M2 Epidemiology
Literature Critiques

Session #3
Tuesday, 12/1/09
5:00 p.m.

You have been assigned to literature critique session #3, Tuesday, 12/1/09, at 5:00 p.m. Individual paper assignments are given below. Electronic versions of the papers can be found on the course website under the heading of “TA Handouts.” Remember, in addition to organizing and writing a critique of your assigned paper, you must come prepared to discuss all of the papers that will be presented during your session - at the very least, you must read all four papers included in this packet. If you have any questions, please let me know.

Best regards,
John

Jill Gunther -
“Acid-Suppressive Medication Use and the Risk for Hospital-Acquired Pneumonia”

Matthew Sharrock -
“Association Between 5-α Reductase Inhibition and Risk of Hip Fracture”

Daniel Votava -
“Red Yeast Rice for Dyslipidemia in Statin-Intolerant Patients: A Randomized Trial”

Patrick Mathias -
“News Media Coverage of Medication Research Reporting Pharmaceutical Company Funding and Use of Generic Medication Names”
Acid-Suppressive Medication Use and the Risk for Hospital-Acquired Pneumonia

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WITH THE ADVENT OF PROTON-PUMP INHIBITORS, the use of acid-suppressive medications has increased significantly over the last several years, particularly in the inpatient setting. Studies evaluating the prevalence of acid-suppressive medication estimate that between 40% and 70% of medical inpatients receive some form of acid-suppressive medication during their hospitalization, approximately 50% of which are initiations.1,2 Furthermore, approximately half of those newly prescribed acid-suppressive medication in the hospital are subsequently discharged with a prescription for these medications.1,3,4

The high prevalence of acid-suppressive medication use in the inpatient setting is of particular concern for several reasons. First, up to 70% of inpatient use is for indications that have not been investigated or supported by literature, most commonly stress ulcer prophylaxis in low-risk patients.3-7 Second, recent data in the outpatient setting suggest an increased risk for community-acquired pneumonia in current users of acid-suppressive medication (both proton-pump inhibitors and histamine, receptor antagonists).8-10 More concerning for the inpatient population are the findings in a cohort of outpatients in the United Kingdom11, the highest risk for community-acquired pneumonia was within the first 2 days of proton-pump inhibitor therapy, and there was a statistically significant association up to 30 days after newly started therapy but no significant association thereafter. Another study8 similarly found higher risk among persons who started proton-pump inhibitor use within the prior 7 days. This is particularly concerning given the large proportion of patients who are newly prescribed acid-suppressive medication in the inpatient setting, when they are debilitated and more susceptible to infection.

Context The use of acid-suppressive medication has been steadily increasing, particularly in the inpatient setting, despite lack of an accepted indication in the majority of these patients.

Objective To examine the association between acid-suppressive medication and hospital-acquired pneumonia.

Design, Setting, and Patients Prospective pharmacoepidemiologic cohort study. All patients who were admitted to a large, urban, academic medical center in Boston, Massachusetts, from January 2004 through December 2007; at least 18 years of age; and hospitalized for 3 or more days were eligible for inclusion. Admissions with time spent in the intensive care unit were excluded. Acid-suppressive medication use was defined as any order for a proton-pump inhibitor or histamine2 receptor antagonist. Traditional and propensity-matched multivariable logistic regression were used to control for confounders.

Main Outcome Measure Incidence of hospital-acquired pneumonia, defined via codes from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), in patients exposed and unexposed to acid-suppressive medication.

Results The final cohort comprised 63,878 admissions. Acid-suppressive medication was ordered in 52% of admissions and hospital-acquired pneumonia occurred in 2219 admissions (3.5%). The unadjusted incidence of hospital-acquired pneumonia was higher in the group exposed to acid-suppressive medication than in the unexposed group (4.9% vs 2.0%; odds ratio [OR], 2.6; 95% confidence interval [CI], 2.3-2.8). Using multivariable logistic regression, the adjusted OR of hospital-acquired pneumonia in the group exposed to acid-suppressive medication was 1.3 (95% CI, 1.1-1.4). The matched propensity-score analyses yielded identical results. The association was significant for proton-pump inhibitors (OR, 1.3; 95% CI, 1.1-1.4) but not for histamine2 receptor antagonists (OR, 1.2; 95% CI, 0.98-1.4).

Conclusions In this large, hospital-based pharmacoepidemiologic cohort, acid-suppressive medication use was associated with 30% increased odds of hospital-acquired pneumonia. In subset analyses, statistically significant risk was demonstrated only for proton-pump inhibitor use.

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tinue to be frequently prescribed. To our knowledge, no large prospective study has yet examined the association between acid-suppressive medication and hospital-acquired pneumonia in nonventilated patients. We examined this association in a large, prospective pharmacoepidemiologic cohort.

METHODS

Setting and Data Collection
An inception cohort of all patients admitted to a large, urban, academic medical center in Boston, Massachusetts, from January 1, 2004, through December 31, 2007, was investigated. The study was approved by the institutional review board at the medical center and granted a waiver of informed consent. Data were collected from electronic medical information databases maintained at the medical center. These databases, collected prospectively for clinical purposes, contain patient-specific information related to each admission during the study time period. They also include a record of all inpatient medications ordered during each admission.

Inclusion Criteria
All admissions of patients at least 18 years of age and hospitalized for 3 or more days were eligible for inclusion. A cutoff of 3 days was chosen based on the rationale that it would take at least 24 hours of exposure to reliably attribute pneumonia to the acid-suppressive medication exposure, and it would take at least 48 hours of inpatient hospitalization to classify the pneumonia as hospital-acquired, consistent with current criteria of the American Thoracic Society and the Infectious Diseases Society of America. To restrict the analysis to the nonventilated, general hospital patient population, admissions with any time spent in the intensive care unit (ICU) were excluded.

Medication Exposure and Outcomes
Acid-suppressive medication exposure was defined as any order for a pharmacy-dispensed proton-pump inhibitor or histamine2 receptor antagonist during the admission. The day on which these medications were ordered was identified.

The primary outcome was hospital-acquired pneumonia, defined as any discharge code from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) for bacterial pneumonia listed as a secondary discharge diagnosis (ie, not listed as the primary discharge diagnosis). ICD-9-CM codes used for primary and secondary discharge diagnoses indicating bacterial pneumonia are listed in the box. Secondary outcomes included subcategories of hospital-acquired pneumonia: aspiration and nonaspiration pneumonia, also defined via specific ICD-9-CM codes.

Covariates
Covariates were included that were thought to predict use of acid-suppressive medications, as well as variables thought to increase the risk of hospital-acquired pneumonia. These included age; sex; race; season and day of the week of admission; admitting service (medicine vs other); admission type (elective, urgent, emergent); length of hospitalization; any ICD-9-CM code for gastrointestinal hemorrhage; any ICD-9-CM code for nausea and/or vomiting; and use of specific classes of medications, including drugs with sedating effects (benzodiazepines, barbiturates, antipsychotics, opiates, anesthetics), paralytics, nonsteroidal anti-inflammatory drugs (NSAIDs), inhaled and systemic steroids, and anticoagulant medications (enoxaparin, warfarin, heparin).

Race/ethnicity data were obtained by patient self-report at the time of registration by employees who had received specific training in obtaining and coding this information into fixed categories. These data were included as a variable in the analyses because they may be associated with pneumonia risk.

All of the comorbidities included in the Charlson Comorbidity Index, as operationalized from administrative data by Quan et al, were controlled for except where noted here. Rather than

Box. ICD-9-CM Codes Used for Outcomes and Comorbidities

Outcomes
- Primary outcome
  - Any pneumonia: 481, 482, 483, 485, 486, 507
- Secondary outcomes
  - Aspiration pneumonia: 507
  - Nonaspiration pneumonia: 481, 482, 483, 485, 486

Comorbidities
- The comorbidities in the Charlson Comorbidity Index, as operationalized by Quan et al, were used for the analysis. Following are only the comorbidities that were either added (not already present in the Charlson Comorbidity Index) or enhanced as described in the text.

- Comorbidities not already included in the Charlson Comorbidity Index
  - Gastrointestinal hemorrhage: 578
  - Nausea/vomiting: 643, 787.0, 564.3
  - Alcohol/drug use: 291, 292, 303, 304, 305
  - Psychiatric disorder: 296, 300, 301, 306, 311, 307.8
  - Neurologic disorder: 332, 333, 335, 340, 341, 345, 352.1, 352.2, 438.82
  - Enhanced comorbidities (includes ICD-9-CM codes recommended by Quan et al, as well as added ICD-9-CM codes as described in the text)
    - Delirium/dementia: 290, 294.1, 331.2, 293, 294, 331, 797
    - Peptic ulcer disease: 530, 531, 532, 533, 534, 535, 536, 787.1, 306.4
ACID-SUPPRESSIVE MEDICATION AND HOSPITAL-ACQUIRED PNEUMONIA

use a summary index score, each co-

morbidity was incorporated into the

model as a separate, independent mea-

sure, as advocated by Elixhauser et al. Several ICD-9-CM codes were added to

the diagnostic categories of dementia

and peptic ulcer disease already pre-

sent in the Charlson comorbidity list to

increase the capture rate of these con-

ditions, both hypothesized to have im-

portant associations with both acid-

suppressive medication exposure and

hospital-acquired pneumonia. Addition-

al comorbidities were controlled for,

including any ICD-9-CM code for al-

cohol and/or drug abuse, psychiatric

disorders, and neuromuscular disor-

ders, because of the hypothesized as-

sociation with both acid-suppressive

medication use and hospital-acquired

pneumonia.

Statistical Analysis

The Fisher exact test was used to com-

pare categorical variables and a non-

parametric median test for continu-

ous variables. Unadjusted incidence

rates of the primary and secondary out-

comes in exposed and unexposed pa-

tients were compared using the Fisher

exact test.

Patients with multiple admissions

would violate the assumption of inde-

pendence when using logistic regres-

sion to analyze the data, so repeated ad-

missions were approached in 2 ways. First,
an analysis was performed that in-

cluded all admissions during the time

interval but controlled for confound-

ers and within-participant correlated

data using a multivariable generalized

estimating equation (GEE) model with

logit link and exchangeable working

dependence when using logistic regres-

sion. This approach was performed that

in-

ccluded only the first admission during

the time interval. Because the results ob-

tained with these approaches did not

differ, only the results of the first analy-

sis are presented.

In addition, a propensity score was de-

rived using a GEE model with the use

of acid-suppressive medication as the de-

pendent variable. In this model, the same

set of covariates was used as in the first

approach. The fitted probability from this

model was used as the propensity score.

This score was assigned to each patient

admission reflecting the propensity to

have received the exposure of interest.

The c statistic for the propensity score

model was 0.83, indicating a good abil-

ity to discriminate between admissions

with and without an order for acid-

suppressive medication.

Admissions were then matched on

their propensity score using a greedy

matching technique. With this tech-
nique, each admission in which acid-

suppressive medication was ordered

was matched to the admission with the

closest propensity score in which acid-

suppressive medication was not or-

dered, thus addressing confounding by

indication. The algorithm specified

looking initially for a match out to 6 dig-

its of the propensity score. If a 6-digit

match could not be found, the pro-

gram then moved to 5 digits, then 4, and

so on, until the closest match was

found. Once admissions were matched

on their propensity to have received

acid-suppressive medication, baseline

characteristics were compared within

the matched groups to gauge the effec-

tiveness of the matching. Any baseline

characteristics with residual imbal-

ance ($P \leq .05$) were incorporated into

a GEE regression model to obtain the

adjusted odds ratio (OR) for hospital-

acquired pneumonia in the 2 groups.

A 2-sided type I error of 0.05 or less

was used to indicate statistical signifi-
cance for all comparisons. Assuming a

rate of 1 hospital-acquired pneumo-

nia per 100 admissions, an estimated

sample size of 53,000 admissions would

be necessary to achieve 90% power to

detect a relative risk of 1.3 in exposed

vs unexposed patients. All analyses were

conducted to ensure that the observed mag-
nitude of any outcome misclassification

would not affect interpretation of the re-

sults. A sensitivity analysis was con-
ducted to assess the thresholds at which

misclassification of the outcome would

cause the point estimate of the in-

creased risk of pneumonia to lose clin-

cal significance, which was defined as a

10% increase in the odds of pneumo-

nia. In this simulation, it was sequen-
tially assumed that the misclassifica-
tion rate of the presence (or absence) of

hospital-acquired pneumonia was 1%,

2%, 5%, 7%, and 10%. For example,

when the misclassification rate was set

at 1%, 1% of the admissions were ran-
domly selected and their outcome was

switched from 1 (presence of pneumo-

nia) to 0 (absence of pneumonia) or vice

versa. The multivariable model was then

rerun using this simulated data to ob-
tain the adjusted OR at each rate of mis-
classification. This process was re-
peated to obtain estimates of the OR for

all possible combinations of misclassifi-
cation rates.

In this manner, the misclassifica-
tion rates (patients coded as having had

a pneumonia who on record review did

not, and vice versa) that would de-
crease the effect estimate below the pre-
defined threshold of 1.1 were identi-
fied. Once these 2 threshold rates were

known, a validation study was per-
duced using medical record review on a

randomly selected sample of admis-
sions to estimate the true misclassifi-
cation rates and their 95% confidence

intervals (CIs). If the upper bound of

either of these rates exceeded the pre-
determined thresholds, the implica-
tion would be that the estimation re-
sult would not be reliable; otherwise the

model estimation would be accepted.

