Treatment of Mild Depression in Elderly Patients

To the Editor: Dr Williams and colleagues[1] found that paroxetine was superior to psychotherapy in treating dysthymia and minor depression among older patients in a primary care setting. However, their study was seriously flawed in the choice and administration of the psychotherapy component.

The patients who received psychotherapy were provided a previously unknown and untested protocol called problem-solving treatment–primary care (PST-PC). Although PST-PC is reportedly based on cognitive-behavioral principles, the authors noted that the procedure is unpublished, making it an unknown entity that has been not peer reviewed. Furthermore, although the study used psychotherapists from a variety of disciplines, these practitioners presumably were not allowed to use more common psychotherapeutic interventions. Thus, this was a test of PST-PC, not psychotherapy.

The authors also report that the psychotherapy patients received a total of 6 sessions during 10 weeks, the first session lasted 1 hour and the remaining 5 treatment sessions lasted 30 minutes each. In total, these patients received 3½ hours of therapy during a 10-week period. This is an extremely "low-dose" intervention, and it is little wonder that the patients had such a poor response to it.

I believe it is misleading to claim that the study compares a well-known antidepressant drug regimen with "psychotherapy." It merely demonstrates that PST-PC, whatever it might be, is ineffective in a regimen that offers short and infrequent treatment sessions.

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1. Williams JW Jr, Barrett J, Oxman T, et al. Treatment of dysthymia and minor depression in primary care: a randomized controlled trial in older adults. *JAMA*. 2000;284:1519-1526.

To the Editor: Although I applaud the effort by Dr Williams and colleagues[1] to recognize and treat depression in elderly patients, I am concerned about their choice of paroxetine for this study population. Patients enrolled in this study had a mean age of 71 years. Patients with moderate or severe cognitive impairment, as defined by a Folstein Mini-Mental State Examination (MMSE) score of 23 or less, were excluded. A low MMSE score is a nonspecific finding and could indicate either dementia or delirium.

Dementia affects approximately 5% to 8% of individuals older than 65 years and 15% to 20% of individuals older than 75 years.[2] It has been shown that cell loss in the nucleus basalis of Meynert may be involved in the etiology of Alzheimer disease and other related disorders. The cells of the nucleus basalis of Meynert are cholinergic.[3] Treatment of these disorders may involve cholinesterase inhibitors to prevent cognitive and functional losses.[4] Paroxetine has the strongest anticholinergic effect of all the selective serotonin reuptake inhibitors. Thus, this treatment may worsen underlying medical conditions in elderly patients. Unless clinicians are as stringent as the investigators of this study in detecting elderly patients with MMSE scores of 23 or less before initiating paroxetine treatment, such patients may not be identified.

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1. Williams JW Jr, Barrett J, Oxman T, et al. Treatment of dysthymia and minor depression in primary care: a randomized controlled trial in older adults. *JAMA*. 2000;284:1519-1526.
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To the Editor: Dr Williams and colleagues[1] concluded that paroxetine showed moderate benefit for depressive symptoms and mental health functioning in elderly patients with dysthymia and more severely impaired elderly patients with minor depression. We feel that this conclusion is more optimistic than would be suggested by more precise expressions for the treatment effect, namely the absolute risk reduction (ARR) and the number needed to treat (NNT).[2] It is possible to calculate the NNT from the authors' Table 3, which shows remission rates for patients attending 4 or more treatment sessions. For both dysthymia and minor depression, 52 of 106 (49.1%) patients receiving paroxetine reached remission, compared to 53 of 119 (44.5%) patients receiving placebo. The ARR is therefore 4.6%. In other words, the individual patient has a 4.6% chance of benefiting from paroxetine. However, the 95% confidence interval (CI) of the ARR is –8.5% to 17.6%.[3] The interval contains 0 and so it can be concluded that the ARR is not statistically significant. Even the 90% CI does not reach significance (–6.6%

