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Responding to Requests of Families for Unproven Interventions in Neurodevelopmental Disorders: Hyperbaric Oxygen "Treatment" and Stem Cell "Therapy" in Cerebral Palsy

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Faced with the limitations of currently available mainstream medical treatments and interventions, parents of children with neurodevelopmental disorders often seek information about unproven interventions. These interventions frequently have undetermined efficacy and uncertain safety profiles. In this article, we present a general background and case vignettes that highlight the use of hyperbaric oxygen chambers and stem cells in cerebral palsy, the leading cause of pediatric physical disability. We then review the current evidence about these interventions as exemplars of unproven therapies. Building on the background and cases, we explore and review two important questions related to unproven interventions: (1) How should clinicians respond to requests for innovative and alternative interventions? (2) What should clinicians keep in mind when such requests come from online sources?
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Key Words: neurodevelopmental disorders; cerebral palsy; neuroethics; hyperbaric oxygen therapy; stem cell; unproven treatments; pediatric neurology; best interests

INTRODUCTION

Faced with the limitations of currently available mainstream medical interventions, parents of children with neurodevelopmental disorders frequently seek information about unproven interventions. For common neurodevelopmental disorders like cerebral palsy, autism, and Down syndrome, few therapeutic options currently meet the high expectations of parents who, cherishing the best interests of their children, seek the most promising therapeutic avenues. Studies suggest that in various developmental disorders, as many as 50% of patients may use complementary and/or alternative medicine (CAM) [Hyman and Levy, 2005]. Given difficulties in defining the boundaries of conventional, allopathic, and CAM therapies [Liptak, 2005], in this article, we consider the range of therapies available as falling into the broad categories of proven or unproven interventions. Sanderson et al's. [2006] model of "therapeutic footprint" describes conventional medicine and CAM intervention as occupying different but overlapping places on scales of level of risk and amount of available evidence. The American Academy of Pediatrics has stated that "[t]he distinctions among unproven interventions, CAM and biomedicine may become especially blurred" [Committee on Children with Disabilities, American Academy of Pediatrics, 2001]. The way we approach unproven and proven therapies in this paper has the merit of evaluating interventions based on their potential effects on the individu-

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al's body function and structure, activities and participation [Liptak, 2005] regardless of the intervention's nature (e.g., biomedical, complementary). This also allows us to focus our discussion on balancing the ethical principles of autonomy, trust, nonmaleficence, and beneficence in individual cases based on specific risks and benefits of interventions.

In this article, we review some major questions raised by parental requests for unproven interventions for neurodevelopmental disorders. We present two illustrative cases about the use of hyperbaric oxygen "treatment" (HBOT) and stem cells in the context of cerebral palsy, the leading cause of pediatric physical disability, and we review current evidence for these interventions. Using this background, we then explore two important questions related to unproven interventions: (1) How should clinicians respond to requests for innovative and alternative interventions? (2) What should clinicians keep in mind when such requests come from online sources? To answer these common clinical and ethics questions, we reviewed relevant neuroscience and medical literature, professional guidelines, and the interdisciplinary health ethics literature. Although we focus on cerebral palsy, our discussion bears on the general medical approach in dealing with families seeking unproven treatments for a range of disorders.

UNPROVEN INTERVENTIONS IN NEURODEVELOPMENTAL DISORDERS: THE ILLUSTRATIVE CASES OF HYPERBARIC OXYGEN CHAMBERS AND STEM CELLS

Cerebral Palsy

The essential core feature of cerebral palsy is an objective neuromotor impairment of early onset, typically before the age of 2 [Shevell, 2009]. This impairment may manifest itself through delays in gross and fine motor skills or objective findings on neurologic examination, that is, posture, balance, tone, stretch reflexes, preservation of primitive reflexes [Rosenbaum et al., 2007] and is a result of either an anomaly or an acquired injury to the not yet mature, that is, fetal, neonatal, or early infantile brain. Apart from these elements, heterogeneity exists in all aspects of cerebral palsy: presentation, pathogenesis, severity, and natural history [Shevell, 2009]. Furthermore, up to 50% of individuals with cerebral palsy will also have a coexisting feature or comorbidity such as epilepsy, cognitive impairment, behavioral disturbances, substantial perceptual difficulties, speech/language/feeding limitations, or orthopedic deformities [Himmelmann et al., 2006; Rosenbaum et al., 2007; Shevell et al., 2009]. Ultimately, the motor impairment, together with these coexisting features, impact activity and participation, causing limitations in these domains and an increased individual and familial burden of care [Rosenbaum and Stewart, 2004].

