Effects of an Increase in Prescription Copayment on Utilization of Low-Sedating Antihistamines and Nasal Steroids

Identification of Allergic Disease Among Users of Antihistamines

Frequency of Simvastatin Prescriptions With Potentially Interacting Medications in a Veterans Affairs Health Care System

Quantifying the Effect of Applying the NCEP ATP III Criteria in a Managed Care Population Treated With Statin Therapy

Cost-Effectiveness Analysis of Simvastatin and Lovastatin/Extended-Release Niacin to Achieve LDL and HDL Goal Using NHANES Data

A Comparison of the Cost-Effectiveness of Almotriptan and Sumatriptan in the Treatment of Acute Migraine Using a Composite Efficacy/Tolerability End Point
CONTENTS

ORIGINAL RESEARCH

226 Effects of an Increase in Prescription Copayment on Utilization of Low-Sedating Antihistamines and Nasal Steroids
Brian L. Meissner, PharmD; W. Mark Moore, PharmD, MBA; Judith A. Shinogle, PhD, MSc; C.E. Reeder, PhD; and John M. Little, Jr., MD

234 Identification of Allergic Disease Among Users of Antihistamines
Sheryl L. Szeinbach, PhD; P. Brock Williams, PhD; Pieter Muntendam, MD; and Richard D. O’Connor, MD

239 Frequency of Simvastatin Prescriptions With Potentially Interacting Medications in a Veterans Affairs Health Care System
Jerilyn B. Petropoulos, BSPharm, PharmD, BCPs, and Cristina E. Bello-Quintero, PharmD

244 Quantifying the Effect of Applying the NCEP ATP III Criteria in a Managed Care Population Treated With Statin Therapy
Brian J. Quilliam, PhD; H. Ed Perez, PharmD; Vickie Andros, PharmD; and Peter Jones, MD, FACP

FORMULARY MANAGEMENT

251 Cost-Effectiveness Analysis of Simvastatin and Lovastatin/Extended-Release Niacin to Achieve LDL and HDL Goal Using NHANES Data
Edward P. Armstrong, PharmD; Woodie M. Zachry III, PhD; and Daniel C. Malone, PhD

259 A Comparison of the Cost-Effectiveness of Almotriptan and Sumatriptan in the Treatment of Acute Migraine Using a Composite Efficacy/Tolerability End Point
Paul Williams, MBA, MD, FRCPsych, and C.E. Reeder, PhD

DEPARTMENTS

216 Cover Impressions
Whirlwind (2000)
Alicia Binda
Sheila Macho

266 Editorial Subjects—In This Issue
• Which Triptan?—Opportunity for Same or Better Outcomes at Lower Cost
• Does Member Cost Sharing Pose a Threat to Desirable Patient Outcomes?
• Alternate Managed Care Approaches to Disease Management of Allergic Rhinitis
• Methods to Attain Optimal Outcomes With Lipid-Lowering Drug Therapy
Frederic R. Curtiss, PhD, RPh, CEBS
Editor-in-Chief

AMCP HEADQUARTERS
100 North Pitt St., Suite 400
Alexandria, VA 22314
Tel: (703) 683-8416
Fax: (703) 683-8417

BOARD OF DIRECTORS
President: James R. (Rusty) Hailey, PharmD, DPh, MBA, Coventry Health Care, Inc., Franklin, TN
President-Elect: Dianne A. Kane Parker, PharmD, Amgen Inc., Thousand Oaks, CA
Past President: Michael E. Bailey, RPh, MedImpact Healthcare Systems, Inc., San Diego, CA
Treasurer: Peter M. Penna, PharmD, Formulary Resources, LLC, University Place, WA
Director: Elizabeth L. Brouig, PharmD, BCPhS, Optima Health Plan, Virginia Beach, VA
Director: Janeen McBride, RPh, MedImpact Healthcare Systems, Inc., San Diego, CA
Director: Mark J. Rubino, RPh, Aetna, Inc., Hartford, CT
Director: Doug W. Stephens, RPh, Midwestern University, Glendale, AZ (JMCP liaison)
Director: Richard A. Zabinski, PharmD, UnitedHealthcare Corporation, Edina, MN

ADVERTISING
Advertising for Journal of Managed Care Pharmacy is accepted in accordance with the advertising policy of the Academy of Managed Care Pharmacy.
For advertising information, contact:
Professional Media Group, Inc., P.O. Box 189, 40 N. Woodbury Rd., Pitman, NJ 08071
Tel: (800) 486-5454 or (856) 589-5454
Fax: (856) 582-7611
E-mail: peter@promedgroup.net

EDITORIAL
Correspondence related to editorial content should be mailed to:
Managing Editor, JMCP
AMCP
100 North Pitt St., Suite 400
Alexandria, VA 22314
Tel: (703) 683-8416
Fax: (703) 683-8417

SUBSCRIPTIONS
Annual subscription rates: USA, individuals, institutions—$60; other countries—$80. Single copies cost $10. Missing issues are replaced free of charge up to 6 months after date of issue. Send requests to AMCP headquarters.

REPRINTS
For article reprints, contact Diana Sholl, Reprint Management Services, (717) 560-2001, ext. 162; dsholl@reprintbuyer.com. Microfilm and microfiche editions of Journal of Managed Care Pharmacy are available from University Microfilms, 300 N. Zeeb Rd., Ann Arbor, MI 48106. Reprint Guidelines are available at www.amcp.org.

All articles published represent the opinions of the authors and do not reflect the official policy of the Academy of Managed Care Pharmacy or the authors’ institutions unless so specified.

Copyright © 2004 Academy of Managed Care Pharmacy, Inc. All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, without written permission from the Academy of Managed Care Pharmacy.
JMCP publishes peer-reviewed original research manuscripts, subject reviews, and other content intended to advance the use of the scientific method, including the interpretation of research findings in managed care pharmacy. JMCP is dedicated to improving the quality of care delivered to patients served by managed care pharmacy by providing its readers with the results of scientific investigation and evaluation of clinical, health, service, and economic outcomes of pharmacy services and pharmaceutical interventions, including formulary management. JMCP strives to engage and serve professionals in pharmacy, medicine, nursing, and related fields to optimize the value of pharmaceutical products and pharmacy services delivered to patients.

JMCP employs extensive bias-management procedures intended to ensure the integrity and reliability of published work.

EDITORIAL MISSION

JMCP employs extensive bias-management procedures intended to ensure the integrity and reliability of published work.

EDITORIAL STAFF

Editor-in-Chief
Frederic R. Curtiss, PhD, RPh, CEBS
(817) 491-3593, fcurtiss@amcp.org

Managing Editor, Tamara C. Faggen, (703) 323-0170, tfaggen@amcp.org
Associate Editor, Shane P. Desselle, PhD, RPh, (412) 396-6363, desselle@duq.edu
Peer Review Administrator, Jennifer A. Booker, (703) 317-0725, jmcpreview@amcp.org
Graphic Designer, Laura J. Mahoney, (703) 917-0737, laura@gilbertgordon.com
Cover Editor, Sheila Macho, (952) 431-5993, jmcpcoverart@amcp.org

Publisher
Judith A. Cahill, CEBS, Executive Director, Academy of Managed Care Pharmacy

EDITORIAL ADVISORY BOARD

The JMCP Editorial Advisory Board is chaired by Marvin D. Shepherd, PhD, Director of the Center for Pharmacoeconomic Studies of the College of Pharmacy at the University of Texas at Austin. Dr. Shepherd and the other advisers review manuscripts and assist in the determination of the value and accuracy of information provided to readers of JMCP.

Emily Ann Baker, PharmD, ACS State Health Care, Atlanta, GA
John P. Barbuto, MD, HealthSouth Rehabilitation Hospital, Sandy, Utah
Diana L. Brixner, RPh, PhD, Department of Pharmacy Practice, University of Utah, Salt Lake City
Jeanne Carlson, CPA, Blue Care Network, BlueCross BlueShield of Michigan, Southfield
Timothy Covington, PharmD, MS, McWhorter School of Pharmacy, Samford University, Birmingham, Alabama
Leslie Fish, PharmD, Fallon Community Health Plan, Worcester, Massachusetts
Feride Frech, MPH, Novartis Pharmaceuticals Corp., East Hanover, New Jersey
Zafar Hakim, PhD, Hoffman-La Roche, Nutley, New Jersey
Joel Hay, PhD, School of Pharmacy, University of Southern California, Los Angeles
Alan Heaton, PharmD, BlueCross BlueShield of Minnesota, Eagan
Brent C. James, MD, MStat, Institute for Healthcare Delivery Research, Intermountain Health Care, Salt Lake City, Utah
Richard A. Kipp, MAAA, Milliman USA, Radnor, Pennsylvania
Katherine Knapp, PhD, Center for Pharmacy Practice Research, Western University of Health Sciences, Pomona, California
Michelle Modrijan, PharmD, Medica Health Plan, Minnetonka, Minnesota
Robert P. Navarro, PharmD, Campbell Alliance, Raleigh, North Carolina
Eduardo Ortiz, MD, Washington, DC, VA Medical Center
Steven Pepin, PharmD, Express Scripts, Inc., Bloomington, Minnesota

Founding Editor
Louise J. Sargent Heuer, MS, RPh

Editor-in-Chief, 1998-2001
Craig S. Stern, RPh, MBA, PharmD

Steven R. Peskin, MD, MBA, Pharmaceutical Research Plus, Severna Park, Maryland
Cathlene Richmond, PharmD, Kaiser Permanente, Oakland, California
J. Warren Salmon, MS, PhD, College of Pharmacy, University of Illinois at Chicago
Michael J. Sax, PharmD, The Pharmacy Group, LLC, Glastonbury, Connecticut
Fred L. Sego, Jr., JD, RPh, Reliant Pharmaceuticals, LLC, Poulsbo, Washington
Fadia T. Shaya, PhD, MPH, School of Pharmacy, University of Maryland, Baltimore
Joshua Spooner, PharmD, Advanced Concepts Institute, Philadelphia, Pennsylvania
Andy Stergachis, RPh, PhD, University of Washington and Formulary Resources, LLC, Seattle
Sean D. Sullivan, PhD, Pharmaceutical Outcomes Research and Policy Program, University of Washington, Seattle
Kent H. Summers, PhD, School of Pharmacy, Purdue University, Lafayette, Indiana
Robert J. Valuck, RPh, PhD, School of Pharmacy, University of Colorado Health Sciences Center, Denver
George J. Wan, PhD, MPH, McNeil Consumer & Specialty Pharmacy, Fort Washington, Pennsylvania
William J. Waugh, PharmD, WellPoint Pharmacy Management, West Hills, California
Bill Yates, RPh, PhD, CaremarkPCS, Columbia, South Carolina
Alicia Binda's Whirlwind is an energetic vortex of color, form, light, and shadow. At first glance, it appears to be an abstract painting, but it is actually a photograph of Italian blown glass.

For this piece, Binda employed the technique of macrophotography, which is defined as close-up photography of small objects using supplementary or macro lenses. (The magnification ranges from 1:1 [life-size] to 20:1, image size to object size ratio.) She also backlit the glass for the shoot to achieve the luminescent effect and intensify the colors.

To create this type of glass, the glassblower used millefiori (Italian for “thousand flowers”) glass dowels, which consist of multicolored rods bundled together and heated until they fuse. The bundle is then pulled thin, cooled, and sliced to produce small disks with flowerlike designs. These disks are subsequently combined with hot blown glass to produce vivid designs. The technique was developed by the Romans in the 1st century B.C. and is used to make glassware such as vases, bowls, plates, figurines, and paperweights.

Binda’s photography is truly a “snapshot of a snapshot”—the formerly molten and fluid glass eventually cools to the point where it becomes motionless and frozen in time (the first snapshot). For the second snapshot, she has to choose the best angle and most appealing section of her subject. Through this process, Binda inexplicably transforms images of glass into mesmerizing works of fine art.

Dorothy Roatz Myers of Art Talk—New York Art wrote in the exhibit catalog of Binda’s 2001 Italian Glass exhibit at the Montserrat Gallery in New York City, “The photographic art exhibited by Alicia Binda definitely falls within the definition of fine art. Her training in both fine art and traditional photography meet on a common ground that is innovative and unique . . . working in a personal style that lies between fantasy and realism.” New York art critic Wilson Wong also wrote in the exhibit catalog, “Alicia Binda employs photography as a medium, but goes far beyond the limitations of its documentary function. Her color photographs evoke otherworldly landscapes—she makes rivers, mountains and skies merge in rhythmic waves, with luminous rainbow hues converging simultaneously to create some of the most painterly photographic imagery in recent memory.”

In her artist’s statement, Binda said, “light and shadow playing together, and the pure, brilliant colors of the glass are my tools. They help me to ‘paint’ my images, using my camera as if it were a brush.” She went on to say, “Shapes and colors combine to produce images that are very near to dreams—of our past and of our feelings. Trying to capture the images is a difficult task—it demands a focused mind, patience and speed; for they might escape and disappear in a few seconds, just like our dreams when we wake up in the morning.”

A resident of Buenos Aires, Argentina, Binda calls herself an “Argentinean Photographer-Artist.” Her training has included photography courses with noted Argentinean, Italian, and American photographers as well as complementary studies in Latin American Art Museum in Miami, Florida. She has also been an expert juror in numerous photographic competitions.

Binda has had more than 60 exhibitions in Argentina and has exhibited her works in Uruguay, Brazil, France, Spain, Italy, Germany, and the United States, including the Euroamérica Gallery in New York’s Soho district and the Design Gallery of the Americas in Miami. She has received many notable awards, including first prize at the National Salon of Photography in Argentina and the “Punta del Este 1996” award, given by the government of Uruguay to artists with an “Outstanding Trajectory in the Field of Photography.” She was also granted a “Certificate of Appreciation” by the United States Department of Justice in 2000. Binda has been a professional photographer for over 25 years, and her photographs are in public and private collections in Argentina and abroad, including Miami’s Latin American Art Museum.

In addition to her photographs of glass, Binda takes pictures of stones and metal. She casts colored lights upon the objects, achieving a striking effect. To see more examples of Binda’s unusual photography, visit Arte Contemporaneo’s Web site at www.artecontemporaneo.com.ar and click on “fotógrafos” in the index.

Sheila Macho
JMCP Cover Editor

COVER CREDIT

SOURCES
Interview with the artist. Alicia Binda Italian Glass Montserrat Gallery exhibit catalog. www.artecontemporaneo.com.ar
Editorial Content and Peer Review

All articles and editorials in JMCP undergo blinded peer review. Letters may be peer reviewed to ensure accuracy. The fundamental departments for manuscript submission are:

- Original Research
- Subject Reviews
- Formulary Management
- Contemporary Subjects
- Editorials
- Letters

For manuscript preparation requirements, see “JMCP Author Guidelines” in this Journal or at www.amcp.org.

Original Research

These are well-referenced articles based on original research that has not been published elsewhere and reflects use of the scientific method. The research is guided by explicit hypotheses that are stated clearly by the authors.

Subject Reviews

These are well-referenced, comprehensive reviews of subjects relevant to managed care pharmacy.

Formulary Management

These are well-referenced, comprehensive reviews of subjects relevant to formulary management methods or procedures in the conduct of pharmacy and therapeutics (P&T) committees and may include description and interpretation of clinical evidence.

Contemporary Subjects

These are well-referenced submissions that describe pilot projects or other subjects that are not intended to be comprehensive reviews of the subject.

Editorials

These submissions should be relevant to managed care pharmacy and address a topic of contemporary interest.

Letters

If the letter addresses a previously published article, an author response may be appropriate. (See “Letter to the Editor” instructions at www.amcp.org.)
JMCP Author Guidelines

The Journal of Managed Care Pharmacy is indexed by Index Medicus/MEDLINE and International Pharmaceutical Abstracts (IPA).

Manuscript Preparation

Manuscripts should include, in this order: title page, abstract, text, references, tables, and figures (see Submission Checklist for details).

JMCP abstracts should be written narratives that contain the information described for each type of article shown below, where applicable. For descriptions of editorial content, see “JMCP Editorial Policy” in this Journal or at www.amcp.org.

Original Research
An abstract is required in the format of:
- Objective
- Results
- Keywords

Subject Reviews
An abstract is required, generally in the format of:
- Objective
- Conclusion

Formulary Management
An abstract is required in the format of Original Research or Subject Reviews, depending upon the subject matter.

Contemporary Subjects
An abstract is required in the format of Original Research or Subject Reviews, depending upon the subject matter.

Editorials
These submissions require no abstract but should include references.

Letters
These submissions require no abstract or title page.

Please note:
- A subsection in the Discussion labeled “Limitations” is generally appropriate for articles published in Original Research and sometimes appropriate for articles published in Subject Review, Formulary Management, or Contemporary Subject.
- Most articles published in JMCP, particularly Subject Reviews, should incorporate or at least acknowledge the relevant work of others published previously in JMCP (see “Article Index by Subject Category” at www.amcp.org).

For articles in Original Research, a figure is recommended for making the effects of the inclusion and exclusion criteria clear to readers (see JMCP examples in 2003;9(4):320 [Figure 1] or 2003;9(3):258 [Table 1]).
- Product trade names may be used only once, for the purpose of providing clarity for readers, generally at the first citation of the generic name but not in the Abstract.

Reference Style

References should be prepared following modified AMA style. All reference number in manuscript should be superscript (e.g., ‘1’). See examples of common types of references below:

1. Standard journal article
(List all authors when 6 or less; if more than 6, list only the first 3 and add et al.)


2. No author given

3. Journal paginated by issue

4. Book or monograph by authors

5. Book or monograph with editor, compiler, or chairman as author

6. Chapter in a book

7. Government agency publication

8. Dissertation or thesis

9. Paper (or Poster) presented at a meeting
Reagan ME. Workers’ compensation, managed care, and reform. Paper (poster) presented at: 1995 AMCRA Midyear Managed Care Summit; March 13, 1995; San Diego, CA.

Manuscript Submission

A paper copy of the manuscript, including orignals of figures and tables and author attestation forms (see Submission Checklist), should be submitted to the JMCP Peer Review Administrator at the Academy of Managed Care Pharmacy, 100 North Pitt Street, Suite 400, Alexandria, VA 22314; Tel: (800) 827-2627 or (703) 683-8416 or Fax: (703) 683-8417. The paper copy is necessary to ensure proper presentation and placement of text, figures, tables, and graphs. Please send an electronic version of the manuscript, either on a disk or via e-mail, to jmcp@www.amcp.org.

All text should be in a word processing program (preferably Microsoft Word). Tabular material also should be in a word processing program using the tab function to create columns, not using “tables” or “cells.” Figures should be saved in Photoshop or Illustrator and may be re-created by us. We can accept Power-Point graphics. Please identify the format (PC or MAC), all programs used, and all file names.

Cover letter: the corresponding (lead) author should include a cover letter with the manuscript, which • briefly describes the importance and scope of the manuscript; • certifies that the paper has not been accepted for publication or published previously and that it is not under consideration by any other publication, and • identifies the nature and extent of any financial interest or affiliation that any author has with any company, product, or service discussed in the manuscript.

All manuscripts are reviewed prior to peer review. Manuscripts may be returned to authors prior to peer review for clarification or other revisions. Peer review generally requires 4 weeks but may extend as long as 8 weeks in unusual cases. Solicited manuscripts are subject to the same peer-review standards and editorial policy as unsolicited manuscripts.

Submission Checklist

Before submitting your manuscript to the Journal of Managed Care Pharmacy, please check to see that your package includes the following:
- Cover letter
- Manuscript: prepared in 12-point type, 1.5 line spacing (on disk or sent via e-mail to jmcp@www.amcp.org), including
- title page with identification of all authors (with academic degrees and preferred credentials, position title, name of employer, city and state) and complete contact information for the corresponding author (mailing address, telephone and facsimile numbers, and e-mail address)
- abstract: no more than 500 words
- keywords: follows the abstract
- references: cited in numerical order as they appear in the text (use superscript numbers) and prepared following modified AMA style
- tables and figures (generally no more than a total of 6). Submit referenced tables and figures on separate pages with titles (and captions, as necessary); match symbols in tables and figures to explanatory notes, if included. May use 10-point font.
- Disclosures and conflict-of-interest forms: completed and signed author attestation forms (available at www.amcp.org); clearly indicate source(s) of funding and financial support.

For “Manuscript Submission Checklist,” see www.amcp.org.

REFERENCE

Effects of an Increase in Prescription Copayment on Utilization of Low-Sedating Antihistamines and Nasal Steroids

BRIAN L. MEISSNER, PharmD; W. MARK MOORE, PharmD, MBA; JUDITH A. SHINOGLE, PhD, MSc; C.E. REEDER, PhD; and JOHN M. LITTLE, JR., MD

ORIGINAL RESEARCH

ABSTRACT

BACKGROUND: Health plans are using 3-tier copayment designs and other methods to control utilization that shifts drug costs to plan members. There is a need to determine the effects of increased member cost sharing on drug utilization and drug costs.

OBJECTIVE: To assess the impact of a $10 increase in prescription copayment in a public employer health plan for 2 classes of drugs used for allergic rhinitis.

METHODS: Changes in the number of prescriptions dispensed for 2 therapeutic classes—low-sedating antihistamines (LSAs) and nasal steroids (NSs)—were examined 1 year prior to and 1 year after copayment increase. Relative price effects were measured as arc price elasticity, the ratio of the percent change in prescription utilization over the percent change in price, an indicator of how responsive patients are to the copayment increase.

