Percentage Set Straight

In her editorial, Dr Fitzgerald discusses the limitations to the generalizability of the findings reported in our article. Dr Fitzgerald correctly stresses the important issue that an individualized treatment regimen does not apply to the usual population of alcoholic patients admitted to most hospitals in the United States. However, it is not correct to say that only 6% of eligible patients (117 of 2000) were ultimately included in the study since the final inclusion rate was 48.1% (117 of 243, see the article’s “Results” section, p 1119).

Because such misinterpretation of the results might reduce the interest of the study, would the journal consider publishing an erratum?

Jean-Bernard Daeppen, MD
Lausanne, Switzerland

In reply

I thank Dr Daeppen for the opportunity to clarify my editorial. When I wrote that “Only 117 (6%) of 2000 consecutive patients admitted to the treatment program in Switzerland were ultimately included for analysis in the study,” I meant just that. As Dr Daeppen and his colleagues pointed out in their article, 2000 patients were consecutively admitted in a little over 1 year to the inpatient alcohol treatment programs of 2 university-affiliated clinics with a combined capacity of 22 beds. For what the authors call “staff organization” reasons, only 2 patients per week per clinic could be included in the study, a total of 243 persons.

Dr Daeppen is correct when he says that my statement of this was possibly confusing. What I should have said was that “Of the 2000 patients admitted for alcoholism, 243 could be evaluated for the study, of whom 48% (117) were finally included.”

It is still important to note that whatever the staff organization issues were, they limited the total number of possible entrants into the study to so few of the presenting population of alcoholic patients admitted for treatment that it might indeed affect the generalizability, and so the impact, of this excellent work. I look forward to reports of studies of larger patient groups to assess feasibility of the PRN (as the occasion requires) approach to therapy of alcohol withdrawal: it won’t matter how good the therapy is if it cannot be practically done for the majority of those who would benefit.

Faith T. Fitzgerald, MD, MACP
Davis, Calif

Statin Use and Fracture Risk

We were fascinated by the reduction in fracture risk with statin therapy reported by the Geelong Osteoporosis Study (odds ratio, 0.40; adjusted odds ratio, 0.45). These striking results are in concordance with 3 other published observational studies that found fracture risk reductions of similar magnitudes associated with statin exposure. However, they are in conflict with the results of a randomized clinical trial that found no association between pravastatin use and fracture risk.

The explanation offered for the difference between these results is heterogeneity of effect on bone morphogenic protein-2 production between statins, and this contention is supported by in vitro data showing that pravastatin does not have the same effect as other statins on this biological marker. This intriguing hypothesis and its role in the divergence between the observational results and the pravastatin clinical trial results could be supported by presenting a subgroup analysis of effect according to specific statin, and we encourage the authors of the Geelong Osteoporosis Study to present such a subgroup analysis if data on specific statins are available. Since the other observational studies showing substantially reduced fracture risk with statin therapy included some pravastatin exposure, demonstrating that pravastatin is ineffective at preventing fracture would imply that the other statins are even more effective than the combined results would suggest.

Interestingly, another randomized clinical trial of statin therapy also reported no association between statin use and fracture risk. These results from a randomized clinical trial of simvastatin suggest that the heterogeneity of effect on fracture risk between studies is not statin dependent but rather study design dependent, with clinical trials finding no effect while observational studies find substantial effect. However, this dichotomy between randomized clinical trials and observational studies is complicated by one observational study reporting no association between statin use (all statins combined) and fracture risk.

With proper control of confounding, results from observational studies should not differ from those of randomized controlled trials. Instead of differences between statins being the source of heterogeneity in results across studies, some uncontrolled confounding variable (or suite of them) might be responsible for the divergent observational and clinical trial results. Such a divergence represents an opportunity to learn something new: some unexpected variable might be confounding the observed association between statin use and fracture risk, and observational researchers would welcome its elucidation.

John D. Seeger, PharmD, DrPH
Hyon K. Choi, MD, MPH
Newton, Mass

In reply

As Seeger and Choi have pointed out, pravastatin does not share the in vitro effect of other statins on bone morphogenetic protein-2 production. Subgroup analysis of data from the Geelong Osteoporosis Study for pravastatin alone was not performed because the subsample size was too small for statistical analysis. From a group of 69 statin users, 10 used pravastatin (3 from the fracture group and 7 from the nonfracture group). However, the original data set has been reanalyzed with pravastatin users excluded, and results are presented in the Table.

After exclusion of pravastatin, the substantial reduction in fracture risk associated with statin use was maintained. Moreover, the point estimates show a consistent trend toward greater protection against fracture. Confounding by differences in age, weight, dietary calcium intake, smoking, level of physical activity, exposure to hormone replacement therapy, and use of alcohol, glucocorticoids, and calcium and/or vitamin D supplements again failed to explain the reduced fracture risk associated with statin use.

