Ethical dilemmas in hyperbaric medicine

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Chan ECY, Brody B. Ethical dilemmas m hyperbaric medicine. Undersea Hyper Med 2001; 28(3):123–130.—Although hyperbaric oxygen therapy (HBO_2T) is the primary or adjunctive treatment for a limited number of clinical conditions, off-label use is increasing as a result of public demand. Because of unusual research problems and limited regulatory mechanisms to ensure patient safety, physicians question whether it is ethical to provide HBO_2T for an unproven indication. An ethical approach to the off-label use of HBO_2T is proposed. This approach requires combining a physician's clinical judgment with guidelines written by recognized organizations in hyperbaric medicine and patient informed consent. Scientific guidelines can identify which off-label uses of HBO_2T are not therapeutic, which are potentially therapeutic, and to what degree. Registries or a central repository for the systematic collection of data can promote research. Ethical guidelines should require patient informed consent for approved indications, for potentially therapeutic off-label indications, and for registry or research participation. The creation of a consortium of hyperbaric clinics may improve the validity of information disseminated to the general public and promote the ethical practice of HBO_2T.

ethics, hyperbaric medicine, informed consent, off-label therapy

Although hyperbaric oxygen therapy (HBO_2T) is the primary or adjunct treatment for a limited number of clinical conditions, off-label use is rising in response to public demand. At present, HBO_2T is the primary medical treatment for decompression sickness, arterial gas embolism, and serious carbon monoxide poisoning. It is also an adjunct treatment for chronic refractory osteomyelitis, clostridial myonecrosis (gas gangrene), crush injury and other acute traumatic ischemias, selected wounds, severe anemia, necrotizing soft tissue infections, radiation tissue damage, compromised skin grafts and flaps, thermal burns, and some types of intracranial abscesses (1). These comprise the 13 "approved" indications that the Food and Drug Administration (FDA) recognizes. The FDA calls all other indications "off-label". But the public has become increasingly interested in the off-label uses of HBO_2T, which have been reported for over 130 other clinical conditions (2). This situation prompts physicians to ask whether it is ethical to use HBO_2T for any clinical condition for which the benefit is unproven.

For physicians, the off-label use of HBO_2T is an issue fraught with intense controversy and ambiguity. Some off-label uses appear potentially therapeutic; some do not. Determining just which conditions are more potentially therapeutic than others requires guidance from experts in hyperbaric medicine. There is an ethical problem when HBO_2T is offered to patients and their families as a "cure" for a condition that has virtually no scientific basis (e.g., aging). The ethical principle at issue is that of nonmaleficence, expressed as *primum non nocere,* or first do no harm. HBO_2T does carry the potential for medical harm because there are medical risks (1,3,4). There is also the risk of financial harm (2). A patient and family could be misled to pay in cash for a series of treatments that they believe work, when in fact there is no scientific evidence to support that opinion. That is why we recommend that experts in hyperbaric medicine provide scientific and ethical guidelines for the off-label use of HBO_2T.

Research for off-label indications, as well as research that might support additional approved indications, has been slow. It has been impeded by technical and financial constraints. Until randomized, controlled clinical trials have been conducted and demonstrate the net benefit of HBO_2T for a particular off-label indication, physicians need guidelines on how to respond to patients requesting the use of HBO_2T for an off-label indication. We recommend that experts of HBO_2T develop scientific guidelines to determine which off-label uses of HBO_2T are potentially beneficial for their patients.

For patients, the off-label use of HBO_2T is increasingly popular (2,5). Hyperbaric chambers now appear not only in hospitals and freestanding facilities, but also in private homes (5). Some parents with chambers installed in homes or garages have been reportedly treating their own and other children (5). In effect, they may be practicing medicine and incurring unsuspected liabilities. Busi-

nesses with aggressive advertising are stirring public demand, spilling information onto the Internet, and recruiting more people to the off-label use of HBO_2T [Caroline Fife, then president, Undersea and Hyperbaric Medical Socierty (UHMS), personal communication]. There has been limited regulation of this and other areas related to hyperbaric medicine. As a result, patients and their families have become increasingly vulnerable. Consequently, we recommend that HBO_2T experts develop *ethical* practice guidelines to meet the growing public demand for off-label HBO_2T use.