The pathogenic heterogeneity of cerebral palsy, together with the inevitable delay between the timing of acquisition of the central nervous system (CNS) dysfunction and accurate clinical diagnosis, offers considerable challenges for effective therapeutic primary intervention. This is further complicated because the majority of causal factors related to cerebral palsy occur prenatally and there is a relative lack of reliable methods to assess fetal CNS integrity. Therapeutic efforts thus far have been directed at improving the identification of risk factors and have assumed primarily a preventative strategy. Current therapeutic efforts address symptoms of the disorder and include minimizing spasticity [Tilton, 2004], decreasing the likelihood of seizures [Hadjipanayis et al., 1997], improving function through aids and adaptation [Majnemer, 1998], and enhancing attention skills [Gross-Tsur et al., 2002]. These efforts are beneficial in improving outcome, but a "cure" for cerebral palsy remains an elusive goal in spite of the legitimate high expectations of parents. The following two cases featuring HBOT and stem cell "therapy" in cerebral palsy illustrate some of the tensions and substantial ethical questions surfacing when parents request information and guidance about unproven interventions in the specific context of cerebral palsy. The cases are featured with the purpose of illustrating common questions and to support further discussion.

Case of HBOT in Cerebral Palsy

Thomas is a 7-year-old boy diagnosed with spastic diplegic cerebral palsy. Despite regular physiotherapy intervention as well as the application of ankle foot orthosis and Botox administration into his lower extremities, Thomas uses a rear walker for ambulation and a wheelchair for longer distances. He requires some assistance with respect to activities of daily living in reference to dressing and toileting, but he self-feeds. He socializes well, has no behavioral issues, is in a regular Grade 1 classroom where he has learned to read and write. Thomas's neurologist has discussed with his parents that there is no further functional improvement expected for Thomas. Unsatisfied by this response, Thomas's parents have intensified searches for online information about CAM treatments. They have come across a local HBOT provider whose website claims that most patients with cerebral palsy will benefit from HBOT, although this is described as an off-label use. The website features basic risk information, favorable citations from scientific studies suggesting clear benefits from HBOT, corporate videos, and patient testimonials. Thomas's parents would like to enroll him for five courses of HBOT. The entire course of HBOT will cost $20,000 and because it is considered experimental it will not be covered by the father's health insurance plan. They have been told by the facility that HBOT will eliminate Thomas's need for a walker by stimulating the development of new blood vessels in his cerebellum. Thomas's parents are working with members of their church's congregation to raise the funds through church-based activities.

Evidence About HBOT in Cerebral Palsy

The basis for HBOT in cerebral palsy is the supposition that dormant cells in an ischemic penumbra can be reactivated both metabolically and electrically to resume normal function by enhancing oxygen availability. HBOT involves the delivery of 95–100% inhaled oxygen at pressures greater than 1 atm. Changes in brain metabolism and electrical activity following HBOT have been demonstrated in some animal models of acquired brain injury, which may be analogous to cerebral palsy in humans. A large number of private facilities providing HBOT exist, with costs estimated in a US government report (2000) at 400.00 US dollars per session, amounting to 12,000 to 16,000 US dollars per patient [U.S. Department of Health and Human Services Office of the Inspector General, 2000].

A systematic review of HBOT in cerebral palsy identified only two randomized controlled trials (RCTs) and four observational studies with sufficient scientific rigor to merit inclusion in the review [McDonagh et al., 2007]. The best evidence was derived from a RCT conducted in the Canadian province of Quebec that compared two groups of children (n = 111 overall) with cerebral palsy. One group received

Box 1. Conclusion of a systematic review on the use of HBOT for cerebral palsy

"While some case reports and before-and-after studies indicate improvements in function after HBOT, the best evidence to date indicates that HBOT and pressurized room air improved function to a similar degree, as shown in the observational studies, with no significant difference between groups. A proportion of children undergoing HBOT will experience adverse events, including seizures and the need for ear pressure equalization tube placement, but due to poor quality methods of assessment, estimates of the prevalence of these are uncertain."

