Draft Oxygen

In order to supplement my sagging income, I have decided to open a chain of oxygen bars. This seems to me to be a worthwhile business venture for a board-certified pulmonologist. It will satisfy two of the major dictums of modern medicine:

1. Alternative medicine is worthwhile when traditional research-based medical results are unsatisfactory or more expensive; and
2. The most financially successful physicians are entrepreneurs and businessmen.

Although current oxygen bars provide pleasant aromas with the oxygen such as lemon or cherry, I plan to use more medicinal flavors for authenticity. To start with, I am considering menthol eucalyptus, hydrogen sulfide, and “dentist office” flavors.

There is a statistical chance that some of the people actually paying for and going to my oxygen bars will actually need oxygen. They are likely to feel better transiently, and I can use these patrons to provide “testimony” at promotional meetings and in advertisements. If necessary, I can give free passes to some patients with pulmonary fibrosis or COPD.

Although my oxygen bars would be outside the scope of third-party insurance coverage initially, health-maintenance organizations may come to realize that a visit to one of my facilities is cheaper than a visit to a physician. Here comes the big money. All I need to do is to get my oxygen bars on a few local protocols or critical pathways. This may not be as difficult as it sounds. In this age of downsizing competence and transferring care from specialists to primary care physicians, nurse practitioners, and physician assistants, the next step down may likely involve care by practitioners who know little if anything about oxygen. As soon as Dr. Pied Piper realizes that he will be accused of poor quality for not using my alternative therapy, it is likely to be in widespread use.

Once my oxygen bars are successful, I suspect that certain controversies will arise. Is humidification of the oxygen necessary for its full therapeutic effect? Is “natural” oxygen from a concentrator healthier than oxygen obtained from chemical means or tanks? One fear that I have is that once this is established therapy, there will be the assumption that if a little oxygen is good, perhaps a lot is better. Hyperbaric chambers are already being used for treating “senility” and maintenance of youthfulness. My only hope is that these chambers won’t seem as “natural” as my products. There will, of course, have to be a warning for people with chronic hypercapnia or recent chemotherapy. Perhaps I can sell antioxidant vitamins on site to prevent side effects.

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Off-Label Use of Approved Drugs

Throughout the 1980s and continuing into the 1990s, drug pipelines in the biotechnology and pharmaceutical sectors expanded at an unprecedented rate. To expedite the safety and efficacy assessment of these products by the Food and Drug Administration (FDA), the 105th Congress passed the FDA Modernization Act of 1997.

Section 401 of the Act permits drug manufacturers to disseminate reprints of journal articles reporting “off-label” use—unapproved indications, populations, doses, or routes of administration for marketed drugs—directly to the medical community. A key element of the drug regulatory process is the package insert, or “labeling.” The labeling serves two important functions: it presents the indications for which a drug is approved, and it summarizes the
safety and efficacy information obtained from clinical trials conducted by the manufacturer (the “sponsor”). Drug labeling is an ongoing process, with frequent revisions being made to expand or restrict the indications for a drug, or even its availability, as more clinical experience is gained.2

Once a product has been approved by the FDA, individual investigators frequently undertake clinical trials that explore off-label uses, some of which ultimately are reported in peer-reviewed journals. Occasionally, an article may be so compelling that it changes clinical practice. Nevertheless, sponsors must still conduct their own phase IV postmarketing trials, and they must demonstrate to the FDA that the drug is safe and effective for the desired purpose, if they wish to advertise the use directly to the medical community.

With this new rule from HHS, sponsors can, in effect, promote off-label use to practitioners before they formally begin phase IV trials. Effective November 29, 1998, sponsors may disseminate “directly to a health care practitioner, pharmacy benefit manager, health insurance issuer, (or) a group health plan . . .” reprints of clinical investigations that appear in peer-reviewed reference textbooks and journals listed in Index Medicus. These articles report unapproved uses that the manufacturer intends to study and submit to the FDA within 36 months. Sponsors can receive an exemption from conducting these studies if they demonstrate that it would be “economically prohibitive,” ie, the costs of the studies would exceed the estimated total revenue from the product minus the costs of goods sold and marketing and administrative expenses.

In return, manufacturers are bound by certain restrictions: (1) reprints must be submitted to the FDA for approval before dissemination; (2) each reprint must display a statement advising readers that the off-label use(s) described in the article has not been reviewed by the FDA; and (3) the publication must be scientifically sound, ie, it must be “prospectively planned, enroll the appropriate population for the condition of interest, account for ‘drop-outs,’ utilize meaningful end points that are likely to predict safety and effectiveness, include appropriate controls, report adverse events, and analyze the data in a scientifically appropriate manner.”