Exposure Subgroup

and Sensitivity Analyses

In a prespecified subgroup analysis the

independent effects of each class of

medication on the primary outcome

were evaluated. A stratified analysis

was performed in which 2 separate mul-
tivariable GEE models were run: one ex-

amining the effect of proton-pump in-
hibitor exposure excluding patients with exposure to histamine2 receptor antagonists, and a second examining the effect of histamine2 receptor antagonist exposure excluding patients with exposure to proton-pump inhibitors. This assessed the independent effects of each of these medication subgroups.

Because there was no information on the date of occurrence of the hospital-acquired pneumonia, it could not be determined whether the acid-suppressive medication was started before or after the onset of pneumonia (if one occurred), raising the possibility of exposure misclassification (ie, if the pneumonia actually occurred before the acid-suppressive medication was started, then the patient should not be considered to have received acid-suppressive medication in accordance with our hypothesis). Therefore, the percentage of orders for acid-suppressive medication that occurred within the first 48 hours of admission was determined, a sensitivity analysis reclassified all admissions in which acid-suppressive medication was not started within the first 48 hours as not having received acid-suppressive medication. The percentage of orders for acid-suppressive medication that occurred within 48 hours of discharge was also ascertained.

Although there was no information on smoking status for the majority of the cohort, there were data in 20,030 admissions (31%). For these admissions, a secondary analysis was performed using a 3-category variable for smoking status (yes, no, and unknown) and running the multivariable GEE model after incorporation of this variable.

RESULTS

Patient Admission Characteristics

There were 136,529 admissions to the medical center from January 1, 2004, through December 31, 2007. After excluding admissions with any time spent in the ICU (n=18,531), as well as admissions with a length of stay less than 3 days (n=54,120), 63,878 admissions comprised the final cohort. Out of 63,878 admissions, there were 42,093 unique patients, indicating repeated admissions ranging from 1 to 61 admissions per patient during the time frame. The median age of the cohort was 54 years (range, 18-107 years), and 23,801 (37%) were men.

Exposure to Acid-Suppressive Medication

Overall, acid-suppressive medication was ordered in 32,922 admissions (52%). Of the group exposed to acid-suppressive

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acid-Suppressive Medication (n = 32,922)</th>
<th>No Acid-Suppressive Medication (n = 30,956)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, No. (%)</td>
<td>14,759 (45)</td>
<td>9,042 (29)</td>
</tr>
<tr>
<td>Race or ethnic group, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>24,709 (75)</td>
<td>21,025 (68)</td>
</tr>
<tr>
<td>Black</td>
<td>3,473 (11)</td>
<td>3,486 (11)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1,065 (3)</td>
<td>1,242 (4)</td>
</tr>
<tr>
<td>Asian</td>
<td>607 (2)</td>
<td>1,660 (5)</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>3,068 (9)</td>
<td>3,541 (11)</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>62 (18-106)</td>
<td>40 (18-107)</td>
</tr>
<tr>
<td>Comorbidities, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2,399 (7)</td>
<td>1,176 (4)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>6,324 (19)</td>
<td>2,611 (8)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>2,546 (8)</td>
<td>1,453 (5)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1,573 (5)</td>
<td>831 (3)</td>
</tr>
<tr>
<td>Delirium/dementia</td>
<td>1,687 (5)</td>
<td>1,097 (4)</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>6,205 (19)</td>
<td>2,865 (9)</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>1,165 (4)</td>
<td>384 (1)</td>
</tr>
<tr>
<td>Peptic ulcer disease/reflux</td>
<td>7,678 (23)</td>
<td>874 (3)</td>
</tr>
<tr>
<td>Mild liver disease</td>
<td>2,483 (8)</td>
<td>819 (3)</td>
</tr>
<tr>
<td>Moderate or severe liver disease</td>
<td>721 (2)</td>
<td>97 (&lt;1)</td>
</tr>
<tr>
<td>Diabetes without complications</td>
<td>6,662 (20)</td>
<td>3,486 (11)</td>
</tr>
<tr>
<td>Diabetes with complications</td>
<td>2,578 (8)</td>
<td>1,364 (4)</td>
</tr>
<tr>
<td>Paraplegia/hemiplegia</td>
<td>340 (1)</td>
<td>196 (1)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>4,622 (14)</td>
<td>1,811 (6)</td>
</tr>
<tr>
<td>Cancer</td>
<td>5,332 (16)</td>
<td>2,316 (7)</td>
</tr>
<tr>
<td>Metastatic carcinoma</td>
<td>3,119 (9)</td>
<td>941 (3)</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>493 (2)</td>
<td>376 (1)</td>
</tr>
<tr>
<td>Alcohol/drug abuse</td>
<td>2,712 (8)</td>
<td>1,943 (6)</td>
</tr>
<tr>
<td>Psychiatric disorder</td>
<td>4,499 (14)</td>
<td>3,455 (11)</td>
</tr>
<tr>
<td>Neuromuscular disorder</td>
<td>1,436 (4)</td>
<td>1,043 (3)</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>808 (2)</td>
<td>66 (&lt;1)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>808 (2)</td>
<td>176 (1)</td>
</tr>
<tr>
<td>Admitting service, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicine</td>
<td>18,702 (57)</td>
<td>8,518 (28)</td>
</tr>
<tr>
<td>Other</td>
<td>14,220 (43)</td>
<td>22,438 (72)</td>
</tr>
<tr>
<td>Admission type, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elective</td>
<td>6,606 (20)</td>
<td>4,116 (13)</td>
</tr>
<tr>
<td>Emergent</td>
<td>25,163 (76)</td>
<td>14,599 (47)</td>
</tr>
<tr>
<td>Urgent</td>
<td>1,153 (4)</td>
<td>12,241 (40)</td>
</tr>
<tr>
<td>Season of admission, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Winter</td>
<td>7,870 (24)</td>
<td>7,401 (24)</td>
</tr>
<tr>
<td>Spring</td>
<td>8,396 (26)</td>
<td>7,606 (25)</td>
</tr>
<tr>
<td>Summer</td>
<td>8,315 (25)</td>
<td>8,165 (26)</td>
</tr>
<tr>
<td>Fall</td>
<td>8,341 (25)</td>
<td>7,694 (25)</td>
</tr>
<tr>
<td>Length of hospitalization, median (range), d</td>
<td>5 (3-164)</td>
<td>4 (3-170)</td>
</tr>
<tr>
<td>In-hospital medications, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedative</td>
<td>27,015 (82)</td>
<td>23,842 (77)</td>
</tr>
<tr>
<td>NSAID</td>
<td>5,924 (18)</td>
<td>14,351 (46)</td>
</tr>
<tr>
<td>Steroid, systemic</td>
<td>7,314 (22)</td>
<td>1,986 (6)</td>
</tr>
<tr>
<td>Steroid, inhaled</td>
<td>3,840 (12)</td>
<td>1,858 (6)</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>22,699 (69)</td>
<td>10,926 (35)</td>
</tr>
</tbody>
</table>

Abbreviations: HIV, human immunodeficiency virus; NSAID, nonsteroidal anti-inflammatory drug.
medications, 27,236 (83%) received proton-pump inhibitors and 7,548 (23%) received histamine2 receptor antagonists, with some exposed to both. The majority of these medications were ordered within 48 hours of admission (29,176; 89%), and an order was still present within 48 hours of discharge in 30,965 (94%). There were significant differences in baseline characteristics between those exposed and unexposed to acid-suppressive medication (Table 1).

**Relationship of Acid-Suppressive Medication to Hospital-Acquired Pneumonia**

Table 2 shows the unadjusted incidence rates of hospital-acquired pneumonia relative to acid-suppressive medication status. The primary outcome of hospital-acquired pneumonia occurred in 2,219 admissions (3.5%). The unadjusted incidence of hospital-acquired pneumonia was higher in the group exposed to acid-suppressive medication relative to the unexposed group (4.9% vs 2.0%; OR, 2.6; 95% CI, 2.3–2.8). There was a stronger association between acid-suppressive medication and aspiration pneumonia in particular; however, the association remained significant for both aspiration and nonaspiration pneumonia (Table 2).

After adjusting for potential confounders as well as clustering of admissions with a multivariable GEE, the OR of hospital-acquired pneumonia in the group exposed to acid-suppressive medication was 1.3 (95% CI, 1.1–1.4) (Table 2). With respect to the secondary end points of aspiration and nonaspiration pneumonia, the ORs remained significant for each after adjustment, with a stronger association between acid-suppressive medication and aspiration pneumonia than nonaspiration pneumonia (Table 2).

**Propensity-Matched Analysis**

There was a successful match of 16,396 patient admissions with acid-suppressive medication exposure to 16,396 patient admissions without exposure. After matching admissions by propensity score, the group exposed to acid-suppressive medication was much more similar in baseline characteristics to the unexposed group (Table 3). A significant association between exposure to acid-suppressive medication and hospital-acquired pneumonia again existed, with an OR of 1.3 (95% CI, 1.1–1.4) (Table 2). The same association held for the secondary end points of aspiration and nonaspiration pneumonia (Table 2).

**Outcome Sensitivity Analysis and Validation**

Varying the rate of patients misclassified as having had a pneumonia did not change the point estimate of the OR substantially. This was consistent with only 2,219 admissions coded as having had a pneumonia (vs 61,659 without pneumonia); a simulated misclassification rate of 10% among patients originally coded as having had a pneumonia resulted in a movement of only 222 admissions to the group without pneumonia and a small change in the OR. Conversely, a simulated misclassification rate of 10% among patients originally coded as not having had a pneumonia resulted in movement of 6,166 admissions to the group with pneumonia. In the latter scenario, a misclassification rate of 5% or greater would cause the OR estimate to fall below the predefined threshold of 1.1 and render the results unreliable.

To estimate the actual rate of admissions misclassified as not having had a pneumonia, the discharge summaries of 100 randomly selected admissions that had been classified as not having hospital-acquired pneumonia were reviewed. In the event that there was no discharge summary, the chest radiographs from the admission were reviewed for presence or absence of an infiltrate. Of these 100 admissions, there was 1 case of hospital-acquired pneumonia. This yielded a standard error of 0.01 and a 95% CI upper bound of 2.95%, less than the threshold of 5%.

**Exposure Subgroup and Sensitivity Analyses**

When examining the association between the subcategories of acid-suppressive medication and hospital-acquired pneumonia in the stratified analysis, the same significant association with hospital-acquired pneumonia held for those exposed to proton-pump inhibitors but not histamine2 receptor antagonists (Table 4). After reclassifying admissions in which acid-suppressive medication was ordered after the first 48 hours of the hospitalization as not having received acid-suppressive medication, the multivariable GEE-derived OR of hospital-acquired pneumonia in an admission with acid-suppressive medication exposure in the first 48 hours was 1.2 (95% CI, 1.04–1.3).
After incorporation of the 3-category variable for smoking into the multivariable GEE model, the adjusted OR and 95% CI for the main effect were unchanged from the baseline analysis (OR, 1.3; 95% CI, 1.1-1.4).

**COMMENT**

In this large hospital-based pharmacoepidemiologic cohort, use of acid-suppressive medication was associated with 30% increased odds of hospital-acquired pneumonia in nonventilated patients. This association was stronger for aspiration pneumonia than for nonaspiration pneumonia. In a prespecified subgroup analysis, the association was significant for proton-pump inhibitor use but not histamine2 receptor antagonists.24,27

There are accumulating data implicating an association between acid-suppressive medication and various disease states, including *Clostridium difficile* colitis,17-20 ventilator-associated pneumonia,21-26 and community-acquired pneumonia.8,10 Only 2 of the studies undertaken in critically ill patients have examined the association between proton-pump inhibitors and hospital-acquired pneumonia (the remainder focused exclusively on histamine, receptor antagonists, sucralfate, and/or antacids), and neither found a statistically significant association when compared with placebo or histamine, receptor antagonists.24,27

Both studies, however, were small, and one did not include an unexposed reference group. Given the increased risk of stress-related gastric mucosal ulceration in ventilated patients, acid-suppressive medications continue to be used for prophylactic purposes in this patient population, consistent with current consensus guidelines.28

The theory that non–critically ill hospitalized patients would benefit from stress-ulcer prophylaxis has not been examined in a large, well-designed trial. Accordingly, current guidelines do not support the use of these medications in nonventilated hospitalized patients.28

Studies showing an association between current proton-pump inhibitor use and community-acquired pneumonia found that risk was highest within the first week of use,8,10 of potential importance for the inpatient population in whom initiation of these medications is frequent. The lack of availability of outpatient medication records in our database precluded assessing...
whether this relationship held in our patient population.

The recent finding of highest risk within the first 2 days of use\textsuperscript{10} raises pathophysiologic questions. Acid-suppressive medications have been thought to increase the risk of pneumonia via modification of the upper gastrointestinal flora (and, as a result, respiratory flora) in the setting of a less acidic intestinal flora (and, as a result, respiratory flora).\textsuperscript{27,28} It is possible that even early in this process, pneumonia risk is elevated. The risk might then be expected to remain elevated indefinitely thereafter. However, pneumonia risk appears to decrease with increasing duration of use.\textsuperscript{8,10} These findings should therefore prompt consideration of alternative explanations, such as impairment of white blood cell function associated with proton-pump inhibitor therapy, which has been demonstrated to occur within hours.\textsuperscript{33-35} Further studies are necessary to elucidate the mechanism of increased pneumonia risk in patients prescribed acid-suppressive medications in general and proton-pump inhibitors in particular.