Source: McDonagh MS, Morgan D, Carson S, Russman C. 2007. Systematic review of hyperbaric oxygen therapy for cerebral palsy: the state of the evidence. Dev Med Child Neurol 49: 942–947.

HBOT at 1.7 atm, and the other group received room air pressurized to 1.3 atm. Both groups received 40 treatments for 2 months. Blinded outcome assessors did not detect any statistical or clinically meaningful difference between the two groups in either the gross motor function primary outcome measure or secondary outcome measures assessed in this trial [Collet et al., 2001]. An improvement in the Gross Motor Function Measure of roughly 5–6% over baseline was noted in both groups 6 months subsequent to treatment initiation, which strongly suggests that HBOT is not more effective than pressurized room air. This improvement has been attributed to the participation (i.e., Hawthorne) effect [McCarney et al., 2007].

The second RCT identified by the systematic review was judged to be of poor quality, and hampered by small subject numbers ($n = 26$), a lack of blinded outcome assessment, vague subject ascertainment, a lack of important details regarding randomization and baseline comparability, and the absence of a true control group which did not undergo the HBOT intervention. Interestingly, this small RCT has never been published in the peer review literature and is available on a website alone [Packard, 2000]. Similarly, the four observational studies identified by the systematic review were all felt to be of poor quality, limited by retrospective design, lacking blinded outcome assessment, vulnerable to potential selection biases and confounder effects, and used no actual control groups for direct comparison [Machado, 1989; Montgomery et al., 1999; Chavdarov, 2002; Waalkes, 2002].

At present, as stated by the 2007 systematic review, "the evidence is inadequate for establishing a significant benefit for HBOT" in the setting of cerebral palsy (see Box 1 for further detail on this conclusion) [McDonagh et al., 2007]. While the trials and observational studies identified by the review did indicate an increase in the occurrence of either seizures or inner ear problems in children undergoing HBOT, "accurate estimates of the prevalence" of these adverse events was deemed at present uncertain [McDonagh et al., 2007]. In 2003, the Agency for Healthcare Research and Quality (U.S. Department of Health and Human Services) reviewed the evidence on HBOT in cerebral palsy and concluded that there was "insufficient evidence to determine whether the use of HBOT improves functional outcomes in children with cerebral palsy" [U.S. Department of Health and Human Services Agency for Healthcare Research and Quality, 2003].

Thus, it appears that HBOT for cerebral palsy has moderate risks without an expected demonstrable benefit. Still, different advocacy groups advance the value of HBOT in cerebral palsy and, accordingly, parents regularly inquire about the value of this intervention. The case of Thomas illustrates the attractiveness of allegedly powerful interventions falling outside mainstream medicine as well as the claims confronted by parents and, indirectly, clinicians. The following case about stem cell therapy exemplifies how conventional biomedical research itself can spur hope and requests for unproven interventions.

Case of Stem Cell Use in Cerebral Palsy

Sarah is 4 years old. She has been diagnosed with a spastic quadriparetic cerebral palsy, she is unable to roll, and she gets her head and chest up only to a limited degree in the prone position. She does not have a grasp or functional hand use and there is some question regarding her visual capabilities. She babbles but does not exhibit language comprehension. On their own initiative, Sarah's parents have located through online searches a clinic in Germany for which they can receive stem cell "treatment" for their child. The cost for this stem cell injection procedure has been estimated to be $40,000. The company offering this intervention claims to be a world leader in the use of human stem cells with hundreds of patients having undergone surgery. Powerful testimonials of parents capture the benefits of stem cells injections in cerebral palsy (e.g., patients walking independently, better posture, increase in cognitive abilities, and reduction of spasticity). The parents expressed a wish to do everything they can for Sarah and do not expect her to be "normal" due to this intervention, but instead hope to improve Sarah's quality of life. The cost will be entirely self-financed by the parents.