(These restrictions were recently challenged in federal court. In a landmark decision issued on July 30, 1998, District of Columbia Federal Judge Royce Lamberth ruled that, even though the FDA can mandate that sponsors conduct postmarketing studies before making off-label marketing claims, FDA criteria for what kind of articles can be disseminated are too restrictive. In a subsequent ruling on July 28, 1999, Judge Lamberth further declared that the FDA’s restrictions are indefensible violations of the Constitution, amounting to “Constitutional blackmail.”)

One advantage of the rule for the pharmaceutical industry is obvious: name recognition. During a new product launch, manufacturers ramp-up their advertising campaign in order to gain a foothold in the marketplace. Permitting drug representatives to distribute reprints of the latest off-label studies directly to physicians provides high-profile visibility in a professionally acceptable format, thereby improving the market position of the product. Of perhaps even greater importance to manufacturers than name recognition, however, is the possibility that the ruling could serve as a cost-effective strategic planning tool. By analyzing which articles resulted in increased sales, upper management would have a financial criterion that it could use to make rational decisions about future budgeting of off-label trials.

As a regulatory document, the rule sets forth some “interesting” notions. For example, the FDA agrees that “all journal articles . . . in peer-reviewed publications are scientifically sound (except letters to the editor, abstracts, phase I trials in healthy people, publications that contain little or no substantive discussion of the relevant clinical investigation, and reports in four or fewer people)” Inferring that editorial boards use identical criteria in judging whether to accept or reject a given manuscript is an oversimplification of the peer-review process that minimizes factors such as reviewer bias, the intended audience, differing journal standards, and competition for subscribers within the medical publishing industry. Additionally, the rule states that it is the intent of the FDA that scientifically sound articles can include “historically-controlled studies, retrospective analyses, (and) open label studies,” whereas most individuals in the research and regulatory communities regard such studies as inherently flawed and biased trial designs.

A key concern for clinicians is the impact the rule may have on patient safety. Studies show that some physicians base their prescribing decisions on promotional materials rather than scientific research, prescribing inappropriate or dangerous drugs when there are more effective, safer alternatives available.3–6 Because individual investigator-initiated off-label studies typically enroll too few subjects to generate a reliable safety profile, a rise in off-label use could increase the number of individuals at risk of serious adverse events. Drugs recently withdrawn from the marketplace by the FDA for this reason include “Fen-Phen”—an unapproved combination of two weight-reduction drugs (fenfluramine [Pondimin; Wyeth-Ayerst Laboratories; Philadelphia, PA]
and phentermine [Redux; Wyeth-Ayerst Laboratories]) that is associated with cardiac valvular insufficiency—and the analgesic bromfenac (Duract; Wyeth-Ayerst Laboratories), which led to fulminant liver failure when it was prescribed to patients for months, instead of the 10-day maximum as directed in the labeling. Clearly, the more “untested” the use, the greater the risk for serious and unexpected side effects.

Does this mean that drugs should never be prescribed for unapproved purposes? I believe the answer to this question is “No.” For millions of patients, the benefits of off-label use clearly outweigh the risks, especially for drugs with a long track record of safety. It is not widely appreciated, however, that new drugs are being approved by FDA at a faster rate today than ever before, even when medical experts on its own advisory panels raise serious safety questions.7

Each year, > 100,000 Americans die from serious adverse drug events when these products are used as the labeling indicates.8 Practitioners should bear this in mind the next time they consider using a drug “off-label.”

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Difficulties With Diagnosing Asthma in the Elderly

National trends in the morbidity and mortality associated with asthma have demonstrated that this is a common disease in the elderly. Evans et al1 reported in 1987 that the rate for active asthma was 10.4% for 65- to 74-year-olds, with lower rates found in all other age groups. Mortality studies in the United States from 1977 and 1982, respectively, demonstrated a higher per capita death rate of 3.0 and 4.9 per 100,000 for adults 65 to 74 years old, compared to 0.5 and 0.6 per 100,000 for younger adults >35 years old.1 Similar findings have been reported elsewhere. Burr et al2 reported on a south Wales town where there was a 6.5% rate for history of asthma for persons >70 years old, and 2.9% with active disease. A review of asthma mortality in England found that 58% of the male patients and 71% of the female patients whose deaths were attributable to asthma were >70 years old.3 A study by Barger et al4 in 1982 showed similar findings, where 80% of asthma deaths were in persons >55 years old. However, there were many confounding factors in these deaths, including COPD and non-respiratory problems, and only 33% of these patients died from pure asthma. Since these reports, the National Institutes of Health (NIH) published initially in 1991 and again in 1997 several guidelines for all clinicians on the diagnosis and management of asthma. The NIH published another guideline in 1996 to specifically address asthma diagnosis and management in the elderly.