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Letters Section Editors: Stephen J. Lurie, MD, PhD, Senior Editor; Phil B. Fontanarosa, MD, Executive Deputy Editor.

to 15.5%). The NNT is 100/4.6=21.7. This indicates that about 22 older patients with minor depression or dysthymia need to be treated with paroxetine rather than standard or placebo treatment for 1 additional patient to benefit after 11 weeks of treatment. The 95% CI of the NNT goes to infinity because 0 is part of the 95% CI for the ARR. Thus, the 95% CI of the NNT (benefit) is 5.68 to infinity and the NNT (harm) is 11.7 to infinity.[4] Given the ARR and NNT with their 95% CIs, we believe that paroxetine did not show benefit.

Finally, because the usual care in this group of patients is often less extensive than the care received by patients in the current study regardless of group, it is unfortunate that a group receiving usual care was not included in the design. In this type of more realistic experiment, it is possible that the magnitude of the effect for paroxetine would have been more substantial.

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1. Williams JW Jr, Barrett J, Oxman T, et al. Treatment of dysthymia and minor depression in primary care: a randomized controlled trial in older adults. *JAMA*. 2000;284:1519-1526.
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In Reply: In response to Mr Freeny, PST-PC is a promising, behaviorally based, psychological treatment developed specifically for primary care. In 1 randomized trial, it was superior to placebo for major depression.[1] In another trial, PST delivered by telephone showed clinically important effects.[2] We built on previous studies by evaluating the effectiveness of PST-PC in patients with minor depression or dysthymia, using a relatively limited, but feasible dose for primary care (6 sessions). We agree that PST-PC is best categorized as a psychological treatment, not psychotherapy, and that the dose may have been too low for patients with dysthymia. In an ongoing study, we are evaluating the effect of more sessions of PST-PC. Until more definitive data are available, we consider it a psychological treatment in development.

We agree with Dr Leard-Hansson that paroxetine, like many antidepressants, has anticholinergic and other potential adverse effects. Despite this, the dropout rate due to adverse effects was only 8.7% (12/137) among the patients who received paroxetine. This compares favorably to the average dropout rate of 6% to 11% due to adverse effects that we cited.[3] Although we agree that medications with strong anticholinergic properties should be avoided in patients with cognitive impairment, paroxetine is certainly not contraindicated in elderly patients.

Drs Terluin and van Hout's calculations of ARR and NNT are correct but only consider remission from depression, which was a secondary outcome. Paroxetine showed a significantly better effect than placebo for the primary outcome, including change in depressive symptoms and effects on mental health functioning. When considering all 3 outcomes, we conclude that paroxetine showed a moderate benefit for patients with dysthymia. Finally, we agree that the inclusion of patients receiving usual care would have yielded valuable information. Patients in our placebo group received more visits and more support than is typical in primary care, which may have diminished the observed treatment effect.

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1. Mynors-Wallis LM, Gath DH, Lloyd-Thomas AR, Tomlinson D. Randomised controlled trial comparing problem solving treatment with amitriptyline and placebo for major depression in primary care. *BMJ*. 1995;310:441-445.
2. Lynch DJ, Tamburrino MB, Nagel R. Telephone counseling for patients with minor depression: preliminary findings in a family practice setting. *J Fam Pract*. 1997;44:293-298.
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Quality of Care at Teaching and Nonteaching Hospitals

To the Editor: Dr Allison and colleagues[1] found that teaching hospitals have better processes of care and outcomes for patients with acute myocardial infarction (AMI). This is quite different from the results of our study[2] of the same Cooperative Cardiovascular Project (CCP) data set. We found no independent association between teaching status and survival.