Acid-suppressive medications, and proton-pump inhibitors in particular, remain frequently prescribed in the inpatient setting outside of the ICU. Our study demonstrated use in 52% of admissions (83% of which were proton-pump inhibitors), similar to the rate estimated in the literature.\textsuperscript{1,2,4-7} With an estimated 40 million discharges from US medical centers each year,\textsuperscript{36} this suggests approximately 20 million patients are exposed to these medications annually in the inpatient setting, with potentially important cost implications.\textsuperscript{3} Estimating that exposure to these medications increases the risk of developing a hospital-acquired pneumonia by 30% (and using OR as relative risk given the rarity of the outcome), with an overall rate of 3.5% and an exposure rate of 52%, this suggests an attributable risk of 0.9%, a number needed to harm of 111, and an excess of more than 180,000 cases of hospital-acquired pneumonia annually that could be attributed to acid-suppressive medication use. With an estimated mortality rate of 18% for hospital-acquired pneumonia,\textsuperscript{39,40} exposure to these medications could result in 33,000 preventable deaths annually. Reduction in the rates of nosocomial infection is one of the top-20 Priority Areas for National Action proposed by the Agency for Healthcare Research and Quality in association with the Institute of Medicine.\textsuperscript{41}

However, this analysis did not take into account the potential benefits of acid-suppressive medication with respect to prophylaxis of gastrointestinal bleeding. One study examining the incidence of hospital-acquired gastrointestinal bleeding in non–critically ill patients found an incidence of less than 0.5%.\textsuperscript{42} It therefore seems unlikely that the benefit of these medications for gastrointestinal bleed prophylaxis would offset the risk found in our study, but further research is necessary to determine the net clinical effect.

As with all studies using administrative data, there is concern over the validity of ICD-9-CM coding. Additionally, coding of whether or not a discharge diagnosis was present on admission began toward the end of the study period, and the inability to incorporate this new coding is a limitation of our analysis. To address this, we performed a sensitivity analysis that varied the degree of misclassification of outcomes to investigate the potential effect on the findings. This analysis suggested that our effect estimate was quite robust to even a very high rate of admissions misclassified as having had a pneumonia; although sensitive to a rate of 5% or greater of patients misclassified as not having had a pneumonia, the medical record review suggests that the actual rate of this type of misclassification was below this threshold.

The lack of information on the temporal association between acid-suppressive medication and date of diagnosis of hospital-acquired pneumonia is another study limitation. This was addressed through a sensitivity analysis in which all patients who received their first dose of acid-suppressive medication more than 48 hours into their hospitalization were reclassified as not having received acid-suppressive medication. Although the OR for the main effect decreased from 1.3 to 1.2, some attenuation was expected because this approach biased the result toward the null. Furthermore, for 89% of patients prescribed acid-suppressive medications, they were prescribed within 48 hours of admission, and 94% were still prescribed these medications within 48 hours of admission. Some patients were exposed to medications outside of the ICU.

Table 4. Rates of Hospital-Acquired Pneumonia According to Type of Acid-Suppressive Medication

<table>
<thead>
<tr>
<th></th>
<th>Acid-Suppressive Medication</th>
<th>No Acid-Suppressive Medication</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total admissions, No.</td>
<td>25,374</td>
<td>30,956</td>
<td>56,330</td>
<td>56,330</td>
</tr>
<tr>
<td>Hospital-acquired pneumonia, No. (%)</td>
<td>1,340 (5.3)</td>
<td>610 (2.0)</td>
<td>2.8 (2.5-3.1)</td>
<td>1.3 (1.1-1.4)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.

\textsuperscript{a}Patients prescribed histamine, receptor antagonists were excluded from this analysis.

\textsuperscript{b}Adjusted for all variables listed in Table 1, plus admission day of the week, using a multivariable generalized estimating equation (GEE) to take into account dependency of the data due to repeated admissions.

\textsuperscript{c}Patients prescribed proton-pump inhibitors were excluded from this analysis.
hours of discharge, indicating that the duration of use typically spans the hospitalization.

The possibility of unmeasured confounders remains, particularly in light of the large difference between unadjusted and adjusted ORs. There was no available information on activity order, presence of a nasogastric tube, or socioeconomic status, all of which could have an association with both acid-suppressive medication use and hospital-acquired pneumonia. While data on smoking status were not available for the entire cohort, the analysis was repeated after incorporating this information in the subgroup for which it was available; smoking did not confound the observed relationship. Several approaches were used to control for confounders, and 50 covariates were included in the models. The inclusion of length of hospitalization as a covariate introduced a very conservative bias, since hospital-acquired pneumonia itself can prolong length of hospitalization. Despite this, the association between acid-suppressive medication and hospital-acquired pneumonia remained significant after adjusting for length of stay, with no attenuation in effect size. A randomized controlled trial would be helpful to more definitively evaluate the observed relationship, but given the effect estimate, a well-powered trial would require a prohibitively large sample size (approximately 17,000 patients). Although almost 70,000 admissions were studied over a 4-year period, the single-center nature of the study limits generalizability. These findings should thus be validated at other institutions.

While the increased odds of hospital-acquired pneumonia in patients exposed to histamine₂ receptor antagonists was not statistically significant, this subgroup analysis was not adequately powered to detect significance for an OR of less than 1.3. Thus, a small but increased risk associated with this medication subclass cannot be excluded.

CONCLUSIONS

This study found that acid-suppressive medication use was associated with 30% increased odds of hospital-acquired pneumonia, and this result was significant for proton-pump inhibitor use. These results occur in the context of an increasing body of literature suggesting an association between acid-suppressive medication and pneumonia. Further scrutiny is warranted regarding inpatient prescribing practices of these medications.

Author Contributions: Dr Herzig had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Herzig, Howell, Ngo, Marcantonio.

Acquisition of data: Herzig, Howell.

Analysis and interpretation of data: Herzig, Howell, Ngo, Marcantonio.

Drafting of the manuscript: Herzig, Ngo, Critical revision of the manuscript for important intellectual content: Herzig, Howell, Ngo, Marcantonio.

Statistical analysis: Herzig, Howell, Ngo.

Obtained funding: Herzig, Marcantonio.

Administrative, technical, or material support: Howell, Ngo, Marcantonio.

Study supervision: Herzig, Marcantonio.

Financial Disclosure: None reported.

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Role of the Sponsor: The funding organization had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Disclaimer: The study contents are solely the responsibility of the authors and do not necessarily represent the official views of the Department of Health and Human Services.

REFERENCES


Let me consider this as a resolution by which I pledge myself to act in all variety of circumstances and to which I must recur often in times of carelessness and temptation—to measure my conduct by the rule of conscience.
—Ralph Waldo Emerson (1803-1882)
ENIGM PROSTATIC HYPERPLASIA (BPH) is a common condition in aging men. It has been estimated that more than 8 million US men aged 50 through 79 years will meet current guidelines for discussing treatment options for BPH by 2010.1 Treatments for BPH include surgical procedures, minimally invasive procedures, and pharmacological agents.2 Most often, the first-line therapy is pharmacological, using either α-blockers or 5-α reductase inhibitors (eg, finasteride). The former work through adrenergic pathways in the bladder, prostate, or both, whereas the latter work through hormonal mechanisms. The use of these agents has been increasing, and annual spending on prescriptions for BPH therapy in 1996 to 1998 totaled nearly $200 million; this is likely much greater now, with the availability of additional pharmacological agents.

The biological effects of 5-α reductase are fairly broad, since it is responsible for the conversion of testosterone to dihydrotestosterone. Dihydrotestosterone is the more powerfully active androgenic agent; with approximately 10 times the binding affinity for the androgen receptor, it is biologically active in pathways leading to secondary sex characteristics, BPH, acne, and male pattern baldness. Several adverse effects have been associated with the use of 5-α reductase inhibitors, including erectile dysfunction, decreased ejaculate volume, breast pain or tenderness, and gynecomastia.3 It is not clear, however, if these are the result of a decrease in dihydrotestosterone levels, a relative increase in testosterone levels, or a relative increase in estradiol levels due to shunting of testosterone through the aromatization pathway.4 Moreover, it is not clear how 5-α reductase inhibition affects long-term bone health, which has multiple androgenic and estrogenic steroid-dependent pathways.5-7

Previous work has suggested that inhibition of 5-α reductase may have little effect on bone metabolism, despite biological plausibility in either direction. The evidence in human cell-line studies is mixed. Testosterone appears to be related to bone mineral density (BMD) only in older men,8 which suggests that 5-α reductase inhibition may lead to increased bone density due to increases...
in testosterone levels. Simultaneous administration of testosterone and 5α reductase inhibitors compared with testosterone alone does not appear to have any differential effect on BMD in men with low testosterone levels.9 A sub-study of a large clinical trial for BPH showed no difference in BMD after 4 years of finasteride therapy,10 but this was examined in only 117 patients, and substantial dropout during the trial might have introduced bias. A small study of 71 men with BPH randomized to receive 5α reductase inhibitors vs control found no difference in markers of bone formation, turnover, or BMD.11 Of interest, however, is that human osteoblast-like cells predominantly express 5α reductase type 1,12 and dihydrotestosterone appears to have a modest regulatory role in the production of 1α-hydroxylase, which in turn increases levels of 1,25 dihydroxyvitamin D.13 Together, these observations suggest that dihydrotestosterone might have a role in bone metabolism, but no clear evidence exists to support this theory.

Some of this lack of clarity is owing to several limitations in the existing literature. Most of the studies have included a fairly limited number of individuals and therefore had limited power to detect differences. Most have included fairly short-term follow-up, and most have focused on BMD and not fracture. The latter outcome is of great public health import, given the morbidity and costs associated with fracture. If 5α reductase inhibition has an effect on fracture risk, it could be important from a societal perspective. Thus, to help clarify the potential adverse role of 5α reductase inhibitors in bone metabolism, we conducted a case-control study of hip fracture among men enrolled in a large managed care organization.

METHODS

Setting

Kaiser Permanente Southern California (KPSC) is a large managed care organization that covers the region from Bakersfield to San Diego. In 2006, KPSC had a membership of more than 3.2 million, with a racial/ethnic composition similar to that of the source population. The majority of health care for members is delivered in 1 of 12 medical centers or in more than 100 affiliated outpatient facilities. A small fraction of emergent and specialty care is obtained from other institutions through contractual arrangements or through a claims reimbursement system. Health plan members are assigned a primary medical center based on geographic proximity. All health care encounters are tracked through electronic data systems, including detailed information on diagnoses applied and procedures performed during those encounters, regardless of setting. Most members have pharmacy benefits as well. All dispensed prescriptions are electronically tracked, with information on drug, dose, frequency, amount, and date dispensed.

Patients

Case patients included men identified from KPSC membership rolls from 1997 to 2006 who had a new diagnosis of hip fracture (International Classification of Diseases, Ninth Revision, Clinical Modification code 820.x) coded in the encounter information and who were 45 years or older at the time of fracture. Control patients were selected from the same population and who were optimally matched14 to case patients at a 1:1 ratio on age, membership in the health plan on the index (fracture) date, and medical center; because of the known association of age and race/ethnicity with risk of fracture, patients also were matched on these factors. Race/ethnicity was determined by an administrative code primarily assigned to members at the time of enrollment or during health care encounters.

Measurements

The primary exposure measure was the dispensing of a 5α reductase inhibitor (dutasteride or finasteride) from 1991 (the year the electronic pharmacy files were established) forward. Information was recorded on the start of the prescription (date), dose, total doses, amount dispensed, and the total dose dispensed. Prescriptions for α-blockers (terazosin, tamsulosin, doxazosin, alfuzosin, prazosin) were also assessed as a second comparison exposure.

Information on additional variables was collected for consideration of these variables as potential confounders or effect modifiers. Among these were comorbid conditions, determined by the Deyo modification15 of the Charlson Comorbidity Index16 and based on diagnoses made during inpatient and outpatient encounters from 1981 until the index date. A diagnosis of BPH or surgical treatment of BPH also were considered potential confounders. The matching factor of race/ethnicity was considered a potential effect modifier.

Analysis

The primary analysis was the comparison of the off-diagonal frequencies of exposure to 5α reductase inhibitors for the matched case-control pairs. Differences were tested with the McNemar test. The association between 5α reductase inhibition and hip fracture was estimated with a matched-pairs odds ratio (OR) and its respective 95% confidence interval (CI). Conditional logistic regression was used to estimate the OR, taking into account potential confounders. Potential effect modifiers were tested by introducing appropriate interaction terms to the conditional logistic regression models.

A series of secondary analyses were conducted as well. Additional analyses used α-blockers, a diagnosis of BPH, or surgical treatment of BPH as alternative exposures. The association between hip fracture and α-blocker use was explored further, separating selective vs nonselective α-blocker, recency of initiating use, and current vs past use. A dose-response relationship between cumulative drug exposure and hip fracture was evaluated by Cochran-Armitage test for trend; P < .05 was considered statistically significant. With
type I and type II error rates fixed at .05 and .20, respectively, 7076 case patients, and an exposure prevalence of 0.20, the minimal detectable OR was 1.37. All analyses were performed by one investigator (J.M.S.) using SAS version 9.1.3 (SAS Institute Inc, Cary, North Carolina). The protocol for this study was reviewed and approved by the KPSC institutional review board.