Although there are no published guidelines for the ethical use of off-label therapies in general, the use of HBO_2T for off-label indications may require such guidelines from expert practitioners. Unlike other therapies (e.g., drugs), HBO_2T is not just a therapy, it is also a field of tnedicine. Although other fields of medicine have practitioners who use drugs on an off-label basis, the credibility of those fields does not depend on the administration of a single therapy. The credibility of HBO_2T as a field of medicine does. Ethical guidelines are needed to guide the ethical practice of HBO_2T and to identify professional practitioners of hyperbaric medicine if HBO_2T is to remain a field of medicine. Just as the practice of medicine requires an ethical code of conduct, the practice of hyperbaric medicine requires ethical guidelines too.

THE CALL FOR AN ETHICS REVIEW

In the fall of 1998, the president of the UHMS identified the off-label uses of HBO_2T as an area requiring expert ethics consultation after receiving multiple e-mails, phone calls, and letters from concerned practitioners and the general public. By that time, requests for the treatment of unapproved or off-label indications had become an almost daily occurrence at the University of Texas–Houston Medical Center.

The president of the UHMS invited the major nonprofit professional organizations in hyperbaric medicine to designate representatives who could speak with us and to contribute to a grant fund administered by the Office of Development at the University of Texas–Houston Health Science Center. The purpose of the grant fund was to reimburse the authors for their time. All invited organizations (*see* Acknowledgements) responded, and their representatives were part of the Working Group on Ethics in Hyperbaric Medicine. After meeting with representatives of these organizations, we began a systematic review of the literature. In addition to the published literature on currently accepted indications for HBO_2T (1), we reviewed the literature relating to HBO_2T in general plus other sources of information. These other sources included FDA regulations regarding the advertising of hyperbaric chambers and directives for the use of oxygen, advertisements (both Internet and in print) soliciting patients for the treatment of conditions not approved by the UHMS, information about informed consent practices from patients who were treated for off-label indications, and informal case reports written by mothers of children who were treated with HBO_2T. We subsequently identified three main issues confronting hyperbaric medicine and made four recommendations for organizations to consider as they develop guidelines for the off-label use of HBO_2T .This report constitutes our work and represents only our opinions.

Issue 1

Research difficulties impede the investigation of off-label uses of HBO_2T: Significant challenges and obstacles impede research in hyperbaric medicine. Difficulties in organizing clinical trials center on the issues of creating conditions for a control population, blinding, randomization, and patient consent. In clinical trials that do not have extramural funding, investigators wonder if it is appropriate to charge patients randomized to control groups and wonder what the requirements of informed consent should be (2). Additionally, funding is scarce. Although oxygen is widely considered to be a drug, it is not manufactured by a pharmaceutical company. Consequently, there is no ready source of funding from industry. Such issues decrease the likelihood that treatment decisions in the near future can be based on scientific data from randomized, controlled clinical trials.

Meanwhile, proponents for the off-label use of HBO_2T in conditions where it may be potentially therapeutic argue that the growing number of successful anecdotal reports justify adding such conditions to the approved list. They have asked, "How many anecdotal reports are needed to approve an indication?"

Issue 2

Public demand and profits spur growth of off-label uses of HBO_2T, endangering the ethical and safe practice of HBO_2T: With the expansion of off-label uses for HBO_2T, non-hospital facilities offering HBO_2T have proliferated (6,7). Hyperbaric oxygen chambers have also expanded into private homes, raising concerns about safety. In the current Internet era, information about HBO_2T spreads quickly. Several grassroots organizations support the use of HBO_2T for conditions that have no medical cure in the belief that HBO_2T can offer some benefit (5).