The 2 studies differ in several respects. Allison et al seem to exclude all 39025 patients subsequently transferred to other hospitals, whom we assigned to the initial admitting hospital. The CCP hospitals without the ability to perform bypass surgery transferred 29.9% of patients, usually for angiography and revascularization. These patients had a 30-day mortality of 8.6%, which is half the rate of patients who were not transferred, and had higher compliance with process-of-care guidelines. Hospitals with high levels of technology transferred only 1.9% of their patients. Because availability of technology is strongly correlated with teaching status (in the study by Allison et al, 28.6% of nonteaching vs 69.7% of major teaching hospitals had onsite bypass surgery), the exclusion of patients who subsequently were transferred might explain much of the mortality difference between nonteaching and teaching hospitals.

Allison et al included patients regardless of their preadmission status, while our study included only patients admitted directly from home. In the CCP data, patients admitted from nursing homes comprised 6.8% of patients at hospitals without angiography vs 4.5% at hospitals with bypass surgery ($P<.001$) and had a 30-day mortality of 41.4% compared with 18.8% for the overall CCP cohort. Conversely, patients admitted from outpatient clinics comprised 8.5% of patients at hospitals with low levels of technology vs 10.1% at hospitals with

high levels of technology ($P<.001$) and had a low 30-day mortality of 13.4%. Unlike Allison et al, our analysis also adjusted for several health care system factors that may confound studies of teaching status, including hospital volume of AMI cases, hospital technological capability, physician specialty,[3] and rural vs urban patient residence.

The cumulative effect of such methodological differences can be substantial. When we applied the methods of Allison et al to our published analysis, the 30-day mortality hazard at hospitals with on-site coronary bypass surgery vs those without angiographic capability decreased from 0.98 ($P=.56$) to 0.78 (95% confidence interval, 0.76-0.81; $P<.001$), roughly matching the odds ratio of 0.80 for major teaching vs nonteaching hospitals that Allison et al reported.

The reported survival advantage at teaching hospitals may be overstated or even illusory. It would be important to know 2 things: the results of analysis stratified by level of hospital technology, and the number of outgoing transfer patients excluded and their 30-day mortality for each teaching status category. Valid analysis of hospital traits such as teaching status requires comprehensive adjustment for confounding health care system variables and patient characteristics.

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1. Allison JJ, Kiefe CI, Weissman NW, et al. Relationship of hospital teaching status with quality of care and mortality for Medicare patients with acute MI. *JAMA*. 2000;284:1256-1262.
2. Thiemann DR, Coresh J, Oetgen WJ, Powe NR. Association between hospital volume and survival after acute myocardial infarction in the elderly. *N Engl J Med*. 1999;340:1640-1648.
3. Jollis JG, DeLong ER, Peterson ED, et al. Outcome of acute myocardial infarction according to the specialty of the admitting physician. *N Engl J Med*. 1996; 335:1880-1887.

In Reply: As stated in our original article, we recognized that selection bias might be an issue, and we analyzed the data with and without transfer patients separately. Our results did not change appreciably: unadjusted 30-day mortality rates for major teaching, minor teaching, and nonteaching hospitals were 17.0%, 18.2%, and 20.1%, respectively ($P<.001$), with transfer patients included and 18.7%, 20.3%, 23.3%, respectively ($P<.001$), with transfer patients excluded. We noted the difficulty in attributing transfer patient mortality to a particular hospital when the patients may have received the majority of their care at another hospital, especially when the events are not recorded in the CCP data set, and we described our approach to transfer patients explicitly.

In response to the criticism that we failed to adjust for hospital volume, level of technology, and physician specialty, we followed sound practices of multivariable modeling. These principles demand a clear rationale for selection of independent variables and caution against overadjustment. In addition to being associated with both the main independent variable and the dependent variable, a confounder must not be on the "etiologic path" linking the 2 variables.[1] Total AMI volume, physician specialty, and hospital technological capability are all highly correlated with teaching status and potentially on the etiologic path between hospital teaching status and mortality. Adjustment for these constructs in our analysis would mask important differences, perhaps leading Dr Thiemann and colleagues to erroneously dismiss the importance of teaching status. Furthermore, inclusion of multiple collinear variables adversely affects coefficient estimates.[2]

Our analysis suggests that higher overall quality of care (a mediating construct, not a confounder) explains most of the variation in 30-day, 60-day, 90-day, and 2-year mortality. There may be other mediators of this association, such as hospital volume or physician specialty. However, adding these constructs to our models would have obscured the picture and answered a different question from the one we posed.