There is little evidence that clinicians are doing well with the management of asthma in the elderly. Banerjee et al5 clearly documented in 1987 that although there is a higher frequency of asthma in the elderly, it is usually underdiagnosed and undertreated. Similar reports have confirmed these findings. A retrospective cohort study in Rochester, Minnesota from 1964 to 1983 identified 98 elderly patients with asthma. Their diagnostic evaluation was less intensive than recommended guidelines, and there was infrequent use of pulmonary function testing to guide therapy.6 In this issue of CHEST (see page 603), Enright and colleagues highlight the ongoing problem that clinicians still lack the proper approach to the diagnosis and management of asthma. The authors expanded their original research from the Cardiovascular Health Study done in from 1989 to 1990 to develop more data on respiratory complaints in the elderly. They originally reported on this group of elderly patients in 1994, noting that dyspnea on exertion and wheezing was common and airway obstruction was frequently un-
diagnosed. The group of patients from the Cardiovascular Health Study was expanded to include more minority patients and more questions on asthma and sleeping habits. The expanded cohort reported in this study underwent a repeat evaluation to include a baseline spirometry and a 1-week serial peak flow measurement.

This article demonstrates several important points about asthma in the elderly. The responses given by these patients demonstrate that elderly asthmatics rated themselves lower on functional status, well-being, and general health than did those without asthma. Furthermore, they were more likely to report usual daytime sleepiness. These data suggest that asthma symptoms are fairly common and definitely impact on the quality of life. There are also many common medical problems that cause dyspnea and make spirometry measurements in the elderly difficult to interpret. A fixed obstructive defect can be due to either COPD or chronic asthma, and congestive heart failure (CHF) may demonstrate restrictive changes. Elderly patients with asthma have been shown to have chronic persistent airflow obstruction on pulmonary function testing. The authors have attempted to better identify their patients who only have asthma by excluding those with CHF and a significant prior smoking history. Several prior studies, such as the Tucson community study, did not exclude smokers from the analysis.

There are several limitations to this study that may alter the validity of the conclusions presented by the authors. They did not evaluate these patients specifically to confirm the presence of asthma, nor was it the intent of the Cardiovascular Health Study to do so. There was no attempt to confirm the presence or absence of airway hypersensitivity by either broncho-provocation testing or serial spirometry in association with symptoms. As such, there is no true incidence of asthma in this study as defined by spirometric data. However, 92 participants were defined as “definite asthma” based on three factors: previous diagnosis of asthma, current diagnosis of asthma, and confirmation by a physician. There are no data presented that identify which patients had asthma previously confirmed by spirometry. This information is essential in establishing if asthma was correctly diagnosed on the basis of airway obstruction and not solely on subjective findings. With such a subjective basis for the definition of asthma, it is not surprising that 59% of these patients with “definite asthma” had normal spirometry. Forty-two percent of these patients with “definite asthma” had normal spirometry and a 1-week serial peak flow measurement.

The data suggest several alternatives that are not addressed by the authors. First, the historical diagnosis of asthma in their cohort of patients could be incorrect. While given the diagnosis of asthma, did their primary physician properly evaluate these patients and did they meet NIH criteria? It would be interesting to know what percentage of these patients actually had spirometry done in the previous year or during their initial evaluation. The data presented suggest that there was an incomplete initial evaluation and treatment despite the frequency of symptoms. Furthermore, if the diagnosis of asthma is incorrect, what is the true diagnosis in these patients? While diseases such as COPD and CHF were eliminated from the study analysis, there still may be many possibilities for the cause of their reported symptoms.

The extent of symptoms described in this group of patients in the Cardiovascular Research Study emphasizes that respiratory complaints are common in the elderly. It has been well documented that there is a significant incidence of asthma in the elderly. Clinicians must ensure that there is a complete and proper evaluation of these complaints. Utilization of the established guidelines to effectively diagnosis and treat asthma in the elderly would lessen their symptoms and comorbidity. A study of the treatment of elderly asthma patients based on both symptoms and evidence of airway obstruction since the publication of the NIH guidelines would further define how well these patients are being managed.