RESULTS: Of 8,643 continuously enrolled health plan beneficiaries, 2,150 patients (24.8%) received at least 1 NS or LSA during the 2-year period of the study, from January 1, 1998, through December 31, 1999. An average $10 increase in copayment per prescription was associated with no statistically significant change in utilization of combined LSA and NS prescriptions, 2.89 per patient in 1998 and 2.94 in 1999 (P = 0.597). Health plan costs for study drugs, unadjusted for inflation, decreased by 16.3% from $66.86 per patient in 1998 to $72.68 in 1999 (P = 0.004). Health plan costs per patient per month (PPPM) for all drugs for the 2,150 allergic rhinitis patients decreased by 13% from $41.33 PPPM in 1998 to $35.93 in 1999 (P<0.001), and health plan drug costs for all 8,643 members decreased by 13% from $14.93 per member per month (PMPM) in 1998 to $12.99 in 1999 (P<0.001). The actual average copayment increase was $7.23 (a 41% increase) for LSAs, which was associated with a 14.8% increase in utilization of LSAs and an 11.8% increase in the number of patients using LSAs; the number of LSA prescriptions per patient per year was unchanged at 2.68 in 1999 versus 2.61 in 1998 (P = 0.429). The actual average copayment increase was $10.98 (71%) for NSs, which was associated with an 11.3% decrease in utilization of NSs and a 10.2% decrease in the number of users of nasals steroids in 1999; the number of nasal steroid prescriptions per patient per year was unchanged at 2.05 in 1999 versus 2.07 in 1998 (P = .842). The combined utilization of LSA and NS prescriptions increased by 8.9% following the increase in copayments for these 2 therapeutically interchangeable drugs for allergic rhinitis. LSA prescriptions were less elastic, with an unadjusted arc elasticity of 0.39, while nasal steroid prescriptions were more responsive to the copayment change, with an unadjusted arc elasticity of –0.22.

CONCLUSIONS: An average $10 increase in patient cost sharing per prescription (46.9% copayment increase) was associated with an increase in combined utilization of 2 drug classes used for allergic rhinitis (LSAs and NSs) but no change in the number of prescriptions per patient. Health plan costs decreased significantly for allergic rhinitis drugs, all drugs used by allergic rhinitis patients, and all drugs used by continuously enrolled health plan members. NSs exhibited a greater arc price elasticity compared with low-sedating oral antihistamines. LSAs were less elastic, with an unadjusted arc elasticity of 0.39.

KEYWORDS: Prescription copayment, Utilization, Elasticity, Allergic rhinitis

J Manag Care Pharm. 2004;10(3):226-233

H ealth care administrators are struggling to provide quality care while controlling costs. New advancements in the treatment of highly prevalent diseases contributed to the $1.2 trillion spent on health care in the United States in 1999. Moreover, during 1999, the growth in prescription drug expenditure led all other health care services, at 16.9%. The Centers for Medicare & Medicaid Studies (CMS) projected that by 2010, health care expenditure will total $2.6 trillion and account for 15.9% of the gross domestic product. These increases are fueled in part by the rising drug cost and increased utilization of pharmaceuticals.

The increase in pharmacy expenditure can be attributed to a number of factors. For instance, over the past 30 years, the number of third parties expanding prescription benefits has increased, as evidenced by the decrease in the average percentage of prescription costs paid out-of-pocket by the consumer. Based on national estimates from CMS, 96.2% of medication costs were paid out-of-pocket (cash purchases) by consumers in 1960 compared with 26.6% in 1998. Expanding coverage of prescription drugs lowers the effective price to the patient and may lead to increased utilization. Also, as medical knowledge grows, newer, more expensive pharmaceutical agents are becoming the “standard of care” for more illnesses. Furthermore, there has been an increase in the number of diseases treated with multiple drug therapies, and, as a result of improved medical technology, life expectancy is being extended, allowing patients to utilize medications for longer periods of time. Many other factors, including direct-to-consumer advertising, can also be associated with an increase in prescription drug

Authors

BRIAN L. MEISSNER, PharmD, is a graduate student and C.E. REEDER, PhD, is a professor, College of Pharmacy, Department of Pharmaceutical and Health Outcomes Sciences, University of South Carolina, Columbia; W. MARK MOORE, PharmD, MBA, is director of admissions, Campbell University, Buies Creek, North Carolina; JUDITH A. SHINOGLE, PhD, MSc, is an assistant professor, College of Pharmacy, Department of Pharmaceutical and Health Outcomes Sciences, School of Public Health, Department of Health Administration, University of South Carolina, Columbia; JOHN M. LITTLE, Jr., MD, is vice president for managed care services, Companion HealthCare, Columbia, South Carolina.

AUTHOR CORRESPONDENCE: Brian L. Meissner, PharmD, College of Pharmacy, Department of Pharmaceutical and Health Outcomes Sciences, University of South Carolina, 1425 Richland St., Columbia, SC 29201. Tel: (215) 431-7447; Fax: (803) 777-2820; E-mail: meissner@csp.sc.edu

Copyright© 2004, Academy of Managed Care Pharmacy. All rights reserved.
Effects of an Increase in Prescription Copayment on Utilization of Low-Sedating Antihistamines and Nasal Steroids

In addition to increased utilization of pharmaceuticals, the use of higher-priced brand-name drugs has contributed to rising pharmacy expenditure when these are substituted for older, lower-cost products.ville and multi-tier formularies, prior authorization, generic substitution, and therapeutic interchange. CMS estimated that out-of-pocket expenditure for prescription drugs increased from $26.3 billion in 1994 to $43.1 billion in 2001. These increased costs are being shifted to the consumer in the form of higher cost-sharing provisions. Copayments, deductibles, and coinsurance require the patient to pay a certain amount of money to obtain prescriptions covered by the drug benefit. Copayments represent a fixed charge that must be paid for each prescription and are typically not related to the full price of the prescription. Copayments may place the patient in a state of uncertainty where they must decide if the benefits from the drug outweigh the cost of purchasing the prescription. When the perceived marginal benefit of the medication is less than the copayment (marginal cost), the patient will not purchase the prescription.

Price elasticity is a measure of consumer responsiveness to price changes. In a competitive market, an elastic demand will be seen if utilization decreases after a small increase in the copayment (i.e., the absolute price elasticity is greater than 1). An elastic demand depends on many factors, including the availability of viable therapeutic alternatives and consumer preferences. For example, a drug class such as the beta-adrenergic blockers would likely have an elastic demand given the abundance of generically and therapeutically equivalent alternatives. However, there are instances in which the demand is inelastic or does not change appreciably with a change in copayment, such as the demand that would be expected for HIV antivirals or chemotherapy medications.

A limited number of studies have assessed the impact of increased patient cost sharing on prescription utilization or expenditure. Results from these studies are mixed. Variations in study designs and differences among patient populations make generalizations difficult. Harris et al. used a longitudinal cohort to study the impact of increasing copayments from zero to $1.50 and $3.00 in a staff model health maintenance organization (HMO) in the late 1980s. As part of the analysis, drugs were stratified into essential and discretionary use classifications. The authors reported an overall reduction in prescription demand from 10% to 12% among the copayment tiers. More specifically, they noted a much greater decline in drugs categorized as discretionary compared with drugs defined as essential. In addition, after controlling for potential confounders, they found that a $3 copayment was associated with a 13% decrease in use of essential drugs compared to a zero copayment.

Soumerai et al. assessed the impact of prescription quantity limitations on drug utilization in a New Hampshire Medicaid population. Using 3 classification systems (effective-essential medication; effective-nonessential; and nonessential, symptomatic-relief medications), this study assessed prescription use following the transition from a no-prescription limit to a 3-prescription limit and from a 3-prescription limit to a $1 prescription copayment without a prescription limit. Multivariate analysis indicated that the 3-prescription limit was associated with decreased use of both essential and nonessential medications. After instituting a $1 copayment, prescription utilization increased to just below the levels prior to the imposition of the quantity limits.

Johnson et al. analyzed the impact of prescription utilization within a Medicare population after copayment increases and stratified the analysis by drug classes. This study used a combination of matching, random-sample generation, and multivariate models to control for potential confounders. Results indicated that after the copayment increased, prescription utilization for self-limiting and chronic disease states did not change.

In 1983, Nelson et al. compared the impact of a $.50 copayment increase within the South Carolina Medicaid population with a control cohort (Tennessee Medicaid) using ordinary least squares to control for confounders. The results indicated an overall decrease in prescription utilization. They also demonstrated a lower average monthly expenditure after instituting a prescription copayment. Using these same data, Reeder and Nelson (1985) examined the effect of the copayment change within 10 therapeutic categories and found a differential effect among therapeutic categories. Little change in monthly expenditure occurred in the drug therapy groups—analgesics and hypnotics—while the cardiovascular, diuretic, and psychotherapeutic drug groups had significant declines in both the level and growth (slopes) of monthly expenditure after copayment increase. While this study is only generalizable to the Medicaid population and examined a small change in copayment, it did highlight that an increase in patient copayments for prescription drugs may have a differential effect among therapeutic categories. And yet, few present-day studies have examined the effects of increased cost sharing within therapeutic categories of drugs.

Joyce et al. studied the impact of an increased prescription copayment within multiple formulary designs (1-tier, 2-tier, and 3-tier) using claims from a working population and its beneficiaries aged 18 to 64 years. A 2-part probit model was used to examine the impact on the provider and patients. The results indicated that the average annual decrease in drug cost per member ranged from 22.3% (P<0.001) to 32.9% (P<0.001), depending on formulary design. In addition, out-of-pocket costs increased from 17.6% to 25.6% after doubling the copayment within a 2-tier drug plan. Thus, the magnitude of drug
cost savings exceeded the magnitude of increase in copayments for the 2-tier plan.

A few studies have assessed the impact of insurance coverage on the demand for pharmaceuticals. Using data from the RAND Health Insurance Experiment, Leibowitz et al.,4 assessed the effects of copayment on prescription utilization. They found that patients randomized to more generous insurance plans (richer benefits) utilized more medications. This finding is theoretically consistent with a change in quantity demanded following a change in price. Coulson et al.24 analyzed the impact of various types of insurance coverage and access to care on prescription utilization. They used both instrumental variables to control for unobserved heterogeneity and a Heckman 2-stage model to address selection issues common in administrative claims datasets. The results indicated that patients with medical or prescription drug coverage (insurance) consume, on average, more prescriptions than do patients with limited physician access or drug coverage.

In summary, all of these studies measured the effects of relatively small increases in prescription copayment. Additionally, very few studies assessed utilization by individual drug therapy class. The majority of prior research was performed within a Medicaid or other public drug plan, which limits the generalizability of the findings. To address some of these limitations, we investigated the impact of a $10 copayment increase within a working population of a public employer with health benefits administered by a private, for-profit managed care organization.

## Methods

This study examined drug utilization of LSAs and nasal steroids (NSs) 1-year prior to a copayment increase (January 1, 1998, to December 31, 1998) and 1-year after the copayment increase (January 1, 1999, to December 31, 1999). Data were extracted from a pharmacy claims database for a public employer with health benefits administered by a private, for-profit, network model HMO with a total of approximately 130,000 lives, located in the southeastern United States. Of the 130,000 lives, a total of approximately 15,000 beneficiaries are enrolled in a single health plan funded by a large public employer. This analysis was further limited to select nonfederal employer segments within this health plan. The study inclusion criteria were members from (a) select groups covered by the single large nonfederal public employer who (b) had a pharmacy claim in 1998 or 1999 for either an LSA or an NS and (c) were enrolled continuously in the HMO for the 2-year period from January 1, 1998, to December 31, 1999. A mail-service pharmacy benefit was not provided to health plan members during the study period.

Prior to January 1, 1999, copayments were $5 for each for generic prescription, $15 for a prescription for a preferred drug, and $25 for nonpreferred drugs, for a maximum 30-day supply of the prescription. On January 1, 1999, copayments rose to $10 for generic drugs, $25 for preferred drugs, and $35 for nonpreferred drugs, each for a maximum 30-day supply prescription for all beneficiaries from the single large employer group enrolled in the HMO. This copayment increase represents relative price increases of 100%, 67%, and 40%, respectively, for the 3 tiers. If the full price of the prescription was below the copayment amount, patients were charged the lower price. For example, if a patient received a prescription for nine 10 mg tablets of a “preferred drug” during 1999 and the price was $19, the patient would pay the lesser of the 2 amounts ($19 versus $25).
Concurrent with copayment changes, formulary status for certain drugs was modified. From 1998 to 1999, the formulary status for loratadine plus pseudoephedrine (Claritin-D) and fexofenadine plus pseudoephedrine (Allegra-D) was changed from nonpreferred to preferred; the single agent formulation of each, loratadine or fexofenadine, remained preferred (tier-2 copay) drugs throughout the 2-year period. In addition, triamcinolone nasal spray was converted from preferred status in 1998 to nonpreferred (tier-3 copay) status in 1999. The changes in formulary status of these 3 agents accounted for less than 24% of the overall prescription utilization for LSAs and NSs combined (Table 1). Nonetheless, a subanalysis was conducted, excluding those medications that changed formulary status, to assure minimal influence on overall results.

LSAs included in the analysis were the brand-name products for loratadine (Claritin), loratadine plus pseudoephedrine (Claritin-D), fexofenadine (Allegra), fexofenadine plus pseudoephedrine (Allegra-D), and cetirizine (Zyrtec). NSs were included in this analysis since they are considered reasonable therapeutic alternatives for LSAs and included the brand-name products for flunisolide, budesonide, fluticasone, triamcinolone, and beclomethasone. The data were also combined for the entire cohort to assess the overall effect of the copay change between 1998 and 1999. Cost was defined as the amount of money paid (including a dispensing fee) by the health plan to the pharmacy for each prescription dispensed before consideration of member cost-share.

A 2-sample $t$ test was used to assess differences after the copayment increase and across therapeutic categories for the following variables: mean age, mean prescriptions per patient per month (PPPM), and mean number of study prescriptions PPPM. A chi-square test was used to assess gender differences between therapeutic groups and the percent of new versus refill prescriptions within the 2 groups after copayment increase. A paired $t$ test was used to test differences between the mean number of prescriptions dispensed per year (study drug), mean drug costs per patient (both study drug and all other drugs for allergic rhinitis patients), and PPPM (all drugs for allergic rhinitis patients) drug costs, mean copayments, and the per-member-per-month (PMPM) cost to the health plan. A 2-tailed significance level of 0.05 was used to determine statistical significance. Data management and statistical analyses were performed using SAS (Cary, North Carolina) version 8.0.

## Results

Of the approximately 15,000 members enrolled in the single large public employer health plan, 8,643 nonfederal members were continuously enrolled from January 1, 1998, to December 31, 1999. A total of 2,150 patients (24.8% of continuously eligible members) received either 1 or more prescriptions for an LSA (N = 1,931) and/or an NS (N = 688) during the 2 years (Table 2); a total of 469 patients (5.4% of eligible members and 21.8% of allergic rhinitis patients who received pharmacotherapy with LSAs or NSs received at least 1 LSA and 1 NS during the 2-year study period. The number of patients who received an LSA or NS increased from 1,451 (16.8% of eligible members) in 1998 to 1,553 (18.0% of eligible members) in 1999. The mean age for patients receiving an NS was 39.8 years compared with 38.3 years for patients receiving LSAs (P = 0.10). Females comprised approximately 71% of patients who received a prescription for an LSA compared with almost 67% of patients who received NSs during the 2-year study period (P = 0.03).

The mean number of all prescriptions (study and nonstudy medications) dispensed PPPM was higher for patients who received an NS prescription than patients who received an LSA prescription (1.95 prescriptions PPPM versus 1.64 prescriptions PPPM; P < 0.0001). On average, more LSA prescriptions PPPM were dispensed than NSs (0.15 LSA prescriptions PPPM versus 0.11 NS prescriptions PPPM; P < 0.0001).

Although the sum total of LSA and NS prescriptions increased 8.9% after the change in copayment (4,570 in 1999 versus 4,198 in 1998), no statistically significant difference was noted for the average number of prescriptions dispensed per patient. The total number of LSA prescriptions dispensed during the 2 years was 6,962 compared with 1,806 NS prescriptions. The number of patients who received an LSA increased by 11.8% in 1999 (Table 3), the year in which there was a 41.1% increase in the average copayment amount (Table 4). The number of patients who received an NS prescription declined by 10.2% (Table 3), the year in which there was a 41.1% increase in the average copayment amount (Table 4). The number of prescriptions increased by 14.8% for LSAs in 1999, but the number of NS prescription claims decreased by 11.3.

### Study Population Characteristics (Two-Year Period, 1998 and 1999)

<table>
<thead>
<tr>
<th></th>
<th>Low-Sedating Antihistamines</th>
<th>Nasal Steroids</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>1,931</td>
<td>688</td>
<td>−</td>
</tr>
<tr>
<td>Age (SD)</td>
<td>38.3 (16.0)</td>
<td>39.8 (15.2)</td>
<td>0.102</td>
</tr>
<tr>
<td>Female (%)</td>
<td>1,372 (71.0)</td>
<td>459 (66.7)</td>
<td>0.033</td>
</tr>
<tr>
<td>Male (%)</td>
<td>559 (28.9)</td>
<td>229 (33.2)</td>
<td></td>
</tr>
<tr>
<td>Total number of Rxs dispensed†</td>
<td>76,004</td>
<td>32,198</td>
<td>−</td>
</tr>
<tr>
<td>Mean Rxs PPPM (SD)</td>
<td>1.64 (1.53)</td>
<td>1.95 (1.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of study Rxs dispensed†</td>
<td>6,962 (9.1)</td>
<td>1,806 (5.6)</td>
<td>−</td>
</tr>
<tr>
<td>Mean study Rxs PPPM (SD)</td>
<td>0.15 (0.18)</td>
<td>0.11 (0.12)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* A total of 469 patients had both a low-sedating antihistamine and nasal steroid prescription dispensed during the 2-year period.
† This value includes all prescriptions dispensed for this population (study and nonstudy drugs), per patient per month (PPPM).
‡ This value includes only low sedating antihistamines or nasal steroid prescriptions.

### Effects of an Increase in Prescription Copayment on Utilization of Low-Sedating Antihistamines and Nasal Steroids

A 2-sample $t$ test was used to test differences between the mean number of prescriptions dispensed per year (study drug), mean drug costs per patient (both study drug and all other drugs for allergic rhinitis patients), and PPPM (all drugs for allergic rhinitis patients) drug costs, mean copayments, and the per-member-per-month (PMPM) cost to the health plan. A 2-tailed significance level of 0.05 was used to determine statistical significance. Data management and statistical analyses were performed using SAS (Cary, North Carolina) version 8.0.
rhinitis (LSA plus NS) increased by 8.8% after the $8.02 (46.9%) average increase in copayment in 1999.

The average 46.9% increase in out-of-pocket expense for prescriptions for allergic rhinitis patients from 1998 to 1999 was associated with a 13% decrease in the total PMPM drug cost for this continuously enrolled group, from $14.93 in 1998 to $12.99 in 1999 (P < 0.001) (Table 5). In comparison, the national increase in out-of-pocket expenses rose 31% ($15.57 in 1998 versus $22.61 in 1999) for all prescriptions from 1998 to 1999.27,28 The total drug cost PPPM for allergic rhinitis patients (NS or LSA) decreased from $41.33 in 1998 to $35.93 in 1999 (P < 0.0001). The PPPM cost decreased similarly by 11.4% ($41.97 in 1998 versus $37.16 in 1999, P = 0.0010) and 11.1% ($32.69 in 1998 versus $29.07 in 1999, P < 0.0001) for the NS and LSA cohorts, respectively.

As noted in the methods section, the formulary status (and copayment) changed from nonpreferred status to preferred status for loratadine plus pseudoephedrine and fexofenadine plus pseudoephedrine. Despite this change, utilization of LSAs and NSs remained consistent throughout the 2-year study period. The subanalysis, which excluded those medications that changed formulary status, indicated that the total number of LSA prescriptions increased by 9% (2,359 in 1998 versus 2,574 in 1999). In contrast, the total number of NS prescriptions decreased by 12% (878 in 1998 versus 765 in 1999), which resulted in a total increase of 3.1% (3,237 in 1998 versus 3,339 in 1999) for the combined cohort. The number of prescriptions per patient for the combined group was 2.89 in 1998 as compared with 2.94 in 1999, which was not statistically significant. Similarly the mean copayment increased by 65% ($14.96 in
1998, $24.81 in 1999; P < 0.0001) in the LSA cohort and 64% ($15.43 in 1998, $25.42 in 1999; P < 0.0001) in the NS group.

The unadjusted arc elasticities for both drug classes were calculated. (The elasticities are the ratio of the percent change in prescriptions over the percent change in price. Arc elasticity can be calculated as 
\[
\frac{(Q_2 - Q_1)}{(P_2 - P_1)} / \frac{(Q_2 + Q_1)}{(P_2 + P_1)}
\]

Those estimated in this paper have not been adjusted for potential confounders such as age, gender, etc. These arc elasticities indicate the population change in prescription utilization given the increase in out-of-pocket expense. If demand is elastic (price sensitive), a given increase in price will be associated with a smaller expenditure. Similarly, if demand is inelastic (price insensitive), a price increase will be associated with greater expenditure. LSAs were less price sensitive, with an arc elasticity of 0.39, while NSs were more responsive to the copayment change, with an arc elasticity of ~0.22.

### Discussion

The $10 estimated ($8.02 actual) average increase in prescription copayment appeared to have no effect on the combined utilization measures for these 2 principal drug categories for allergic rhinitis, although the 14.8% increase in LSA utilization overshadowed the 11.3% decrease in NS use. The results also indicated more price sensitivity for NS users compared with LSA users after the copayment increase. The overall PMPM and PPPM drug plan costs declined, which can be attributed to the increase in patient out-of-pocket expenses.