We found that the higher quality of care at teaching hospitals resulted from more appropriate use of aspirin, angiotensin-converting enzyme inhibitors, and β-blockers. It is possible for all hospitals to increase the use of these life-saving therapies without radical changes in the US health care delivery system or expensive technology.

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1. Hennekens C, Buring J. *Epidemiology in Medicine*. Boston, Mass: Little Brown & Co; 1987.
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Health Consequences of Eclipse Cigarettes

To the Editor: A recent Medical News & Perspectives article[1] raised a number of criticisms about Eclipse cigarettes. It is impossible in letter format to either describe the scientific data developed to characterize Eclipse or to address the criticisms raised in that article. At R. J. Reynolds Tobacco Company, we are committed to developing new cigarettes that have the potential to present less health risk to smokers. However, no cigarette is without risk, including Eclipse.

Our advertising for Eclipse states: "The best choice for smokers who worry about their health is to quit. But Eclipse is the next best choice for those who have decided to continue smoking." Our advertising also makes it clear that R. J. Reynolds does not claim that Eclipse presents less risk of cardiovascular disease or complications with pregnancy. There is some evidence suggesting that, compared with other cigarettes, Eclipse may pose less risk to smokers of developing cardiovascular disease.[2] However, other evidence suggests that smokers who already have cardiovascular disease may further increase their

health risk by switching to Eclipse.[3] We advise smokers to consult their physicians with questions about their health.

R. J. Reynolds has conducted an extensive comparative evaluation of Eclipse. Many of these studies have been published in the peer-reviewed literature, presented at scientific meetings, or both; and a complete bibliography is available from the authors. The results of these and other studies may be reviewed on the Eclipse Web site (http://www.eclipse.rjrt.com). An independent panel of scientific experts has reviewed our science and reached conclusions consistent with our claims.[4]

As indicated in the news article,[1] some scientists have expressed concern that continuous filament glass may be present on the outer surface of Eclipse cigarettes. R. J. Reynolds has previously responded to these concerns.[5] Transfer data and the physical characteristics of the filaments indicate that significant exposure of the smoker to continuous filament glass will not occur. Environmental survey data demonstrate that Eclipse smokers are extremely unlikely to be exposed to continuous filament glass at a level representing an increase relative to background exposure. The chemical composition of the filament used in Eclipse is generally similar to glass fiber compositions that have failed to produce either tumors or fibrosis in chronic inhalation studies conducted in rats. Furthermore, in vitro dissolution data demonstrate that these filaments are more soluble than biologically active fibers such as asbestos and rock wool. In short, exposure of Eclipse smokers to continuous filament glass is extremely unlikely to occur at a level that may be construed to be of biological significance. A safety assessment addressing this topic has been published.[6]

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1. Stephenson J. A "safer" cigarette? prove it, say critics. *JAMA*. 2000;283:2507-2508.
2. Borgerding MF, Bodnar JA, Chung HL, et al. Chemical and biological studies of a new cigarette that primarily heats tobacco, part I: chemical composition of mainstream smoke. *Food Chem Toxicol*. 1998;36:169-182.
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In Reply: Drs Burger and Swauger do not substantively address any of the major criticisms of R. J. Reynolds' new Eclipse brand cigarette.[1] First, the only appropriate body to evaluate and regulate nicotine delivery devices, including Eclipse, is the US Food and Drug Administration (FDA)—the only entity with the expertise, objectiveness, and appropriate authority to determine whether, and on what terms, such devices should be available in the marketplace. Pharmaceutical companies must meet rigorous scientific review and approval by the FDA before they market nicotine replacement devices such as gum, patch, and nasal spray. The public is unaware that Eclipse, like other tobacco products, remains unregulated merely because a tobacco company manufactures it and wraps it in white paper to look like a cigarette. Notably absent from the authors' comments is any discussion as to why Eclipse "cigarettes" should not be considered smoke-flavored nicotine delivery devices, subject to jurisdiction by the FDA, as we believe they should be.