Evidence About Stem Cell Therapy in Cerebral Palsy

The replacement of lost nerve cells can be considered the contemporary "Holy Grail" of research efforts in neuroscience. Stem cells are naturally occurring cellular elements that retain the capacity to differentiate into various cell lines including neural cells. Potential stem cell sources include mesenchymal (i.e., bone marrow or umbilical cord) using either allogenic or autologous sources, neural precursors, or pluripotent cells (embryonic or induced). Allogenic mesenchymal stem cells require immunosuppression due to the substantial risk of graft versus host disease. Induced pluripotent stem cells are derived from an individual's own fibroblasts and are "embryonic-like" without some of the concurrent ethical concerns or the possibility of immune rejection [Carroll and Borlongan, 2008].

In the setting of cerebral palsy, it has been suggested that the functional replacement of even a small portion of irretrievably lost or damaged neurons may result in a clinically significant benefit. As noted by Carroll and Mays [2011], experimental stem cell injections have shown success in acute injury animal models of cerebral palsy. However, these acute models do not accurately reflect the chronic nature of cerebral palsy. The mechanism of action of stem cells could include (1) actual nerve cell replacement, (2) differentiation into astrocytes or microglia, (3) promotion of blood vessel regeneration, (4) greater survival and function of remaining intrinsic cells, and (5) a reduction of splenic release of inflammatory cells and subsequent mediators. What has been demonstrated to date is that the actual survival of transplanted stem cells is mini-

mal, with few cells showing actual nervous tissue functionality [Peled et al., 2000; Riess et al., 2002; Zhao et al., 2002].

At present, no peer review publication of injections with stem cells in humans with cerebral palsy exists. Four current ongoing clinical trials are registered at ClinicalTrials.gov (http://clinicaltrials.gov/). Two are US based and use autologous banked umbilical cord blood as a source of mesenchymal stem cells. Both feature a double-blind cross-over protocol that focuses on cerebral palsy resulting from a clear antecedent hypoxic ischemic injury. A third trial is based in South Korea and uses allogenic umbilical cord blood in combination with erythropoietin. This trial has a prospective double-blind randomized control design with rehabilitation, and groups with and without erythropoietin administration, as comparisons. In Mexico, the fourth registered clinical trial, which is not currently recruiting patients, uses autologous bone marrow as a stem cell source subsequent to intensive (granulocyte colony-stimulating factor) stimulation.

Although a number of centers are offering stem cell injections for cerebral palsy outside of North America, outside of clinical trials none of these are clearly carried out to rigorously assess efficacy or adverse effects. There is considerable variation between these centers in source of stem cells, mechanism of stem cell administration, and immunosuppression protocol. Most administer multiple doses of stem cells although costs vary considerably. Clinical trials are needed to determine both the safety and risk of stem cell therapies across medical conditions, especially because purported risks include the development of graft-host disease, infection, seizure, or stroke [Iguchi et al., 1999; Woodard et al., 2004; Rubin et al., 2005] and because adverse events from stem cells procedures performed outside of clinical trials may remain unreported. This case brings up important ethics questions not only about the mechanisms for responsibly and ethically translating basic science to clinical care but also about the responsibility of parents and clinicians to critically consider unproven interventions and, under which conditions they should do so.

HOW SHOULD CLINICIANS RESPOND TO REQUESTS FOR UNPROVEN INTERVENTIONS?

The cases above illustrate some of the difficulties faced by clinicians when responding to requests for unproven interventions. In response to requests for unproven interventions, competing interpretations of ethical principles come into play. For example, respect for the young pediatric patient does not necessarily rely solely on respect for autonomy but also on valuing individuals with physical or cognitive disabilities. Moreover, the principle of beneficence may be interpreted by the parents as requiring the use of unproven alternatives while the physician may think that the principle of nonmaleficence indicates avoiding the use of treatments with uncertain safety and efficacy profiles.

"For approved therapies or unproven interventions, a combination of ethical principles, including respect for autonomy, beneficence, nonmaleficence, [Beauchamp and Childress, 2009] as well as other considerations such as the level of evidence supporting the recommendation, guides physicians' recommendations for action.