Health plan PMPM and PPPM drug costs, unadjusted for inflation, decreased by $1.94 (13%) and $5.40 (13%), respectively, after the copayment increase took effect January 1, 1999. These cost reductions would have been larger if adjusted for inflation in prescription drugs in 1999. Patient cost sharing did not affect utilization to the same extent in the 2 drug classes since utilization of LSAs increased by 14.8% and NS utilization decreased by 11.3%. These differences in utilization can be attributed in part to an 11.8% increase in the number of patients receiving an LSA compared with a 10.2% decrease in the number of NS users. Nonetheless, these findings are consistent with several other studies that compared medication utilization by therapeutic drug class and emphasize the need to examine, separately, therapeutic classes when assessing drug utilization after price changes.\(^{19,21}\) The differences in utilization between therapeutic alternatives need to be quantified to assist decision makers in designing drug formularies that reduce inappropriate or unnecessary drug use while realizing the benefits of appropriate medication use.

Although the percentage of patients using LSAs or NSs appears to be relatively high (24.8%) compared with other published estimates, the number of prescriptions per 1,000 members is similar to that of other reports. The 2001 Novartis Pharmacy Benefit Report\(^{29}\) estimated that 390 LSA prescriptions were dispensed per 1,000 members (0.0325 Rxs PMPM), which is consistent with our range of 374 (0.031 Rxs PMPM in 1998) to 430 (0.036 Rxs PMPM in 1999) antihistamine prescriptions per 1,000 members. In our study, almost 70% of the patients received only 1 or 2 LSA prescriptions during the 2-year study period. It is also important to note that the study population consisted of relatively high pharmacy benefit users, considering the LSA prescriptions accounted for only 9.1% of total prescriptions for LSA patients and 5.6% of total prescriptions for the NS patients.

### Limitations

One of the several assumptions required to perform a 2-sample \(t\) test is that the 2 samples are independent. Violation of this assumption may produce biased estimates. This analysis violated the assumption when a 2-sample \(t\) test was used since patients may have either been receiving both an LSA or NS drug concomitantly. As a result, our \(P\) values for the mean age, mean prescriptions PPPM, and mean number of study prescriptions PPPM should be interpreted with caution. In contrast, a paired \(t\) test was used to test the differences between PPPM costs, which generated a more conservative \(P\) value estimate. Nevertheless, these findings were statistically significant and consistent with other studies that assessed the impact of an increased prescription copayment.\(^{17,30}\)

Our study did not have a control group, and while there appears to be an association between changes in copayment and utilization, no causality can be inferred given our study design. The arc price elasticity estimates have not been adjusted for potential confounders such as age, gender, income level, disease severity, and self-selection since the objective was more descriptive in nature. However, work is being done to develop more robust multivariate models. It is also important to note that it is not possible to assess the price elasticity in the presence of an overall increase of all drugs without examining cross-price elasticities. A current research project is addressing this issue. These limitations make extrapolation of these results into public health policy difficult. It was not possible to control for any clinical treatment changes that may have altered prescribing.

### Table 5: Drug Costs Per Member Per Month for All Members*

<table>
<thead>
<tr>
<th></th>
<th>1998</th>
<th>1999</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible members</td>
<td>8,643</td>
<td>8,643</td>
<td>–</td>
</tr>
<tr>
<td>Total drug cost</td>
<td>$1,548,479</td>
<td>$1,347,270</td>
<td>–</td>
</tr>
<tr>
<td>PPPM cost (SD)</td>
<td>$14.93 (40.2)</td>
<td>$12.99 (41.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Cost is defined as the health plan cost (drug cost plus dispensing fee minus the member copayment amount) for each prescription dispensed and expressed as cost per continuously enrolled beneficiary (member) per month (PMPM).
patterns for the medications under study.

The formulary status for loratadine plus pseudoephedrine and fexofenadine plus pseudoephedrine was changed from nonpreferred in 1998 to preferred in 1999. This had the effect of negating the increase in copayment that affected other drugs in this study since these 2 drugs had the same copayment in 1999 as in the prior year. However, it appears, based on the subanalysis, that this change did not have a significant impact on the number of additional prescriptions utilized or mean copayments in 1999 compared with 1998.

To more fully understand the impact on prescription cost-sharing changes, it is necessary to evaluate the impact of additional health care use in the form of emergency room visits and physician visits.11 Such analyses will allow policy makers to structure a prescription drug benefit that is efficient and effective for both the managed care organization and the patient.

Conclusions

This study provides preliminary findings that health plan drug costs per member and per patient declined significantly when the prescription copayment per month (30-day supply) is increased by an average of $10. No change in utilization of LSAs and NSs as measured by the number of prescriptions per patient was observed when the average actual copayment per prescription increased by $7.23 and $10.98, respectively. However, there was a significantly different outcome in utilization between these 2 drug classes used to treat allergic rhinitis. The number of patients who used an LSA increased by 11.8% in the year following the copayment increase while the number of patients who used an NS decreased by 10.2%; the number of prescriptions for LSAs increased by 14.8% in the year following the copayment increase while the number of prescriptions for NSs decreased by 11.3%; the net changes in LSAs per patient, NSs per patient, and combined LSA/NS prescriptions per patient were insignificant. In terms of price sensitivity, the arc price elasticity differed between the 2 therapeutic classes (0.39 for LSA prescriptions and −0.22 for NS prescriptions). Further study is needed to assess the cumulative price elasticity following an increase in copayment within individual drug classes.

DISCLOSURES

No outside funding supported this research. Author Brian L. Meissner served as principal author of the study. Study concept and design were contributed by Meissner and authors W. Mark Moore, Judith A. Shinogle, C.E. Reeder, and John M. Little. Jr. Analysis and interpretation of data were contributed by Meissner, Moore, Shinogle, and Reeder. Drafting of the manuscript was the work of all authors, and its critical revision was the work of Meissner, Shinogle, and Reeder. Statistical expertise was contributed by Meissner and Shinogle.

REFERENCES


Effects of an Increase in Prescription Copayment on Utilization of Low-Sedating Antihistamines and Nasal Steroids


Identification of Allergic Disease Among Users of Antihistamines

SHERYL L. SZEINBACH, PhD; P. BROCK WILLIAMS, PhD; PIETER MUNTENDAM, MD; and RICHARD D. O’CONNOR, MD

ABSTRACT

OBJECTIVE: Patients exhibit a multitude of symptoms that may or may not be allergy related. In this study, we examined the consistency between results obtained by a multiallergen-specific immunoglobulin E (IgE) test and frequent use (3 months or more) of prescribed antihistamines.

METHODS: A retrospective examination of 1-year prescription claims records from January 1, 2000, through December 31, 2000, for 4,643 patients enrolled in a 115,000-member managed care organization who received 1 or more prescriptions for an oral antihistamine (loratadine, fexofenadine, or cetirizine).

RESULTS: A total of 1,343 health plan enrollees who received an oral antihistamine prescription were continuously enrolled during the year 2000 and diagnosed with allergic rhinitis. Of these patients, 246 (18%) consented to a multiallergen-specific IgE test, and 159 patients (64.6%) had a negative IgE test result. A total of 163 patients were classified as frequent antihistamine users (3 or more antihistamine prescriptions), and 101 (62.0%) of these patients had negative test results. Our study demonstrated no relation between prescribed antihistamine use and patient sensitization status.

CONCLUSIONS: Only 35.4% of the patients who used an oral antihistamine and were diagnosed with an allergy tested positive to the multiallergen-specific IgE test, and only 38% of the patients with records of frequent antihistamine use and who were diagnosed as allergic tested positive to the multiallergen-specific IgE test. Apparently, there are patients taking medications prescribed for allergic rhinitis who are, in fact, not allergic, which is both wasteful economically and not indicated medically. Additional evaluation may be advisable to support the clinical diagnosis of allergy for patients presenting with allergy-like symptoms who use antihistamines frequently.

KEYWORDS: Allergic rhinitis, Multiallergen-specific IgE testing, Low-sedating antihistamines

J Manag Care Pharm. 2004;10(3):234-238

S

ymptoms compatible with allergic (immunoglobulin E [IgE] mediated) disease are common and have multiple etiologies. Thus, effective treatment depends on clinical evaluation and an accurate diagnosis. According to the American Academy of Allergy, Asthma, and Immunology (AAAAI), treatment measures such as allergen avoidance and pharmacotherapy should be based on positive history and diagnostic testing.1 Although that report emphasizes the important role of professional referral and skin testing, the use of multiallergen-specific IgE testing by family physicians has been acknowledged as an accurate tool, useful in identifying specific allergen sensitivities and helpful in focusing further investigation and referral.2,3 With allergy prevalence estimates of 10% to 30%, antihistamine drugs such as fexofenadine (Allegra), loratadine (e.g., Claritin), and cetirizine (Zyrtec) have gained widespread acceptance as a strategy to help patients cope with allergic symptoms.4,5

Positive benefits of prescribed antihistamines for allergic rhinitis include increased airway caliber, improved breathing, and significantly reduced symptoms.6 Other studies suggest that medications prescribed to treat allergic rhinitis may alleviate symptoms of asthma.7 While these medications appear to reduce symptoms and improve patient health, consideration must be given to their total cost, estimated at $8.4 billion per year.8 For some patients, however, the use of allergy medication may not be effective or offer only a short-term solution for an ongoing problem.9 For example, the authors in one study asserted that although these medications may alleviate symptoms, an accurate diagnosis suggests more appropriate clinical management, less frequent medication changes, and improved quality of life.10

Decisions to prescribe these medications are usually predicated on clinical evaluation, including patient history and perhaps some diagnostic testing. In the process of patient evaluation, patient history can be subjective and influenced by perceptual interpretation with respect to clinical experience and expectations. Moreover, pertinent information may be selectively filtered or overlooked in the communication process. Besides patient history, diagnostic tools include avoidance, specific allergen challenges, medication trials, and those that indicate immunological sensitization.11 Successful medication trials with antihistamines are often interpreted as proof of an allergic etiology even though their activity is rather nonspecific. An example of a test that indicates sensitization is the multiallergen-specific IgE test, which contains about 15 different common allergens that identify approximately 98% of the patients with allergic rhinitis. This specific IgE test is highly specific and selective for IgE antibodies to a mixture of the most prevalent inhalant allergens.12

Authors

SHERYL L. SZEINBACH, PhD, is professor, Ohio State University, College of Pharmacy, Columbus; P. BROCK WILLIAMS, PhD, is clinical professor, University of Missouri Medical School, Kansas City; PIETER MUNTENDAM, MD, is director, biopharma and healthcare practice, netNumina, Cambridge, Massachusetts; RICHARD D. O’CONNOR, MD, is director, quality management, Sharp Rees-Stealy Medical Group, San Diego, California.

AUTHOR CORRESPONDENCE: Sheryl L. Szeinbach, PhD, Professor, Department of Pharmacy Practice and Administration, College of Pharmacy, Ohio State University, Columbus, OH 43210-1291. Tel: (614) 688-4249; Fax: (614) 292-1335; E-mail: szeinbach.1@osu.edu

Copyright© 2004, Academy of Managed Care Pharmacy. All rights reserved.
Only recently has evidence surfaced to suggest that patient history and symptoms may not align well with the results obtained from diagnostic tests such as skin testing or multiallergen-specific IgE testing. In one study, the accuracy of the diagnosis of a patient for a specific allergic condition by history alone compared with concordant skin testing and specific IgE measurements rarely exceeded 50% and, in some cases, was below 25%. Given this potential for discrepancy between history and true diagnosis, questions arise regarding the existence of similar discrepancies between prescribed antihistamine use and multiallergen-specific IgE testing.

In this study, we investigate whether the patterns of prescribed antihistamine use in a managed care facility were consistent with results obtained from a multiallergen-specific IgE test for allergy. Specifically, the UniCAP Phadiatop is a single laboratory test designed to determine the presence or absence (e.g., positive or negative) of specific IgE to a variety of common inhalant allergens (e.g., grass, ragweed, cat, and mite). In this study, the cut-off point for positivity for the specific IgE assays was 0.35 kUA/L, with test sensitivity and specificity reported at 100%. Test results were categorized as either positive or negative.

**Methods**

Prescription claim records for 4,643 patients enrolled in a 115,000-member health plan located in the southeast United States were examined retrospectively by 2 pharmacists to identify patients who received at least 1 prescription for a low-sedating antihistamine (LSA) in tablet or capsule form ( cetirizine 5 mg or 10 mg, fexofenadine 60 mg, loratadine 10 mg, and all combinations with pseudoephedrine). Of these 4,643 patients, there were 1,343 patients with a diagnosis of allergic rhinitis (ICD-9-CM 477.0, 477.8, and 477.9 for pollen, other allergens, and unspecified, respectively). Antihistamine use was defined...
Identification of Allergic Disease Among Users of Antihistamines

**Table 1**

Cross Tabulation of Laboratory Multiallergen Specific IgE Test Results (Yes) and Frequent Antihistamine Use (Yes/No)

<table>
<thead>
<tr>
<th>Screening Result:†</th>
<th>Frequent Use*</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Negative test</td>
<td>58</td>
<td>101</td>
<td>159</td>
<td></td>
</tr>
<tr>
<td></td>
<td>36.5% nonallergic</td>
<td>63.5%</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>69.9% within frequent use</td>
<td>30.1%</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>62.0% of total</td>
<td>38.0%</td>
<td>64.6</td>
<td></td>
</tr>
<tr>
<td>Positive test</td>
<td>25</td>
<td>62</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td></td>
<td>28.7% within allergic</td>
<td>71.3%</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30.1% within frequent use</td>
<td>69.9%</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>38.0% of total</td>
<td>62.0%</td>
<td>64.6</td>
<td></td>
</tr>
<tr>
<td>Nonallergic and allergic</td>
<td>83</td>
<td>163</td>
<td>246</td>
<td></td>
</tr>
<tr>
<td></td>
<td>33.7% of total</td>
<td>66.3%</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

* Frequent antihistamine use defined as 3 or more prescriptions for low-sedating antihistamines during the continuous 12-month enrollment period.
† Screening test results available only for those who were lab tested. All tests conducted with the multiallergen-specific IgE test.

Chi-square test \( \chi^2 = 1.5; P \leq 0.225 \) for the convenience sample \( N = 246 \); IgE is immunoglobulin E.

---

As infrequent if fewer than 3 prescriptions for LSAs during the 12-month period from January 1, 2000, to December 31, 2000.18

Once these patients were identified, a convenience sample yielded 246 patients who completed a consent form and desired confirmation of their allergy diagnosis with a free multiallergen-specific IgE test (Phadiatop by Pharmacia Diagnostics, Current Procedural Terminology Code [CPT] 86005)17,18 (Figure 1). Patients were offered a mailed summary of their survey responses and, based on these replies, personalized allergy-management information.

Age and gender were the only demographic data available for the study participants, and there was not a significant difference for age or gender between the convenience sample and the plan enrollees who used at least 1 LSA \( N = 1,343 \); average age = 43.65 years \( [11.7 \text{ SD}] \) for plan enrollees versus \( N = 246 \); age = 45.02 years \( [11.4 \text{ SD}] \) for the convenience sample. The chi-square test of independence was used to assess differences between infrequent and frequent users of prescribed LSAs. Values of \( P \leq 0.05 \) for a 2-tailed test were considered significant.

### Results

Of the 163 frequent LSA users, 62 (38%) had evidence of specific IgE that would be consistent with a diagnosis of allergy, and 30.1% (25 of 83) of infrequent users also had similar evidence of specific IgE. Results from the chi-square statistical test revealed no significant difference between the observed and expected frequencies among patients undergoing specific IgE testing and prescribed LSA use \( \chi^2 = 1.5; P \leq 0.225 \). Thus, our hypothesized relation between prescribed antihistamine use and sensitization status was not supported. However, further examination of the data in Table 1 revealed that 64.6% (159 of 246) of the laboratory-tested group did not have significant levels of specific IgE (the cut-off for positivity for the specific IgE assays was 0.35 kU/L), and 63.5% (101 of 159) of these patients were classified as frequent LSA users over the last year. Stated differently, approximately two thirds of those patients with records of frequent LSA use were tested as negative for specific IgE.

### Discussion

The initial clinical diagnosis of an allergic condition was supported for 35.4% of the patients who had the multiallergen-specific IgE test. Although the treatment of rhinitis with antihistamines is often used to provide diagnostic evidence of an allergic etiology, it has been estimated that as many as 50% of patients with rhinitis may not have allergic rhinitis.19,20 Thus, in some situations, short-term or intermittent use of these medications is warranted to treat conditions such as nasal congestion, rhinorrhea, sneezing, itching, and hyposmia. However, frequent use (3 months or more) of prescribed antihistamines would suggest the need for more specific evaluation or additional follow-up.

The lack of a significant difference in frequent antihistamine use and the presence or absence of inhalant allergy in this patient population suggest that routine history and physical examination may not always provide accurate evidence to discern allergic from nonallergic rhinitis.3 Considering that the results of this study are consistent with findings from previous reports of confirmed allergy (43%, \( n = 975 \))21,22 our findings suggest the need for more extensive patient evaluation criteria. Although patients provide a comprehensive overview of their current health status, additional opportunities exist for clinicians in patient screening and evaluation. For example, patients who present with multiple allergic-like symptoms would undergo preliminary evaluation by trained clinicians and practitioners. Decision protocols can be developed and standardized to ascertain whether perceptual differences in judgment have possibly influenced conclusions drawn from the patient history and evaluation.13 After examining patient history and evidence of allergic etiology, or patients appear unresponsive to medications, objective tests such as the multiallergen-specific IgE test may be performed.

At the time of this study, loratadine was available only by prescription, but the availability of loratadine over the counter (OTC) at year-end 2002 begs examination of the means to attain the optimum cost benefit from verification of true allergy in frequent users of antihistamines. While OTC loratadine costs less than $20 per month of therapy, most drug plans in managed care organizations (MCOs) cover prescription oral antihistamines that have average wholesale prices that range from $75 to $105 for a 30-day supply.23 The average price paid per spe-
cific IgE determination ranges from $10 to $12 per allergen ($7.23 for Medicare). The Medicare median patient charge for allergen testing, which includes 12 to 16 profile allergens and total IgE ($20) was approximately $150 to 175 per profile and ranged from $50 to $500, depending on the type of test (e.g., skin, blood) and the number of allergens evaluated. 24 Although these costs, to some extent, may be covered by a third-party plan, patients, providers, and MCOs should evaluate short-term and long-term benefits of serum allergen testing.

From a managed care perspective, optimal strategies for therapy would begin by accurately identifying patients who would benefit from specific IgE testing. Results from this study suggest that confirmation of allergic disease may be more complex, perhaps involving the cooperation of both family physicians and allergists. Primary care physicians might perform initial evaluation, testing, and treatment involving the short-term use of antihistamines and, with patients, evaluate patient responsiveness to drug therapy. Persistent or more-severe symptoms may require further evaluation and referral. Allergy testing may be more beneficial when patients are stratified by severity and persistence of allergy symptoms, magnitude of direct costs (e.g., physician visits, oral antihistamines), and indirect costs (e.g., diminished productivity). These suggestions present opportunities for managed care physicians and pharmacists to work together efficiently to create an environment to improve patient management through initiatives that focus on diagnostic accuracy. Hence, consideration should be given to the additional benefits of testing and the contribution that appropriate prescribing would make toward improving patient outcomes and possibly reducing health care and social costs.

Limitations
The extent to which patients are affected by allergic rhinitis may be a function of seasonal fluctuations characteristic of the geographic region (southeastern United States) of this MCO. Additionally, survey completion was not designed to necessarily coincide with the annual period during which symptoms were experienced. Hence, the absence of particular symptoms at that time did not preclude the presence of seasonal allergic rhinitis. However, seasonal affects may be of no consequence since the IgE test is unaffected by antihistamine use. Moreover, the presence of IgE is not affected by the season in which the test is performed.

Conclusions
By far, the most common—but not only—reason for prescribing LSAs is for symptoms with a suspected allergic etiology. Our data suggest that either LSAs are prescribed indiscriminately or that the sequencing of testing and treatment needs further evaluation. Notwithstanding consideration of medication side effects, economic considerations, and the potential for escalating costs associated with the advent of more expensive allergy treatment options (e.g., leukotriene receptor antagonists, anti-IgE), assuring the existence of allergic etiology may be more beneficial to patients (e.g., reduced office visits, improved quality of life) and increasingly important to managed care providers. Practitioners and clinicians might use objective means such as multiallergen-specific IgE testing in conjunction with other evidence such as patient symptoms and history to confirm the allergic basis of disease.

DISCLOSURES
Funding for this study was provided by an unrestricted grant from Pharmacia Corporation and was obtained by author Pieter Muntendam. Results from this study were presented at the American College of Osteopathic Family Physicians (ACOFP) Meeting, Philadelphia, Pennsylvania, March 28, 2001, and at the Aspen Allergy Conference, Aspen, Colorado, July 26, 2001. Author Sheryl L. Szeinbach served as principal author of the study. Study concept and design were contributed primarily by Szeinbach and Muntendam. Analysis and interpretation of data were contributed by Szeinbach and authors P. Brock Williams and Richard D. O’Connor. Drafting of the manuscript was primarily the work of Szeinbach and Williams, and its critical revision was the work of all authors. Statistical expertise was contributed by Szeinbach and Williams, and administrative, technical, and/or material support was provided by Szeinbach and Muntendam.

REFERENCES


Frequency of Simvastatin Prescriptions With Potentially Interacting Medications in a Veterans Affairs Health Care System

JERILYN B. PETROPOULOS, BSPharm, PharmD, BCPS, and CRISTINA E. BELLO-QUINTERO, PharmD

ABSTRACT

OBJECTIVE: The primary objective of this review is to quantify the proportion of patients on simvastatin, an HMG-CoA reductase inhibitor (commonly known as statin), who received concurrent prescriptions for potentially interacting chronic-use medications. The secondary objective is to determine the frequency with which simvastatin was prescribed above its recommended dose when administered concomitantly with known interacting medications.

METHODS: A retrospective review of computerized outpatient pharmacy records from a Veterans Affairs Medical Center and its associated ambulatory clinics was performed in September 2002.