The apparent dilution by pravastatin of the effect of statins may be consistent with the observations of Reid et al., who reported no association between pravastatin use and fracture risk in a randomized clinical trial. It should be noted that the reanalysis by Reid et al of the LIPID cohort (Long-term Intervention With Pravastatin in Ischaemic Disease) and the post hoc analysis of the 4S study (Scandinavian Simvastatin Survival Study) involved cohorts selected on the basis of coronary artery disease and were not designed to assess fracture as a primary outcome. The ascertainment of fractures and effect of increased mortality in the placebo groups potentially reduced the power of these studies.

Observational studies may be subject to unrecognized confounding. We and others have used statistical methods to adjust for potential confounding and have observed a reduction in fracture risk, whereas van Staa et al reported no reduction in fracture risk among statin users. It is unlikely that dyslipidemia, or a suite of confounders associated with dyslipidemia, is responsible for any decrease in fracture risk associated with statin use because none of the reported studies has reported an effect with nonstatin therapy or hypercholesterolemia. We agree with Seeger and Choi that identification of any uncontrolled confounding in the association between exposure to statins and protection against fracture would be illuminating. Furthermore, a definitive, randomized, placebo-controlled study examining a population at high risk of fracture is yet to be published.

Julie A. Pasco, PhD
Mark A. Kotowicz, MBBS, FRACP
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The Geelong Osteoporosis Study, of which this reanalysis is a part, was supported by the Victorian Health Promotion Foundation, Melbourne, Australia.

Odds Ratios (95% Confidence Intervals) for Bone Fracture Associated With Statin Treatment With and Without Pravastatin in Subjects of the Geelong Osteoporosis Study

<table>
<thead>
<tr>
<th>Pravastatin Treatment</th>
<th>Unadjusted</th>
<th>Adjusted*</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Femoral Neck</td>
<td>Spine (L2-L4)</td>
</tr>
<tr>
<td>Included (n = 69)†</td>
<td>0.40 (0.23-0.71)</td>
<td>0.45 (0.25-0.80)</td>
</tr>
<tr>
<td>Not included (n = 59)‡</td>
<td>0.38 (0.20-0.71)</td>
<td>0.42 (0.22-0.79)</td>
</tr>
</tbody>
</table>

*Adjusted for bone mineral density at the indicated measurement location.
†Sixteen subjects in the fracture group; 53 in the nonfracture group.
‡Thirteen subjects in the fracture group; 46 in the nonfracture group.

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Falls and 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors

In a recent issue of the ARCHIVES,1 we reported lower fracture risk among women taking 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) for hypercholesterolemia. The research was prompted by the finding that statins increase bone morphogenetic protein-2, leading to osteoblast differentiation and bone formation.2 The substantial 60% reduction in fracture risk we reported persisted after adjusting for potential confounders and was greater than expected from increases observed in bone mineral density alone.

Recent data from Britain3 and Australia4 support a role for statins in preventing age-related macular degeneration. The authors suggest that statins might prevent the accumulation of basal linear deposit in the Bruch membrane, protect the retina from oxidative damage, and maintain a competent vascular supply to the macula.5 Statins have also been reported to protect against dementia, which may be explained, at least in part, by the protective effect of statins on vascular disorders.6 Given that poor vision and impaired cognitive function are independently associated with increased risk of falls and fracture,6,7 we hypothesized that statins may reduce fracture risk by protecting against maculopathy and dementia. We did not collect visual acuity or dementia data, but we could examine falls data.

Of 1375 women studied,1 self-reported falls data were available for 1345 women (563 with incident fractures and 782 selected at random from the population without incident fractures), including 50 women who had used statins for at least 12 months (age range of all women, 50-95 years; median age, 70.0 years). Women who reported not falling or rarely falling during the previous 12 months were classified as nonfallers, whereas those with few, several, or regular falls were classified as fallers. Of the 1345 women assessed, 331 (24.6%) were classified as fallers. There were 16 (4.8%) statin users in the fallers group and 34 (3.4%) in the nonfallers group (P = .20, 2 test). After adjusting for age and fracture status, the odds ratio for falls among statin users was 1.63 (95% confidence interval, 0.88-3.03).

Our study indicates that statins do not protect against falls, and the point estimate suggests that falls risk may be increased. It is possible that patients prescribed statins have preexisting vascular conditions that predispose them to falls. Myotoxic effects of statins ranging from mild nonspecific myalgia to myositis with raised concentrations of creatine kinase have been reported.8 Although rare, these adverse reactions are shared by all statins and may predispose users to increased falls. Given that falls increase the risk of fracture, these observational data suggest that the protective effect of statins on bone fragility may have been underestimated. The results of prospective randomized trials are awaited with interest.