Ethical principles guiding decision making in pediatric clinical care

For approved therapies or unproven interventions, a combination of ethical principles, including respect for autonomy, beneficence, nonmaleficence [Beauchamp and Childress, 2009] as well as other considerations such as the level of evidence supporting the recommendation, guides physicians' recommendations for action. To facilitate ethical discussion and concerted action in response to ethical questions, most contemporary commentators and medical societies concur on recommending a shared decision-making approach. In this model, the physician provides information on the medical aspects, answers the parents' questions, and will eventually make a recommendation. As much as possible, input from children themselves is sought to ascertain their own preferences in medical care. Parents provide their input, convey and discuss their personal values and views of the child's best interests, which may differ from that of the physician, and consider the physician's recommendation. Ideally, the parents, together with the physician, reach a mutually acceptable consensus regarding the treatment plan [Committee on Bioethics, American Academy of Pediatrics, 1995; Bell, 2007]. When caring for infants and young children, the primary goal of this process is to identify treatment that is in the child's best interest [Spence, 2000] because of the absence of patient capacity and autonomous decision making.

In these cases, parents are assigned as surrogate decision makers and the "best interests" approach is applied, that is, parents are presumed to make decisions in accordance with the best interests of the child [Spence, 2000]. Several factors are included in the determination of a child's best interest, including their medical condition and overall well-being, questions about quality of life for the child and the family, and information about prognosis and future impact of the current decisions that families and physicians are faced with. Parents are expected to weigh these factors carefully, otherwise their legitimacy as proxy decision makers can be questioned and their decision-making responsibility can be revoked [Bernat, 2008; Wade et al., in press].

The tenets of shared decision making may be challenged by requests for unproven interventions. Typically little information can guide clinicians to inform the parent's decision (autonomy), to mitigate and warn about harms (nonmaleficence), or to discuss potential benefits (beneficence). However, the shared decision-making model, or at least some of its core aspects, may be upheld even in cases where many unknowns plague the clinical conversation, such as in the cases of HBOT and stem cells. The importance of shared decision making regarding treatment options including unproven, innovative, or alternative interventions are particularly important when the decision is being made for someone else.

Clinical and ethical approaches for dealing with requests from families for unproven therapies

The increased use of CAM or desire for unproven interventions

Box 2. Recommendations for pediatricians who discuss alternative, complementary, and unproven therapies with families

Seek information for yourself and be prepared to share it with families
Evaluate the scientific merits of specific therapeutic approaches
Identify risks or potential harmful effects
Provide families with information on a range of treatment options (avoid therapeutic nihilism)
Educate families to evaluate information about all treatment approaches
Avoid a dismissal of CAM in ways that communicate a lack of sensitivity or concern for the family's perspective
Recognize feeling threatened and guard against becoming defensive
If the CAM approach is endorsed, offer to assist in monitoring and evaluating the response
Actively listen to the family and the child with chronic illness

Source: Taken and formatted into a table from American Academy of Pediatrics Committee on Children with Disabilities. 2001. Counseling families who choose complementary and alternative medicine for their child with chronic illness or disability. Pediatrics 107: 598–601.

among patients requires a responsive approach by physicians to incorporate discussions about these into their consultations [Pappas and Perlman, 2002]. By responding to patients' questions and concerns about CAM or unproven interventions, physicians can help ensure that patients or parents are making informed decisions about risks and benefits. These discussions are particularly important because they may reveal that patients have limited or unreliable information about the intervention [Pappas and Perlman, 2002]. They can also contribute to the patient–physician relationship and foster open communication [Pappas and Perlman, 2002]. The AAP Committee on Children with Disabilities, in 2001, put forth recommendations for pediatricians discussing CAM and unproven interventions with families (see Box 2). These recommendations can be compared with the step-by-step strategy proposed by Eisenberg [1997] (Box 3). Both identify common obligations of physicians in consultation with patients and families including, providing an analysis of possible risks and benefits of the intervention, paying close attention to the patient's perspective and their preferences and expectations, and maintaining a continuing therapeutic relationship during and after treatment. Reasons why patients are seeking CAM should also be probed [Pappas and Pearlman, 2002]. The motivations for seeking CAM can include needing or wanting to control side effects of medications and dissatisfaction with attitudes of their providers of standard medical care [Pappas and Perlman, 2002]. Moreover, when patients desire CAM or unproven approaches to treatment, physicians should inform them about the alternative to participate in current open clinical trials and should discuss the potential negative impacts of the use of unproven therapies on future research participation.