RESULTS: A total of 12,240 patients had an active prescription for a statin. The majority of patients (95%, N = 11,677) were on simvastatin therapy, and 1,231 (10.5%) of the patients on simvastatin were prescribed at least 1 potentially interacting medication. More than one half (57.8%) of simvastatin doses were above the maximum recommended daily dose when prescribed with potentially interacting medications.

CONCLUSION: This analysis supports the need for vigilance in reviewing the dose of simvastatin in patients receiving interacting medications. Health care systems should consider strategies to educate health care professionals on prevention of drug interactions and adverse patient outcomes.

KEYWORDS: Simvastatin, Statins, Myopathy, Drug use review

J Manag Care Pharm. 2004;10(3):239-243

Elevated low-density lipoprotein (LDL) cholesterol has been identified as a primary risk-reduction target in patients at risk for coronary heart disease (CHD). Numerous epidemiological studies have demonstrated a relationship between elevated LDL and the incidence of CHD. Use of LDL-lowering therapy, including hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors, also known as statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin), has been shown to significantly reduce risk for major coronary events and coronary deaths. Statins are recommended as standard treatment for elevated LDL and are widely used in clinical practice. Results from clinical trials with statins show a decrease in CHD and total mortality, revascularization procedures, and stroke. A meta-analysis demonstrates a decrease of 31% in major coronary events and 21% in total mortality with use of statins compared with placebo. Statins are generally well tolerated, with elevated liver enzymes and myopathy reported as the most common adverse effects.

Myopathy is a general term for muscle disease and includes myalgia, myositis, and rhabdomyolysis (Figure 1). The prevalence of statin rhabdomyolysis is rare. A review of adverse drug events reported to the U.S. Food and Drug Administration (FDA) showed an overall reporting rate of 0.15 cases of fatal rhabdomyolysis per 1 million statin prescriptions. However, the true incidence of statin rhabdomyolysis is unknown because of the underreporting of adverse drug reactions during the postmarketing period of medications. All statins seem to have a potential for causing rhabdomyolysis. The risk of myopathy is dose related and increases with statin serum concentration. Most myopathy associated with statins occurs in patients of older age, small body frame, multisystem disease (including chronic renal insufficiency), multiple medications, perioperative periods, or specific drug-drug interactions.

Several medications have been identified that increase the risk of myopathy when administered concurrently with statins, primarily by decreasing the metabolism of the statin (Figure 2). Although these drug-drug interactions are well documented as increasing risk for myopathy, published studies documenting the frequency of prescribing interacting drugs are lacking. Einarson and colleagues studied the extent of drug interactions and health care utilization in patients receiving statins. However, Einarson focused on concomitant drugs whose levels increased from the statin therapy and short-term concomitant therapy, which could increase statin serum concentrations.

The primary objective of this review is to quantify the proportion of patients in a primary care setting on simvastatin, the...
Methods

This was a retrospective analysis of computerized outpatient records from a Veterans Affairs Medical Center and its associated ambulatory clinics, which had 429,500 outpatient visits in fiscal year 2002. Patients were included in the analysis if they had an active prescription for simvastatin at the time of review (September 2002). Pharmacy records, laboratory results, and patient demographics were retrieved for analysis from the computerized patient record.

The product labeling for simvastatin was reviewed to identify potentially interacting medications and dosage recommendations for concurrent use (Figure 3). At the time of this review, the manufacturer recommended a maximum daily dosing of 10 mg for simvastatin when used concurrently with fibrates, niacin, or cyclosporine. A maximum daily simvastatin dose of 20 mg is recommended when used concurrently with amiodarone or verapamil. The product labeling does not provide a maximum daily dose for simvastatin when administered concurrently with potent CYP3A4 inhibitors (cytochrome P450, family 3, subfamily A, polypeptide 4) inhibitors. The manufacturer recommends generally avoiding the use of potent CYP3A4 inhibitors (Figure 2) unless the benefit of combined therapy outweighs the increased risk of myopathy and rhabdomyolysis.

At the time of this review, manufacturers did not provide specific dosage recommendations for atorvastatin and pravastatin, 2 other statins used in the study population, when prescribed concurrently with interacting medications. Although lovastatin did have new dosage recommendations for use with interacting drugs, simvastatin was the most frequently prescribed statin due to its formulary status at the time of this study. Therefore, atorvastatin, lovastatin, and pravastatin were excluded from the analysis.

Pharmacy records were queried for presence of concurrent prescriptions for potentially interacting chronic-use medications. The secondary objective is to determine the frequency with which simvastatin was prescribed above its recommended daily dose when administered concomitantly with known interacting medications.

### Table of Recommended Maximum Doses of Simvastatin When Administered With Interacting Medications

<table>
<thead>
<tr>
<th>Interacting Medication</th>
<th>Maximum Recommended Dose of Simvastatin (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>20</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>10</td>
</tr>
<tr>
<td>Fibrates (gemfibrozil or fenofibrate)*</td>
<td>10</td>
</tr>
<tr>
<td>Niacin*</td>
<td>10</td>
</tr>
<tr>
<td>Verapamil</td>
<td>20</td>
</tr>
</tbody>
</table>

* Subsequent to preparation of this manuscript, the FDA approved a label change for simvastatin to eliminate the maximum-dose warnings concerning concomitant use with fenofibrate and niacin. The revised label still warns that the benefit of further alterations in lipid levels by the combined use of simvastatin with fibrates or niacin should be carefully weighed against the potential risks.

## Results

A total of 12,240 patients had an active prescription for a statin in the specified time period. Simvastatin was the most frequently prescribed statin (Table 1). Of the 11,677 patients receiving simvastatin, 1,231 (11%) were prescribed at least 1 potentially interacting medication. Of these 1,231 patients, 1,176 (96%) were prescribed 1 interacting medication, 54 patients (4%) were prescribed 2 potentially interacting medications, and 1 patient was prescribed 3 potentially interacting medications. Overall, the majority (57.8%) of simvastatin doses were above the maximum daily recommended dose when given with potentially interacting medications (Table 2).

A total of 75 simvastatin patients (mean dose 42 ± 24 mg) also received nefazodone. Of these patients, 49 (65%) received a dose greater than 10 mg and 22 (29%) received a dose greater than 20 mg. Two simvastatin patients also received protease inhibitors (1 patient was ordered nelfinavir, while the other was ordered both amprenavir and ritonavir); both of these patients were ordered a daily simvastatin dose of 40 mg. Pravastatin has less potential for interaction with potent inhibitors of CYP3A4 due to its lack of metabolism via the CYP450 pathway. It was prescribed for 14 patients who were also receiving protease inhibitors and 2 patients who were receiving nefazodone.

## Discussion

This analysis supports the need for vigilance in reviewing the dose of simvastatin in patients receiving interacting medications. The dose-related nature of statin rhabdomyolysis is well established. Interactions with statins are also well documented in the literature as increasing the patient’s risk for myopathy, primarily through decreasing the metabolism of statins and increasing their serum levels. The American College of Cardiology (ACC), American Heart Association (AHA), and National Heart, Lung, and Blood Institute (NHLBI) advise that “particular attention . . . be given to drug interactions” when using statin therapy. Merck submitted a supplemental new drug application to the FDA in May 2001, with subsequent labeling changes in response to postmarketing adverse event reports. Revisions to the simvastatin product label, effective May 2002, included additional warnings to describe the increased risk of rhabdomyolysis with use of specific concomitant drugs; maximum dose recommendations when simvastatin is used with cyclosporine, fibrates, niacin, amiodarone, and verapamil; recommendations to avoid concomitant use of simvastatin with potent CYP3A4 enzyme inhibitors; instructions to warn patients about the risk of myopathy; and a quantification of the dose-related effects of myopathy and rhabdomyolysis.

This study demonstrates a need to heighten awareness of dose-related simvastatin drug interactions. A significant number of simvastatin prescriptions were ordered at doses higher than the recommended maximum dose. The updated product labeling and ACC/AHA/NHLBI Clinical Advisory were published.

---

**TABLE 1** Patient Demographics

<table>
<thead>
<tr>
<th>Patients n (%)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>70 ± 11 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11,978 (98)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>262 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>3,270 (27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>787 (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>513 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian</td>
<td>11 (0.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>4 (0.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>7,655 (63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most Recent CPK Result* (reference range 55 U/L -170 U/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not available</td>
<td>10,460 (85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;170 U/L</td>
<td>1,388 (11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between 171U/L and 1,700 U/L</td>
<td>389 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1,700 U/L</td>
<td>3 (0.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HMG-CoA Reductase Inhibitor (“Statin”)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>283 (2.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lovastatin</td>
<td>233 (1.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>47 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>11,677 (95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average Statin Dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>42 ± 29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lovastatin</td>
<td>27 ± 16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>27 ± 19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>27 ± 20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Most recent result from 9/1/01 to 9/1/02.

**TABLE 2** Simvastatin Dose With Concomitant Potentially Interacting Medications

<table>
<thead>
<tr>
<th>Patients n</th>
<th>Concomitant Drug</th>
<th>Dose of Simvastatin Mean in mg ± SD</th>
<th>Patients Above Maximum Daily Dose* n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>509</td>
<td>Gemiibrozil</td>
<td>28 ± 23</td>
<td>362 (71)</td>
</tr>
<tr>
<td>3</td>
<td>Fenofibrate</td>
<td>23 ± 16</td>
<td>2 (66)</td>
</tr>
<tr>
<td>335</td>
<td>Verapamil</td>
<td>25 ± 19</td>
<td>92 (27)</td>
</tr>
<tr>
<td>280</td>
<td>Niacin</td>
<td>32 ± 24</td>
<td>212 (76)</td>
</tr>
<tr>
<td>98</td>
<td>Amiodarone</td>
<td>30 ± 20</td>
<td>39 (40)</td>
</tr>
<tr>
<td>6</td>
<td>Cyclosporine</td>
<td>18 ± 4</td>
<td>5 (83)</td>
</tr>
<tr>
<td>1,231</td>
<td></td>
<td></td>
<td>712 (58)</td>
</tr>
</tbody>
</table>

* Maximum dose recommended by the manufacturer in product labeling (May 2002). A total of 57.8% (712/1,231) of patients receiving concomitant potentially interacting medications were prescribed simvastatin at a daily dose higher than the maximum recommended.
lished very shortly before initiation of this review. Electronic interaction alerts currently display during the order-entry process to warn prescribers of these identified drug interactions with statins. As a result of this data, dose recommendations for simvastatin were added to the formulary information that is accessible when simvastatin is electronically ordered. A follow-up review is planned to compare it with the baseline data obtained from this analysis.

In this retrospective review, 11% of patients on simvastatin were prescribed at least 1 potentially interacting drug. Einarson and colleagues\(^1\) found a 15% prescribing rate for concomitant medications that can increase HMG-CoA reductase inhibitor concentrations and risk of myopathy. However, Einarson focused on acute therapy medications (erythromycin, clarithromycin, fluconazole, and ketoconazole) and antiulcer medications (cimetidine and omeprazole). Our review focused on chronic-use medications known to increase risk for HMG-CoA inhibitor (statin) myopathy.\(^5\)\(^,\)\(^6\) Patients prescribed short-term, potent CYP3A4 inhibitors were excluded from our review. Patients who receive short-term therapy with potent CYP3A4 inhibitors (e.g., clarithromycin, erythromycin, itraconazole, and ketoconazole) should be counseled to temporarily withhold their statin therapy.

In this analysis, 85% of patients did not have a creatine phosphokinase (CPK) level measured within the previous year. This is consistent with standard practice recommendations, as routine measurement of CPK levels is not required in asymptomatic patients receiving statins.\(^6\) Baseline CPK measurement is recommended to assist in the evaluation of subsequent myopathy. However, the date of initiation of statin therapy was not collected for analysis in this review.

Patients receiving statins should be asked at each follow-up visit if they are experiencing any unusual or unexpected muscle pain or tenderness. A follow-up CPK level should be obtained if the patient reports muscle symptoms, and it should be compared with baseline levels. Statin therapy should be discontinued if a patient with muscle pain has a CPK greater than 10 times the upper normal limit. If a patient experiences muscle pain with no CPK elevation or a moderate elevation in CPK, the patient’s symptoms and CPK level should be followed weekly until there is no longer medical concern or symptoms worsen to the situation previously described.\(^6\) It should be noted that some statin patients do experience muscle weakness and histopathologic findings of myopathy despite a normal CPK.\(^2\)

As with any medical therapy, the risks and benefits of statin use must be carefully considered. In patients with hyperlipidemia, statin therapy has demonstrated an approximate one-third decrease in coronary deaths and major coronary events compared with placebo in clinical trials. Conversely, the absolute risk of rhabdomyolysis is low, with fewer than 0.15 cases of fatal rhabdomyolysis reported per 1 million statin prescriptions. Careful patient selection, counseling, and monitoring can reduce the risk of statin myopathy while allowing patients to receive the positive benefits of statin therapy. High-dose statin therapy should be avoided in patients at increased risk of myopathy, including those on potentially interacting medications. In patients who are prescribed medications that inhibit the CYP3A4 enzyme system, using statins that are not metabolized by the CYP3A4 enzyme system (fluvastatin, pravastatin, and rosvastatin) may minimize risk of rhabdomyolysis.

Limitations
The primary objective of this analysis was to quantify the proportion of patients on simvastatin who had received concurrent prescriptions for potentially interacting medications. Although the existence of potential drug interactions was identified, patient progress notes were not reviewed for outcomes of potential myopathy. Review of reported adverse drug reactions revealed 25 patients with simvastatin myopathy during fiscal year 2001 and fiscal year 2002 at our institution; these include 3 reports of rhabdomyolysis, 4 of myositis, and 18 of myalgias. Twenty percent of these patients (5 of 25) were also receiving interacting medications. High-dose simvastatin with an interacting medication, 80 mg daily with concurrent gemfibrozil, was implicated in 1 of the reports of rhabdomyolysis. The other reports with interacting medications were all cases of myalgia. These adverse drug reactions are voluntarily reported and may underestimate the actual numbers of patients with statin myopathy. Further research should be conducted to quantify the outcome of statin drug interactions in the managed care setting.

This analysis is limited by its retrospective design and method of data collection. Information was retrieved from a computer search of prescription, laboratory, and demographic records. Patient race was not identified in 63% of cases; therefore, no ethnic analysis can be performed. Patient progress notes were not reviewed to determine the extent of patient counseling that was provided. Medication adherence was also not determined.

Conclusion
The risk of HMG-CoA reductase inhibitor (statin) myopathy is often associated with concomitant use of other medications. This retrospective analysis in a population of elderly males demonstrates a high frequency of coadministration of simvastatin with potentially interacting drugs, often above the recommended maximum dose of simvastatin. Health care systems need to initiate strategies to educate health care professionals on minimizing or preventing drug interactions, in an effort to reduce the risk of negative patient outcomes.

Acknowledgments
The authors gratefully acknowledge Richard Spekis, computer programmer, Department of Veterans Affairs Medical Center, Miami, Florida, for his expertise in information technology.
DISCLOSURES

No outside funding supported this research. Author Jerilyn B. Petropoulos served as principal author of the study. Study concept and design and statistical expertise were contributed by Petropoulos. Analysis and interpretation of data and drafting of the manuscript were contributed by Petropolous and author Cristina E. Bello-Quintero, critical revision of the manuscript was the work of Bello-Quintero.

REFERENCES

Quantifying the Effect of Applying the NCEP ATP III Criteria in a Managed Care Population Treated With Statin Therapy

BRIAN J. QUILLIAM, PhD; H. ED PEREZ, PharmD; VICKIE ANDROS, PharmD; and PETER JONES, MD, FACP

ABSTRACT

OBJECTIVE: Revised treatment goals suggested by the third report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III) represent a challenge to both physicians and the health care industry. We sought to quantify the impact of these changes in a large managed care population being treated with statin therapy.

METHODS: Using data collected from a retrospective chart review of 1,962 managed care enrollees who received statin drug therapy between February 2001 and August 2001, we quantified the low-density lipoprotein cholesterol (LDL-C) goals and goal attainment of this population according to both the NCEP ATP II and ATP III criteria and further identified independent predictors of ATP III goal attainment using multivariable logistic regression modeling.

RESULTS: Overall, 21.1% (n = 414) of statin patients moved to a more stringent LDL-C goal when ATP III criteria were applied over ATP II. Substituting ATP III criteria for ATP II criteria resulted in a 6.8% decrease in the percentage of participants who had their most recent LDL-C value below the suggested goal, from 59.8% under ATP II to 53.0% under ATP III. Persons with existing coronary heart disease, diabetes, obesity, and stroke or transient ischemic attack were all less likely to meet the suggested NCEP ATP III LDL-C goal.

CONCLUSION: Taking into account the revised risk stratification of the ATP III guidelines and the lack of LDL-C goal attainment in patients currently taking statins, there will be an increase in the number of statin patients who require dose or agent adjustment, combination therapy, or compliance counseling to achieve their lower LDL-C goal.

KEYWORDS: Hyperlipidemia, Managed care, Statin, Coronary heart disease

J Manag Care Pharm. 2004;10(3):244-250

Coronary heart disease (CHD) is the number one cause of death in males and females in the United States.

The objective of the Framingham Heart Study (FHS), initiated in 1948 by the National Heart, Lung, and Blood Institute (NHLBI) was to identify the common factors that contributed to cardiovascular disease over a long period of time in a cohort of patients who were free of known cardiovascular disease at baseline. The FHS has identified high blood pressure, high blood cholesterol, smoking, obesity, diabetes, and physical inactivity as major cardiovascular risk factors and has established a direct association between elevated low-density lipoprotein cholesterol (LDL-C) and coronary artery disease. The FHS and other observational studies have also provided evidence implicating low levels of high-density lipoprotein cholesterol (HDL-C) and high triglyceride levels in atherosclerotic risk.

In 1985, the NHLBI created the National Cholesterol Education Program (NCEP), and the Adult Treatment Panel (ATP) of the NCEP released its first guidelines in 1988 with an evidence-based emphasis on primary prevention of CHD. In 1993, the second set of guidelines was published (ATP II), with the focus on secondary prevention (preventing coronary events in patients with established CHD). In 2001, the ATP published the preliminary report of its third set of guidelines, with a focus on better methods to identify high-risk primary prevention candidates, such as those with multiple CHD risk factors. The final report of the third set of guidelines (ATP III) was published in December of 2002. A major change from ATP II to ATP III criteria was the introduction of CHD risk equivalents, conditions that carry a >20% risk of having a major coronary event in the next 10 years. Among the risk equivalents suggested by ATP III criteria are diabetes, carotid artery disease, peripheral arterial disease, and abdominal aortic aneurysms.

Targeting of patients with multiple (≥2) risk factors results in a greater percentage of the population who are candidates for lipid-lowering measures, including lifestyle changes and possibly drug therapy. It has been estimated that 1 out of every 5 adults may need lipid-lowering drugs, representing an increase from 15 million to 36 million adults between the lipid goals in ATP III versus ATP II criteria.

To our knowledge, this is the first study to quantify the percentage of patients shifted to lower LDL-C goals suggested by the introduction of ATP III criteria in a managed care population as well as the percentage of patients who are meeting their target ATP III LDL-C goals.
Methods

We performed secondary data analysis on data originally collected from a quality improvement (QI) initiative designed to identify inefficiencies in the care and management of patients with hyperlipidemia on drug therapy. Patients eligible for study inclusion in the original QI initiative were identified from pharmacy claims databases of commercial members prescribed statin therapy in 4 managed care organizations (MCOs) located in the southeastern, north central, and northeastern United States. Since this QI initiative involved review of the medical chart in the physician’s office, the top 200 physicians based on volume of statin therapy use were identified and the patients randomly selected from among these 200 higher-volume prescribers. The target was random selection of approximately 500 patients in each MCO.

For the QI initiative, nurses with prior data abstraction experience who were trained in the use of standardized data abstraction methods collected the data from the patients’ medical records using a standardized data collection form. Approximately 20 nurses were performing chart reviews among all sites from February through August 2001. The data collection form solicited information on patient demographics, clinical history (family history of heart disease and smoking history), comorbid disease states (coronary heart disease, diabetes, hypertension, ischemic stroke, obesity, transient ischemic attack [TIA], and peripheral vascular disease), drug therapies (hypertension and cholesterol-lowering agents), and results of clinical examinations (blood pressure readings) and laboratory tests (total cholesterol, LDL-C, HDL-C, and triglycerides) pertinent to the management of hyperlipidemia.

This research project compares the data collected as part of this retrospective chart review from 1,962 patients with guidelines set forth by the Second and Third Panels of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. We determined each patient's risk status and corresponding LDL-C goal according to these guidelines by accounting for the presence of CHD, CHD risk factors, and the presence of CHD risk equivalents.7,8 Table 1 summarizes risk factors and risk equivalents identified by each of these guidelines. Information on carotid artery disease was not abstracted in the original QI initiative; therefore, for the current analyses, we used chart documentation of ischemic stroke or TIA as a proxy for carotid artery disease. Likewise, information on abdominal aortic aneurysms was not abstracted during the initial QI chart review. For our analyses, we assumed that abdominal aortic aneurysm would be rare within this population and therefore would not unduly influence NCEP goal categorization.11

In Table 1, we present the LDL-C goals recommended by NCEP ATP II and ATP III criteria based on the presence of CHD, CHD risk factors, and CHD risk equivalents. Using information abstracted from the chart as part of the QI initiative, we determined an LDL-C goal for each patient according to both the NCEP ATP II and NCEP ATP III criteria. Patients’ individual LDL-C goal attainment success was determined by comparing their most recent LDL-C value documented in the chart (within the 2 years prior to chart review) with their LDL-C goal as defined by their risk status according to both guidelines.