Grass-roots interest has also been on the rise for the use of HBO_2T for muscle contusions and other soft tissue

injuries sustained by professional and amateur athletes. Perhaps extrapolating from data about the benefit of HBO_2T in ischemia reperfusion and crush injury, professional athletes in Europe, Canada, and the United States have used hyperbaric chambers purportedly to shorten their recovery time from soft tissue injuries (8–11). Although HBO_2T for such muscle and soft tissue injuries remains unproven (11,12), the net effect has been to thrust HBO_2T into the public limelight and to increase demand. Amateur athletes have reportedly used HBO_2T to enhance performance, an indication for which there is no scientific rationale. Nevertheless, hyperbaric chambers are available in some health clubs.

For conditions approved by the UHMS, Medicare and all third-party payers cover the cost of HBO_2T. For off-label uses, patients usually pay cash. Even if the cost of an individual treatment is less than the usual clinical rate, the total cost for a series can quickly escalate to tens of thousands of dollars. Furthermore, as payers begin to reduce reimbursement for approved indications, hospitals may treat unapproved conditions for cash to help sustain their programs for approved therapy. Even with significant reductions in approved charges, a cash-based system, which obviates the need for staff to manage insurance claims, could make off-label HBO_2T a profitable business for hyperbaric facilities.

Patients and their families are susceptible to overlooking the risks of HBO_2T. Marketing efforts suggest that HBO_2T at pressures less than twice atmospheric pressure can be performed without any complications or side effects. Although the operation of a hyperbaric chamber appears straightforward, the use of compressed oxygen is not without risks. The risk of chamber fires is well known (13–15). Although the incidence of fires has been low worldwide, the increasingly common practice of installing home or garage chambers operated by family members raises the concern that a tragedy will occur .The potential side effects of HBO_2T are also well known. They include otic, sinus, and pulmonary barotrauma (which can lead to tension pneumothorax, arterial gas embolism, and death); central nervous system symptoms of oxygen toxicity; and ocular changes such as myopia, which can still occur at the lower treatment pressures currently advocated for some off-label indications (1,3,4).

Issue 3

Limited regulatory mechanisms to ensure safety: Patients are also vulnerable to system-wide risks in the current practice environment. Limited regulatory mechanisms exist to prevent misleading advertising and to ensure that hyperbaric facilities are safe. There is no centralized site from which patients can obtain information about regulatory issues, safety, or training standards for facilities. No procedure is in place for registering complaints about questionable practices.

According to the FDA, chamber manufacturers must limit their advertising to indications approved by the UHMS. This limitation also applies to hyperbaric facility operators unless they can present sufficient data to the FDA proving the benefit of HBO_2T for a new indication. The FDA has the legal authority to shut down facilities that fail to comply with this advertising requirement (16). In practice, the FDA lacks the resources to police such breeches, now common on the Internet. Therefore, it seems unlikely that misleading advertising regarding HBO_2T can be controlled in the near future.

Although regulatory oversight to ensure safety at hospital facilities is strict, there is less oversight at freestanding hyperbaric facilities and no oversight of chambers in homes and garages. Hospital hyperbaric facilities must comply with all hospital regulations plus those of the Joint Commission for Accreditation of Healthcare Organizations and the National Fire Protection Administration, the latter being enforceable by the local fire marshall or other authority having jurisdiction. Hospital facilities are expected to use equipment that conforms to Pressure Vessel for Human Occupancy standards. Freestanding facilities and chambers in private homes are not subject to the same rigid oversight.

Another issue is that of expert supervision at hyperbaric facilities. Physicians who operate facilities or supervise patients undergoing hyperbaric treatments must be licensed in the United States and are accountable to their state licensing board. State boards are sensitive to physician activities involving unproven therapies and interventions that may be considered experimental. But many freestanding facilities have no physician involvement (Caroline Fife, personal communication, 1998), thus removing a powerful type of oversight from program operation. The UHMS Operations Committee Report (17) outlines in detail the requirements for staffmg and training personnel in hospital facilities.