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The Definition of Survival

Physicians, surgeons, and other health professionals often use survival data to guide the treatment of patients with cancer. Such data (especially when stratified by stage and cell type) allow the evaluation of competing therapies and help patients gain a perspective on their illness. In most instances, a statistical discussion between patients and caregivers occurs around the time of diagnosis, and cumulative survival data are cited. However, as the course of a patient’s disease unfolds, information related to the patient’s prognosis following an initial period of survival becomes more appropriate. In this issue of CHEST (see page 697), Merrill and colleagues provide us with such “conditional” survival data for patients with lung cancer. From their analysis of data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, one can predict, for example, the likelihood that a patient who presents for 2-year follow-up after lobectomy for early stage lung cancer will survive an additional 5 years. Clearly, such information allows for a more enlightened evaluation and discussion. It may also help determine how aggressively to intervene in other health problems.

Unfortunately, the manner in which the SEER data are collected does not provide as much information as we might like. Instead of using the International Staging System, patients are divided into localized, regional, distant, and unstaged disease. Whereas localized disease translates into stages IA and IB, patients with regional disease include those in stages II, IIIA, and IIIB, a heterogeneous group with differing cumulative survivals. In addition, observed survival (from all causes) rather than survival relative to the overall population is reported. This makes it seem that the disease causes more deaths than is actually the case.

Aside from the obvious scientific utility of this information, it is interesting to speculate on the use of survival data in discussing treatment options with an individual cancer patient. Patients with cancer often ask for survival statistics, and their doctors are more than willing to provide that information. In contrast, patients with equally serious benign illnesses (such as diabetic ketoacidosis or dilated cardiomyopathy, for example) are less likely to engage in these detailed statistical discussions. I believe that there are reasons for this discrepancy and that our patients’ welfare may be jeopardized by our complicity with their wish for numerical prognostications.

Statistical description may represent an attempt to gain a sense of control over illness when our therapeutic success is limited. Despite improvements in surgical therapy, better chemotherapy, and modern radiation oncology, the likelihood of successfully treating patients with lung cancer has changed little over the past decades. This frustration and seeming lack of ability to impact on the disease process may, I believe, lead to an emphasis on the statistical description of the illness. Concern over these often-negative statistics may serve to mask the positive interventions that can prolong life and ease suffering. A preoccupation with data may dehumanize rather than help patients and their loved ones.

These survival curves can also be destructive when they create (inevitably) a perception that cancer is an “all or none” disease. Patients and their doctors forget that many patients who are not “cured” can in fact live healthy and productive lives with cancer. Newer therapeutic strategies such as antiangiogenic metalloproteinase inhibitors may help improve the lives of patients with metastatic disease. Treatment does not have to be curative to be effective. Neither coronary artery bypass surgery nor angioplasty nor medical therapies cure coronary artery disease. Insulin does not cure diabetes. However, there is no doubt that these therapies are worthwhile. They decrease suffering and prolong healthful lives.

When faced with nonmalignant chronic illness, caregivers are typically concerned with prolonging good health (diabetics are not only given insulin but are encouraged to lose weight, stop smoking, and exercise). However, when the chronic illness is cancer, it is often “survive or die.” Framing the disease in this way not only robs patients of the hope of living well with either persistent or recurrent disease, it may lead to inappropriate risk taking in an attempt at cure. In addition, interventions not destined to “cure” may be rejected even though they have a substantial chance of improving survival. The needs of patients who cannot be cured should be given more rather than less of our attention.

Most patients do not understand the implications of statistical analyses on their particular situation. Unlikely events may be thought of as impossible. A
risk of 1%, for example, is usually discounted completely. When a low chance of survival is cited, the patients may see their situation as hopeless. They do not realize that the people who survive are 100% alive. When using numbers, we must be careful to relate them to a patient’s particular situation in an understandable fashion. We should discuss not only survival but also quality of life. Patients should be given the opportunity to contribute their perspectives as well.

Studies of large groups of patients such as this one by Merrill and colleagues, as well as detailed studies of smaller groups, are invaluable for improving the care of patients with cancer. For the individual, these data can be a helpful guide in facing life’s inevitable choices. However, we must be careful to interpret this information for our patients and to keep their overall best interests foremost in mind. Cancer, like life, is not an “all or none” phenomenon. As physicians, we have the privilege of helping patients deal with life’s complexity. Let’s not oversimplify the task.

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