Lastly, we developed a logistic regression model to identify independent predictors of NCEP ATP III goal attainment among a subsample of the population with an LDL-C value documented in the 2 years prior to the date of chart review (n = 1,647). We considered demographic and clinical characteristics of the population as potential variables for model inclusion. The odds ratios (OR) and 95% confidence intervals (CI) derived from the final model provide estimates of effect for each of the factors while controlling for the influence of the other factors included in the model.

Results

Demographics

Of the 1,962 patient charts reviewed, 55.7% (n = 1,092) were males and 44.3% (n = 870) were females. The mean age was 59.7 years and median age was 59.2 years. Among the study sample, 916 of the 1,962 patients were at least aged 60 years, accounting for 46.7% of the study population (Table 2). Weight was recorded in the chart for more than 97% (n = 1,907) of the study population, yet height was only recorded in 58.8% (n = 1,154) of the patient charts reviewed. For women, the average height and weight in charts with this information recorded

<table>
<thead>
<tr>
<th>Guideline/Risk Category</th>
<th>Suggested LDL-C Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ATP II Criteria</strong></td>
<td></td>
</tr>
<tr>
<td>With CHD</td>
<td>≤100 mg/dL</td>
</tr>
<tr>
<td>Without CHD and ≥2 risk factors*</td>
<td>&lt;130 mg/dL</td>
</tr>
<tr>
<td>Without CHD and &lt;2 risk factors*</td>
<td>&lt;160 mg/dL</td>
</tr>
<tr>
<td><strong>ATP III Criteria</strong></td>
<td></td>
</tr>
<tr>
<td>With CHD and/or CHD risk equivalents†</td>
<td>&lt;100 mg/dL</td>
</tr>
<tr>
<td>Without CHD and ≥2 risk factors†</td>
<td>&lt;130 mg/dL</td>
</tr>
<tr>
<td>Without CHD and &lt;2 risk factors†</td>
<td>&lt;160 mg/dL</td>
</tr>
</tbody>
</table>

* ATP II risk factors include: current tobacco smoking, hypertension, HDL-C <35 mg/dL, family history of premature CHD, age (men ≥45; women ≥53 or those with pre-mature menopause) and diabetes mellitus.
† ATP III CHD risk equivalents include: abdominal aortic aneurysm, carotid artery disease, diabetes mellitus, peripheral arterial disease, and multiple risk factors that confer a 10-year risk for CHD ≥20%.
‡ ATP III risk factors include: current tobacco smoking, hypertension, HDL-C <40 mg/dL, family history of premature CHD, and age (men ≥45; women ≥53).
LDL-C = low-density lipoprotein cholesterol.
HDL-C = high-density lipoprotein cholesterol.
NCEP ATP = National Cholesterol Education Program Adult Treatment Panel.
CHD = coronary heart disease.
Quantifying the Effect of Applying the NCEP ATP III Criteria in a Managed Care Population Treated With Statin Therapy

**TABLE 2** Demographic and Clinical Characteristics of the MCO Population Treated With Statin Therapy

<table>
<thead>
<tr>
<th>Comorbid Condition</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>870</td>
<td>44.3</td>
</tr>
<tr>
<td>Male</td>
<td>1,092</td>
<td>55.7</td>
</tr>
<tr>
<td><strong>Age Category (Years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td>7</td>
<td>0.4</td>
</tr>
<tr>
<td>30-39</td>
<td>69</td>
<td>3.5</td>
</tr>
<tr>
<td>40-49</td>
<td>307</td>
<td>15.7</td>
</tr>
<tr>
<td>50-59</td>
<td>663</td>
<td>33.8</td>
</tr>
<tr>
<td>60-69</td>
<td>520</td>
<td>26.5</td>
</tr>
<tr>
<td>70-79</td>
<td>309</td>
<td>15.8</td>
</tr>
<tr>
<td>≥80</td>
<td>87</td>
<td>4.4</td>
</tr>
<tr>
<td><strong>Clinical Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1,222</td>
<td>62.3</td>
</tr>
<tr>
<td>Male ≥45 years</td>
<td>954</td>
<td>48.6</td>
</tr>
<tr>
<td>Female ≥55 years</td>
<td>632</td>
<td>32.2</td>
</tr>
<tr>
<td>Existing CHD</td>
<td>596</td>
<td>30.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>478</td>
<td>24.4</td>
</tr>
<tr>
<td>Early family history of CHD*</td>
<td>350</td>
<td>17.8</td>
</tr>
<tr>
<td>Current smoker</td>
<td>231</td>
<td>11.8</td>
</tr>
<tr>
<td>Framingham risk &gt;20% †</td>
<td>97</td>
<td>4.9</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>82</td>
<td>4.2</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>62</td>
<td>3.2</td>
</tr>
</tbody>
</table>

**Laboratory Monitoring**

| HDL-C <60 mg/dL ‡                  | 461  | 23.5 |
| HDL-C <40 mg/dL ‡                 | 455  | 23.2 |
| HDL-C <35 mg/dL ‡                 | 204  | 10.4 |

* CHD (coronary heart disease) in a male first-degree relative aged <55 years or in a female first-degree relative aged <65 years. ††
† Calculated using the Framingham Scoring System as identified in NCEP ATP III criteria, which identifies patients with multiple comorbidities who have a greater than 20% risk of a major coronary event over the next 10 years.
‡ Assessed using the most recent HDL-C value documented in the chart in the 2 years prior to the date of chart review.
MCO = managed care organization.
TIA = transient ischemic attack.
HDL-C = high-density lipoprotein cholesterol.

Documentation of Recent LDL Cholesterol Readings

Of the 1,962 patients included, 315 (16.1%) did not have an LDL-C value measured in the 2 years prior to chart review. Therefore, in these patients, we were unable to determine whether their LDL-C target was attained.

Cholesterol-Lowering Medication Use

At the time of chart review, 93% of the study population was documented as being treated with cholesterol-lowering medica-

was 54” and 179 pounds compared with 5’10” and 207.2 pounds for men. Using available information on height and weight, we calculated body mass index (BMI) for 58.2% (n = 1,142) of the population; the average BMI was 30.2 (30.8 for women and 29.8 for men). Race and ethnicity were not documented in the chart for more than 60% of study participants; therefore, further presentation of this information is not possible.

NCEP CHD Risk Factors, Risk Equivalents, and Corresponding LDL-C Goals

The prevalence of NCEP ATP II and ATP III risk factors and ATP III risk equivalents is presented in Table 2. Further, both ATP II and ATP III guidelines recognize an HDL cholesterol level of >60 mg/dL as protective against CHD and counted as 1 negative risk factor. In this population, 23.5% had a recent HDL-C cholesterol reading (in the 2 years prior to chart review) above this cutpoint. According to ATP III criteria, there was a shift in the population to lower LDL-C goals (Figure 1). Overall, 21.1% (n = 414) of the population moved to lower suggested LDL-C goals when switching from ATP II guidelines to ATP III guidelines.

Intermediate Outcomes—NCEP Goal Attainment

When discussing outcomes related to hyperlipidemia management, intermediate end points and final end points need to be considered. Attainment of NCEP goal is considered an intermediate end point, and prevention of a first or second coronary event is considered a final end point. For the purpose of this study, NCEP goal attainment was the primary outcome. According to NCEP ATP II criteria, 59.8% of the population met their suggested LDL-C goal, compared with 53.0% of the population using LDL-C goals as suggested by NCEP ATP III criteria. Thus, 6.8% of the population (n = 134) who would have met goal according to ATP II guidelines did not meet their new LDL-C goal according to NCEP ATP III guidelines.

As expected, the percentage of patients with goal attainment according to both NCEP ATP II and ATP III criteria was greater among those with the least intensive LDL-C goal of <160 mg/dL. Additional information on goal attainment is presented in Figure 1. Further, among the 607 persons not achieving goal according to NCEP ATP III criteria, 60.3% required <20% reduction from their most recent LDL-C value to attain the suggested LDL-C cholesterol goals (Figure 2).

Independent Predictors of NCEP Goal Attainment

Results of multivariable logistic regression modeling are presented in Table 3. Persons with existing CHD were 64% less likely to meet their suggested NCEP ATP III LDL-C goal compared with persons without existing CHD (OR = 0.36, 95% CI 0.28-0.45). Similarly, persons with diabetes, carotid artery disease (stroke and/or TIA), obesity, smoking, and those with a Framingham risk >20% were less likely to meet their suggested LDL-C goal according to ATP III criteria. Age and gender did
not significantly predict NCEP ATP III goal attainment.

Discussion

The care and management of patients with hyperlipidemia is an increasingly important aspect of the managed care industry. As suggested by the NCEP ATP III guidelines, more patients will be identified as high risk and need more intensive treatment to reach their suggested LDL-C goal in order to reduce cardiovascular events.7 To our knowledge, this is the first study quantifying the differences in LDL-C goals required and the changes in goal attainment as suggested by NCEP ATP III criteria. Our findings suggest that an additional 6.8% of our managed care population taking statin therapy were not at the lower LDL-C goals: 24.1% under ATP II versus 30.9% under ATP III.

In this large population of managed care enrollees taking statin therapy, the prevalence of CHD, CHD risk factors, and CHD risk equivalents was considerable. More than 30% of the population had existing CHD, 24% had diabetes, and 60% had greater than 2 CHD risk factors. Based on the presence of these factors, approximately 21% of this cohort shifted to more stringent LDL-C goals when ATP III criteria were used rather than ATP II criteria. In addition, a greater percentage of these patients had a recent LDL-C reading that, while at or below their ATP II LDL-C goal, did not meet their suggested ATP III LDL-C goal.

In our sample, 59.8% of the population was at or below their ATP II LDL-C goal while 53.0% were at or below the ATP III LDL-C goal, a 6.8% decrease in goal attainment. Previous data published from the Lipid Treatment Assessment Project (L-TAP) indicated that only 38% of their overall study population, 37% of the high-risk patients (≥2 risk factors without CHD), and 18% of patients with existing CHD who were also on stable diet or lipid drug therapy were meeting their desired LDL-C goals when ATP III criteria were used rather than ATP II criteria. In addition, a greater percentage of these patients had a recent LDL-C reading that, while at or below their ATP II LDL-C goal, did not meet their suggested ATP III LDL-C goal.

Of the 596 persons (30%) with existing CHD included in our sample, only 38.1% were meeting LDL-C goals (<100 mg/dL) according to ATP III criteria, and 39.4% were meeting LDL-C goals according to ATP II criteria (≤100 mg/dL). Further, in multivariable logistic regression modeling, CHD was an independent predictor of nongoal attainment. Only 18% of persons with existing CHD in the L-TAP study were meeting their ATP II goal of ≤100 mg/dL.12 In a randomized controlled trial with CHD patients who had “normal” total cholesterol, the authors showed that many needed combination drug therapy to reach desired LDL-C goals.18 In a large claims analysis, Straka et al. demonstrated that only 23.3% of persons with existing CHD were meeting their LDL-C goal according to ATP II criteria. Also, the majority of CHD patients who were not meeting goal were already prescribed lipid-lowering therapy.17 Future
strategies to manage patients with existing CHD may include dose titration, switching to another statin, or the use of combination lipid drug therapy.

In this study, the documented presence of risk factors for CHD was common. According to ATP II criteria, diabetes is a risk factor for CHD, while in ATP III, diabetes is a risk equivalent for CHD since the probability of a diabetic patient developing a major CHD event in the next 10 years is greater than 20%. The high prevalence of diabetes in the U.S. population identifies a new high-risk group requiring more intensive therapy to achieve LDL-C goals. In our sample, 289 of the 478 (60.5%) diabetic patients who did not have existing CHD fell in the lowest LDL-C goal of ≤100 mg/dL, as opposed to an LDL-C goal of either <130 mg/dL or <160 mg/dL, depending on the presence of other CHD risk factors in other ATP criteria. Among these diabetic patients without existing CHD who were identified as taking statin therapy, only 33% attained an LDL-C of <100 mg/dL. Straika and colleagues reported that 21% of their diabetic population without CHD attained an LDL goal of ≤100 mg/dL, although only 29% of those meeting goal were identified as taking cholesterol-lowering medication. Other studies assessing the proportion of diabetic patients meeting ATP II goals also indicate a low goal attainment within this population. While changes in other risk factors between ATP II to ATP III may have a smaller impact on the numbers of patients that need more intensive management, our data indicate that changing diabetes from a risk factor for CHD to a CHD risk equivalent is quite significant. As the size of the diabetic population continues to increase, a greater emphasis on primary CHD prevention within this population will become more important for MCOs.

During this chart review process, approximately 16% of the population did not have an LDL-C laboratory value documented in their chart, despite the fact that all patients were identified for inclusion in the QI initiative on the basis of receipt of at least 1 prescription for a statin drug. With an increase in the percentage of high-risk patients who need a lower LDL-C goal, it is disappointing that LDL-C is not being followed more closely by primary care physicians in an outpatient managed care setting. Greater educational efforts should focus not only on routine lipid screening but also on regular follow-up of lipid laboratory testing. Further, it is important to note that while we chose to collect data on LDL-C values in the 2-year period prior to chart review, we found that only 75% of our sample had an LDL-C reading documented within the 1 year prior to chart review.

While our population was already being treated with lipid drug therapy, there is undoubtedly a greater percentage of the untreated population who will need to be treated to meet NCEP ATP III goals. Both treatment and monitoring may increase costs to the health care industry; however, the increased cost savings in the prevention of major CHD events and revascularizations will potentially make such endeavors cost effective.

Despite the shifts to more aggressive LDL-C goals suggested by changes from ATP II to ATP III guidelines, the average additional percent reduction in LDL-C was 18.1% among the 607 participants not meeting goal according to ATP III criteria. More than 60% needed a reduction in their current LDL-C value (within the previous 2 years) by 20% or less to meet goal. Therefore, in those persons not meeting goal, additional treatment strategies could quite reasonably include more attention to lifestyle modification, increased counseling on medication compliance, dose titration or switching to another statin, and combining lipid-lowering drugs that are complementary in reducing LDL-C levels (e.g. statins and bile acid-binding resins).

Limitations

Among the limitations of this study was our reliance on medical chart documentation to ascertain the presence of CHD, CHD risk factors, CHD risk equivalents, and LDL-C values. As part of the original QI initiative, trained nurses reviewed the medical

---

### TABLE 3 Predictors of NCEP ATP III Goal Attainment Among a Subsample of the MCO Statin Population With a Recent LDL-C Value Documented

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NCEP ATP III Goal Attainment (n = 1,040)</th>
<th>NCEP ATP III Nongolden Goal Attainment (n = 607)</th>
<th>Adjusted Odds Ratio*</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Gender</td>
<td>574 (55.2)</td>
<td>336 (55.4)</td>
<td>1.08</td>
<td>0.86-1.35</td>
</tr>
<tr>
<td>Age Category</td>
<td>&lt;40</td>
<td>36 (3.5)</td>
<td>19 (3.1)</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>41-50</td>
<td>159 (15.3)</td>
<td>76 (12.5)</td>
<td>1.15</td>
</tr>
<tr>
<td></td>
<td>51-60</td>
<td>351 (33.8)</td>
<td>190 (32.8)</td>
<td>1.24</td>
</tr>
<tr>
<td></td>
<td>61-70</td>
<td>302 (29.0)</td>
<td>150 (24.7)</td>
<td>1.62</td>
</tr>
<tr>
<td></td>
<td>71-80</td>
<td>153 (14.7)</td>
<td>124 (20.4)</td>
<td>1.30</td>
</tr>
<tr>
<td></td>
<td>&gt;80</td>
<td>39 (3.8)</td>
<td>39 (6.4)</td>
<td>0.79</td>
</tr>
<tr>
<td>Existing CHD</td>
<td>227 (21.8)</td>
<td>276 (45.5)</td>
<td>0.36</td>
<td>0.28-0.45</td>
</tr>
<tr>
<td>Obesity</td>
<td>135 (13.0)</td>
<td>125 (20.6)</td>
<td>0.62</td>
<td>0.46-0.83</td>
</tr>
<tr>
<td>Diabetes</td>
<td>177 (17.0)</td>
<td>210 (35.6)</td>
<td>0.39</td>
<td>0.30-0.49</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>25 (2.4)</td>
<td>39 (6.4)</td>
<td>0.44</td>
<td>0.25-0.78</td>
</tr>
<tr>
<td>Framingham risk &gt;20%†</td>
<td>23 (2.2)</td>
<td>60 (9.9)</td>
<td>0.25</td>
<td>0.14-0.43</td>
</tr>
<tr>
<td>Current smoker</td>
<td>97 (9.3)</td>
<td>90 (14.8)</td>
<td>0.62</td>
<td>0.44-0.88</td>
</tr>
</tbody>
</table>

* Adjusted for all factors listed in the table.
† Calculated using the Framingham Scoring System as identified in the NCEP ATP III criteria, which identifies patients with multiple comorbidities who have a greater than 20% risk of a major coronary event over the next 10 years.
NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III.
LDL-C = low-density lipoprotein cholesterol.
MCO = managed care organization.
CHD = coronary heart disease.
TIA = transient ischemic attack.
records of eligible patients in the office of the physician identified in the pharmacy claims data as the prescriber for statin drug therapy. Since several physicians may be involved in the care of any given patient, all the information of interest may not have been available in the particular prescriber’s office where the medical chart was reviewed. It is possible that some of the missing LDL-C values could have been recorded in the medical charts of other physicians who cared for these MCO patients.

Another important limitation is the lack of information regarding dose titration and patient compliance to their cholesterol-lowering medication regimen. Although the study population was identified for the original QI initiative from a pharmacy claims database, these original claims data were not available for the current research project. As part of the original QI project, trained nurses abstracted information on the patient’s current cholesterol-lowering drug regimen as documented in the chart at the time of chart review. A history of dose titration and information about switching between antilipid agents were not collected. Therefore, we did not measure compliance with treatment or adherence or persistence with drug therapy and did not record the number of days of statin drug therapy that were dispensed. However, since nearly 31% of the population was not meeting its NCEP ATP III goal, there is a clear opportunity to improve goal attainment through mechanisms such as increased emphasis on physician monitoring and management of these patients and increased patient compliance to improve goal attainment.

Lastly, the patients randomly selected in these analyses were identified in pharmacy claims data as receiving prescriptions for statin drug therapy. The high prevalence of hypertension, diabetes, obesity, and other comorbidities within this population suggests that patient selection on the basis of drug therapy captures a relatively more complex population compared with patients being managed with diet and other lifestyle modifications alone. Therefore, the results of this study may not be generalizable to the general population of patients with hyperlipidemia.

**Conclusion**

The advent of the more rigorous NCEP ATP III guidelines will likely result in more patients on cholesterol medication requiring additional interventions-management to attain LDL-C goals. In this study of MCO patients receiving statin drug therapy (the most common treatment for hyperlipidemia), the percentage of patients achieving their LDL-C goal dropped by 6.8% from 59.8% under the criteria of ATP II to 53.0% under the criteria of ATP III. Conversely, the proportion of statin patients not at LDL-C goal rose from 24.1% under ATP II to 30.9% under ATP III criteria.

**ACKNOWLEDGMENTS**

The authors would like to thank Barry Patel, PharmD, and Thomas Stacy, PharmD, for their assistance in editing and revising the text of the manuscript and Allison Egger, MPH, for her assistance with statistical analysis; all are employed by Total Therapeutic Management, Kennesaw, Georgia.

**DISCLOSURES**

Funding for this research was provided by Sankyo Pharma and was obtained by author H. Ed Perez. Perez and author Vickie Andros are employed by Total Therapeutic Management, Inc., which currently has research grants from Sankyo and numerous other pharmaceutical and health care companies; author Brian J. Quilliam was employed by TTM at the time of this study. Author Peter Jones has received grants from Sanlevo, Pfizer, AstraZenec, and GlaxoSmithKline and honoraria from Pfizer and AstraZeneca. Quilliam served as principal author of the study. Study concept and design and drafting of the manuscript were the work of Quilliam, Perez, and Andros. Critical revision of the manuscript and analysis and interpretation of data were contributed by all authors; statistical expertise was contributed by Quilliam.

**REFERENCES**

5. Castelli WP. Epidemiology of triglycerides: a view from Framingham. Am J Cardiol. 1992;70:3H-9H.


Cost-Effectiveness Analysis of Simvastatin and Lovastatin/Extended-Release Niacin to Achieve LDL and HDL Goal Using NHANES Data

EDWARD P. ARMSTRONG, PharmD; WOODIE M. ZACHRY III, PhD; and DANIEL C. MALONE, PhD

ABSTRACT

OBJECTIVE: The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, Adult Treatment Panel III (ATP III) encouraged reduced low-density lipoprotein (LDL) cholesterol levels for a greater number of patients and reemphasized the benefits of high-density lipoprotein (HDL) cholesterol. The purpose of this study was to compare 2 regimens achieving simultaneous LDL and HDL goals.

METHODS: A decision-analytic model compared the cost-effectiveness of simvastatin and lovastatin/extended-release niacin. The perspective of the analysis was that of a health system. Product labeling was used to determine changes in cholesterol concentrations and frequencies of clinically important adverse events. The Third National Health and Nutrition Examination Survey (NHANES III) adult data were used for baseline cholesterol levels. Each product was titrated to achieve LDL and HDL goals unless an adverse effect occurred. Direct medical costs were determined for each treatment to determine cost-effectiveness.

RESULTS: For both the 130 mg/dL and 100 mg/dL LDL goal analyses (and HDL ≥40 mg/dL), lovastatin/extended-release niacin had higher success rates and lower estimated direct-medical costs than simvastatin. Simvastatin had the highest success rate in achieving LDL level <160 mg/dL and HDL ≥40 mg/dL; however, its estimated direct-medical cost was approximately twice that of lovastatin/extended-release niacin ($665 versus $333).