OVERVIEW OF THE FOUR RECOMMENDATIONS

In the context of these issues, physicians have asked whether it is ethical to use HBO_2T for an indication for which its benefit is unproven. This question is not unique to HBO_2T as it is common for physicians to use other drugs and therapies on an off-label basis. But because HBO_2T is also a field of medicine, scientific and ethical guidelines may be needed. Until results from randomized, controlled clinical trials definitively answer the

question of whether HBO_2T confers net benefits for a particular off-label indication, physicians need guidelines on what to do. There is some line that prohibits physicians from prescribing HBO_2T for every conceivable unproven indication, some line that makes it unethical for a physician to recommend HBO_2T for some unproven indications—such as wrinkles. Until results from randomized, controlled clinical trials definitively answer the question of whether HBO_2T confers net benefits for a particular off-label indication, physicians need guidelines on how to evaluate the different unproven indications and how to approach requests from patients about treatments for them. Physicians need guidelines on where to draw the line.

Deciding where to draw the line for a particular case will depend on a combination of a physician's individual clinical judgment, clinical guidelines from organizations in hyperbaric medicine, and patient informed consent. To develop such guidelines, organizations in hyperbaric medicine will first need to develop *scientific* guidelines to identify which off-label indications are clearly not therapeutic for any patients, which off-label indications are potentially therapeutic for some, and to what degree. A physician and patient considering an off-label indication deemed potentially therapeutic by these organizations can weigh the *type* and *level* of scientific data justifying its categorization, potential benefits and risks to the patient, and determine where the line ought to be drawn for a particular patient through informed consent.

Scientific guidelines are also important to direct research efforts. Proponents for the off-label use of HBO_2T have asked: "How many anecdotal reports are needed to make an indication 'potentially beneficial'"? We suggest reformulating this question as: "What *level* and what *kind* of scientific proof is needed to distinguish between a potentially therapeutic indication from one that is not?" We also recommend collecting anecdotal reports in a systemic fashion as part of a coordinated effort to promote research in the off-label uses of HBO_2T. This can be accomplished by establishing a registry or, in the absence of one, a central repository of case reports.

Once established, scientific guidelines will help guide the development of *ethical* guidelines for the potentially therapeutic off-label use of HBO_2T incorporating informed consent. In general, physicians have a duty to disclose the risks and benefits of HBO_2T treatment, regardless of whether the indication is approved or off-label, so that patients can make an informed decision about whether to undergo treatment. But this naturally leads to the question of what physicians should say to their patients during the process of informed consent when patients request a potentially therapeutic off-label use of HBO_2T. We recommend an approach to this question.

Finally, we recommend a concerted effort to bring together the scientific and ethical approaches to the issues discussed above. This can be encouraged on an individual level, by developing a set of clinical guidelines for individual physicians to follow in response to off-label requests for HBO_2T, and on a profession-wide level by creating a consortium of hyperbaric clinics.

Recommendation I

Develop scientific guidelines to determine which off-label uses of HBO_2T are potentially therapeutic and which are not: Although we do not intend to delineate specific scientific guidelines, we recommend developing criteria with a scoring system for the off-label use of HBO_2T. Such criteria (Table 1) would identify which off-label uses are potentially therapeutic and which are not, and the degree to which a use is potentially therapeutic. For example, criteria might include

- there are no alternative treatments that are cost-efficient and successful for the proposed indication,
- there are human or animal data to support the potentially therapeutic use of HBO_2T, and
- the benefits of administering HBO_2T outweigh the risks.

Under the category of benefits and risks, special consideration should be given to a patient's co-morbid conditions and the technical capability and safety of the facility administering the treatment.

A scoring system might recognize different *levels* and *types* of scientific data. As an example of how different levels of data might be considered, one end of the spectrum might point to the absence of animal data or published case reports, and the other end of the spectrum might point to the presence of double-blinded, randomized, case controlled clinical trials. Furthermore, a scoring system could allocate different point values to different types of clinical trials. Some trials are not blinded, while others compare an intervention with standard treatment rather than with a placebo (18,19). Instead of clinical trial data, registry data supporting the

Table 1: Criteria for Potentially Therapeutic, Off-Label Use of Hyperbaric Oxygen Therapy

1.	Alternative treatments neither cost-efficient nor successful Human or animal study data supports use
2.	Benefits greater than risks
3.	a. patient co-morbid conditions b. technical capability and safety of the facility

therapeutic benefit of HBO_2T for a particular indication might also be recognized. The fact that a therapy does not have a randomized, controlled clinical trial to support its use, does not by itself determine whether a therapy is ethical or not. A scoring system recognizes that there are other kinds of data (e.g., registry data) and research designs (20) that can lead experts to support, to varying degrees, the off-label use of HBO_2T for a particular indication until randomized, controlled clinical trial data becomes available.