RESULTS

Overall, 7076 men had a diagnosis of hip fracture over the 10-year period. The median age at fracture was 77 (interquartile range, 67-84) years (Table 1). Approximately 70% of men were white, with 11% identified as Hispanic and 7% as black. Compared with men without hip fracture, those with hip fracture were more likely to have multiple comorbid conditions (P < .001), despite being matched by age. A modest direct association was observed between comorbidity and use of 5-α reductase inhibitors (Spearman correlation coefficient, 0.057; P < .001).

Use of 5-α reductase inhibitors was fairly low in this population. During this period (1991 to 2006), finasteride was the only 5-α reductase inhibitor dispensed to study patients, and only 109 case patients (1.5%) and 141 control patients (2%) had a history of any exposure to these compounds (Table 2). The matched OR was 0.77 (95% CI, 0.59-1.00; P = .04). There was no suggestion of a dose-response relationship between exposure to 5-α reductase inhibitors when the exposure was stratified into tertiles of total exposure (P = .12). In multivariate models, there was little effect of adjustment for comorbidity.

There was no evidence for an association between a diagnosis of BPH or surgical treatment of BPH and hip fracture (Table 3). Of the 7076 case and control patients, 2547 (36%) and 2488 (35%), respectively, had a prior diagnosis of BPH (P = .30). The use of α-blockers was slightly greater in men with hip fracture (2250/7076 [32%]) compared with those without hip fracture (2139/7076 [30%]) (P = .04). There also was no evidence of a dose response in the association with α-blocker use. The risk associated with α-blocker use was increased only among those with the most recent prescriptions (within 30 days vs none: OR, 2.04; 95% CI, 1.19-3.49). In comparing the selective vs nonselective α-blockers, the effect was slightly stronger in men using selective α-blockers (OR, 1.23; 95% CI, 0.97-1.56) vs nonselective α-blockers (OR, 1.07; 95% CI, 1.00-1.16), although neither attained statistical significance.

**COMMENT**

These data demonstrate no evidence of a direct association between 5-α reductase inhibitors and hip fracture. In fact, there appears to be an inverse association. This does not appear to be due to the men having BPH, which in and of itself may be the manifestation of an altered hormonal milieu. Similarly, the inverse association does not appear to be due to confounding by indication, because there was no suggestion of an inverse association between α-blocker use, a diagnosis of BPH, or surgical treatment for BPH and hip fracture. Thus, the inverse association between 5-α reductase inhibitors and risk of hip fracture may be real and deserves additional consideration.

This observed association is biologically plausible. The role of sex steroids in bone health has been long recognized. Testosterone levels in men have been shown to be directly correlated with bone density in older men, although serum levels of bioavailable estradiol were more strongly correlated. However, the pathway through which 5-α reductase inhibitors may work is not clear, and the association may not necessarily be affected by bone metabolic pathways. The predominant form of 5-α reductase in osteoblasts is type I, whereas finasteride inhibits the type II isoenzyme, suggesting alternative pathways. It has been noted that finasteride is associated with higher serum levels of estradiol, which may be due to shunting of testosterone through the aromatization pathway. In addition, increased levels of bioavailable testosterone have been shown to be indirectly related to the risk of falling. Even if the inverse association between finasteride and fracture risk is due to a decreased risk of falls, it is not clear if decreased risk of fracture represents a direct effect of androgen or an increase in estrogen levels due to increased levels of substrate for aromatase. And while previous studies of 5-α reductase inhibitors have not
shown an association with bone density or with markers of bone metabolism, many of these studies may have been underpowered, may have had limited follow-up, or both.

While the size of the effect is modest, it could have important public health implications if it represents a cause-and-effect relationship. It has been projected that approximately 8.1 million US men aged 50 through 79 years will have BPH by 2010.1 If 10% of these men are taking 5-α reductase inhibitors,19 approximately 2000 would be expected to sustain hip fractures in the following year.20-21 Based on the inverse association observed in this study, these men may avoid 500 of these hip fractures, owing to the effects of 5-α reductase inhibition. In this study population, however, the use of these agents was fairly low, and the use of dutasteride almost nonexistent. Thus, it is not clear if these results would be sustained with wider use of finasteride or with the use of 5-α reductase inhibitors that affect both forms of the enzyme, such as dutasteride. In addition, the duration of exposure in this study was somewhat limited, given the availability and uptake of finasteride within the KPSC health plan. It will be important to assess men who start taking 5-α reductase inhibitors at earlier ages for BPH or other indications.

The finding of a modest direct association with 5-α blockers, although not an a priori hypothesis, is also of interest. These agents are often used as a first-line medication for the treatment of lower urinary tract symptoms often associated with BPH.2 A well-known adverse effect of these agents, particularly when the dose is first being titrated, is orthostatic hypotension.22 A consequent increase in falls could therefore represent the cause of the increase in hip fracture observed in this study. This hypothesis is supported by the observation that the increase in risk was primarily in men who started taking an α-blocker more recently. It was surprising, however, that the effect was somewhat stronger in men receiving selective α-blockers, because the systemic adverse effects are supposed to be less common with these agents. This may represent confounding by indication (men at higher risk of falling being given the selective agents) or a false sense of security and less careful titration of dose.

While these results provide no evidence of a detrimental effect of 5-α reductase inhibitors on the risk of hip fracture, this study does have some limitations. While it does not appear that the observed association is due to the underlying disease—i.e., BPH—or to confounding by indication or comorbidity, an unmeasured confounder may be responsible for the observed association. The replication of these results with other fracture sites may provide additional evidence as to whether this is a true association. Also, it is important to

### Table 2. Association Between Finasteride Exposure and Hip Fracture in Men—Kaiser Permanente Southern California, 1997-2006

<table>
<thead>
<tr>
<th>Finasteride Exposure</th>
<th>Fracture (n=7076)</th>
<th>No Fracture (n=7076)</th>
<th>P Value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude</td>
<td>Model 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Model 2&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6967 (98.5)</td>
<td>6925 (98.0)</td>
<td>.04&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1 [Reference] 1 [Reference] 1 [Reference]</td>
</tr>
<tr>
<td>Yes</td>
<td>109 (1.5)</td>
<td>141 (2.0)</td>
<td></td>
<td>0.77 (0.59-1.00) 0.72 (0.56-0.94) 0.71 (0.55-0.93)</td>
</tr>
<tr>
<td>Total dispensed, mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>6967 (98.5)</td>
<td>6925 (98.0)</td>
<td>.12&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1 [Reference] 1 [Reference] 1 [Reference]</td>
</tr>
<tr>
<td>Low (1-499)</td>
<td>34 (0.5)</td>
<td>54 (0.8)</td>
<td></td>
<td>0.64 (0.41-0.98) 0.60 (0.38-0.94) 0.60 (0.39-0.96)</td>
</tr>
<tr>
<td>Medium (500-2749)</td>
<td>50 (0.7)</td>
<td>55 (0.8)</td>
<td></td>
<td>0.91 (0.62-1.33) 0.87 (0.58-1.29) 0.86 (0.58-1.27)</td>
</tr>
<tr>
<td>High (≥2750)</td>
<td>25 (0.3)</td>
<td>32 (0.4)</td>
<td></td>
<td>0.78 (0.46-1.32) 0.72 (0.42-1.23) 0.75 (0.44-1.28)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.
<sup>a</sup>Adjusted for age, medical center, enrollment, race/ethnicity, and comorbidity.
<sup>b</sup>Adjusted for factors in model 1 plus α-blocker use.
<sup>c</sup>Exact test.
<sup>d</sup>Armitage test for trend.

### Table 3. Prevalence of Diagnosis of Benign Prostatic Hyperplasia and α-Blocker Use Among Men With and Without Hip Fracture—Kaiser Permanente Southern California, 1997-2006

<table>
<thead>
<tr>
<th>BPH diagnosis</th>
<th>Fracture (n=7076)</th>
<th>No Fracture (n=7076)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>4529 (64)</td>
<td>4588 (65)</td>
<td>.30</td>
</tr>
<tr>
<td>No</td>
<td>2547 (36)</td>
<td>2488 (39)</td>
<td></td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>BPH surgery</th>
<th>Fracture (n=7076)</th>
<th>No Fracture (n=7076)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>6344 (90)</td>
<td>6286 (89)</td>
<td>.12</td>
</tr>
<tr>
<td>No</td>
<td>732 (10)</td>
<td>790 (11)</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>α-Blocker exposure</th>
<th>Fracture (n=7076)</th>
<th>No Fracture (n=7076)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>4826 (68)</td>
<td>4937 (70)</td>
<td>.04</td>
</tr>
<tr>
<td>No</td>
<td>2250 (32)</td>
<td>2139 (30)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>α-Blocker, total dispensed, mg</th>
<th>Fracture (n=7076)</th>
<th>No Fracture (n=7076)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>4826 (68)</td>
<td>4937 (70)</td>
<td>.64</td>
</tr>
<tr>
<td>Low (1-400)</td>
<td>788 (11)</td>
<td>670 (10)</td>
<td></td>
</tr>
<tr>
<td>Medium (401-5199)</td>
<td>985 (14)</td>
<td>942 (13)</td>
<td></td>
</tr>
<tr>
<td>High (≥5200)</td>
<td>257 (3)</td>
<td>217 (3)</td>
<td></td>
</tr>
</tbody>
</table>

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remain cognizant that dispensed medications are not necessarily ingested. However, any misclassification of exposure status due to medication received but not ingested is likely to bias the results to the null and thereby lead to an underestimate of the true association. The KPSC population represents an insured population; therefore, the results may be limited in their generalizability. However, the characteristics of the KPSC member population are very similar to those of the California population, with the exception of a modest underrepresentation of the lowest and highest socioeconomic brackets. Finally, this study relied on the diagnostic codes for fracture and on pharmacy codes for exposure. While some modest misclassification might exist with these codes, it seems unlikely that misclassification would introduce a systematic bias on the basis of either exposure or outcome.

These data suggest that 5α-reductase inhibitors do not confer a negative risk for bone health and in fact may lower the risk of hip fracture. While presumably this lower risk is related to hormonal mechanisms, further understanding of the biological mechanisms underlying this phenomenon may lead to new insights that can be exploited for preventive measures. The increased risk of fracture associated with recent receipt of an α-blocker highlights the need for careful titration of these agents.

Author Contributions: Dr Jacobsen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Jacobsen.

REFERENCES


Red Yeast Rice for Dyslipidemia in Statin-Intolerant Patients
A Randomized Trial
David J. Becker, MD; Ram Y. Gordon, MD; Steven C. Halbert, MD; Benjamin French, PhD; Patti B. Morris, RD; and Daniel J. Rader, MD

Background: Red yeast rice is an herbal supplement that decreases low-density lipoprotein (LDL) cholesterol level.

Objective: To evaluate the effectiveness and tolerability of red yeast rice and therapeutic lifestyle change to treat dyslipidemia in patients who cannot tolerate statin therapy.

Design: Randomized, controlled trial.

Setting: Community-based cardiology practice.

Patients: 62 patients with dyslipidemia and history of discontinuation of statin therapy due to myalgias.

Intervention: Patients were assigned by random allocation software to receive red yeast rice, 1800 mg (31 patients), or placebo (31 patients) twice daily for 24 weeks. All patients were concomitantly enrolled in a 12-week therapeutic lifestyle change program.

Measurements: Primary outcome was LDL cholesterol level, measured at baseline, week 12, and week 24. Secondary outcomes included total cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, liver enzyme, and creatinine phosphokinase (CPK) levels; weight; and Brief Pain Inventory score.

Results: In the red yeast rice group, LDL cholesterol decreased by 1.11 mmol/L (43 mg/dL) from baseline at week 12 and by 0.90 mmol/L (35 mg/dL) at week 24. In the placebo group, LDL cholesterol decreased by 0.28 mmol/L (11 mg/dL) at week 12 and by 0.39 mmol/L (15 mg/dL) at week 24. Low-density lipoprotein cholesterol level was significantly lower in the red yeast rice group than in the placebo group at both weeks 12 ($P < 0.001$) and 24 ($P = 0.011$). Significant treatment effects were also observed for total cholesterol level at weeks 12 ($P < 0.001$) and 24 ($P = 0.016$). Levels of HDL cholesterol, triglyceride, liver enzyme, or CPK; weight loss; and pain severity scores did not significantly differ between groups at either week 12 or week 24.

Limitation: The study was small, was single-site, was of short duration, and focused on laboratory measures.

Conclusion: Red yeast rice and therapeutic lifestyle change decrease LDL cholesterol level without increasing CPK or pain levels and may be a treatment option for dyslipidemic patients who cannot tolerate statin therapy.

Primary Funding Source: Commonwealth of Pennsylvania.