The AAP Committee on Children with Disabilities [2001] and Eisenberg [1997] procedural recommendations can be useful for guiding discussions related to CAM approaches or to deal with parental requests for interventions in which no good evidence exists (unproven interventions). However, their ability to support informed decisions will sometimes be threatened by a limited understanding of the potential benefits and risks associated with interventions. This tension exists because, as Cohen [2006] describes, on the one hand, when the safety and efficacy of an approach is known to be low, it violates the principles of nonmaleficence and beneficence leading physicians to discourage use of the intervention. But on the other hand, in many instances, the evidence is not clear or has not yet been systematically reviewed leaving more room for respecting patient autonomy but with unclear assessments of beneficent or nonharmful effects of the intervention. Of course, physicians have to balance these unknowns with estimates of probable risks and benefits that do exist. This should also include an assessment of the consequences associated with the high costs of many CAM or unproven interventions.

How can we apply these considerations to our cases? In our first case, Thomas's parents have indicated that they wish to seek out HBOT at a nearby HBOT facility. The limited evidence available does not support any evidence-based claims for the benefit of HBOT in cerebral palsy but at the same time, evidence indicates tolerable physical risks. Additionally, the costs of the intervention and the energy and hope invested in it are significant. In the second case, Sarah's parents indicate that they have been considering going abroad for stem cell injections to treat her cerebral palsy. Little current evidence exists regarding the effectiveness of stem cells to treat cerebral palsy, in part because the area of stem cell research is still being developed and because a lack of adequate animal models of cerebral palsy for preclinical work has slowed translation to clinical trials in the US [Carroll and Mays, 2011]. However, the potential physical risks of stem cell interventions are still unknown but could be unacceptably high. Cases like that of a child who developed tumors in the brain and spinal cord after stem cell injection in Moscow highlight the potential impact of still undefined serious risks [Amariglio et al., 2009]. Grounding our ethical analysis in an approach based on evidence, it might be appropriate in Thomas' case to permit the family access to HBOT and maintain a close evaluation of its impacts. In Sarah's case, because of a lack of evidence for efficacy and estimates of potential serious risks, it may be more appropriate to strongly discourage travel for stem cell therapy. However, an analysis such as this, which does not take into account other potential factors in the interpretation of beneficence and nonmaleficence (e.g., presence of unrealistic hope, important financial consequences), overlooks important issues. In the cases of Thomas and Sarah, the high cost of both procedures could impact the families' financial situation; this requires more discrete appraisal in collaboration with each family. Other atypical risks of

Box 3. A step-by-step strategy to "discuss the use or avoidance of alternative therapies"

Ask the patient to identify the principal symptom
Ask the patient to maintain a symptom diary
Discuss the patient's preferences and expectations
Review issues of safety and efficacy
Identify a suitable licensed provider
Provide key questions for patients to ask the alternative therapy provider during initial consultation
Schedule a follow-up visit (or telephone call) to review the treatment plan
Follow up to review the response to treatment
Provide documentation [of how decisions were reached]

Source: Taken and formatted into a table from Eisenberg DM. 1997. Advising patients who seek alternative medical therapies. Ann Intern Med 127: 61-69.

Box 4. Characteristics of alternative "therapy" practices likely to magnify consumer risks

Focus is on cure – this is regardless of the disease being treated; the therapy may be presented as a universal panacea
Denial of responsibility – promotes treatments in terms of inherent goodness, naturalness or safety without acknowledging any potential for risk or treatment failure. Adverse effects or failure of therapy may be explained as patients' failure to follow the therapy regimen properly or starting therapy too late
Exclusive relationships – highlights opposition of standard medicine to alternative therapy and discourages use of some or all standard medical care
Exploitative relationships – encourages psychological dependence in treatment users
No objective scrutiny of outcomes – existing evidence about the therapy is discounted and the "medical model" and its basis in scientific knowledge is discredited