CONCLUSION: For the LDL goals <130 mg/dL and <100 mg/dL (and HDL ≥40 mg/dL) required of the majority of U.S. residents, lovastatin/extended-release niacin was both more successful and less costly than simvastatin.

KEYWORDS: Cholesterol, ATP III, LDL, HDL, Niacin, Lovastatin, Simvastatin

J Manag Care Pharm. 2004;10(3):251-258

The treatment of dyslipidemia is of tremendous importance to patients, clinicians, and health systems. New cholesterol guidelines—the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, Adult Treatment Panel III (ATP III)—have created treatment challenges by encouraging reduced low-density lipoprotein (LDL) cholesterol levels for a greater number of patients. These guidelines have also reemphasized that a low level of high-density lipoprotein (HDL) cholesterol is a major risk factor for coronary heart disease (CHD) events.

This recommendation is supported by the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) that was conducted to determine whether drug therapy to increase HDL levels would decrease the incidence of major CHD events in patients with CHD and low LDL levels. During a median follow-up of 5.1 years, this study demonstrated that CHD events were significantly reduced in the patients who received gemfibrozil therapy when the predominant lipid abnormality was low HDL level. The HDL-Atherosclerosis Treatment Study (HATS) also supports aspects of this finding. The HATS study compared simvastatin-niacin and antioxidant-vitamin therapy, alone and together or placebo, in patients with coronary disease and low plasma levels of HDL. The HATS study found that simvastatin plus niacin provided marked clinical and angiographically measurable benefits in patients with coronary disease and low HDL levels.

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor regimens, commonly referred to as “statins,” have become the standard treatment to achieve lower LDL concentrations. This product class has been shown to be quite effective and safe in lowering LDL levels and provides a modest improvement in HDL concentrations. In addition, niacin is an established product that has been demonstrated to raise HDL levels along with lowering LDL concentrations. However, flushing associated with immediate-release formulations of niacin has limited its adoption as a common therapy. The availability of an extended-release formulation of niacin with reduced occurrence of adverse events, along with the ATP III emphasis on the role of HDL, has renewed interest in niacin’s role in improving both LDL and HDL levels. When niacin is utilized, it is often added to a statin regimen that has not achieved LDL and HDL goals as monotherapy.

Simvastatin is an established statin product that has been used in several pivotal dyslipidemia studies. It has demonstrated efficacy in reducing overall deaths (0.7 relative risk), coronary deaths (0.58 relative risk), and the risk of undergoing
Cost-Effectiveness Analysis of Simvastatin and Lovastatin/Extended-Release Niacin to Achieve LDL and HDL Goal Using NHANES Data

### Methods

#### Overview of Models

Decision-analytic models were created to compare the cost-effectiveness between simvastatin and lovastatin/extended-release niacin. The perspective of the analysis was that of a health system (e.g., a managed care organization). Simvastatin was selected because it has true clinical outcomes data available with its use. Publication of the 4S and HATS studies was crucial to support its inclusion in the model. The simvastatin pathway started with 20 mg per day and was titrated monthly to a maximum dosage of 80 mg per day. The lovastatin/extended-release niacin pathway started with 20 mg/500 mg per day and was titrated monthly to a maximum dosage of 40 mg/2,000 mg per day. Patients in either treatment pathway were titrated to maximum dosage unless ATP III-designated LDL and HDL targets were realized or major side effects (myopathy, liver toxicity, or major flushing) were experienced (Figure 1). Manuscripts cited in the product package labeling were used to estimate the change in cholesterol concentrations (LDL and HDL) and the frequency of clinically important adverse events with each regimen.

Three separate models were created for the different patient populations that required LDL goals of <160 mg/dL, <130 mg/dL, or <100 mg/dL. For each decision tree, the model incorporated the titration scenarios for the changes in LDL and HDL concentrations with each dosage increase. The side-effect frequencies for each product were also included as indicated in the product labeling during the dosage titration. The model defined the effectiveness rate (i.e., successfully treated patient) as a patient achieving LDL and HDL goals and not experiencing a significant adverse event. Health care resource units and their respective costs were estimated for each pathway in the model. Cost-effectiveness was calculated by determining the direct-medical costs to achieve a successfully treated patient. The decision-analytic model framework is summarized in Figure 1.

#### Model Specifications

Cholesterol levels for the U.S. population were obtained from the Third National Health and Nutrition Examination Survey (NHANES III) 1988-1994 adult data file, a publicly available sample of health care information for U.S. residents from the National Center for Health Statistics and the Centers for Disease Control and Prevention. This database was designed to provide national estimates of the health and nutritional status of the U.S.’s civilian, noninstitutionalized population. Data elements relevant to this study included patient-level data on cholesterol levels, smoking history, presence of CHD, presence of diabetes mellitus, age, and gender. These data fields were applied to the ATP III guidelines to estimate each patient’s estimated 10-year CHD risk. Within the ATP III major risk factors (exclusive of LDL) that modify LDL goals, the only data element not included in the data set was the presence or absence of a family history of premature CHD. Following the ATP III framework, patients with CHD or a CHD risk equivalent (10-year CHD risk >20%) were assigned an LDL goal of <100 mg/dL. Patients with multiple (2 or more) risk factors and an estimated risk ≤20% (using the Framingham risk assessment tool) were assigned an LDL goal of <130 mg/dL; and patients with no or 1 risk factor(s) were assigned an LDL goal of <160 mg/dL. HDL goal was defined as ≥40 mg/dL for all patients. Patients were included in the model only if they had LDL levels above their calculated target goal. An HDL level less than 40 mg/dL was not used as a concomitant inclusion criterion.

The percent change in LDL and HDL at each dosing range of simvastatin or lovastatin/extended-release niacin was applied to the database to estimate the proportion of NHANES patients achieving LDL and HDL goal at each decision node (Table 1). Since no data were available in the product labeling for lovastatin.

### Table 1: Lipid Changes From Baseline

<table>
<thead>
<tr>
<th>Medication</th>
<th>LDL Change (% Change From Baseline)</th>
<th>HDL Change (% Change From Baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin 20 mg</td>
<td>-38</td>
<td>+8</td>
</tr>
<tr>
<td>Simvastatin 40 mg</td>
<td>-41</td>
<td>+9</td>
</tr>
<tr>
<td>Simvastatin 80 mg</td>
<td>-47</td>
<td>+8</td>
</tr>
<tr>
<td>Lovastatin 20 mg/extended-release niacin 500 mg</td>
<td>-25</td>
<td>+11</td>
</tr>
<tr>
<td>Lovastatin 20 mg/extended-release niacin 1,000 mg</td>
<td>-30</td>
<td>+20</td>
</tr>
<tr>
<td>Lovastatin 40 mg/extended-release niacin 1,000 mg</td>
<td>-36</td>
<td>+20</td>
</tr>
<tr>
<td>Lovastatin 40 mg/extended-release niacin 1,500 mg</td>
<td>-37</td>
<td>+27</td>
</tr>
<tr>
<td>Lovastatin 40 mg/extended-release niacin 2,000 mg</td>
<td>-42</td>
<td>+30</td>
</tr>
</tbody>
</table>

LDL = low-density lipoprotein cholesterol. HDL = high-density lipoprotein cholesterol.
Lovastatin/extended-release niacin 20 mg/500 mg formulation, the results from Kashyap26 (lovastatin/extended-release niacin 10 mg/500 mg) were used as an estimate of cholesterol level changes. Data 3.5 software (TreeAge Software, Inc., Williamstown, MA) was used to construct the models. The time frame of the model was 4 months, assumed to be sufficient time to complete titration, if necessary. Resource units and their respective direct-medical costs to complete the titration schedule for each pathway were determined and entered into the model (Table 2). A minor problem physician visit (CPT [Current Procedural Terminology] code 99212) was assumed if no dosage change was made. A moderate/high problem physician visit (CPT code 99214) was assumed if the patient suffered an adverse event or when the dosing schedule required modification. If the patient suffered an adverse event, the medication was assumed to have been discontinued and appropriate laboratory tests conducted.16 This study was conducted from the perspective of a health care system. Table 2 summarizes the resource unit costs used in the analyses. Medicare’s national average allowance fees were used to estimate 2002 costs associated with physician visits and laboratory tests.27 Average wholesale prices (AWP) (Medispan, fall 2002) were used to estimate medication costs. The AWP values were averaged across package size and manufacturer/relabeler. The costs calculated from the model were the estimated total health care costs (medications, physician visit costs, and laboratory costs) to use each regimen for 4 months.

Sensitivity analysis testing was conducted to determine the impact of variable uncertainty on the models. Tornado diagrams were constructed for sensitivity analysis to determine which variables produced the greatest variation in end points. (A tornado diagram is useful to identify the range of model results...
TABLE 2  Resource Unit Costs Used to Populate the Decision-Analytic Model

<table>
<thead>
<tr>
<th>Resource Unit (Current Procedural Terminology Code)*</th>
<th>Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician visit 10 minute, minor problem (99212)*</td>
<td>36</td>
</tr>
<tr>
<td>Physician visit 25 minute, moderate/high severe (99214)*</td>
<td>79</td>
</tr>
<tr>
<td>Lipid panel (80061)*</td>
<td>58</td>
</tr>
<tr>
<td>Transaminase (84460 or 84450)*</td>
<td>19</td>
</tr>
<tr>
<td>Creatine kinase (82550)*</td>
<td>25</td>
</tr>
<tr>
<td>Simvastatin 20 mg (AWP)*</td>
<td>4.24</td>
</tr>
<tr>
<td>Simvastatin 40 mg (AWP)*</td>
<td>4.30</td>
</tr>
<tr>
<td>Simvastatin 80 mg (AWP)*</td>
<td>4.46</td>
</tr>
<tr>
<td>Lovastatin 20 mg/extended-release niacin 500 mg (AWP)*</td>
<td>1.45</td>
</tr>
<tr>
<td>Lovastatin 20 mg/extended-release niacin 750 mg (AWP)*</td>
<td>1.77</td>
</tr>
<tr>
<td>Lovastatin 20 mg/extended-release niacin 1,000 mg (AWP)*</td>
<td>1.89</td>
</tr>
</tbody>
</table>

* Costs determined using Physicians Fee and Coding Guide. 27
† Average wholesale price (AWP) determined using Medispan Fall 2002.

TABLE 3  Baseline Demographic Characteristics of the Treatment Groups

<table>
<thead>
<tr>
<th></th>
<th>Goal LDL &lt;160 mg/dL + HDL ≥40 mg/dL N = 256</th>
<th>Goal LDL &lt;130 mg/dL + HDL ≥40 mg/dL N = 1,268</th>
<th>Goal LDL &lt;100 mg/dL + HDL ≥40 mg/dL N = 906</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, SD)</td>
<td>61.9 (14.8)</td>
<td>61.5 (13.1)</td>
<td>65.9 (13.7)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>92 (35.9)</td>
<td>85.7 (66)</td>
<td>342 (37.7)</td>
</tr>
<tr>
<td>Total serum cholesterol mg/dL (mean, SD)</td>
<td>273.7 (33.9)</td>
<td>229.1 (28.5)</td>
<td>231.9 (39.0)</td>
</tr>
<tr>
<td>Serum triglycerides mg/dL (mean, SD)</td>
<td>146.4 (68.9)</td>
<td>130.6 (61.0)</td>
<td>167.3 (71.8)</td>
</tr>
<tr>
<td>Serum LDL cholesterol mg/dL (mean, SD)</td>
<td>188.7 (27.7)</td>
<td>156.2 (24.2)</td>
<td>154.4 (35.3)</td>
</tr>
<tr>
<td>Serum HDL cholesterol mg/dL (mean, SD)</td>
<td>55.7 (12.9)</td>
<td>46.7 (11.9)</td>
<td>44.0 (10.6)</td>
</tr>
</tbody>
</table>

LDL = low-density lipoprotein cholesterol. HDL = high-density lipoprotein cholesterol.

obtained with a series of model variables.) Since statins have been shown to have a coefficient of variation of 17% in their LDL reduction, all clinical end point variables (lipid changes and adverse events) were modified by 25% higher and lower from the point estimates in the models. 28 Cost-sensitivity analyses were conducted by decreasing the medication costs by 25% for the most costly treatment strategy. In addition, sensitivity analyses were conducted to estimate cost changes over a 1-year study horizon. In the 1-year sensitivity analyses, it was assumed that there was 1 additional minor problem physician visit and 365 days of drug therapy based upon the dose for each pathway, 1 more lipid (laboratory) panel, and that previous treatment remained discontinued if a patient encountered a significant adverse drug event.

Results

The analysis of the NHANES data based on LDL goal stratification revealed that, among dyslipidemic persons, there were 256 patients (10.5%) who required a goal of <160 mg/dL, 1,268 (52.2%) patients who required a goal of <130 mg/dL, and 906 patients (37.3%) who required a goal of <100 mg/dL. The baseline demographic characteristics of the patients are summarized in Table 3. Table 4 summarizes the success rate (i.e., proportion of patients achieving both LDL and HDL goals and not having a significant adverse event) and the cost for each regimen. It was noted that the proportion of patients achieving both LDL and HDL goals decreased with the more restrictive goal requirements for both regimens.

Figure 2 summarizes the cost-effectiveness ratios for both regimens at each treatment goal. These data demonstrate that lovastatin/extended-release niacin had lower (more favorable) cost-effectiveness ratios at each treatment LDL/HDL goal than did simvastatin.

Simvastatin had the highest clinical success rate in achieving both LDL and HDL goals in patients that required a LDL level <160 mg/dL and a HDL ≥40 mg/dL (97.2% versus 89.7% for lovastatin/extended-release niacin). However, the estimated total direct-medical cost (medications, physician visit costs, and laboratory costs) to use simvastatin was approximately twice that of lovastatin/extended-release niacin ($665 versus $333). Based on these estimates, the incremental cost-effectiveness ratio for each additional patient to reach LDL and HDL goals without an adverse event with simvastatin was $4,427 when compared with lovastatin/extended-release niacin.

For both the 130 mg/dL and 100 mg/dL goal analyses, lovastatin/extended-release niacin had higher success rates than simvastatin (85.6% versus 76.7% and 63.7% versus 60.3%, respectively). In addition, for both the 130 mg/dL and 100 mg/dL goal analyses, lovastatin/extended-release niacin had lower estimated costs than simvastatin. Thus, in the incremental cost-effectiveness analyses for 130 mg/dL and 100 mg/dL LDL goal levels (plus HDL goal ≥40 mg/dL), lovastatin/extended-release niacin combination therapy dominated simvastatin monotherapy.

In the <160 mg/dL LDL and ≥40 mg/dL HDL goal model, sensitivity analysis demonstrated that 2 variables impacted the model success rates. Lowering the proportion of patients on simvastatin 20 mg who reach LDL and HDL goals from 0.891 to 0.730 and 0.991 to 0.741, respectively, lowered the overall simvastatin success rate to 0.897. Thus, lowering the simvastatin 20 mg lipid effects by 25% resulted in the same success rate as the baseline lovastatin/extended-release niacin. In another sensitivity analysis, when simvastatin medication costs were reduced by 25%, the estimated total direct-medical cost was reduced from $665 to $538. This yielded an incremental cost-
effectiveness ratio of $2,733 for simvastatin for each additional patient to reach LDL and HDL goals without an adverse event compared with lovastatin/extended-release niacin. For the <130 mg/dL LDL and ≥40 mg/dL HDL goal model, tornado diagram sensitivity analyses suggested that the clinical success rates were most sensitive to changes in HDL levels from either 20 mg of simvastatin or 20 mg/500 mg of lovastatin/extended-release niacin. When more than 86.8% of patients achieved HDL goal with simvastatin 20 mg, simvastatin was more successful than lovastatin/extended-release niacin. In the remaining sensitivity analyses, lovastatin/extended-release niacin was the most successful strategy throughout the range of other variables. When the simvastatin medication costs were reduced by 25%, the estimated total direct-medical cost was reduced from $675 to $548. Lovastatin/extended-release niacin continued to dominate simvastatin even when the simvastatin cost was lowered by 25% and was both more successful and less costly.

For the models with goals of <100 mg/dL LDL and ≥40 mg/dL HDL, tornado diagram sensitivity analyses suggested that the clinical success rates were most sensitive to the effect of simvastatin 20 mg on HDL, the LDL reduction with lovastatin/extended-release niacin 40 mg/1,000 mg, and the LDL lowering with lovastatin/extended-release niacin 40 mg/2,000 mg. When more than 76.6% of patients achieved HDL goal with simvastatin 20 mg, simvastatin was more successful than lovastatin/extended-release niacin. In sensitivity analyses with the other variables, lovastatin/extended-release niacin remained more successful throughout the variable ranges. When the simvastatin medication costs were reduced by 25%, the estimated total direct-medical cost was reduced from $773 to $645. Lovastatin/extended-release niacin remained more successful throughout the variable ranges. When the simvastatin cost was lowered by 25% and was both more successful and less costly.

One-year sensitivity analysis demonstrated an expansion in the estimated treatment cost differences between simvastatin and lovastatin/extended-release niacin. For the <160 mg/dL LDL and ≥40 mg/dL HDL goal model, the estimated cost of simvastatin was $1,793 compared with $792 for lovastatin/extended-release niacin. In the <130 mg/dL LDL and ≥40 mg/dL HDL goal model, the estimated cost of simvastatin was $1,804 compared with $829 for lovastatin/extended-release niacin. In the <100 mg/dL LDL and ≥40 mg/dL HDL goal model, the estimated cost of simvastatin was $1,911 compared with $1,354 for lovastatin/extended-release niacin. Figure 3 demonstrates the decision-tree variables with the greatest impact on treatment costs using the <100 mg/dL LDL and ≥40 mg/dL HDL goal model.

For drug costs, this study used AWP costs across package size and manufacturer/relabeler. A sensitivity analysis was also conducted by assuming flat pricing across all strengths of simvastatin and was assumed to be $4.41 per tablet. Using the <100 mg/dL LDL and ≥40 mg/dL HDL goal model, the average cost of simvastatin increased from $773 to $789. Therefore, using flat dose pricing did not change the rank order of the alternatives.

**Discussion**

The ability to achieve goal cholesterol levels has enormous implications for patients, clinicians, and health care systems. This analysis demonstrated that, in the NHANES sample, most patients with dyslipidemia require LDL goals of less than either 130 mg/dL or 100 mg/dL. In targeting patient populations for LDL levels below 130 mg/dL or 100 mg/dL and HDL ≥40 mg/dL, lovastatin/extended-release niacin was both more successful and...
Cost-Effectiveness Analysis of Simvastatin and Lovastatin/Extended-Release Niacin to Achieve LDL and HDL Goal Using NHANES Data

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL + HDL ≥40 mg/dL</td>
<td>Success Rate (%) a</td>
<td>Cost ($)</td>
<td>Success Rate (%) a</td>
<td>Cost ($)</td>
<td>$4,427 per additional successfully treated patient</td>
</tr>
<tr>
<td>&lt;160 mg/dL</td>
<td>97.2</td>
<td>665</td>
<td>89</td>
<td>333</td>
<td>Lovastatin/extended-release niacin dominates simvastatin</td>
</tr>
<tr>
<td>&lt;130 mg/dL</td>
<td>76.7</td>
<td>675</td>
<td>85.6</td>
<td>400</td>
<td>Lovastatin/extended-release niacin dominates simvastatin</td>
</tr>
<tr>
<td>&lt;100 mg/dL</td>
<td>60.3</td>
<td>773</td>
<td>63.7</td>
<td>616</td>
<td>Lovastatin/extended-release niacin dominates simvastatin</td>
</tr>
</tbody>
</table>

*Success rate is defined as a patient achieving LDL and HDL goals and not experiencing a significant adverse event. LDL = low-density lipoprotein cholesterol. HDL = high-density lipoprotein cholesterol.

Cost-effectiveness analysis of simvastatin monotherapy andLovastatin/Niacin combination therapy for each designated lipid goal.

<table>
<thead>
<tr>
<th>Clinical and Cost Outcomes for Simvastatin Monotherapy and Lovastatin/Niacin Combination Therapy for Each Designated Lipid Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>LDL + HDL ≥40 mg/dL</td>
</tr>
<tr>
<td>&lt;160 mg/dL</td>
</tr>
<tr>
<td>&lt;130 mg/dL</td>
</tr>
<tr>
<td>&lt;100 mg/dL</td>
</tr>
</tbody>
</table>

*Success rate is defined as a patient achieving LDL and HDL goals and not experiencing a significant adverse event. LDL = low-density lipoprotein cholesterol. HDL = high-density lipoprotein cholesterol.

Cost-effectiveness analysis of simvastatin monotherapy and Lovastatin/Niacin combination therapy for each designated lipid goal.

Less costly than simvastatin monotherapy.

The promotion of the ATP III treatment guidelines has importantly emphasized the goal of LDL levels. In addition, this guideline has encouraged an examination of HDL levels, too. The VA-HIT and HATS studies suggest that patients may benefit from optimization of both LDL and HDL levels.6,7 Further research is needed to examine whether these long-term benefits are also observed with lovastatin/extended-release niacin.

The 3 decision-analytic models demonstrate that both treatment regimens had fewer patients achieve LDL and HDL goals as the goals became more restrictive. These results also indicate that the short-term direct-medical costs are larger, regardless of regimen, to achieve tighter lipid control. Long-term studies are needed to determine the clinical and economic outcomes with the goals being applied following publication of the ATP III guidelines.

These data are consistent with research from other investigators. Statins are highly regarded treatments and considered cost effective in the treatment of both secondary and primary prevention of dyslipidemia.29-40 Numerous evaluations have been conducted that support the important role of these products.41-43 In addition, based on the VA-HIT trial, treatment with gemfibrozil to raise low HDL levels has been shown to be quite cost effective.44 The complementary nature of extended-release niacin in combination with statin treatment has also been demonstrated.14-15 The data from this study support the rationale of using extended-release niacin in combination with statins. The formulation evaluated in this study (lovastatin/extended-release niacin) appears to be a cost-effective treatment alternative to simvastatin monotherapy in the majority of patients.