Second, none of the industry-sponsored studies mentioned by Burger and Swauger provides convincing evidence that smokers who switch to Eclipse will experience a lower risk of cancer or other smoking-related diseases than those who do not. The lack of substantiation of any health claims is deftly sidestepped in the product advertisement[1] that Eclipse are "new cigarettes that have the potential to present less risk to smokers." It is clear that lawyers and public relations experts have crafted the language so that it implies more than it actually says. One of the greatest dangers of Eclipse is the public's belief that these products are less hazardous than conventional cigarettes, which may discourage smokers from genuine cessation efforts. This could increase, not decrease, the overall disease burden caused by tobacco products. Moreover, fiber glass fragments inhaled by Eclipse smokers may prove more hazardous than Burger and Swauger suggest, just as the asbestos Micronite filters proved to be an imprudent addition to Kent cigarettes in the 1950s.[2] The higher carbon monoxide concentrations generated from Eclipse cigarettes[3] may actually increase the cardiovascular hazard.

Finally, even if the engineering changes in Eclipse have in fact achieved a 30% to 80% reduction in the risk of cancer compared with conventional cigarettes,[4] this leaves the 42% of tobacco-related deaths due to cardiovascular disease undiminished. Also, these changes might or might not affect the additional 22% of respiratory diseases induced by smoking.

No one can dispute that "the best choice for smokers who worry about their health is to quit." Rather than Eclipse, however, "the next best choice" for a smoker involves medical counseling on the broad array of evidence-based pharmacological and behavioral approaches available to treat tobacco dependence.[5]

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1. Stephenson J. A "safer" cigarette? prove it, say critics. *JAMA*. 2000;283:2507-2508.
2. Longo WF, Rigler MW, Slade J. Crocidolite asbestos filters in smoke from original Kent cigarettes. *Cancer Res*. 1995;55:2232-2235.
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5. A clinical practice guideline for treating tobacco use and dependence: a US Public Health Service report. *JAMA*. 2000;283:3244-3254.

Non-English Reports of Medical Research

To the Editor: In their systematic review and meta-analysis, Drs Wu and Colford[1] examined the role of chorioamnionitis

as a risk factor for cerebral palsy and cystic periventricular leukomalacia (cPVL). They concluded that chorioamnionitis is a risk factor for both conditions, a finding with potentially important clinical and economic implications. The authors carefully examined potential sources of heterogeneity, which is of crucial importance in meta-analysis of observational studies.[2] It is ironic, however, that they used sophisticated statistical methods to examine the possible presence of publication bias while completely ignoring an obvious source of reporting bias: a priori exclusion of studies published in languages other than English. An unknown number of relevant studies are thus missing from their review. This likely reduced the precision of their estimates and, more worrisome, may have introduced bias. For example, it has been shown that investigators based in German-speaking countries tend to publish clinical trials in English-language journals if the results are statistically significant but choose German-language journals if results are negative.[3]

We performed a brief search of the non–English-language literature in MEDLINE and EMBASE. We identified a case-control study[4] from Switzerland that met all the inclusion criteria of the meta-analysis by Wu and Colford. Not surprisingly, this study did not find a significant association between chorioamnionitis and cPVL. Earlier this year, the consensus statement from the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group examined the reporting of meta-analyses of observational studies and made recommendations that, if followed, should facilitate the proper evaluation of the quality and completeness of meta-analyses of observational studies.[5] One of the recommendations included in their checklist stated that authors should provide "justification for exclusion (eg, exclusion of non–English-language citations)."