Source: From Sanderson CR, Koczwara B, Currow DC. 2006. The 'therapeutic footprint' of medical, complementary and alternative therapies and a doctor's duty of care. MJA 185: 373-376.

pursuing CAM or unproven interventions, such as the possible detrimental effects of delaying (or pausing) conventional treatments, and the possible negative effects of disappointment among patients and families expecting a cure, need to be taken into account [Eisenberg, 1997]. Unfortunately, while approaches to deal with requests for CAM or unproven therapies have been proposed in the academic literature (see above), there is little or no evidence to our knowledge that any mechanism to deal with patient or family requests for alternative or unproven therapies has actually been evaluated. This could represent an important area for future research.

Defining the obligations of physicians to pediatric patients seeking unproven interventions

Importantly, for pediatric physicians and clinicians there could be obligations to support and follow closely the role of parents who are making requests for CAM or unproven interventions on behalf of children. Zarzeczny and Caulfield [2010] have looked at the specific case of stem cell tourism by parents for their children. As they describe, even in cases where physicians are not themselves involved in the treatment being pursued (such as stem cell injection carried out abroad), physicians may have fiduciary, legislative, and professional obligations to minor patients whose parents wish to engage in stem cell tourism [Zarzeczny and Caulfield, 2010]. However, the obligation to act in each of these areas may be associated with how well a physician can actually gauge or demonstrate the significance of physical risk posed by the unproven intervention as well as whether the patient refuses or denies recommended treatments in order to pursue unproven ones. They suggest that, as it relates to parents seeking stem cell tourism for their children, parents should be given as much risk information as is available in the consultation and should also be referred to other helpful resources [Zarzeczny and Caulfield, 2010]. Essentially, they advise that physicians evaluating their obligations to act on behalf of the child must conduct case-by-case analyses taking into account the state of the patient's current disease, conventional therapies tried and or available, the potential for risk or harm, quality of life, and parents' wishes [Zarzeczny and Caulfield, 2010].

WHAT SHOULD CLINICIANS KEEP IN MIND WHEN REQUESTS ABOUT UNPROVEN INTERVENTIONS COME FROM ONLINE SOURCES?

The cases we feature and the broader context of parental requests for unproven interventions immediately highlight how, in our times, parents and children acquire information about such interventions. Traditional media like newspaper reports and radio and television broadcasts carry important challenges, which have been reviewed previously. Notable traits of traditional forms of media (e.g., print media) include publication of non-peer-reviewed findings presented by researchers at scientific meetings, dissemination of hype, and lack of appropriate explanation of neurological disorders and neuroscience research methods [Zuckerman, 2003; Caulfield, 2004; Bubela, 2006; Racine et al., 2010; Racine, 2011]. Today, patients and families commonly use the Internet to obtain health information [Tuffrey and Finlay, 2002; Semere et al., 2003; Wainstein et al., 2006; Khoo et al., 2008; Fox, 2011]. It is therefore important for physicians to be aware of the content patients are exposed to on product websites or through online advocacy sites. Guidelines for patients to evaluate therapeutic claims are also necessary.

Several studies show that direct to consumer advertising (DTCA) of health products (both approved and alternative) can lead to compromised patient safety and overutilization of specific medications [Mintzes et al., 2003; Frosch et al., 2010; Liang and Mackey, 2011]. Common attributes in the marketing of alternative practices on the Internet include several strategies that augment risks for patients (see Box 4) [Sanderson et al., 2006]. An analysis of patient blogs discussing unregulated stem cell injection found that although many patients were aware of physicians' skepticism about stem cell injection, the views of these physicians were dismissed because of positive testimonials offered on clinic websites and other sources [Ryan et al., 2010]. Moreover, websites, especially those marketing products, often provide unrealistic claims about the benefits, risks, and evidence available about their products and services [Racine et al., 2007]. Stem cell medicine clinics have been found to feature undue benefits and present procedures as routine and ready for public access [Lau et al., 2008]. For instance, one study has shown that information obtained from stem cell providers on the internet depicts stem cell interventions as available to be used for a range of disorders; some of the information even suggests the benefits of stem cell interventions exceed those of current treatments in certain disorders, including in CP (Regenberg et al., 2009). Key information is also missing from the websites of stem cell clinics [Carroll and Mays, 2011]. These websites often give little information on how the stem cells are obtained and prepared, and clinics rarely collect systematic evidence about the intervention and outcomes of their patients [Carroll and Mays, 2011].