Although simvastatin had the highest success rate for the LDL <160 mg/dL and HDL ≥40 mg/dL goal levels, this regimen had a total direct-medical cost almost twice that ofLovastatin/extended-release niacin. The explanation for this observation appears to be the pricing of simvastatin that is the same regardless of dose for the 20 mg, 40 mg, and 80 mg doses (Table 2; the AWPs for the 5 mg and 10 mg doses of simvastatin are lower than the 3 doses studied in this research). Although not often recommended, the practice of splitting the tablets of higher-dose simvastatin tablets would partially offset simvastatin’s higher unit cost47; splitting the 80 mg dose would reduce the 40 mg per day cost by 50%.

There are several important limitations that should be kept in mind when interpreting this study. Since no data were available in the product labeling for lovastatin/extended-release niacin 20 mg/500 mg formulation, the results from Kashyap9 lovastatin/extended-release niacin 10 mg/500 mg were used as an estimate of cholesterol-level changes. Therefore, the model likely underestimated the number of patients reaching LDL and HDL goals at this dosage.

When incorporating medication costs, this study used AWP values. In a market economy with negotiated contract prices, actual purchase costs may be lower than AWP but would be similarly discounted across the products studied in this research. In addition, health systems may receive rebates from pharmaceutical manufacturers that would further lower the medication resource unit costs. Since contracts and rebates are confidential and variable by health system, this study relied upon AWP, a reasonable cost basis for this research since none of the products studied are available by generic name.48

Another limitation with this study is the inability to account for variation in a patient’s recommended lipid diet. Since diet can...
independently impact cholesterol levels, this analysis was unable to incorporate this possible variability. A patient who is noncompliant with a recommended diet would be anticipated to have inferior lipid changes that are predicted with this model.

The basis of this study was that the NHANES III database was representative of the U.S. population. In addition, the effectiveness analysis in this study was based on the lipid changes in the product labeling for simvastatin and lovastatin/extended-release niacin. Lipid changes in actual practice may vary from those stated in the product labeling. Furthermore, this study used assumptions concerning the number of physician visits and laboratory tests needed to complete the titration schedules for both products. Actual practice patterns may vary between clinicians and health plans. The significant flushing rate with lovastatin/extended-release niacin was assumed to be a treatment failure in all cases and lowered the overall effectiveness for this product. In practice, it is possible that some patients may have tolerated the product with a slower titration schedule and/or administration of aspirin.

Conclusion

Both simvastatin and lovastatin/extended-release niacin are important agents to attain both LDL and HDL goals. This study demonstrated that simvastatin was more successful in achieving an LDL goal <160 mg/dL and an HDL goal ≥40 mg/dL. However, only a minority of patients requires this goal. The NHANES data demonstrate that the majority of U.S. residents require an LDL goal of <100 mg/dL or <130 mg/dL. For both of these goals—and the desired end point of HDL ≥40 mg/dL—lovastatin/extended-release niacin was both more successful and less costly than simvastatin.

DISCLOSURES

Funding for this study was provided as a grant to the University of Arizona by Kos Pharmaceuticals and was obtained by authors Edward P Armstrong, Woodie M. Zachry III, and Daniel C. Malone. Armstrong and Malone are employed by the University of Arizona, and Zachry was employed by the university at the time of this study. Armstrong attended 2 Kos Pharmaceuticals Advisory Boards and received honoraria from Kos, all authors received grant support from Kos. Armstrong served as principal author of the study. Study concept and design, analysis and interpretation of data, and statistical expertise were contributed by all authors. Drafting of the manuscript was primarily the work of Armstrong, and its critical revision was the work of Zachry and Malone.

REFERENCES

Cost-Effectiveness Analysis of Simvastatin and Lovastatin/Extended-Release Niacin to Achieve LDL and HDL Goal Using NHANES Data


A Comparison of the Cost-Effectiveness of Almotriptan and Sumatriptan in the Treatment of Acute Migraine Using a Composite Efficacy/Tolerability End Point

PAUL WILLIAMS, MBA, MD, FRCPsych, and C.E. REEDER, PhD

ABSTRACT

OBJECTIVE: To use a composite efficacy/tolerability end point to compare the cost-effectiveness, from the perspective of a U.S. health care payer, of almotriptan and sumatriptan in the treatment of an acute migraine attack.

METHODS: The composite end point “Sustained pain free and No Adverse Events” (SNAE) was created from the sustained pain free and adverse event rates obtained in a meta-analysis of 53 placebo-controlled trials of oral triptans. The total direct cost of treating a single migraine attack was calculated from published sources.

RESULTS: In the base-case analysis, the average cost-effectiveness ratios (CERs) were $82, $133, and $138 (per attack at which SNAE is achieved, 2004 prices) for almotriptan 12.5 mg, sumatriptan 50 mg, and sumatriptan 100 mg, respectively; the incremental CERs for almotriptan 12.5 mg were $12 and $16 (compared with sumatriptan 50 mg and sumatriptan 100 mg, respectively) per incremental attack at which SNAE is achieved. Sensitivity analyses were conducted to explore the impact of (1) relaxing the base-case assumptions (independence of efficacy and tolerability, uniform apportionment of health service use costs across attacks, number of tablets used to treat 1 attack); (2) varying input costs; and (3) uncertainty in the efficacy and tolerability estimates from the meta-analysis. In all of these sensitivity analyses, almotriptan 12.5 mg remained cost effective compared with sumatriptan 50 mg and 100 mg.

CONCLUSION: Almotriptan was economically superior to sumatriptan in the treatment of a migraine attack.

KEYWORDS: Migraine, Triptans, Almotriptan, Cost effective, Sumatriptan

J Manag Care Pharm. 2004;10(3):259-265

Methods

Approach

We developed a model to compare the cost-effectiveness of almotriptan 12.5 mg and 2 dose levels of sumatriptan (50 mg and 100 mg) in the treatment of a single migraine attack from a U.S. health care payer perspective. Cost-effectiveness ratios...
A Comparison of the Cost-Effectiveness of Almotriptan and Sumatriptan in the Treatment of Acute Migraine Using a Composite Efficacy/Tolerability End Point

**TABLE 1** Summary of Relevant Results From Ferrari et al.’s Meta-analysis

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Almotriptan 12.5 mg</th>
<th>Sumatriptan 50 mg</th>
<th>Sumatriptan 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute 2 hour headache response rate</td>
<td>61% (95%CI 58%-65%)</td>
<td>63% (95%CI 60%-65%)</td>
<td>59% (95%CI 57%-61%)</td>
</tr>
<tr>
<td>Absolute 2 hour pain-free rate</td>
<td>36% (95%CI 32%-39%)</td>
<td>29% (95%CI 27%-31%)</td>
<td>29% (95%CI 27%-31%)</td>
</tr>
<tr>
<td>Absolute sustained pain-free rate</td>
<td>26% (95%CI 23%-29%)</td>
<td>20% (95%CI 18%-22%)</td>
<td>20% (95%CI 18%-21%)</td>
</tr>
<tr>
<td>Absolute recurrence rate</td>
<td>26% (95%CI 22%-30%)</td>
<td>28% (95%CI 25%-31%)</td>
<td>30% (95%CI 27%-33%)</td>
</tr>
<tr>
<td>Placebo-corrected adverse event rate—CNS events</td>
<td>-1.5% (95%CI -3.9%-1.0%)</td>
<td>-2.4% (95%CI -3.7%-0.8%)</td>
<td>-3.4% (95%CI -4.4%-2.3%)</td>
</tr>
<tr>
<td>Placebo-corrected adverse event rate—chest events</td>
<td>-0.4% (95%CI -1.6%-0.8%)</td>
<td>1.9% (95%CI 0.4%-3.3%)</td>
<td>1.7% (95%CI 0.8%-2.5%)</td>
</tr>
<tr>
<td>Placebo-corrected adverse event rate—all events</td>
<td>1.8% (95%CI -2.7%-6.2%)</td>
<td>7.8% (95%CI 2.6%-13.1%)</td>
<td>13.2% (95%CI 8.6%-17.8%)</td>
</tr>
</tbody>
</table>

CNS = central nervous system.

**FIGURE 1** Relationship Between Efficacy and Tolerability

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Tolerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>a (spf-SNAE)</td>
<td>b (ac-[spf-SNAE])</td>
</tr>
<tr>
<td>c (SNAE)</td>
<td>d (1-[ac-SNAE])</td>
</tr>
<tr>
<td>Adverse Events YES</td>
<td>Adverse Events NO</td>
</tr>
<tr>
<td>(ae)</td>
<td>(1-ae)</td>
</tr>
</tbody>
</table>

Adverse Events

Data on sustained pain-free and adverse event rates were obtained from Ferrari et al.’s meta-analysis of 53 double-blind, randomized, controlled, clinical trials of oral triptans. These included data on 719 patients treated with almotriptan and 4,715 patients treated with sumatriptan in placebo-controlled trials. Sustained pain-free and adverse event rates are the marginal totals in Figure 1, so the value of SNAE can be calculated only if the relationship between efficacy and tolerability is known or can be assumed. For the base case, efficacy and tolerability were assumed to be independent so that:

\[ SNAE = (\text{sustained pain-free rate})(1-\text{[adverse event rate]}) \]

The impact of relaxing this independence assumption was explored in the sensitivity analysis, as the true nature of the relationship between efficacy and tolerability of triptan treatment is not known.

Absolute rates are more appropriate than placebo-corrected rates for cost-effectiveness analysis, as the placebo effect is a component of real-world effectiveness. Ferrari et al. published absolute sustained pain-free rates but only placebo-corrected, and not absolute, adverse event rates. The placebo adverse event rates from the same meta-analysis, published elsewhere, were therefore added to the placebo-corrected rates to result in estimated absolute adverse event rates for almotriptan and sumatriptan.

**Costs**

The perspective taken for this analysis was that of a U.S. health care payer, so only direct medical care costs were included. Migraine-related health service use costs were obtained from Hu et al.’s study of the economic burden of migraine in the United States. It was assumed in the base case that these costs could be apportioned uniformly across attacks, so the estimated cost per attack was obtained by dividing the annual per-migraineur health service use costs (physician visits, emergency room attendance, hospitalization) by the annual attack frequency from Hu et al. In the base case, these costs were assumed to be uninfluenced by choice of triptan (an assumption that acts in favor of sumatriptan [which has higher adverse event rates than almotriptan; see Table 1], and is therefore conservative with respect to the cost-effectiveness comparison). This study was conducted in 1999, so their costs have been inflated by 3% for each of the 5 intervening years.

Another base-case assumption was that a migraine attack was treated with 1 tablet, which is consistent with the conditions under which the efficacy and adverse event data were collected (the impact of relaxing the “1 tablet per attack” assumption was explored in the sensitivity analysis). On this basis, estimates for the total direct cost per attack were obtained by adding the drug acquisition cost ($ per tablet) to the estimated health service use cost per attack. The cost per tablet of each

(CERS) were calculated as appropriate, and the robustness of the cost-effectiveness comparisons was tested in a range of sensitivity analyses.

**Effectiveness**

We used a composite “unqualified success” measure as the primary index of effectiveness in this study, i.e., the proportion of patients who achieved sustained freedom from pain (defined as pain free at 2 hours after taking medication with no recurrence of moderate or severe headache and no rescue medication 2 to 24 hours postdose) without experiencing adverse events. We called this end point SNAE (Sustained pain free and No
triptan was obtained from http://www.drugstore.com,18 (whose prices more closely approximate to actual managed care pharmacy prices than average wholesale prices), and take into account the January 2004 price rise for almotriptan.

**Sensitivity Analyses**

**Relationship Between Efficacy and Tolerability**

The calculation of SNAE in the base-case analysis assumed efficacy and tolerability to be independent. In sensitivity analyses, odds ratios (OR) were specified for the relationship between efficacy and tolerability (ranging from OR = 0.1 [strongly negative relationship] to OR = 10 [strongly positive relationship]), SNAE was calculated by the method described in Figure 2, and CERs were calculated across this 100-fold range for the strength and direction of the efficacy/tolerability relationship.

**Health Service Use Costs**

In the base case, health service use costs were apportioned uniformly across attacks. Patients responding to treatment with an oral triptan, however, are unlikely to incur emergency room attendance and hospitalization costs. Therefore, the analyses were repeated assuming that these costs would be incurred only by patients not achieving sustained freedom from pain. Sustained pain-free rates were different for almotriptan and sumatriptan and, consequently, health service use costs were different. Thus, this analysis tested the effect of relaxing the assumption that health service use costs were the same irrespective of triptan choice.

**Tablets per Attack**

As the analysis was based on clinical trials data, it was assumed that an attack was treated with 1 tablet (of almotriptan or sumatriptan) in the base case. The impact of relaxing this assumption was explored separately for positive, negative, and independent relationships between efficacy and tolerability.

**Impact of Uncertainty in the Efficacy and Tolerance Estimates From the Meta-analysis**

An OR for the efficacy/tolerability relationship was first specified. Then the values and confidence intervals from the meta-analysis were used to calculate standard deviations for SNAE. The variance of SNAE was estimated using Haugen analysis were used to calculate standard deviations for SNAE. Then the values and confidence intervals from the meta-analysis were used to calculate standard deviations for SNAE. Haugen

**Results**

**Effectiveness**

Sustained pain-free rates and adverse event rates for almotriptan 12.5 mg, sumatriptan 50 mg, and sumatriptan 100 mg obtained from the meta-analysis11,14 are shown in Table 2. The table also shows the values for SNAE calculated under the base-case assumption that efficacy and tolerability are independent.

**Costs**

Table 3a shows health service use costs ($ per migraineur per year) taken from Hu et al.'s analysis of the burden of migraine

---

**FIGURE 2** Calculating the Value of SNAE

When Efficacy and Tolerability Are Not Independent

In the notation of Figure 1, the odds ratio (OR) that defines the relationship between efficacy and tolerability is

$$\text{OR} = \frac{(a/c)/(b/d)}{a/b}$$

Cells a, b, c, and d in Figure 1 can be expressed in terms of the adverse event rate (ae), the sustained pain-free rate (spf), and SNAE, i.e.,

- $a = \text{spf-SNAE}$
- $b = \text{ae-(spf-SNAE)} = \text{ae-spf+SNAE}$
- $c = \text{SNAE}$
- $d = 1-\text{ae-SNAE}$

Substituting these into equation [1] gives

$$\text{OR} = (\text{spf-SNAE})(1-\text{ae-SNAE})/(\text{ae-spf+SNAE-SNAE})$$

Equation [2] can be manipulated to give a quadratic equation, as follows:

$$0 = (\text{OR}-1)\text{SNAE}^2 + (\text{OR}\times\text{ae}-\text{OR}\times\text{spf}+\text{spf}+1-\text{ae})\text{SNAE} + \text{OR}\times\text{ae}\times\text{SNAE} - \text{spf}\times\text{ae}\times\text{SNAE} + \text{spf}^2 - \text{spf}\times\text{ae} - \text{spf}^2$$

Solving the quadratic equation yields:

$$\text{SNAE} = \frac{\text{spf} - \text{spf}\times\text{ae} - \text{spf}^2 - \text{spf}\times\text{SNAE} - \text{SNAE} + \text{SNAE}\times\text{ae} + \text{SNAE}^2}{\text{ae}\times\text{SNAE} - \text{spf}\times\text{SNAE} + \text{OR}\times\text{SNAE}^2}$$

Equation [3] can be rewritten as

$$0 = x^2 + y^2 + z^2$$

Using the standard approach to solving a quadratic equation, SNAE can be found by solving equation [4] with any value for OR and with known values of spf and ae, as follows

$$\text{SNAE} = \sqrt{\frac{(\text{spf}\times\text{ae} - \text{spf}\times\text{SNAE} + \text{SNAE}\times\text{ae} + \text{SNAE}\times\text{SNAE})}{\text{ae}\times\text{SNAE} - \text{spf}\times\text{SNAE} + \text{OR}\times\text{SNAE}^2}}$$

Equation [5] has 2 solutions, $(-\sqrt{\text{ae}\times\text{SNAE} - \text{spf}\times\text{SNAE} + \text{OR}\times\text{SNAE}^2})/2x$ and $(-\sqrt{\text{ae}\times\text{SNAE} - \text{spf}\times\text{SNAE} + \text{OR}\times\text{SNAE}^2})/2x$. The solution that conforms to the condition 0 < solution < min(spf,ae) is the value of SNAE.
in the United States.\textsuperscript{1} In their analyses, Hu et al. used average annual attack frequencies of 34.0 for men and 37.4 for women obtained from Stewart et al.\textsuperscript{1,20} Applying these frequencies to the data in Table 3a gives $1.92 as the average health service use cost per attack for men and $1.87 for women. The weighted average of these gender-specific costs (weighted for the relative frequency of treated migraine attacks, based on data in Hu et al.)\textsuperscript{1} was $1.88: inflating this figure by 3% per year for 5 years gives $2.18, the figure used in the cost-effectiveness analysis.

Table 3b shows the www.drugstore.com price of the trip-tans\textsuperscript{18} and the total direct costs incurred in treating an attack (under the base-case assumption of 1 tablet per attack).

**Base Case Cost-Effectiveness**

The unit of measurement for the CERs in this analysis (Table 4) is cost in 2004 dollars per attack at which SNAE is achieved following triptan treatment. For convenience, this will be referred to as $ per SNAE.

**Average CERs**

Table 4 shows that the average CER for almotriptan 12.5 mg was $81.75 per SNAE ($18.23 [from Table 3b] divided by 22.3% [from Table 2]). Corresponding calculations for sumatriptan 50 mg and sumatriptan 100 mg yield average CERs of $132.87 and $138.25 per SNAE, respectively.

Consider that $10,000 is available to be spent on treating migraine with either almotriptan or sumatriptan. With almotriptan, approximately 548 attacks ($10,000/$18.23 [Table 3b]) would be treated. SNAE would be achieved in 22.3% of these attacks (Table 2). Therefore, spending $10,000 on treating migraine with almotriptan 12.5 mg would result in approximately 122 successes ($10,000/$18.23*22.3%), at a cost of $81.75 per success (the average CER set out above). With sumatriptan 50 mg, approximately 583 attacks ($10,000/$17.14) would be treated. SNAE would occur in 12.9%, so spending $10,000 on this treatment would result in approximately 75 successes ($10,000/$17.14*12.9%) at a cost of $132.87 each. Spending the equivalent resource on treating migraine with sumatriptan 100 mg would result in approximately 72 ($10,000/$16.59*12.0%) successes at a cost of $138.25 each.

While the focus of our analysis was on SNAE, we recognize that this composite efficacy-tolerability end point is the most stringent of a hierarchy of efficacy end points, and will therefore be achieved in only a minority of patients. For completeness, therefore, Table 5 shows the hierarchy of end points and for each end point, the number of successes that can be purchased for $10,000 (calculated as described above, using rates from Table 1).
17.14)/(22.3%-12.9%) = $11.60 per additional SNAE; the corresponding figure for the comparison with sumatriptan 100 mg was ($18.23-16.59)/(22.3%-12.0%) = $15.92 per additional SNAE. These incremental CERs are substantially smaller than the average CERs for sumatriptan, so in the base case, according to the principle of extended dominance, almotriptan 12.5 mg was economically superior to both strengths of sumatriptan.

**Sensitivity Analyses**

**Relationship Between Efficacy and Tolerability**
The calculation of SNAE in the base case assumed independence between efficacy and tolerability. Values for SNAE and for the CERs were recalculated assuming positive relationships between sustained pain-free and adverse events (responders more likely to experience adverse events) and then assuming negative relationships (responders less likely to experience adverse events).

Figure 3 shows average and incremental CERs calculated across the range of assumptions for the relationship between efficacy and tolerability (strongly negative, OR = 0.1, to strongly positive, OR = 10). The average cost per SNAE was always greater with sumatriptan (both dose levels) than with almotriptan. In incremental analyses, almotriptan remained cost effective (according to the principle of extended dominance) over both dose levels of sumatriptan across the entire range tested.

**Health Service Use Costs**
Health service use costs were apportioned equally across attacks in the base case. Treatment-responsive patients are unlikely to attend emergency rooms or be hospitalized. The analyses were repeated assuming health service use costs were incurred only by patients not achieving sustained freedom from pain. In this analysis, health service use costs and sustained pain-free rates were different for almotriptan and sumatriptan. The impact was trivial; in all cases (OR for the efficacy/tolerability relationship ranging from 0.1 to 10), the impact on the CERs was less than $1 per SNAE. We made no attempt to account for possible differences in health service use costs attributable to treatment of adverse events—not doing so favors sumatriptan (i.e., the cost-effectiveness comparison is conservative), as any such adjustment would favor almotriptan, due to its lower adverse event rate.

**Tablets per Attack**
The base-case assumption was that attacks were treated with a single tablet only, which is appropriate, given that effectiveness was based on clinical trials data. The economic advantage of almotriptan would be reduced if, in the real world, more almotriptan than sumatriptan tablets were used to treat a given attack. In this sensitivity analysis, we held the number of sumatriptan tablets constant (=1) and increased the number of almotriptan tablets (per attack) to identify the threshold at which the 2 treatments became equivalently cost effective. These thresholds are seen in Table 6.