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Integrative Medicine Is a Trojan Horse

Dr Andrew Weil is a strong advocate for integration of complementary alternative medicine (CAM) into medical training and practice.1,2 The purpose of this communication is to respond to a recent position paper on this topic that he coauthored with Snyderman.3 I believe that the rationale they present for integrative medicine is unconvincing, and their depiction of its principles and practices is misleading.

The first part of their article addresses the crisis in the American health care system, “The chassis is broken and the wheels are coming off.” Their analysis of the crisis emphasizes the deterioration in patient-physician relationships, which they attribute to scientific medicine. They acknowledge that the reforms in medical education that followed the Flexner report improved understanding of disease and medical care. However, they state that emphasis on developing a scientific basis for medical practice led to a reductionist model of medicine that emphasizes molecular biology, technology, and subspecialization at the expense of compassion and patient-physician interactions. They also state that because of its “single-minded focus on the pathophysiological basis of disease,” mainstream medicine has turned its back on many complex clinical conditions.

The growing problems in the American health care system have been the subject of countless articles and books during the last 15 years. These commentaries focus on different aspects of health care organization and financing, but none present an analysis as narrow and oversimplified as that presented by Snyderman and Weil. To address only a few points, their analysis ignores the fact that there is no health care system, only a patchwork of private and government insurance that leaves out 40 to 50 million people. There is no mention of the powerful economic and political forces that shape the delivery of health care and obstruct reform. As they point out, economic forces have imposed a corporate structure on the delivery of health care, and severely limited the amount of time physicians can spend with patients. Physicians certainly bear some responsibility for the high cost of health care, but the medical profession has no control of major factors such as the price of medications, or profit-driven hospitals and insurance companies.
In their promotion of CAM, Weil and others present a caricature of medical education and practice, and contrast it with an idyllic picture of alternative medicine. The philosophy of biomedicine is described by leading naturopathic educators as follows, “The body is a machine; the body and mind are separate; the physician should be emotionally neutral and detached.” I have been an educator for almost 40 years, and this version of the medical curriculum has no basis in reality. I have addressed in detail elsewhere these misrepresentations of medical education. The concept that practitioners versed in pathophysiology are “more focused on disease than healing and wellness,” and that practitioners who embrace alternative practices are all sensitive and compassionate, is not supported by data and is not credible.

The remedy prescribed by Snyderman and Weil for the health care crisis is integrative medicine, which includes CAM and an emphasis on patient-centered care, preventive medicine: diet, exercise, and stress management. They state that conventional medicine does not appreciate the importance of a healthy lifestyle. While that might have been true to some extent 20 to 30 years ago, there is now a vast literature on the role of diet, obesity, and exercise in the prevention and management of cardiovascular disease, diabetes, and all-cause mortality. The real problem is how to motivate people to implement this advice, and to exercise more and to eat less. The lifestyle issues are a matter of emphasis, and are not fundamental differences between integrative and conventional medicine. To understand the real differences, which are not evident in their article, it is necessary to examine Weil’s beliefs about disease, and how integrative medicine is practiced in his program.

Dr Weil’s beliefs have been presented in his books and in his daily online column, “Ask Dr. Weil.” In his article, “A Trip to Stonesville,” Relman provided a detailed summary of Weil’s writings. One of Weil’s core beliefs is that one can obtain more insight into disease and healing from intuition, from personal experience, and from states of altered consciousness than from straight thinking. He believes that all healing is natural healing, and in the power of the mind to cure many ailments. A great deal of space in Weil’s recent books is devoted to stories of healing that have the following scenario: a person who is suffering from inept, impersonal medical care, or the adverse effects of medications, is cured by embracing a new lifestyle and alternative treatments. A typical anecdote concerns a person with cancer who was given a “death sentence” by a physician but survived after treatment by an alternative practitioner. Weil is not concerned with scientific data, and his statements about the efficacy of alternative treatments are unsupported by evidence.

Several years ago, Dr Weil established a 2-year fellowship in Integrative Medicine at the University of Arizona for physicians who have completed residency training in primary care. Since he presents his fellowship as a model program, it is important to consider some examples of how patients are treated. During a visit to the program in April 2000, I attended a weekly meeting during which new cases were presented to the fellows and faculty, and treatment plans were formulated. Each patient’s problems and “allopathic” medications were reviewed in a thoughtful manner. In contrast, alternative treatments were then prescribed for each patient without any discussion of specific indications, evidence for efficacy, or potential adverse effects. For example, one patient had complaints of fatigue, insomnia, bloating, and esophageal reflux. Recommendations for alternative treatments included meditation; hypnosis and guided imagery; fennel seeds for gas; calcium, magnesium, and garlic for hypertension; cholesterol for hyperlipidemia; and an investigation of possible dysbiosis (a naturopathic diagnosis) and candidiasis of the gastrointestinal tract. A patient with polymyalgia rheumatica/giant cell arteritis wanted help in discontinuing prednisone. The prescription for this patient included ginger, tumeric, and curcumin to strengthen the immune system.