Even patient advocacy websites, which are assumed to represent patient interests [White and Dorman, 2001], can provide misleading information [Di Pietro et al., submitted]. A study of patient advocacy websites for three neurodevelopmental disorders, including cerebral palsy found that most informa-

Box 5. Frequently asked questions about clinical therapies using stem cells and the availability of stem cell clinical trials

- What are stem cells?
- What is a stem cell therapy?
- For what diseases or conditions are stem cell treatments well established?
- What are some of the special considerations for stem cell therapies?
- What is the usual process for developing a new medical treatment?
- What are the differences between an approved clinical treatment and an experimental intervention?
- What is a clinical trial?
- What is an informed consent form or treatment consent form?
- How do I know if an approved stem cell therapy is safe?
- What should I look for if I am considering a stem cell therapy?
- What should I be cautious about if I am considering a stem cell therapy?
- What else should I ask?
- Should I get a second opinion?
- How can I find out about clinical trials that use stem cells?

Source: From International Society for Stem Cell Research Patient Handbook on Stem Cell Therapies: Appendix I of the Guidelines for the Clinical Translation of Stem Cells. Accessed September 15, 2011. http://www.isscr.org/clinical_trans/pdfs/ISSCRPatientHandbook.pdf

tion was encouraging regardless of whether the intervention was conventional or alternative [Di Pietro et al., 2011]. Few discouraging or cautionary messages were observed. Although the websites analyzed contained no explicit promotion of brand-name products and most contained legal disclaimers, these disclaimers were often difficult to find, yielding an unbalanced endorsement of products [Di Pietro et al., 2011].

Parents like Sarah's, who use online sources to assess the effectiveness of stem cell injections, are very likely to encounter unrealistic claims about the benefits and safety of stem cell injection. The International Society for Stem Cell Research (ISSCR) has published a *Patient Handbook on Stem Cell Therapy* (2008) that contains guidelines to help patients assess potential interventions [International Society for Stem Cell Research, 2008]. These guidelines encourage patients to look for relevant preclinical studies, approval from a regulatory committee, and approval from national or regional regulatory agencies. They also caution patients against service providers that make claims based on testimonials, claim to treat multiple diseases with the same protocol, fail to identify the source of stem cells or procedures they use, or claim there is no risk associated with the procedure. Box 5 features frequently asked questions as reported and discussed by the ISSCR which may serve as an overview of the informational needs of parents. In spite of an interest for online health information, parents largely prefer consulting healthcare professionals directly and accessing institutional online websites in which they have greater confidence than in the results of general search engines [Semere et al., 2003; Wainstein et al., 2006; Khoo et al., 2008]. Studies have reported conflicting data on the level of trust parents have in online health information ["high" by Semere et al., 2003 but lower by Wainstein et al., 2006; Khoo et al., 2008]. Although the impact of online health information is hard to assess and can include positive effects [Murray et al., 2003], clinicians should also keep in mind that in some disorders like cerebral palsy, much of the online information comes from nonclinical sponsors [Kaimal et al., 2008].

CONCLUSION

In the context of neurodevelopmental disorders, requests for unproven interventions are to be expected now and for the foreseeable future. A combination of openness and transparency, sensitivity, engagement of parents in shared decision making, commitment to evidence-based medicine and principles such as beneficence and nonmaleficence can help clinicians deal with parental requests for unproven interventions in this context and others. Various professional societies have proposed approaches that incorporate these principles. In addition, given the evolution of media through which health information can be provided, close attention to how different interventions are marketed reveals important clues about what questions and information parents will bring to the clinical encounter and what additional information they will require to make decisions in the best interests of their child. Healthcare training programs should incorporate discussions about unproven interventions and professional societies should remain continuously abreast of developments in health information technology to support evidence-based responses by clinicians.

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