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1. Wu YW, Colford JM Jr. Chorioamnionitis as a risk factor for cerebral palsy: a meta-analysis. *JAMA*. 2000;284:1417-1424.
2. Egger M, Schneider M, Smith GD. Spurious precision? meta-analysis of observational studies. *BMJ*. 1998;316:140-145.
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4. Bauder FH, von Siebenthal K, Bucher HU. Sonographisch nachgewiesene periventrikuläre Leukomalazie (PVL): Inzidenz und assoziierte Faktoren in der Schweiz 1995-1997 [Ultrasonically established cystic periventricular leukomalacia (PVL): incidence and associated factors in Switzerland 1995-1997]. *Z Geburtsh Neonatol*. 2000;204:68-73.
5. Stroup DF, Berlin JA, Morton SC, et al for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA*. 2000;283:2008-2012.

In Reply: We agree with Dr Bassler and colleagues that the exclusion of non–English-language studies may lead to bias in meta-analysis results. Our MEDLINE search included all languages and revealed 25 publications of potential interest that were not in English. However, we felt that excluding these publications would not lead to significant bias in our meta-analysis. Of the 15 non-English studies that we were able to retrieve, none met our inclusion criteria. The remaining studies were either published prior to 1985, the earliest date that an English-language study was identified as meeting our inclusion criteria, or had an English abstract available online indicating that the study was a case series and therefore could not provide relative risks (RRs).

In their search of the non-English literature, Bassler et al found a single study[1] that met our inclusion criteria. However, this study was published in 2000, and thus could not have been found in our search (1966-1999). Two other pertinent studies published in 2000 also have come to our attention. These found no significant association between clinical chorioamnionitis and cPVL[2] or cerebral palsy.[3] When all 3 new studies[1-3] are added to the meta-analysis, the updated summary RR for clinical chorioamnionitis and cPVL is 1.7 (95% confidence interval [CI], 1.1-2.6) and for cerebral palsy, 1.8 (95% CI, 1.4-2.4).

Bassler et al mention an important source of "language bias" found in clinical trial research published by investigators from German-speaking European countries. Whether such a bias exists for observational studies originating in other non–English-speaking countries is not clear. Of note, our meta-analysis included 7 studies that were performed in countries where English is not the primary language. Five of these studies reported results that were not statistically significant.

We believe that the exclusion of non–English-language studies did not introduce significant bias to our meta-analysis. However, we agree that unless otherwise justified, meta-analyses should include publications in all languages and that literature searches for meta-analyses should include EMBASE, a database that is more inclusive of studies performed in European countries.

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1. Bauder FH, von Siebenthal K, Bucher HU. Sonographisch nachgewiesene periventrikuläre Leukomalazie (PVL): Inzidenz und assoziierte Faktoren in der Schweiz 1995-1997 [Ultrasonically established cystic periventricular leukomalacia (PVL): incidence and associated factors in Switzerland 1995-1997]. *Z Geburtsh Neonatol*. 2000;204:68-73.
2. Ng E, Asztalos E, Rose T, Beyene J, Wylie L, Dunn M. The association of clinical and histologic chorioamnionitis (CA) with cystic periventricular leukomalacia (cPVL) and cerebral palsy (CP) in preterm infants [abstract]. *Pediatr Res*. 2000;47:318A.
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Gender vs Sex

To the Editor: In their Commentary "Gender Verification in the Olympics," Dr Simpson and colleagues[1] were imprecise in

their use of "gender," given that the topic at hand is clearly "sex," not gender. Certainly, *gender* long ago subsumed *sex* as a generic reference in popular culture to all manner of traits associated with the 2 basic sexual divisions. However, proper use of technical terms is not a trivial matter, especially in scientific and clinical publications.

Confusion of *sex* for *gender* blurs significant aspects of their respective meanings.[2] The former denotes objective biological capacities and constraints of a physical organism. The latter denotes more subjective features of sociocultural roles acquired in specific cultural and social milieux. These are not trivial differentiating concepts but, in fact, are analogous to and as important as *genotype* and *phenotype*.