See also: Print Editors’ Notes ........................................ 831 Editorial comment ...................................... 885 Related article ........................................... 858 Summary for Patients ............................... I-28

Web-Only
Appendix
Appendix Figure
Conversion of graphics into slides

Statin-associated myalgias are dose related and typically occur in the absence of myositis. Currently, no optimal treatment exists for patients who develop SAM but still require therapy for hyperlipidemia. Because of SAM, patients may seek alternative therapies to manage their hypercholesterolemia, including red yeast rice (Monascus purpureus), a widely available dietary supplement that has been used as an herbal medication in China for centuries. Red yeast rice decreases low-density lipoprotein (LDL) cholesterol level (5–7), but no trials have investigated its use in patients with SAM.

Our primary goal was to assess the efficacy and tolerability of red yeast rice for hypercholesterolemia in patients with previous SAM. We enrolled all patients in a therapeutic lifestyle change program and compared the lipid-lowering efficacy of red yeast rice with placebo in patients with a history of intolerance to at least 1 statin.

METHODS
Design Overview

We recruited patients from a cardiology practice in suburban Philadelphia. The institutional review board of Chestnut Hill Healthcare approved the trial, and all patients gave written informed consent. All authors had complete access to the primary data.

Statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) are the most effective lipid-lowering medications for primary and secondary prevention of coronary artery disease (1–3). Although statins are generally well tolerated, some patients experience adverse effects, including elevated hepatic enzyme levels; gastrointestinal symptoms; and statin-associated myalgias (SAMs), which include muscle pain and weakness. Myositis (elevated creatinine phosphokinase [CPK] level) and rhabdomyolysis are more serious but rare complications of therapy (4).
Red Yeast Rice for Statin-Intolerant Patients

**Context**

Statin-associated myalgias prevent some patients who would benefit from drug therapy for dyslipidemia from receiving it. Red yeast rice is a dietary supplement that can decrease low-density lipoprotein (LDL) cholesterol level and could be a treatment option for patients with statin-associated myopathy.

**Contribution**

After 12 and 24 weeks, patients who received red yeast rice, 1800 mg twice daily, had significantly larger improvements in both LDL and total cholesterol levels than did patients who received placebo. Pain, creatinine phosphokinase levels, and liver enzyme levels did not differ between groups.

**Implication**

Red yeast rice may be a treatment option for dyslipidemic patients who cannot tolerate statins.

---

**Setting and Patients**

Patients were eligible if they were 21 to 80 years of age; had known hypercholesterolemia; and had discontinued at least 1 statin because of myalgias, with resolution of muscle pain when the medication was discontinued. We excluded patients if they had received a statin or red yeast rice in the month before random assignment; had a history of statin-associated myositis, rhabdomyolysis, chronic pain, or inability to exercise; had myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting in the previous 6 months; had received weight-loss medications or dietary supplements that might mitigate SAM or decrease lipid levels; or had abnormal baseline laboratory values (LDL cholesterol level <2.6 mmol/L [<100 mg/dL] or >5.5 mmol/L [>210 mg/dL], triglyceride level ≥4.4 mmol/L [≥400 mg/dL], CPK level >500 U/L, aspartate transferase or alanine transferase level >1.5 times the upper limit of normal, or an abnormal thyroid-stimulating hormone level).

**Randomization and Interventions**

Figure 1 shows the flow of patients through the trial. We recruited patients between September 2006 and March 2007. We screened 174 patients with SAM; 112 were ineligible for the study or declined to participate. Sixty-two patients were randomly assigned, and baseline laboratory tests were drawn and measurements taken. Table 1 shows baseline characteristics.

We randomly assigned all enrolled patients to receive three 600-mg capsules of red yeast rice (1.8 g by weight) or 3 placebo capsules twice daily for 24 weeks. We randomly assigned patients in blocks of 4 and stratified them into 4 categories to improve power and subgroup analyses: LDL cholesterol level less than 3.9 mmol/L (<150 mg/dL), LDL cholesterol level of 3.9 mmol/L or greater (≥150 mg/dL), body mass index less than 27 kg/m², and body mass index of 27 kg/m² or greater. We generated the random assignment list on a computer by using the blockrand library (8) of the R programming environment with the fixed-block option (9).

We purchased both the red yeast rice and placebo directly from the manufacturer (Sylvan Bioproducts, Kittanning, Pennsylvania); they were identical in size, shape, and color. Participants received a 30-day supply of study product at monthly visits. At the end of the trial, we assessed treatment adherence by self-report of the average number of missed doses per week.

All patients also enrolled in our previously published, multidisciplinary, 12-week therapeutic lifestyle change program (10). Briefly, patients attended weekly 3.5-hour meetings and were taught about cardiovascular disease, nutrition, exercise, and relaxation techniques (Appendix, available at www.annals.org).

After the therapeutic lifestyle change program ended at week 12, we again conducted laboratory tests and took measurements. We then instructed patients to follow the recommendations of the program and continue to take their study medication for an additional 12 weeks. We held meetings each month to review dietary and exercise logs and provide study product. Attendance in the 12-week program and all subsequent monthly meetings was 92%. All patients and study team members were blinded to treatment allocation throughout the 24-week study. At week 24, we conducted the final laboratory tests and took the final measurements.

One patient in the red yeast rice group dropped out at week 10 because he could not attend the program. Two patients in the placebo group dropped out, 1 at week 12 because of newly diagnosed hypothyroidism and 1 at week 16 because of nonadherence to the lifestyle change program. Fifty-nine patients completed the 24-week study: 30 in the red yeast rice group and 29 in the placebo group. We conducted the study between April 2007 and October 2007.

**Outcomes and Follow-up**

The primary outcome was LDL cholesterol level, measured at baseline, week 12 (end of the therapeutic lifestyle change program), and week 24 (end of the study). Other secondary outcomes included total cholesterol level, high-density lipoprotein cholesterol level, triglyceride level, and weight.

**Safety**

All patients completed the Brief Pain Inventory Short Form (BPI-sf) (Appendix Figure, available at www.annals.org) at baseline, week 12, and week 24. The BPI-sf is a validated, widely used, self-administered questionnaire developed to assess the severity of pain and the effect of pain on daily function (11). To assess pain severity, we used a question from the Brief Pain Inventory Pain Severity subscale that asks about average pain severity over the past 24 hours.

The Editors
week (on a 0- to 10-point scale) rather than calculate a mean score across all items. We used this for the secondary outcome of measuring pain severity score at baseline, week 12, and week 24. We also assessed safety by measuring CPK and liver-associated enzyme levels in all patients at baseline, week 12, and week 24. We reviewed the results of laboratory tests independently at week 12 to monitor safety.

**Anthropometry**
We measured weight to the nearest 0.1 kg and height to the nearest centimeter at baseline, week 12, and week 24. We calculated body mass index as weight (kg) divided by height (m)². We measured blood pressure in patients in the sitting position by using standard sphygmomanometry.

**Laboratory**
We obtained a fasting blood sample at baseline, week 12, and week 24 for a lipid panel, complete metabolic profile, and CPK and thyroid-stimulating hormone levels. The Laboratory Corporation of America (Burlington, North Carolina) performed the analyses.

ConsumerLab.com (White Plains, New York) analyzed the red yeast rice (Table 2). The laboratory tested red yeast rice for individual and total monacolins by using high-performance liquid chromatography. They used thin-layer chromatography to detect citrinin, a potential contaminant. We did not disclose the identity of the products to the laboratory performing the testing.

**Statistical Analysis**
We used the intention-to-treat principle for all data analysis on the patients at baseline and week 12. We computed descriptive statistics for primary and secondary outcome measures at baseline, week 12, and week 24. We assumed outcomes were normally distributed and fit a lin-
ear mixed-effects model for each outcome to account for the correlation due to repeated measurements. Each model allowed for patient-specific intercepts. We modeled raw outcomes together (baseline, week 12, and week 24), and the model included an interaction term between treatment indicator and the 3-level categorical variable for week. These models gave an estimate of the treatment effect, which represents the estimated difference in the mean outcome between the red yeast rice and placebo groups at weeks 12 and 24. Specifically, these models provided point estimates and CIs for differences in the mean LDL cholesterol, total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels; BPI-sf pain scores; and body mass index between the treatment and placebo groups at weeks 12 and 24. We also used each model to test for a difference between the treatment effect at weeks 12 and 24 to evaluate any change in the treatment effect over this time. The model for BPI-sf pain severity scores included the number of statins previously not tolerated as a categorical covariate. We performed appropriate model diagnostics. We analyzed safety parameters (CPK and liver-associated enzyme levels) for differences between groups by using linear mixed-effects models.

The amount of missing data was small (<4.8%) and we treated these data as missing in the analysis. We completed all statistical analyses by using Stata, version 9.2 (StataCorp, College Station, Texas).

Role of the Funding Source

Our study was funded by an unrestricted grant from the Commonwealth of Pennsylvania, which had no role in the design, conduct, or analysis of the study or the decision to submit the manuscript for publication.

RESULTS

Table 1 shows the baseline characteristics of enrolled patients. The mean age was 60.5 years (SD, 9.3) in the red yeast rice group and 61.5 years (SD, 8.2) in the placebo group. Forty (65%) of the 62 patients were female. Mean baseline weight was 81.0 kg in the red yeast rice group and

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Red Yeast Rice Group (n = 31)</th>
<th>Placebo Group (n = 31)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), y</td>
<td>60.5 (9.3)</td>
<td>61.5 (8.2)</td>
<td>0.44</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>19 (61)</td>
<td>21 (68)</td>
<td>0.79</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>4 (13)</td>
<td>8 (26)</td>
<td>0.53</td>
</tr>
<tr>
<td>White</td>
<td>26 (84)</td>
<td>22 (71)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>4 (13)</td>
<td>8 (26)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Coexisting disease, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Essential hypertension</td>
<td>12 (39)</td>
<td>16 (52)</td>
<td>0.44</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>6 (19)</td>
<td>4 (13)</td>
<td>0.73</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1 (3)</td>
<td>2 (6)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>0</td>
<td>1 (3)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Mean blood pressure (SD), mm Hg</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>125.9 (8.6)</td>
<td>127.2 (8.2)</td>
<td>0.127</td>
</tr>
<tr>
<td>Diastolic</td>
<td>78.9 (5.8)</td>
<td>79.0 (6.1)</td>
<td>0.85</td>
</tr>
<tr>
<td>Mean fasting glucose level (SD)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>mmol/L</td>
<td>93.0 (9.7)*</td>
<td>100.3 (17.3)</td>
<td>0.21</td>
</tr>
<tr>
<td>mg/dL</td>
<td>5.17 (0.54)</td>
<td>5.57 (0.96)</td>
<td></td>
</tr>
<tr>
<td>Mean body mass index (SD), kg/m²</td>
<td>28.8 (4.3)</td>
<td>29.2 (5)</td>
<td>0.84</td>
</tr>
<tr>
<td>Mean Brief Pain Inventory score (SD)</td>
<td>1.4 (1.9)</td>
<td>2.6 (2.2)</td>
<td>0.026</td>
</tr>
<tr>
<td>Mean creatine phosphokinase level (SD), U/L</td>
<td>122.4 (69.2)</td>
<td>117.5 (87.5)</td>
<td>0.51</td>
</tr>
<tr>
<td>Mean aspartate aminotransferase level (SD), U/L</td>
<td>22.9 (5.4)</td>
<td>24.9 (7.5)</td>
<td>0.35</td>
</tr>
<tr>
<td>Mean alanine aminotransferase level (SD), U/L</td>
<td>24.4 (10.2)</td>
<td>26.0 (10.0)</td>
<td>0.52</td>
</tr>
<tr>
<td>Mean number of statins not tolerated (SD)†</td>
<td>2.0 (1.1)</td>
<td>1.7 (0.87)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

* Available for 30 participants.
† Statin use discontinued before study because of intolerable myalgias.

Table 2. Chemical Analysis*

<table>
<thead>
<tr>
<th>Component</th>
<th>Red Yeast Rice</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monacolins, mg/capsule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2.16</td>
<td>0.0933</td>
</tr>
<tr>
<td>Monacolin IA</td>
<td>0.0120</td>
<td>Not detected</td>
</tr>
<tr>
<td>Monacolin J</td>
<td>0.0186</td>
<td>Not detected</td>
</tr>
<tr>
<td>Monacolin XA</td>
<td>0.0080</td>
<td>Not detected</td>
</tr>
<tr>
<td>Monacolin KA</td>
<td>0.607</td>
<td>0.0041</td>
</tr>
<tr>
<td>Monacolin LA</td>
<td>0.0802</td>
<td>Not detected</td>
</tr>
<tr>
<td>Monacolin X</td>
<td>Not detected</td>
<td>Not detected</td>
</tr>
<tr>
<td>Monacolin K (lovastatin)</td>
<td>1.02</td>
<td>0.0892</td>
</tr>
<tr>
<td>Monacolin L</td>
<td>0.0546</td>
<td>Not detected</td>
</tr>
<tr>
<td>Monacolin M</td>
<td>0.0065</td>
<td>Not detected</td>
</tr>
<tr>
<td>Dihydromonacolin K</td>
<td>0.212</td>
<td>Not detected</td>
</tr>
</tbody>
</table>

Other components, ppm†

<table>
<thead>
<tr>
<th>Component</th>
<th>Red Yeast Rice</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citrinin</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

* Performed by ConsumerLab.com (White Plains, New York). We sent 2 bottles of red yeast rice product (manufactured by Sylvan Bioproducts, Kittanning, Pennsylvania), containing 120 capsules per bottle, for analysis.
† Heavy metals and microbes were undetectable for both red yeast rice and placebo.
81.9 kg in the placebo group. Mean number of statins received before intervention was 2.0 (SD, 1.1) in the red yeast rice group and 1.7 (SD, 0.9) in the placebo group. The groups did not significantly differ at baseline except in BPI-sf score, which was significantly higher in the placebo group ($P = 0.026$).