Herbal medications were prescribed for all patients, which is understandable in view of Dr Weil’s background in botanical medicine. His enthusiasm for herbs seems to be unaffected by accumulating data on the adulteration of herbs by prescription medicines and heavy metals, toxicity, and herb-drug interactions. For example, in 2000 there were case reports of problems that resulted from a decrease in the blood levels of a number of medications, including warfarin, digitalis, theophylline, cyclosporine, and antiretroviral drugs, in patients who took St John’s wort. A subsequent study demonstrated that St John’s wort activated hepatic P450 enzymes that increased the rate of metabolism of many drugs. In an online column on May 7, 2001, some time after these reports, Dr Weil responded to a question about the appropriate dose of St John’s wort. He mentioned only some minor side effects associated with its use, and didn’t refer to possible herb-drug interactions.

In the concluding section of their article, Snyderman and Weil state, “Integrative medicine is not a radical movement, but it can produce major change.” They then present 5 ways in which medical education and practice must change, including promoting research and evaluation of CAM, strengthening patient-physician relationships, and incorporating evidence-based CAM into medical practice. However, there is no valid evidence base for CAM. Recent systematic reviews of publications that are cited to support the efficacy of CAM have concluded that the quality of most of these articles is so poor that no conclusions can be drawn. The depiction of integrative medicine by Snyderman and Weil is misleading because it presents only general principles, and it does not communicate the reality of how integrative medicine is practiced. The CAM component of that practice is a radical departure from science-based medicine: it is a reversion to the pre-Flexnerian era of 100 years ago.

Education about CAM should be incorporated into medical education and postgraduate training. Physicians need to become familiar with the conceptual basis of CAM therapies, and with current data on their efficacy and safety. They should incorporate questions about CAM use into their histories, provide advice to patients who seek guidance, and be sensitive to the needs of patients with chronic, incurable diseases. However, there should be only one standard of evidence for...
medical care, and CAM therapies should meet that standard. Education about CAM should not be entrusted solely to individuals who promote it, who are dismissive of scientific thinking, and who wish to introduce a Trojan horse of belief-based medicine into academic medical centers. Moreover, in institutions where integrative medicine programs are in operation, leaders of clinical departments need to be aware that patients may be receiving unproven and potentially dangerous treatments.

Donald M. Marcus, MD
Houston, Tex

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In reply

Dr Marcus’ response to our article illustrates the difficulties that often arise when one attempts a rational discussion of integrative medicine with some members of the conventional medical community. Dr Marcus raises serious concerns with CAM, but his arguments are not relevant to the points of our article. As we indicated, while the dysfunction in our current health care system is the result of manifold problems, our article addresses the significant erosion of the physician-patient relationship. The restoration of this relationship is necessary to revitalize the core of medical practice and is a major tenet of integrative medicine.

Dr Marcus seems to be confused about our position on science-based medicine, which we fully support. We believe, however, that the greater potential of a treatment to cause harm, the stricter the standard of evidence it should be held to, whether it be conventional or alternative.

Dr Marcus’ attempt to claim ownership of the lifestyle piece of integrative medicine for conventional medicine is laughable. As one example: the food served to patients in American hospitals should be a national scandal and a great percentage of American hospitals have fast food restaurants on their premises.

With regard to CAM, Dr Marcus ignores what we wrote and draws on a radical “straw man” position of CAM not stated or supported by our article. We specifically indicate that CAM approaches need to be scientifically validated. Dr Marcus states that there is no valid basis for CAM—a blanket indictment that speaks of his lack of objectivity regarding this field. He may not be aware that the National Center for Complementary and Alternative Medicine and the National Institutes of Health are currently funding approximately $250 million per year to support research in this area. And in his superficial visit to the program in Integrative Medicine at the University of Arizona, he seems to not have understood the system he witnessed. After listening to the viewpoints of various CAM practitioners, fellows do a literature search to see which treatments are best supported by evidence; this is how they learn to think critically and construct treatment plans that are safe and likely to be effective.

Integrative medicine, as it is being developed by leading academic medical centers, truly does incorporate the best of conventional medicine, but focuses on bringing the patient-physician relationship back to primacy, values a broader range of patient needs, and incorporates selective CAM practices where appropriate. In actuality, despite Dr Marcus’ highly critical tone, we find little if anything he disagrees with in our article. Perhaps he should take several deep breaths and reread it.

RALPH SNYDERMAN, MD
DURHAM, NC
ANDREW WEIL, MD
TUCSON, ARIZ

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