Commonly, gender and sex characteristics closely converge; however, individuals sometimes experience marked contradictions.[3] Moreover, gender entails a degree of self-definition that is impossible for sex. Female "sex" denotes ovate bodily forms productive of offspring whereas gender is a far more fluid matter of self-conceptualization as masculine or feminine. Indeed, a person who asserts a given gender is, in some sense, "verifiably" that gender.

The authors introduce a series of errors by conflating the 2 terms. For example, it was not coherent to assert, "The ostensible goal of gender verification is to ensure that female athletes do not unwittingly compete against men." This confuses gender for sex. It would have been coherent to say the same of sex verification but "gender verification" has to do with issues of self-classification.

Hence, it seems the authors intended to encourage the International Olympic Committee (IOC) to revise its stance on verification of sex, not gender.

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1. Simpson JL, Ljungqvist A, Ferguson-Smith MA, et al. Gender verification in the Olympics. *JAMA*. 2000;284:1568-1569.
2. Paglia C. *Sexual Personae*. New Haven, Conn: Yale University Press; 1990.
3. Wilson DR. The darwinian roots of human neurosis. *Acta Biotheor*. 1994;42:49-62.

In Reply: The purpose of our Commentary was to inform readers that the IOC has abolished laboratory-based gender verification tests, a change in a policy initiated in 1968. Dr Wilson's concerns are semantic, specifically how to designate individuals with disorders of sex differentiation. We are certainly aware of the argument for biological precision using "sex" and thus would acknowledge Wilson's contention that consistency and scientific accuracy should dictate its use. However, convention among health care professionals has long been that *gender* is preferable in describing intersex individuals, given the charged nature of the word *sex* and given that *gender* connotes self-identification of a person's rearing. Of course, it is sometimes necessary to describe both gender and sex when referring to specific individuals. In addition, the IOC has always used the phrase "gender verification" and to have used a different term in our Commentary would have been confusing.

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RESEARCH LETTER

Acute Myocardial Infarction and Prior Antibiotic Use

To the Editor: Chronic infections, particularly with *Chlamydia pneumoniae*, may contribute to the development of atherosclerosis. Use of fluoroquinolones and tetracyclines has been associated with protection against myocardial infarction (MI).[1] We performed a case-control study to determine whether patients receiving antibiotics effective against *C pneumoniae* were less likely to have been admitted for a first acute MI.

Methods. Data were obtained from the PHARMO system, which includes information on hospital admissions and drug-dispensing records for all 450 000 residents of 8 Dutch cities. The drug-dispensing records were obtained from pharmacy files and are linked to a nationwide database of hospital discharge records.[2]

We identified all persons aged 35 to 75 years with a first hospitalization (1985-1995) for MI (*International Classification of Diseases, 9th Revision, Clinical Modification* [*ICD*-9-CM] code 410) and a PHARMO registration period of at least 3 years. For each patient, we identified as many as 4 control patients who were matched on dispensing pharmacy, sex, year of birth, and same date of first entry in the PHARMO system. We included 628 case patients and 1615 age-, sex-, exposure window– and pharmacy-matched control patients. We excluded all cases and controls with a known history of prior MI (*ICD-9-CM* code 412), cardiac aneurysm (*ICD-9-CM* code 414.1), prolonged angina pectoris or other atherosclerotic coronary diseases (*ICD-9-CM* codes 411, 413, 414.0, 414.8, and 414.9), hospitalization for hypertension (*ICD-9-CM* codes 401-405), ischemic and other forms of heart disease (*ICD-9-CM* codes 410-414), or cerebrovascular accidents (*ICD-9-CM* codes 430-438), as well as those with a history of prescriptions for cardiovascular or antihyperglycemic drugs.