**Effects on Lipids and Lipoproteins**

Tables 3 and 4 show descriptive statistics for the primary and secondary outcome measures. In the red yeast rice group, mean LDL cholesterol level was 4.2 mmol/L (163 mg/dL) at baseline, 3.1 mmol/L (120 mg/dL) at week 12, and 3.3 mmol/L (128 mg/dL) at week 24 (Table 3). In the placebo group, mean LDL cholesterol level was 4.3 mmol/L (165 mg/dL) at baseline, 4.0 mmol/L (154 mg/dL) at week 12, and 3.88 mmol/L (149.8 mg/dL) at week 24. The mean percentage of change in LDL cholesterol level from baseline for the red yeast rice group was −27.3% (SD, 16.4%) at week 12 and −21.3% (SD, 22.7%) at week 24. In the placebo group, the mean percentage of change from baseline was −5.7% (SD, 13.3%)

### Table 3. Plasma Lipid Measures at Baseline, Week 12, and Week 24

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Red Yeast Rice Group</th>
<th>Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients, n</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>31</td>
<td>4.23 (0.70) 163.3 (27.0)</td>
</tr>
<tr>
<td>Week 12</td>
<td>29</td>
<td>3.11 (0.95) 120.0 (36.8)</td>
</tr>
<tr>
<td>Week 24</td>
<td>30</td>
<td>3.32 (1.05) 128.3 (40.4)</td>
</tr>
<tr>
<td>Change (baseline to week 12), %</td>
<td></td>
<td>−27.3 (16.4)</td>
</tr>
<tr>
<td>Change (baseline to week 24), %</td>
<td></td>
<td>−21.3 (22.7)</td>
</tr>
<tr>
<td>Total cholesterol level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>31</td>
<td>6.35 (0.79) 245.2 (30.5)</td>
</tr>
<tr>
<td>Week 12</td>
<td>29</td>
<td>5.03 (1.05) 194.1 (40.6)</td>
</tr>
<tr>
<td>Week 24</td>
<td>30</td>
<td>5.41 (1.15) 208.7 (44.3)</td>
</tr>
<tr>
<td>Change (baseline to week 12), %</td>
<td></td>
<td>−21.4 (12.3)</td>
</tr>
<tr>
<td>Change (baseline to week 24), %</td>
<td></td>
<td>−14.9 (15.9)</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>31</td>
<td>1.37 (0.31) 52.8 (12.1)</td>
</tr>
<tr>
<td>Week 12</td>
<td>29</td>
<td>1.33 (0.28) 51.4 (10.9)</td>
</tr>
<tr>
<td>Week 24</td>
<td>30</td>
<td>1.46 (0.32) 56.4 (12.3)</td>
</tr>
<tr>
<td>Change (baseline to week 12), %</td>
<td></td>
<td>−0.6 (13.0)</td>
</tr>
<tr>
<td>Change (baseline to week 24), %</td>
<td></td>
<td>8.6 (17.0)</td>
</tr>
<tr>
<td>Triglyceride level</td>
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<td></td>
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<tr>
<td>Baseline</td>
<td>31</td>
<td>1.64 (0.93) 145.5 (82.3)</td>
</tr>
<tr>
<td>Week 12</td>
<td>29</td>
<td>1.28 (0.48) 113.3 (42.9)</td>
</tr>
<tr>
<td>Week 24</td>
<td>30</td>
<td>1.36 (0.64) 119.9 (57.0)</td>
</tr>
<tr>
<td>Change (baseline to week 12), %</td>
<td></td>
<td>−11.8 (33.2)</td>
</tr>
<tr>
<td>Change (baseline to week 24), %</td>
<td></td>
<td>−7.2 (43.9)</td>
</tr>
</tbody>
</table>
at week 12 and −8.7% (SD, 14.1%) at week 24. Figure 2 displays the mean and 95% CI for LDL cholesterol level at baseline, week 12, and week 24 for the red yeast rice and placebo groups. Mean LDL cholesterol level differed significantly between the red yeast rice and placebo groups (treatment effect) at week 12 (P < 0.001) and week 24 (P = 0.011). Treatment effect for LDL cholesterol was also significantly attenuated at week 24 compared with week 12 (P = 0.041). At week 24, 9 of 30 patients in the red yeast rice group achieved an LDL cholesterol level less than 2.6 mmol/L (<100 mg/dL), compared with 2 of 29 patients in the placebo group.

Mean total cholesterol level differed significantly between the red yeast rice and placebo groups (treatment effect) at week 12 (P < 0.001) and week 24 (P = 0.016). Treatment effect for total cholesterol had a marginally significant attenuation at week 24 compared with week 12 (P = 0.051). The groups did not significantly differ in mean high-density lipoprotein cholesterol or mean triglyceride level at week 12 or week 24.

Weight
In the red yeast rice group, weight decreased an average of 3.7 kg (3.7%) at 12 weeks and 3.5 kg (4.0%) at 24 weeks from baseline. In the placebo group, weight decreased an average of 3.6 kg (4.2%) at 12 weeks and 3.6 kg (5.0%) at 24 weeks from baseline (Table 4). Figure 2 shows mean and 95% CIs for body mass index at baseline, week 12, and week 24 for both groups. The groups did not significantly differ in mean body mass index at either week 12 or week 24 (Table 5).

Safety
Figure 2 displays the mean and 95% CI for BPI-sf scores at baseline, week 12, and week 24 for both groups. Although the BPI-sf score was significantly higher in the placebo group at baseline, the linear mixed-effects model for BPI-sf score, adjusted for the number of statins not tolerated previously, showed no significant differences in pain scores between groups at either week 12 or week 24 (Table 5). However, BPI-sf scores were positively skewed, and a linear mixed-effects model may therefore not be appropriate.

Two (7%) of 29 patients in the red yeast rice group developed persistent intolerable myalgias and discontinued treatment. Their CPK levels were within normal limits. Two other patients discontinued red yeast rice, 1 because of dizziness and 1 because of loose stools. All 4 patients remained in the study and completed the study protocol. One of 30 patients in the placebo group developed persistent intolerable myalgias and discontinued treatment but completed the study protocol. The groups did not significantly differ in the development of intolerable myalgias (P = 0.61) or CPK or liver-associated enzyme level at week 12 or 24 (Table 5).

## Table 4. Secondary Outcome Measures

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Red Yeast Rice Group</th>
<th>Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients, n</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>31</td>
<td>81.0 (12.8)</td>
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<tr>
<td>Week 12</td>
<td>30</td>
<td>77.3 (12.4)</td>
</tr>
<tr>
<td>Week 24</td>
<td>29</td>
<td>77.5 (12.5)</td>
</tr>
<tr>
<td>Change (baseline to week 12), %</td>
<td>−3.7 (2.9)</td>
<td>−4.2 (3.3)</td>
</tr>
<tr>
<td>Change (baseline to week 24), %</td>
<td>−4.0 (3.6)</td>
<td>−5 (4.6)</td>
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<tr>
<td>Brief Pain Inventory score*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>31</td>
<td>1.4 (1.9)</td>
</tr>
<tr>
<td>Week 12</td>
<td>29</td>
<td>1.4 (1.6)</td>
</tr>
<tr>
<td>Week 24</td>
<td>30</td>
<td>1.2 (1.6)</td>
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<tr>
<td>Creatine phosphokinase level, U/L</td>
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<tr>
<td>Baseline</td>
<td>31</td>
<td>122.4 (69.2)</td>
</tr>
<tr>
<td>Week 12</td>
<td>29</td>
<td>135.7 (89.2)</td>
</tr>
<tr>
<td>Week 24</td>
<td>30</td>
<td>128.3 (90.2)</td>
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<td>Aspartate aminotransferase level, U/L</td>
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<tr>
<td>Baseline</td>
<td>31</td>
<td>22.9 (5.4)</td>
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<tr>
<td>Week 12</td>
<td>29</td>
<td>24.8 (11.5)</td>
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<tr>
<td>Week 24</td>
<td>30</td>
<td>22.5 (4.4)</td>
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<td>Alanine aminotransferase level, U/L</td>
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</tr>
<tr>
<td>Baseline</td>
<td>31</td>
<td>24.4 (10.2)</td>
</tr>
<tr>
<td>Week 12</td>
<td>29</td>
<td>24.4 (14.3)</td>
</tr>
<tr>
<td>Week 24</td>
<td>30</td>
<td>21.8 (8.9)</td>
</tr>
</tbody>
</table>

* Scores range from 0 (no pain) to 10 (worst pain imaginable). Score represents the reported average pain over the past month. A change in score of ≥5 points has been cited as a clinically meaningful change.

**DISCUSSION**

To our knowledge, ours is the first randomized, double-blinded, placebo-controlled trial to evaluate red yeast rice in patients with a history of SAM. Red yeast rice significantly decreased LDL and total cholesterol levels compared with placebo and did not increase the incidence of myalgias over a 24-week period. The regimen of red yeast rice and therapeutic lifestyle change may offer a lipid-lowering option for patients with a history of intolerance to statin therapy.

Although the occurrence of myalgias after statin initiation is poorly defined, SAMs are a major clinical issue. An English-language MEDLINE search for *statin myopathy* yielded 1023 articles from July 1983 to April 2009. The incidence of SAM may be as high as 10% (12, 13) and may affect approximately 1.3 million people in the United States (14). The median time of myalgia onset has been reported to be 1 to 6.3 months (12) but it can occur at any time, with a range of 1 week to 48 months (15).

No optimal therapy exists for patients who develop SAM but continue to require therapy for hyperlipidemia. Although alternative or natural therapies have never been tested in this population, several approaches exist for treating hyperlipidemia in patients with SAM (Table 6) (16–
Of note, adding coenzyme Q10 (ubiquinone) to patients with SAM is a popular but controversial practice. Although supplementation with ubiquinone increases serum coenzyme Q10 level, a recent meta-analysis (28) showed no clear-cut benefit in reducing myalgias. Because no definitive treatment for SAM exists, many patients adopt alternative therapies to manage their hypercholesterolemia, including red yeast rice. In 2006, American consumers spent $17 million on this dietary supplement, a 55% increase from 2005 (29). Red yeast rice contains naturally occurring lovastatin (monacolin K) and other monacolins that may inhibit HMG-CoA reductase and reduce LDL cholesterol levels compared with placebo (5–7).

It is unclear why red yeast rice may be better tolerated than statins in patients with SAM. The low rate of myalgias in the red yeast rice group was striking because the recurrence rate of myalgias is as high as 57% when patients are challenged with a second statin (15). One clue may be related to the increasing risk for SAM with higher doses of statins (17). The dose of red yeast rice in our study (3.6 g/d) was equivalent to a daily lovastatin dose of only 6 mg (Table 2), far less than the established therapeutic dose (20 to 40 mg/d) (30). A recent study showed that patients with variants in the \( SLCO1B1 \) gene were more likely to develop statin-associated myopathy with higher doses of simvastatin (31). It is therefore possible that the low dose of monacolin K (lovastatin) in our red yeast rice product was below the threshold necessary to cause SAM.

Another possibility is the presence of compounds in red yeast rice, other than monacolin K, that may inhibit HMG-CoA reductase (Table 2). Little is known about their pharmacodynamics, but these monacolins may either have lipid-lowering effects or potentiate the effects of monacolin K. They may also be less likely to deplete mevalonate metabolites distal to HMG-CoA reductase, such as intracellular isoprenoids (for example, ubiquinone) and guanosine triphosphate–binding regulatory proteins, which are believed to mediate statin-induced muscle injury (32).

Our therapeutic lifestyle change program also played an integral role. It incorporated the Mediterranean diet (33–36), an exercise program, and relaxation techniques, which have been collectively shown to favorably affect serum lipid levels and reduce weight, blood pressure, and mortality (37, 38). The excellent adherence rate seen in our study was probably due to intensive follow-up, education, and support, unlike other studies involving diet and exercise, which reported higher rates of recidivism (39–41).

Our study has limitations. Low-density lipoprotein cholesterol level increased slightly in the red yeast rice group between weeks 12 and 24, probably because of decreased adherence to the red yeast rice regimen after the 12-week lifestyle change program ended and patients were expected to continue taking their study medication. In addition, although red yeast rice was effective in decreasing

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Figure 2. Point estimates and 95% CIs for mean LDL cholesterol level, body mass index, and Brief Pain Inventory score.

Estimates shown for weeks 0 (baseline), 12, and 24 for the placebo and red yeast rice groups. Estimated from separate linear mixed-effect models for each outcome. To convert LDL cholesterol to mmol/L, multiply by 0.0259. LDL = low-density lipoprotein.
LDL cholesterol level, only 30% of patients who received treatment achieved an LDL cholesterol level of 2.6 mmol/L or less (±100 mg/dL). This was probably because of the weak potency of our red yeast rice product (monacolin K, 1.02 mg/capsule; total monacolins, 2.16 mg/capsule). A recent trial (10) showed that a more potent red yeast rice product (monacolin K, 2.53 mg/capsule; total monacolins, 5.3 mg/capsule) reduced LDL cholesterol level by 42% when combined with therapeutic lifestyle change and fish oil. However, more potent red yeast rice products could also increase the incidence of myalgias in patients with previous SAM.

