter factor would appear to be an element in the extent of the benefits provided by the therapy.

As a final point concerning cost and practicality, Microbaric® Oxygen Therapy is administered for 60 minutes per day, five days a week. This compares favorably with the commitment required by ABA interventions which are time intensive, requiring 20 hours or more of treatment per week [6] . In addition, MBO_2 is projected to be more cost-effective requiring, we would expect, no more than about 20-30% of the typical cost of behavior therapies for autism such as ABA, which in 2011 was projected to cost between $40-60,000 annually for a home-based program for pre-school children [75].

Research Requirements

As previously noted, these case studies of MBO_2 were uncontrolled. Thus, before there can be any general application of this modality for ASD, safety and efficacy must be established to the satisfaction of government regulatory authorities. This will require further research with appropriate controls. Fortunately, because MBO_2 is conducted at normal atmospheric pressure, effective controls not involving the breathing of hyperoxic gas mixes will be possible without safety or ethical concerns. To conduct a prospective, randomized, double-blind study, however, some means of safely masking the nature of the gas being breathed by the subjects must be established. We have now worked out a technical solution to this requirement suitable for safe use in subjects' homes. Consequently, if appropriate follow on research is positive, we hope that Microbaric® Oxygen Therapy would not only be recognized by government regulatory authorities, but ultimately by healthcare insurers, as well.

Conclusions

Research concerning both conventional and mild hyperbaric oxygen therapy for autism spectrum disorders has been reported over a wide range of inspired oxygen pressures with predominately successful outcomes. The lower end of these inspired oxygen pressures could easily be administered at normal atmospheric pressure without the involvement of a whole-body chamber. Not being able to identify any potential benefits for conducting such therapy at increased pressure, we wanted to determine if oxygen therapy at normal atmospheric pressure had potential as an intervention for ASD. A pilot study of five cases of preteens and teenagers with autism spectrum disorders were treated with a form of normobaric hyperoxic therapy we have called "Microbaric® Oxygen Therapy." All of the subjects appeared to derive some benefit, and three of them had remarkable improvements over the full range of symptoms of autism, particularly for children of their relatively advanced ages. In the four cases for which we had post-therapy follow-up, the benefits coinciding with MBO_2 have seemed permanent. This follow-up in two cases has extended for approximately six years.

In view of the consistent relationship between changes in the severity of autism and the commencement and termination of MBO_2, it seems highly unlikely that the outcomes achieved could be random in nature and, thus, unrelated to the hyperoxic therapy. Consequently, though anecdotal, this pilot study appears to add to the weight of evidence that hyperoxic therapy can be a beneficial intervention for ASD. Unlike the administration of hyperoxic gases in hyperbaric oxygen therapy, however, MBO_2 has been effective without increases in ambient pressure produced through the use of whole-body chambers and the attendant risks of compression to and decompression from increased pressure.

Thus, MBO_2 appears to be an effective, safe, easy-to-administer, time-efficient, and cost-effective therapy for ASD with no known side effects. If proven to be safe and effective in controlled research, therefore, MBO_2 should be suitable for home administration by the parents or caregivers of individuals with ASD and very much more convenient and cost-effective than hyperbaric oxygen therapy. Though delivered as a home-based therapy in the reported case studies, because of its nature, MBO_2 should also be suitable for administration by non-specialists as part of school, other training, and assisted living programs. As provided in our pilot study, MBO_2 permitted other activities such as additional therapies, schoolwork, and watching TV to take place simultaneously.

The only type of therapy which might conflict with MBO_2 would seem to be administration of drugs that interact with oxygen to present a health risk to the patient. One such pharmaceutical is guanfacine (i.e., Intuniv®), prescribed for ADHD. It reduces systolic and diastolic blood pressure and heart rate while oxygen causes coronary vasoconstriction [76-79]. Thus, the combination of guanfacine and hyperoxic therapy could put the patient's heart at risk of low oxygen delivery. If subsequent research achieves the same results as our pilot study, however, drugs other than oxygen should not be necessary with the hyperoxic therapy. Before MBO_2 can be established as an effective and safe therapy for ASD under any circumstances, though, randomized, prospective, blinded research must be conducted and achieve positive outcomes to the standards necessary for review and approval by government healthcare regulatory authorities such as the US Food and Drug Administration, Health Canada, and their equivalents around the world. Because such research would be done at normobaric pressure, sham control subjects would not have to breathe hyperoxic gases as has been the case for hyperbaric oxygen studies to this point. An approach for safely and effectively blinding this normobaric research in subject homes has already been worked out.

The age range of the subjects who participated in this pilot study suggests that controlled research as described above should not only be conducted with children but with teenagers, young adults, and older adults, as well. If the results we have reported here are reproduced during the course of subsequent controlled trials, MBO_2, alone, or perhaps in combination with other forms of intervention, would seem to have the potential of providing pediatricians and others guiding the treatment of children and possibly even the treatment of adults with autism with a practical intervention meeting the broad objectives set out by Myers and Johnson [80]. "The primary goals of treatment are to maximize the child's ultimate functional independence and quality of life by minimizing the core autism spectrum disorder features, facilitating development and learning, promoting socialization, reducing maladaptive behaviors".

Data availability

Should some person or organization have appropriate purpose for

reviewing the subjective observations of the caregivers used to support the findings of this study and/or a home-made video of one of the mothers telling her story, access may be obtained from the authors upon request by e-mail to mwallen@microbaric.com or repeterson@microbaric.com

Conflict of interest

The authors are the Founding Managers of Microbaric® Oxygen Systems, LLC which was established to provide an organization through which the research described in this paper could be conducted. The data in this paper are reported exactly as gathered during the course of these case studies. Two patents and a trademark have been granted in respect to the provision of the therapy described in this paper.

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