Such a quantifiable system for evaluating scientific data has other advantages. The minimum or threshold number of points that must be earned before an indication gains approval can be defined, thus standardizing the process by which new indications are added to the approved list. Indications that are unproven can have gradations of support, based on the number of points that they earn.

Examples of classification systems include a system proposed by the National Institutes of Health for meta-analyses (21), a classification for using therapeutic interventions in cardiopulmonary resuscitation and emergency cardiac care adopted by the American Heart Association (AHA) (22), and a system for evaluating research protocols for inclusion in practice guidelines (23). Our proposed system, which is based on the strength of supporting scientific evidence, is similar to that used by the AHA.

Recommendation 2

Develop a national registry for conducting research into the potentially therapeutic off-label uses of HBO_2T: When physicians repeatedly using HBO_2T on an off-label basis for a particular indication collect information about it in a systematic fashion with the intent to apply the principles of treatment to other patients, they move from practicing medicine to perfornling research. The Belmont Report (1979), which defined ethical principles and guidelines for research involving human subjects, defined research as an activity "designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge" (18).

As information accumulates, a window of opportunity appears during which an intervention such as HBO_2T can be tested in a prospective, concurrently controlled clinical trial. Early on when information is incomplete, the benefits of an intervention may not be sufficient to justify running a trial. As more information is systematically collected, evidence supporting the potential benefit of an intervention may rise and justify initiating such a trial. But if a preponderance of information has already been collected and clearly establishes the benefits of an intervention, then a clinical trial may not be needed (18).

To facilitate future research conducted through randomized, controlled clinical trials, we recommend collecting information in a systematic manner through a national registry created for the off-label uses of HBO_2T. Such information could contribute to the design of clinical trials in an ethical manner (24). The registry would serve two functions. It would collect specific pilot data for use toward designing a prospective, controlled clinical trial and it would collect general data, a preponderance of which might obviate the need for such a trial in circumstances where a trial is not feasible. In effect, a national registry would help identify that window of opportunity during which a clinical trial could be initiated to examine the potentially therapeutic off-label uses of HBO_2T.

As an example, we considered the case of extracorporeal membrane oxygenation (ECMO) in the management of neonatal respiratory insufficiency. Because of early reports in the 1970s that neonates receiving ECMO improved significantly compared with historical controls, there was a general reluctance to run a controlled clinical trial. Consequently, ECMO increasingly became a standard therapeutic intervention without a controlled clinical trial. By 1992, an International ECMO Registry had demonstrated the overwhelmingly beneficial effect of ECMO. Similar findings were found when a randomized, controlled clinical trial of ECMO in 1993 was aborted 2 yr later. Some have considered that by then, in light of the registry data, it may have been too late to run a trial (18,25–29).

Criteria for including the potentially therapeutic off-label use of HBO_2T for a particular indication in a national registry would include the three criteria proposed for identifying potentially therapeutic, off-label uses of HBO_2T (in Recommendation 1) and others (Table 2). These other criteria would include: a significant incidence of the disease, public pressure or demand for the off-label use of HBO_2T for that disease, the availability of a well-defmed protocol for data collection with defined measures for outcomes, appropriate informed consent forms, and funding for the registry. Points could be assigned to these criteria and a summary score determined for a proposed indication. Specialists could thereby understand why the off-label use of HBO_2T for a particular indication did not get into the registry and where efforts to include it in a registry should be targeted.