Another limitation of the trial is the current regulatory status of red yeast rice as a dietary supplement. Although the chemical composition of red yeast rice was known and controlled in the current study, the lack of consistency between different manufacturers is a major problem (42, 43). There is an ongoing need for the FDA to regulate the manufacturing of red yeast rice products.

Although our trial showed that red yeast rice was well tolerated over the 24-week trial, receiving red yeast rice without a physician’s oversight may be unsafe. Red yeast rice has been reported to cause myopathy (44–48), rhabdomyolysis (49), and hepatotoxicity (50).

It is also possible that our 6-month trial was too short to evaluate the development of SAM in patients receiving red yeast rice. Statin-associated myalgias have been reported as late as 48 months after initiation of statin therapy (15). Future studies are needed to evaluate the risk for SAM in patients receiving red yeast rice for more than 6 months.

Despite the limitations of our small, single-center study, red yeast rice significantly reduced LDL cholesterol level compared with placebo in a cohort with a history of SAM. This raises important questions that need to be addressed in future studies: Does red yeast rice reduce the incidence of myalgias when directly compared with statin therapy? Is red yeast rice effective in patients with previous SAM who are not enrolled in a lifestyle change program? Finally, did the therapeutic lifestyle change program alone play a positive role in decreasing the risk for recurrent myalgias in our cohort (for example, through improved mood or the role of exercise and weight loss).

A final issue raised by our study concerns the relationship between red yeast rice and cardiovascular outcomes. A
Red Yeast Rice for Statin-Intolerant Patients

recent secondary prevention trial (51) showed a decreased incidence of nonfatal myocardial infarction or death from cardiac causes in patients randomly assigned to receive red yeast rice versus placebo. Future trials are needed to confirm this finding and to evaluate cardiovascular outcomes in a primary prevention setting.

Presently, no consensus has been reached on lipid-lowering therapy for patients who develop SAM. In our small, single-center, randomized study, patients with a history of SAM who enrolled in a therapeutic lifestyle change program and received red yeast rice had significantly lower LDL and total cholesterol levels than those who enrolled in the lifestyle program and received placebo over a 6-month period, with no increase in intolerable myalgias. Given our positive results, our approach may provide a therapeutic lipid-lowering option for the large cohort of patients with a history of SAM. A larger, multicenter trial with longer follow-up is needed to determine whether red yeast rice offers a safe and effective solution for this unmet medical need and to evaluate its effects on cardiovascular outcomes.

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Red Yeast Rice for Statin-Intolerant Patients


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Appendix: Therapeutic Lifestyle Change Program

All patients enrolled in the trial participated as a group in a 12-week, multidisciplinary therapeutic lifestyle change program. The group consisted solely of patients enrolled in the trial and involved attending weekly 3.5-hour meetings with a board-certified cardiologist, certified dietitian, exercise physiologist, and several alternative/relaxation practitioners.

During the first part of the session, the cardiologist taught patients about cardiovascular risk factors, the pathogenesis of coronary plaque formation, the importance of preventive measures, and methods to improve communication with their personal physician.

A dietitian taught the group about the basic principles of nutrition and encouraged patients to follow a Mediterranean diet that was modified by reducing saturated fat and limiting total fat to less than 25% of daily caloric intake. Sugars and noncomplex carbohydrates were restricted, and patients learned how to count calories, although no formal caloric restrictions were imposed. Patients were also given dietary advice about shopping for food and eating in restaurants. Individualized advice was given in the form of a question-and-answer session at the end of each teaching period.

An exercise physiologist taught the group about the health benefits of cardiovascular exercise, stretching, and light strength training. Participants were instructed to gradually increase exercise up to 5 to 6 times per week. Aerobic exercise was encouraged and included walking, swimming, or jogging for 30 to 45 minutes at a time. Although the sessions did not involve actual exercise, the exercise physiologist demonstrated proper techniques for various exercises (such as sit-ups, push-ups, and using an exercise ball) and patients were encouraged to track their progress by completing weekly exercise logs. The exercise physiologist reviewed the logs and then gave patients individualized advice about improving their exercise regimen and tolerance.

During the 12-week program, various guest practitioners exposed patients to relaxation methods, including yoga, acupuncture, medical massage, meditation, hypnosis, deep breathing, humor, and tai chi.
Appendix Figure. Brief Pain Inventory Short Form questionnaire.

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain over the past week?
   □ Yes  □ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.

3. Please rate your pain by marking the box beside the number that best describes your pain at its worst over the past week.
   □ 0  □ 1  □ 2  □ 3  □ 4  □ 5  □ 6  □ 7  □ 8  □ 9  □ 10
   No Pain
   Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least over the past week.
   □ 0  □ 1  □ 2  □ 3  □ 4  □ 5  □ 6  □ 7  □ 8  □ 9  □ 10
   No Pain
   Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average over the past week.
   □ 0  □ 1  □ 2  □ 3  □ 4  □ 5  □ 6  □ 7  □ 8  □ 9  □ 10
   No Pain
   Pain As Bad As You Can Imagine

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6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

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<th>1</th>
<th>2</th>
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<td>No Pain</td>
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7. What medications are you taking for your pain?

8. Mark the box beside the number that describes how, during the past week, pain has interfered with your:

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<tr>
<th>A. General activity</th>
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<th>B. Mood</th>
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<th>C. Walking ability</th>
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<th>D. Normal work</th>
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<th>E. Relations with other people</th>
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<td>Completely Interferes</td>
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<th>F. Sleep</th>
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<td>0</td>
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<td>Does Not Interfere</td>
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<td>Completely Interferes</td>
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<tr>
<th>G. Enjoyment of life</th>
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<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>Does Not Interfere</td>
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<tr>
<td>Completely Interferes</td>
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News Media Coverage of Medication Research Reporting Pharmaceutical Company Funding and Use of Generic Medication Names

Michael Hochman, MD
Steven Hochman
David Bor, MD
Danny McCormick, MD, MPH

**Context** The news media are an important source of information about medical research for patients and even some physicians. Little is known about how frequently news articles report when medication research has received funding from pharmaceutical companies or how frequently news articles use generic vs brand medication names.

**Objectives** To assess the reporting of pharmaceutical company funding and generic medication name use in news articles about medication studies and to determine the views of newspaper editors about these issues.

**Design, Setting, and Participants** We reviewed US news articles from newspaper and online sources about all pharmaceutical company-funded medication studies published in the 5 most prominent general medical journals between April 1, 2004, and April 30, 2008. We also surveyed editors at the 100 most widely circulated newspapers in the United States.

**Main Outcome Measures** The percentage of news articles indicating when studies have been pharmaceutical company-funded and the percentage that refer to medications by their generic vs brand names. Also the percentage of newspaper editors who indicate that their articles report pharmaceutical company funding; the percentage of editors who indicate that their articles refer to medications by generic names; and the percentage of newspapers with policies about these issues.

**Results** Of the 306 news articles about medication research identified, 130 (42%; 95% confidence interval [CI], 37%-48%) did not report that the research had received company funding. Of the 277 of these articles reporting on medications with both generic and brand names, 186 (67%; 95% CI, 61%-73%) referred to the study medications by their brand names in at least half of the medication references. Eighty-two of the 93 (88%) newspaper editors who responded to our survey reported that articles from their publications always or often indicated when studies had received company funding (95% CI, 80%-94%), and 71 of 92 (77%) responding editors also reported that articles from their publications always or often referred to medications by the generic names (95% CI, 67%-85%). However, only 3 of 92 newspapers (3%) had written policies stating that company funding sources of medical studies be reported (95% CI 1%-9%), and 2 of 93 (2%) newspapers had written policies stating that medications should be referred to by their generic names (95% CI 1%-8%).

**Conclusion** News articles reporting on medication studies often fail to report pharmaceutical company funding and frequently refer to medications by their brand names despite newspaper editors’ contention that this is not the case.

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newspaper articles discussing studies involving 5 specific medications (atorvastatin, celecoxib, donepezil, oseltamivir, and raloxifene) frequently failed to mention how the studies were funded; however, the authors did not report how many of the cited studies were company sponsored.

Another way the news media may reduce commercial bias in the medical information they present is by using nonproprietary medication names.\textsuperscript{20-22} Generic names may also be preferable because many medications come in multiple brands, and the use of generic names may reduce confusion and even potentially dangerous medication errors.\textsuperscript{23-27} Although pharmacies frequently substitute brand-name medications for less expensive generic versions,\textsuperscript{28} the unnecessary use of brand medications when a related generic could be used may account for as much as $9 billion in wasteful expenditures in the United States annually.\textsuperscript{22,29,30} For these reasons, most medical journals require the use of generic names,\textsuperscript{15} the Institute for Safe Medication Practices recommends that generic medication names be used as the primary nomenclature in electronic ordering systems,\textsuperscript{24} and the US Food and Drug Administration mandates the use of generic names in advertising and on labels and brochures.\textsuperscript{31-33} To our knowledge, no previous studies have examined the use of generic vs brand medication names by the news media.

We sought to determine how frequently and prominently US newspaper and online articles about pharmaceutical company–funded medication studies indicate the funding source and how often they refer to medications by their brand vs generic names. We also surveyed editors at the 100 most widely circulated newspapers in the United States about their publications’ practices on the reporting of company funding and the use of generic medication names.

**METHODS**

**Analysis of News Articles**

Identifying Medical Journal Studies. We identified all pharmaceutical or biotechnology company–funded studies evaluating the effectiveness or safety of medications published between April 1, 2004, and April 30, 2008, in the 5 general medical journals with the highest impact factor (\textit{New England Journal of Medicine}, \textit{JAMA}, \textit{Lancet}, \textit{Annals of Internal Medicine}, and \textit{Archives of Internal Medicine}).\textsuperscript{34} The studies were identified by manually reviewing titles and abstracts of all original articles published in these 5 journals during the specified period. Randomized trials and observational studies were included, but meta-analyses and other review articles were excluded.

Study funding sources were determined by reviewing the “Methods” and “Acknowledgements” sections of the published articles; only studies that received at least partial funding from pharmaceutical companies were included. Studies in which free medications, but no other funding, were provided by a pharmaceutical company were not included. We also excluded studies in which the researchers had personally accepted company payments but the study itself was not company funded.

Identifying News Articles. We then identified news articles that reported on the results of these medication studies by searching major US newspapers and online news sources. The newspapers searched were the 45 non–business-oriented US newspapers included in the Lexis-Nexis database of major newspapers as of November 2006 (See eTable 1 available at http://www.jama.com and http://www.lexisnexis.com for a list of the publications in the database). The online sources we searched were the 7 US-based primary news Web sites that were listed as the top news source for a major news item on “Google News” 10 or more times between January 2006 and November 2006 (ABC News, CNN, Fox News, Time, MSNBC, CBS, and NPR). This list was obtained from Newsknife (http://www.newsknife.com), a commercial advertising agency. Business-oriented news publications were again excluded, as were newspaper Web sites.

For each eligible study, a search was performed in the Lexis-Nexis database of “Major Newspapers.” The generic and brand names of all study medications were entered as search terms along with the name of the medical journal in which the study was published. For medications with multiple brand names, the brand name of the medication made by the sponsoring company was used. These terms were searched in the “Headline, Lead Paragraphs, and Indexing” of all articles in the database. By placing the word “or” between all medication names and the word “and” before the medical journal name, articles were returned that contained any 1 of the medication names as well as the medical journal name.

The date ranges of the search were the 6-month period prior to the publication date of the study until 14 days after the publication date. In a few instances, the authors knew based on results from their online searches that the study results had been released more than 6 months before the date the study was published, and in these instances the date range was modified to include the dates when the study results were first released.

All articles that were returned using this search strategy and were at least 200 words in length were reviewed. Articles that focused on the new research findings were included in the analysis; articles that mentioned the new research only peripherally were not included. There was some judgment on the part of the authors in determining which articles should be included based on the above criteria, but for the most part it was clear whether an article should be included in the analysis.

Online articles were identified in a similar manner by searching the Web sites of the 7 online news sources on http://www.google.com. The only difference in the search strategy was that articles containing either the medication brand or generic name anywhere in the document, rather than just in the headlines or lead paragraph, were returned. For each eligible study, on the...
NEWS MEDIA REPORTING OF MEDICATION RESEARCH

“advanced Google search” in the boxes labeled “one or more of these words,” the generic and brand names of all study medications were entered. In the box labeled “all these words” the name of the medical journal was entered. Again, all articles at least 200 words in length that focused on the new research findings were included in the analysis.

Analysis of News Articles
We reviewed each news article to determine whether the study funding source was listed, and if so whether it was listed in the first 150 words of the article. We also determined whether study medications were referred to by their brand names, generic names, or both. Articles in which both names were used were further classified according to whether brand names were used in at least half of the medication references. When a news article reported on a medication without a brand name, the article was not included in the generic vs brand name analysis.