Exposure to antibiotics was restricted to the calendar time prior to the index date and was classified into 7 classes: tetracyclines, macrolides, sulfonamides, fluoroquinolones, quinolones, penicillins, and cephalosporins. We defined high doses

Table. Hospitalization for Acute Myocardial Infarction for Use of Selected Antibiotics by Dose*

Group of Antibiotics	Cases (n = 628)	Controls (n = 1615)	Matched Odds Ratio (95% CI)
Fluoroquinolones			
Low dose	5 (0.8)	14 (0.9)	1.05 (0.35-3.15)
High dose	5 (0.8)	32 (2.0)	0.34 (0.12-0.93)
Quinolones			
Low dose	1 (0.2)	3 (0.2)	1.01 (0.09-10.8)
High dose	4 (0.6)	11 (0.7)	0.81 (0.24-2.73)
Tetracyclines			
Low dose	170 (27.1)	379 (23.5)	1.13 (0.90-1.42)
High dose	6 (1.0)	13 (0.8)	0.95 (0.35-2.62)
Macrolides			
Low dose	11 (1.8)	25 (1.5)	1.02 (0.48-2.14)
High dose	13 (2.1)	22 (1.4)	1.58 (0.74-3.35)
Other			
Low dose	131 (20.9)	290 (18.0)	1.22 (0.95-1.57)
High dose	100 (15.9)	247 (15.3)	1.04 (0.78-1.38)

*"Use" is defined as receiving a course of antibiotics for more than 5 days; "high dose" as a course longer than 6 days with standard doses. Data are presented as number (percent) of subjects hospitalized for acute myocardial infarction. CI indicates confidence interval.

as courses longer than 6 days with standard doses (details are available from the authors). Patients with several courses of antibiotics were classified as having received a high-dose based on at least a single high dose course. Analysis was by conditional logistic regression analysis using version 2.0.3 for Windows (Cytel Software Corp, Seattle, Wash).

Results. Case and control groups were not different with respect to age, sex, person-years of registration (median, 4.5 years), number of hospitalizations, treatment for respiratory complaints, or presence of chronic diseases. The median age was 57 years (25th-75th percentile, 49-65 years). Nearly 80% of the case and control patients were male.

Only high doses of fluoroquinolones were associated with a lower risk of acute MI (TABLE). For those who took more than 1 course of fluoroquinolones, the odds ratio was 0.12 (95% CI, 0.02-0.94). For all other antibiotics, no significant association was observed.

Comment. Our study found an association of fluoroquinolones in the same direction as Meier et al[1] but our results are not completely compatible with an inhibitory effect on *C pneumoniae*. Particular tetracyclines and macrolides were not associated with a lower risk of acute MI even if given in high doses or given in multiple courses during a sufficient time. These results are consistent with those of Jackson et al.[3] Fluoroquinolones and quinolones have been reported to have a stabilizing effect on the cytoskeleton of endothelial cells[4] and have an effect on chondrocytes in humans.[5] Because calcification also plays a major role in the later stages of plaque formation in atherosclerosis,[6] it is possible that the negative association of fluoroquinolones with MI may be mediated via their nonbacterial inhibitory actions.

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CORRECTIONS

Incorrect Wording: In the Research Letter entitled "Supplemental Oxygen and Mountaineer Death Rates on Everest and K2" published in the July 12, 2000, issue of THE JOURNAL (2000;284:181), the final sentence was worded incorrectly. The sentence that read "Mountaineers considering whether to use supplemental oxygen should consider the risk of death during descent" should have read "Mountaineers considering whether to use supplemental oxygen can now consider the associated fatality risks during descent."

Incorrect Wording: In the Commentary entitled "Current and Future Public Health Challenges" published in the October 4, 2000, issue of THE JOURNAL (2000;284: 1696-1698), there was incorrect wording. On page 1697, under "Achieve a Longer 'Healthspan,'" the sentence that read "In 1900, about 1 in 25 Americans was elderly; in 1990, the proportion was 1 in 8, or 10 times greater than in 1900" should end after "1 in 8." A new sentence should then read, "In absolute terms, the number of elderly Americans had increased 10-fold."