Two operating bodies would need to be created to work with the registry. A registry management team could oversee the daily operations of the registry. This

Table 2: Criteria for the Off-Label Use of Hyperbaric Oxygen Therapy in a National Registry

1.	Alternative treatments neither cost-efficient nor successful
2.	Human or animal study data supports use
3.	Benefits greater than risks
	c. patient co-morbid conditions
	d. technical capability and safety of the facility
4.	Significant incidence of disease
5.	Public pressure or demand
6.	Well-defined protocol with defined measures for outcomes
7.	Informal consent forms
8.	Funding

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team would uphold patient confidentiality and privacy by ensuring that information about individuals would be stored in an anonymous fashion. Coded data and information from links to other databases could be separated to prohibit the identification of a specific individual. Results, based on aggregate rather than individual data, would be reported.

An independent institutional review board (IRE) created specifically for the registry could review applications to the registry by the criteria proposed. A central independent IRE would simplify the application process for investigators and set a single standard for inclusion into the registry. However, this central independent IRE would not replace the functions of local, institutional IREs whose approval would still be required for all research protocols involving the local institution (18).

Recommendation 3

Develop ethical guidelines incorporating informed consent for physicians responding to requests for the potentially therapeutic off-label use: Physicians should get informed consent from their patients for the off-label use of drugs and other major therapies (29). HBO_2T is a medical procedure that involves both a drug (oxygen) and a device (chamber), and informed consent is necessary regardless of whether the indication is approved or off-label. To be legitimate, informed consent may be obtained in oral or written form but, consistent with the practice of medicine, documentation of the key elements of informed consent and that it took place must appear in the medical record.

For the off-label use of HBO_2T, we recommend that organizations in hyperbaric medicine develop scientific guidelines that will help physicians understand which off-label indications are clearly not beneficial for any patients, and which indications are potentially beneficial for some. Such organizations should then develop ethical guidelines incorporating patient informed consent for the potentially therapeutic off-label use of HBO_2T (Table 3).

A physician should discuss five main issues with a patient as part of informed consent:

1. Are there no alternative medical treatments that are cost-efficient and successful for the proposed indication?
2. What is the level and type of scientific data supporting the potentially therapeutic use of HBO_2T?
3. Are the risks of HBO_2T acceptable relative to the potential benefit? (The physician should also review the ability of the facility to handle complications arising from HBO_2T or the primary disease, the risks and side effects of HBO_2T in general and more specifically in light of a patient's co-morbid condition.)
4. Does the patient understand that he/she will be responsible for the cost of a therapy that may offer no benefit?
5. Is there a research protocol or registry available? If a registry exists for an indication, the physician could offer the patient the opportunity to participate in it. The discussion would then include an explanation of the registry, its purpose, and how patient confidentiality and anonymity will be ensured. Separate informed consent for registry participation would be required.

Additionally, informed consent should include physician disclosure of any financial issues that may affect the physician–patient relationship. Physicians have the potential to receive immediate financial benefit for themselves or their facilities when they administer HBO_2T for an off-label indication. After all, in such cases patients often pay in cash. This represents a potential conflict of interest that should be disclosed (30).

Physicians routinely charge for the management (and sometimes for the provision) of the off-label use of drugs, and charging for the off-label use of HBO_2T is no different. The expense of administering the therapy should be reasonable. Patients may pay for unproven treatments that conform to ethical standards and may pay to participate in research trials if they are informed of their financial obligations and accept the fact that they are research subjects.

Recommendation 4

Create a consortium of hyperbaric clinics: To promote the ethical practice of HBO_2T as a field of medicine and to promote the ethical conduct of research using HBO_2T, a Consortium of Hyperbaric Clinics could be created. This consortium would uphold the principles of respect for persons (individuals as autonomous agents), beneficence (maximizing benefits and minimizing harms), and justice (fair distribution of the benefits and burdens of research) (31,32) upon which these recommendations are based. This consortium would uphold these principles by limiting the use of HBO_2T for approved and potentially therapeutic off-label uses. Membership could include freestanding, academic, and other hospital facilities that subscribe to these principles and recommendations. Finally, in addition to advancing the field of hyperbaric medicine, this consortium, by its very existence, would help the general public identify those practitioners of hyperbaric medicine who promote the ethical and safe use of HBO_2T.

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