In some instances, articles came from a newswire source (eg, the Associated Press) and appeared in more than 1 publication (ie, a repeated article). Repeated articles were counted once. When a newswire article appeared in both an online and a newspaper publication, it was counted as either an online or newspaper article on an alternating basis.

The percentage of news articles indicating that the medical journal study was sponsored by a pharmaceutical company was calculated along with 95% exact confidence intervals (CIs). Additionally, the percentages of news articles referring to medications by their brand names exclusively and by brand names in at least half of the references were calculated along with 95% exact CIs. For both of these outcomes, we compared the percentages between the 2 types of news media (ie, newspaper and online articles) using 2-sided \( \chi^2 \) tests with an a priori level of significance of \( P \leq .05 \). To determine whether the increasing recent attention about commercial bias in medical research has affected medical coverage by the news media, we compared the rates of reporting of company funding and generic name usage between news articles published within the final 13 months of the study period and articles published in the first 36 months. Two-sided \( \chi^2 \) tests were used to compare the percentages with an a priori level of significance of \( P \leq .05 \). We used SAS statistical software version 9.1 (SAS Institute Inc, Cary, North Carolina) for all statistical calculations.

Survey of Newspaper Editors
Identification of Newspaper Editors. Between July 1 and September 30, 2007, we surveyed editors at the 100 most widely circulated US newspapers\(^35\) about their coverage of medical studies (eTable 2 available at http://www .jama.com). The name of the health editor at each newspaper was obtained from the News Media Yellow Book.\(^36\) When no health editor was listed, the name of the features editor was obtained. When no features editor was listed, the name of the managing editor or editor-in-chief was obtained.

Survey. Each editor was e-mailed a short survey asking how frequently articles about medical research from his/her publication report when a study has been company funded, report when quoted experts have financial ties to pharmaceutical companies, and refer to medications by their generic vs brand names. We then asked editors whether the news organization has a policy on the reporting of company funding of such studies or on the use of generic medication names. We also asked whether the editor had personally accepted a gift from a pharmaceutical representative within the past year. The e-mail was preceded by a telephone call alerting the editor of the coming e-mail survey. Each nonresponding editor was e-mailed and called weekly for up to 4 weeks. When an editor explicitly opted not to participate or failed to respond after 4 telephone and e-mail contacts, another editor at the publication was contacted. On several occasions, an editor referred us to another editor who could better answer the survey. In 2 instances, an editor referred us to a health reporter; all other surveys were sent to editors. The editors’ tabulated responses to each question were reported along with exact 95% CIs.

Correspondence Between Editor Survey Results and Newspaper Article Analysis. We then determined how well the editor’s responses corresponded to his/her publication’s actual performances. First, we identified all articles from publications at which the editor had indicated that company funding was always reported. Then we determined the percentage of these articles that actually indicated when company funding had occurred. Likewise, we identified all articles from publications at which the editor indicated that generic medication names were always used and determined the percentage of these articles that actually referred to medications by their brand names in at least half of the references.

In addition, we sought to determine whether articles from publications that had policies about the reporting of company funding and the use of generic medication names were more likely to mention when company funding had occurred than articles from publications without policies. We stratified the results of our analysis of news articles according to whether the articles came from publications with written, unwritten, or no policies. Only articles from newspapers that reportedly either had or did not have policies (on the basis of our survey) were included in this analysis.

The survey protocol was approved by the Cambridge Health Alliance Institutional Review Board.

RESULTS
Reporting of Company Funding in News Articles
A total of 358 company-funded medication studies were identified in the 5 medical journals. Of these 358 studies, 117 yielded news articles that met the study inclusion criteria: 68 from New England Journal, 24 from JAMA, 16 from Lancet, 7 from Annals of Internal
names between articles published in the final 13 months of the study period and articles published in the first 36 months (69% of articles published in the final 13 months referred to medications by their brand names in at least half of the medication references compared with 67% of articles published in the first 36 months, \( P = .70 \)).

**Survey of News Media Editors**

Responses to the survey were obtained from editors at 94 of 100 newspapers (94%). Two editors declined the survey because their publications do not regularly cover health stories. Editors at 4 newspaper publications did not respond. Of the 94 responses, 61 were from the first editor at the publication to be contacted.

At 88% (95% CI, 80%-94%) of the newspapers, the editor indicated that his/her publication often or always reported company funding in articles about medical research (93 respondents), and at 82% (95% CI, 72%-89%), the editor reported that his/her publication often or always indicated when cited experts have financial ties to pharmaceutical companies (88 respondents; Table 3). The editor at 77% (95% CI, 67%-85%) of the newspapers responded that his/her publication often or always referred to medications by the generic names in articles about medical research (92 respondents). The editor at 3% (95% CI, 1%-9%) of the newspapers indicated that his/her publication had a written policy stating that company funding should be reported in articles about medical research, while the editor at 62% (95% CI, 51%-72%) of newspapers responded that his/her publication had...
unwritten policies indicating that sponsorship should be reported (92 respondents). The editor at 2% (95% CI, 1%-8%) of newspapers indicated that his/her publication had a written policy stating that medications should be referred to predominantly by their generic names, while the editor at 18% (95% CI, 11%-28%) of newspapers reported that his/her publication had an unwritten policy indicating that generic names should predominately be used (93 respondents). The editor at 4% (95% CI, 1%-11%) of newspapers reported that he/she had received a gift from a pharmaceutical representative within the past year, and 1% (95% CI, 1%-9%) reported that he/she had received a gift valued at more than $5 (93 respondents).

The editors’ perceptions diverged from their publications’ actual performances. A total of 104 newspaper articles were analyzed from publications for which editors reported always identifying company funding. Of these articles, 45% (95% CI, 35%-55%) failed to cite company funding. Additionally, a total of 75 newspaper articles were analyzed from publications for which the editors reported always using generic names. Of these articles, 76% (95% CI, 65%-85%) used brand names in at least half of the medication references.

Table 4 shows the percentages of newspaper articles that indicated when company funding had occurred stratified according to whether the articles

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### Table 2. Reporting of Pharmaceutical Company Funding and the Use of Medication Brand Names in News Articles

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<th>No. of Articles</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Funding Source Not Reported</td>
<td></td>
<td></td>
<td>Brand Names Used to Identify Treatment Drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newspapers</td>
<td>175</td>
<td>75</td>
<td>43 (35-51)</td>
<td>158</td>
<td>104</td>
<td>66 (58-73)</td>
</tr>
<tr>
<td>Online</td>
<td>131</td>
<td>55</td>
<td>42 (33-51)</td>
<td>119</td>
<td>82</td>
<td>69 (60-77)</td>
</tr>
<tr>
<td>Total</td>
<td>306</td>
<td>130</td>
<td>42 (37-48)</td>
<td>277</td>
<td>186</td>
<td>67 (61-73)</td>
</tr>
</tbody>
</table>

*Defined as brand name use in at least half of medication references among articles about medications with brand names.

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### Table 3. Newspaper Editors’ Views on the Reporting of Pharmaceutical Company Funding of Medical Research and the Use of Generic Medication Names in News Articles

<table>
<thead>
<tr>
<th>Question</th>
<th>No. of Respondents (n = 100)</th>
<th>% (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>When you run a story about a medical study that was funded by a pharmaceutical company, do you indicate that the funding source was a pharmaceutical company?</td>
<td>93</td>
<td>69 (58-78)</td>
</tr>
<tr>
<td>When you quote medical experts who have financial connections to pharmaceutical companies in articles about medical research, do you indicate this in your stories?</td>
<td>88</td>
<td>48 (37-59)</td>
</tr>
<tr>
<td>Do your articles refer to medications by their generic names (for example, acetaminophen) as opposed to the brand names (for example, Tylenol) in articles about medical research?</td>
<td>92</td>
<td>39 (29-50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>38 (28-49)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23 (15-33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 (0-4)</td>
</tr>
</tbody>
</table>

---

### Table 4. Correspondence Between Newspaper Policies and the Reporting of Company Funding and the Use of Brand Medication Names

<table>
<thead>
<tr>
<th>News Organization Policy</th>
<th>Organizations With Each Policy</th>
<th>Stories Not Reporting Funding Source, % (95% CI)</th>
<th>Stories Using Brand Names, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reporting of funding source</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>32</td>
<td>35 (25-45)</td>
<td>73</td>
</tr>
<tr>
<td>Unwritten</td>
<td>57</td>
<td>62 (51-72)</td>
<td>58</td>
</tr>
<tr>
<td>Written</td>
<td>3</td>
<td>3 (1-9)</td>
<td>31</td>
</tr>
<tr>
<td>Generic names</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>74</td>
<td>80 (70-87)</td>
<td>114</td>
</tr>
<tr>
<td>Unwritten</td>
<td>17</td>
<td>18 (11-28)</td>
<td>27</td>
</tr>
<tr>
<td>Written</td>
<td>2</td>
<td>2 (1-8)</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

*Defined as brand name use in at least half of medication references among articles concerning medications with brand names.

Additional information and statistics are presented in the text, focusing on the reporting of pharmaceutical company funding and the use of brand versus generic medication names in news articles.
were from publications with written, unwritten, or no policies about the reporting of company funding. Articles from newspapers with written policies were more likely not to report the funding source than articles from newspapers with no or unwritten policies combined (61% with written policies did not report vs 39% without written policies, \( P = .02 \)), however, articles from only 2 publications with written policies were included in this analysis.

Table 4 also shows the percentage of newspaper articles that refer to medications by their brand names in at least half of the references stratified according to whether the articles came from publications with written, unwritten, or no policies about the use of generic medication names. There were no differences among the 3 groups \(( P = .99)\), but articles from only 1 publication with a written policy and 3 publications with unwritten policies were included in this analysis.

**COMMENT**

Our analysis of news articles from US newspapers and online sources suggests that lay media journalists frequently fail to indicate when medical studies have received company funding. Even when this information is reported, it is seldom placed prominently in the text. As a result, those who learn about medical research from the news media may remain unaware of how the research has been funded. In addition, our analysis suggests that news articles usually refer to medications by their brand names rather than their generic names. As a result, those who read about medications in the US news media may frequently learn to refer to medications by their brand names.

In our survey of newspaper editors, most reported their publications always or often indicated when medical research had received company funding. Most also indicated their publications always or often referred to medications by their generic names. These results are discordant with the findings from our analysis of news articles. These discrepancies may be due, in part, to the fact that some of the editors we surveyed worked for publications not included in our analysis of news articles. However, even articles from publications for which the editors reported always including information about company funding or always referring to medications by their generic names frequently failed to do so.

Our study also showed that the majority of major newspapers lacked written policies on the reporting of pharmaceutical company funding and the use of generic medication names. Although most publications had unwritten policies specifying that company funding should be reported, only a few had unwritten policies concerning generic names. These findings may partially explain why journalists so frequently neglect to report when research has received company funding and so frequently refer to medications by their brand names. However, many articles in our analysis from publications with policies about the reporting of company funding and the use of generic names frequently did not follow these policies.

We suspect that journalists may frequently neglect to indicate how medical research has been funded because they are often unaware when a study has been company sponsored. Information about research funding may be buried within the methods section or at the end of journal articles, and unless journalists carefully read the articles—a difficult task for those without a medical background—they are unlikely to discover this information. Additionally, news releases—which many journalists rely on for summaries of technically difficult material—often fail to indicate when a study has been company funded.37 One study published in 2002, for example, found that only 22% of news releases issued by medical journals noted when a study had received company funding.37

Similarly, we speculate that journalists may sometimes refer to medications by their brand names because they do not know whether a drug name is generic or brand. Additionally, several of the newspaper editors in our survey told us informally that they often refer to medications by their brand names because they believe lay readers are more likely to recognize brand names. Moreover, because only a minority of newspapers in our survey had policies (written or unwritten) about generic name use, it is likely that many journalists do not consider generic names to be preferable.

Our study is the most comprehensive analysis that we are aware of that examines the reporting of company funding in medical research by the US news media. It builds on previous research by including a substantially larger number of news articles, a broader array of news sources (including online sources), and survey data from journalists. This is also the first study we are aware of that examines the use of generic vs brand medication names by the US news media.

Our study has several limitations. We only identified studies published in the 5 highest impact medical journals, and only surveyed journalists from the most widely circulated publications; therefore, our results may not be representative of all types of medication studies reported in all types of lay media publications. Additionally, we did not examine news media reports from television and radio sources. Moreover, because the availability of articles in the Lexis-Nexis and online databases varies from time to time, it is possible that our search missed a number of relevant news articles. However, it seems unlikely that such missed articles would differ systematically from the articles in our analysis.

Our findings raise several concerns. For patients and physicians to evaluate new research findings, it is important that they know how the research was funded so they can assess whether commercial biases may have affected the results. Additionally, the use of generic medication names by the news media is preferable so that physicians and patients learn to refer to medications by their generic names, a practice that is likely to reduce medication...
errors and may decrease unnecessary health care costs.

News publications should consider implementing and enforcing written policies stating that all news articles about medical research must indicate study funding and should prominently use generic names. However, as we have shown, this alone is likely to be insufficient. Educational efforts will also likely be needed to help journalists more easily identify how medical studies have been funded. Medical journals can help journalists in this effort by making disclosures of funding sources more prominent and by issuing news releases that include this information. Educational efforts are also needed to encourage the use of generic medication names by the news media because many journalists apparently are unaware of the importance of this practice.

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**REFERENCES**