**Impact of Uncertainty in the Efficacy and Tolerability Estimates**
As described earlier, the exact probability that almotriptan 12.5 mg was economically superior to sumatriptan was

<table>
<thead>
<tr>
<th>Efficacy variable</th>
<th>Almotriptan 12.5 mg</th>
<th>Sumatriptan 50 mg</th>
<th>Sumatriptan 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNAE</td>
<td>122</td>
<td>75</td>
<td>72</td>
</tr>
<tr>
<td>Sustained freedom from pain</td>
<td>142</td>
<td>116</td>
<td>120</td>
</tr>
<tr>
<td>Freedom from pain at 2 hours</td>
<td>197</td>
<td>169</td>
<td>174</td>
</tr>
<tr>
<td>Headache response at 2 hours</td>
<td>334</td>
<td>367</td>
<td>355</td>
</tr>
</tbody>
</table>

These thresholds are seen in Table 6.
estimated, taking uncertainty in the efficacy and tolerability estimates from the meta-analysis into account. These exact probabilities, which can be interpreted as levels of confidence in the result, exceeded 99% across the entire range of efficacy/tolerability relationships tested (from strongly negative, OR = 0.1, to strongly positive OR = 10), for both strengths of sumatriptan.

Discussion

Of the few comparisons of the cost-effectiveness of triptans in the literature, most are based on drug acquisition costs rather than health care resource utilization. Gerth et al. compared the cost per successful treatment using data from 5 randomized controlled trials of rizatriptan 10 mg versus sumatriptan 50 mg or 100 mg, naratriptan 2.5 mg, or zolmitriptan 2.5 mg in acute migraine. Rizatriptan had a lower cost per successful treatment, defined as pain free at 2 hours with no functional disability or associated symptoms. Another study used clinical data from a randomized, double-blind trial of eletriptan 40 mg or 80 mg and sumatriptan 50 mg or 100 mg to perform a cost-effectiveness analysis. Based on drug acquisition costs in the United Kingdom, both strengths of eletriptan were associated with a lower cost than sumatriptan. Similar to our analysis, the efficacy measure was the sustained pain-free rate, but adverse events were not considered.

Reeder et al. combined data from the meta-analysis and drug acquisition costs to determine the cost of attaining 100 sustained pain-free patients with and without adverse events. Almotriptan 12.5 mg was the most cost-effective triptan on both measures. Rothermich et al. performed a cost minimization analysis of almotriptan 12.5 mg and sumatriptan 50 mg. Clinical and resource utilization data were collected from a randomized, double-blind trial of both drugs in acute migraine patients. Among 1,073 patients, health care system costs were significantly lower with almotriptan than with sumatriptan.

Adelman and Belsey conducted their own meta-analysis of triptan treatment trials, focusing on the number needed to treat to achieve freedom from pain within 2 hours. They then used this as the basis for a cost-effectiveness comparison in which almotriptan 12.5 mg and rizatriptan 10 mg were found to be the most cost effective of the triptans.

In this present study, we compared the cost-effectiveness of almotriptan 12.5 mg and sumatriptan 50 mg and 100 mg using a composite measure of effectiveness—SNAE. Sumatriptan was selected for comparison because it is the most widely prescribed oral triptan in the United States and also was used as the standard for comparison in the meta-analysis of triptans. We selected sustained pain free as the efficacy component because it has been described as the ideal measure for assessing response to acute migraine therapy. It is also consistent with what patients desire from treatment because it incorporates features of rapid onset of action, freedom from pain, and absence of recurrence. Freedom from adverse events is also important to patients, hence the composite measure SNAE.

The average CERs for almotriptan 12.5 mg, sumatriptan 50 mg, and sumatriptan 100 mg were $82, $132, and $139 per SNAE, respectively. For decision makers in managed care who administer plans covering thousands of patients who suffer from acute migraine, $10,000 invested in treatment of migraine with a triptan would yield 122 successes (attacks at which SNAE is achieved following triptan treatment) with almotriptan, compared with 75 and 72 successes with the 2 strengths of sumatriptan (50 mg and 100 mg, respectively).

Studies such as this are, in general, constrained by 3 kinds of limitations—those imposed by the data, those imposed by the assumptions, and those inherent in the analytic methods. We have attempted to keep these limitations to a minimum. Our data have come only from published sources. Hu et al.’s study of migraine-related health care costs is comprehensive, population-based, and reasonably up-to-date. Ferrari et al.’s meta-analysis of placebo-controlled triptan treatment trials is the most comprehensive synthesis of currently available knowledge in this area, and analyses of this kind are at the apex of the hierarchy of evidence. However, by using data from published sources only, we were constrained by the analyses and interpretations provided in these publications. For this reason, we were constrained to using placebo-subtracted rates for adverse events from the meta-analysis and had to calculate absolute rates (we should emphasize, however, that all the rates used in this calculation came from the same meta-analysis). The difference in placebo adverse event rates between almotriptan and sumatriptan is perhaps worthy of comment, although the authors of the meta-analysis offer no explanation, except that “there were no differences in study design or population to explain these differences.”

Clearly, the key assumption is that concerning the relationship between efficacy and tolerability, an issue at the heart of the principal limitation inherent in the analytic method (the calculation of SNAE from sustained pain-free and adverse event rates). In the sensitivity analysis, the economic superiority of almotriptan increases as the efficacy/tolerability relationship tends to the positive and decreases as it tends to the negative (although almotriptan remained superior across the 100-fold range tested). Little is known, however, about the true nature of the efficacy/tolerability relationship, so the results of further research on this topic are awaited with interest.

Conclusion

Within the limitations discussed here, we conclude that almotriptan 12.5 mg is more cost effective than either sumatriptan 50 mg or 100 mg in the acute treatment of a migraine attack, a finding that is robust in a range of sensitivity analyses. These findings should help decision makers in managed care and those engaged in designing drug formularies, for whom balancing optimal care with value for money is an ongoing challenge.
DISCLOSURES

Funding for this study was provided by a grant from Pharmacia Corporation and was obtained by author Paul Williams. Author C.E. Reeder has been a paid consultant to Sandofi-Synthelabo, AstraZeneca, and Pfizer within the last 3 years. Williams served as principal author of the study. Study concept and design, analysis and interpretation of data, and statistical expertise were contributed by Williams and Reeder. Drafting of the manuscript was primarily the work of Williams, and its critical revision was the work of both authors. Administrative, technical, and/or material support was provided by Parexel staff.

REFERENCES

Which Triptan?—
Opportunity for Same or Better Outcomes at Lower Cost

With 7 triptans on the market in the United States, there is considerable opportunity for managed care plans to negotiate significant price reductions from manufacturers for preferred formulary status, particularly under 3-tier benefit designs or in closed formularies (i.e., 100% member cost-share for nonformulary drugs). Last year, the Department of Defense and Veterans Affairs released a request for (price) proposal from manufacturers of 4 triptans (the newest triptan, eletriptan [Relpax], was apparently introduced after the RFP was prepared). The drugs under consideration by DOD/VA were almotriptan (Axert), sumatriptan (Imitrex), rizatriptan (Maxalt), and zolmitriptan (Zomig), based, in part, on prices bid in an RFP in October 2002. The RFP found the 4 triptans to be therapeutically equivalent, based on “similar outcomes, similar side-effect profiles, and sufficient safety data.”

In a previous article in this Journal, a meta-analysis showed that the number needed to treat to achieve 1 patient pain free at 2 hours was 3.2 patients for rizatriptan 10 mg, 4.2 patients for zolmitriptan 5 mg, 4.7 patients for either almotriptan 12.5 mg or sumatriptan 100 mg, and 5.9 patients for sumatriptan 50 mg. Naratriptan 2.5 mg required 8.2 patients, and frovatriptan 2.5 mg required 11.3 patients treated to achieve 1 patient pain free at 2 hours. In this issue of the Journal, Williams and Reeder found in their base-case analysis that the average cost-effectiveness ratios, using March 2004 prices, were $82, $133, and $138 per composite end point defined as Sustained pain-free and No Adverse Events (SNAE) for migraine attacks for almotriptan 12.5 mg, sumatriptan 50 mg, and sumatriptan 100 mg, respectively. In other words, sumatriptan had a price premium of 62% to 68% compared with almotriptan. The incremental cost-effectiveness ratios for almotriptan 12.5 mg were $12 and $16 (compared with sumatriptan 50 mg and sumatriptan 100 mg, respectively) per incremental attack at which SNAE is achieved. This research has significant value for managed care pharmacists by determining cost for the combined outcomes of efficacy and safety. Readers should note that this analysis by Williams and Reeder included the 67% price increase for sumatriptan had a price premium of 62% to 68% compared with almotriptan. The incremental cost-effectiveness ratios for almotriptan 12.5 mg were $12 and $16 (compared with sumatriptan 50 mg and sumatriptan 100 mg, respectively) per incremental attack at which SNAE is achieved. This research has significant value for managed care pharmacists by determining cost for the combined outcomes of efficacy and safety. Readers should note that this analysis by Williams and Reeder included the 67% price increase for sumatriptan could be considered superior, the agency's determination that the differences between the drugs were not material for its purposes has not been shown to be unreasonable.

In this issue of the Journal, Meissner, Moore, Shinogle, and Little found that an average $10 (47%) increase in copayment per prescription in a 3-tier drug benefit design for a public employer was associated with no statistically significant change in drug utilization per patient for 2 classes of drugs used to treat allergic rhinitis. The actual average copayment increase was $10.98 (71%) for nasal steroids (NSs), which was associated with an 11.3% decrease in utilization of NSs, primarily the result of a 10.2% decrease in the number of users of NSs in the year following the copay increase. However, the number of NS prescriptions per patient per year was unchanged at 2.68 in the year prior to the copay increase (P = 0.842).

The combined utilization of low-sedating antihistamines (LSAs) and NS prescriptions increased by 8.9% following the increase in copayments for these 2 therapeutically interchangeable drugs for allergic rhinitis. Rather than causing a reduction in the utilization of LSAs, the imposition of a 3-tier copay drug benefit design and an average $7.23 (41%) increase in copayment per prescription was associated with a 14.8% increase in the use of LSAs, including an 11.8% increase in the number of patients using LSAs. The number of LSA prescriptions per patient per year was unchanged at 2.68 in the year following the increase in copayment compared with 2.61 in the year prior to the copay increase; P = 0.429. While not adversely affecting patient use of drugs to treat allergic rhinitis, implementation of the increase in copayment in the 3-tier drug benefit design was associated with the intended outcome of producing cost savings for the health plan. Health plan savings were 16.3% per patient, and these health plan savings would have been larger if the costs had been adjusted for inflation. The health plan costs for all drugs for these allergic rhinitis patients fell by 13%, also understated since the costs were not adjusted for inflation.

Does Member Cost Sharing Pose a Threat to Desirable Patient Outcomes?

Cost sharing by health plan beneficiaries is on the way up, both in dollar amounts or percentages and in the proportion of beneficiaries affected by cost sharing. In 2003, 96% of workers and dependents with health benefits sponsored by employers had either copay or coinsurance requirements for medical office visits, 92% were required to contribute to payment of the monthly family premium, 63% had 3-tier cost sharing for prescription drugs (up from 55% in 2002, 42% in 2001, and 27% in 2000), 79% had an annual deductible, 76% were required to contribute to the monthly premium for individual (single) coverage, 44% had a separate hospital deductible, and 8% had a separate prescription drug deductible.

Research published in late 2003 claimed that the introduction of 3-tier copay designs for prescription drug benefits resulted in patients discontinuing drug therapy. However, careful examination of the data in that study showed mixed and even contradictory results, including the finding that the discontinuation rate for angiotensin-converting enzyme (ACE) inhibitors was twice as high in the comparison (control) group compared with one of the employer 3-tier plans in the study. Wogen and Frech pointed out that there is, in fact, no consensus regarding the impact of patient copay on therapy persistence and adherence.

In this issue of the Journal, Meissner, Moore, Shinogle, Reeder, and Little found that an average $10 (47%) increase in copayment per prescription in a 3-tier drug benefit design for a public employer was associated with no statistically significant change in drug utilization per patient for 2 classes of drugs used to treat allergic rhinitis. The actual average copayment increase was $10.98 (71%) for nasal steroids (NSs), which was associated with an 11.3% decrease in utilization of NSs, primarily the result of a 10.2% decrease in the number of users of NSs in the year following the copay increase. However, the number of NS prescriptions per patient per year was unchanged at 2.05 versus 2.07 in the year prior to the copay increase (P = 0.842).

The combined utilization of low-sedating antihistamines (LSAs) and NS prescriptions increased by 8.9% following the increase in copayments for these 2 therapeutically interchangeable drugs for allergic rhinitis. Rather than causing a reduction in the utilization of LSAs, the imposition of a 3-tier copay drug benefit design and an average $7.23 (41%) increase in copayment per prescription was associated with a 14.8% increase in the use of LSAs, including an 11.8% increase in the number of patients using LSAs. The number of LSA prescriptions per patient per year was unchanged at 2.68 in the year following the increase in copayment compared with 2.61 in the year prior to the copay increase; P = 0.429. While not adversely affecting patient use of drugs to treat allergic rhinitis, implementation of the increase in copayment in the 3-tier drug benefit design was associated with the intended outcome of producing cost savings for the health plan. Health plan savings were 16.3% per patient, and these health plan savings would have been larger if the costs had been adjusted for inflation. The health plan costs for all drugs for these allergic rhinitis patients fell by 13%, also understated since the costs were not adjusted for inflation.

Opportunity for Same or Better Outcomes at Lower Cost

With 7 triptans on the market in the United States, there is considerable opportunity for managed care plans to negotiate significant price reductions from manufacturers for preferred formulary status, particularly under 3-tier benefit designs or in closed formularies (i.e., 100% member cost-share for nonformulary drugs). Last year, the Department of Defense and Veterans Affairs released a request for (price) proposal from manufacturers of 4 triptans (the newest triptan, eletriptan [Relpax], was apparently introduced after the RFP was prepared). The drugs under consideration by DOD/VA were almotriptan (Axert), sumatriptan (Imitrex), rizatriptan (Maxalt), and zolmitriptan (Zomig), based, in part, on prices bid in an RFP in October 2002. The RFP found the 4 triptans to be therapeutically equivalent, based on “similar outcomes, similar side-effect profiles, and sufficient safety data.” In this issue of the Journal, Williams and Reeder found in their base-case analysis that the average cost-effectiveness ratios, using March 2004 prices, were $82, $133, and $138 per composite end point defined as Sustained pain-free and No Adverse Events (SNAE) for migraine attacks for almotriptan 12.5 mg, sumatriptan 50 mg, and sumatriptan 100 mg, respectively. In other words, sumatriptan had a price premium of 62% to 68% compared with almotriptan. The incremental cost-effectiveness ratios for almotriptan 12.5 mg were $12 and $16 (compared with sumatriptan 50 mg and sumatriptan 100 mg, respectively) per incremental attack at which SNAE is achieved. This research has significant value for managed care pharmacists by determining cost for the combined outcomes of efficacy and safety. Readers should note that this analysis by Williams and Reeder included the 67% price increase for sumatriptan (from $10.99 average wholesale price per unit to $18.44 per unit) that was imposed in late 2003 when the drug was transferred from one manufacturer to another.
Alternate Managed Care Approaches to Disease Management of Allergic Rhinitis

Research in this issue of the Journal calls into question several claims for cost-effective disease management of allergic rhinitis. Szeinbach, Williams, Munterdam, and O’Connor found that nearly two thirds of users of low-sedating antihistamines (LSAs) with a medical diagnosis of allergy did not test positive for serum immunoglobulin E (IgE) specific to allergens for allergic rhinitis. Of the 66% of patients defined as frequent users of LSAs (3 or more LSA prescriptions in the 1-year study period), the proportion who tested negative for serum IgE was 62%.

Allergic rhinitis is the fifth most common chronic disease in the United States, affecting 10% to 30% of adults annually and up to 40% of children and contributing to sleep interruptions, lower quality of life, and reduced productivity. Disease-specific patient surveys have been developed and marketed to help measure the magnitude of adverse effect on quality of life and productivity and to guide disease management interventions for allergic rhinitis; the SF-36 and short form SF-12 have been criticized as imprecise for this disease. It is fairly easy to make a case for the use of LSAs or nasal steroids to reduce the social burden of allergic rhinitis, but what is the optimal approach to obtain the most favorable clinical and service outcomes at the lowest cost?

The advent of over-the-counter (OTC) loratadine reduced by more than 90% the average cost to treat allergic rhinitis symptoms with an LSA, now as little as $6.50 per month of therapy with OTC loratadine. Yet, many drug benefit plans have not realized the full value of this dramatic price reduction because they have not implemented managed care tools to steer members to this cost-effective alternative. Most prescription drug benefit plans do not cover OTC drugs, and most drug benefit plans in 2004 included coverage of either fexofenadine (Allegra) or cetirizine (Zyrtec) as a formulary drug (i.e., tier-2 copayment).

Therefore, the work of Szeinbach et al. remains relevant for several reasons. A reasonable argument could be made that unnecessary exposure to any drug, no matter how safe in the incidence of side effects, should be avoided. The use of a serum IgE test to rule out a false diagnosis of allergy would appear to be important if the test is not expensive. Examination of the usual and customary (U&C) charges of a private third-party administrator for Common Procedural Terminology code 86005 (allergen-specific IgE) in March 2004 revealed an allowed price of $140.65 in zip code 80262 (Denver, Colorado) and $121.65 in zip code 30606 (Athens, Georgia). Adding a physician office visit would push the allowed charge to more than $200 to test a patient for serum allergy, more than the net plan cost for 3 LSA prescriptions. However, a countervailing argument would count the costs of repeated physician office visits plus LSA costs for as many as two thirds of patients who may not benefit from LSAs due to the absence of true allergy.

One is left pondering the value of a placebo response in patients without true allergy, but the conclusion is clear for disease management of allergic rhinitis. Stratification of patients by severity of disease, including persistent symptoms, would seem to help define when a serum IgE test to determine true allergy may be warranted and prove to be cost effective when clinical, humanistic, and cost outcomes are considered in total.

Methods to Attain Optimal Outcomes With Lipid-Lowering Drug Therapy

Realizing value-for-money in lipid-lowering drug therapy involves more than selecting the drug with the greatest reduction in low-density lipoprotein cholesterol (LDL-C) per dollar of drug cost. In a previous issue of the Journal, Hay eloquently explored the relationship between cost per quality-adjusted life-year (QALY) and the percentage of annual coronary event risk in the range of less than 1% to more than 9%—cost per QALY drops significantly as the annual coronary risk increases. Hay noted the relative cost-effectiveness of generic lovastatin but also cited the model developed by Stinnett, Mittleman, Weinstein, et al. and concluded that niacin dominates lovastatin as a first-line therapy for hypercholesterolemia. In this issue of the Journal, Armstrong, Zachry, and Malone find, via cost-effectiveness analysis, that lovastatin with extended-release niacin (Advicor) is more successful and less costly than simvastatin for persons with LDL-C goals <130 mg/dL and <100mg/dL (and high-density lipoprotein >40mg/dL); i.e., the majority of Americans.

The market introduction of rosuvastatin in late 2003 increased the attention to ever more powerful statins and the relative cost-effectiveness among these drugs. Yet, managed care pharmacists should not lose sight of the cost per outcome in disease management of coronary heart disease (CHD). For example, comparison of 5 alternative prevention strategies in a patient at 10% coronary risk over 5 years showed that aspirin 75 mg per day is the most cost effective at £3,500 (British pounds per CHD event prevented); 72% lower cost compared with initial treatment for hypertension with a diuretic (benfrofluazide 2.5 mg per day) and beta-blocker (50 mg atenolol per day; 12,500 pounds); 81% lower cost compared with the £18,300 for the initial thiazide + beta-blocker combination + enalapril (angiotensin-converting enzyme inhibitor) 20 mg per day; 94% lower cost than the £60,000 for clopidogrel 75 mg per day or the £61,400 for simvastatin 40 mg per day. In other words, about 20 patients could be treated with aspirin to prevent CHD events for every 1 patient treated with either clopidogrel or simvastatin. Among the many aspects of this thorough analysis, calculation of the costs per outcome recognized that patients taking thiazide diuretics require annual measurement of serum electrolytes and uric acid, patients taking statins require annual measurement of serum lipid concentrations and liver function tests, and major bleeding attributable to aspirin...
had an estimated incidence of 0.3% over 5 years of treatment (0.3% was subtracted from the reduction in absolute coronary risk to account for major adverse effects).

Ohsfeldt observed that the Stinnett, Mittleman, Weinstein, et al. model assumes nearly "ideal" compliance (i.e., the discontinuation rates reported in randomized controlled trials) with niacin, an outcome rarely found in the real world. The oft-reported study of 2,369 new users of lipid-lowering drug therapy in 2 HMOs from 1988 through 1990 found the 1-year probability of discontinuation to be 46% for niacin, 41% for bile acid sequestrants, 37% for gemfibrozil, and 15% for lovastatin, the only statin on the market at the time of the study. Subsequent studies have found lower rates of adherence to lipid-lowering therapy—50% or even much lower. In a study of 29,534 managed care members aged 18 years or older who had CHD or atherosclerosis and were continuously enrolled from January 1, 1998, through December 31, 1999, only 5,943 (46%) continued statin therapy through study end. Only 59% (17,402 patients) had 1 or more cholesterol-monitoring tests during the 2-year study period. For a subgroup of 641 patients with at least 1 coronary event in 1998 and who had LDL-C data available for 1999, only 48% (308) reached National Cholesterol Education Program (NCEP) goal for LDL-C in 1999. In other words, less than one half of the patients on statin therapy were still on the therapy at the end of the 2-year study period, only 59% had at least 1 cholesterol-monitoring test, and only 48% of those on secondary prophylaxis with a statin had reached NCEP goal for LDL-C.

In fact, the real-world adherence to lipid-lowering therapy and attainment of target LDL-C goals appear to be much worse than predicted by the studies noted above. In 454 patients who received care at a preventive cardiology clinic in Cleveland and were prescribed a statin for the first time, 367 (81%) returned for follow-up LDL testing. The observed LDL reduction was less than expected for 3 statins (atorvastatin, simvastatin, and pravastatin), an average of 26% reduction versus 34% expected, and 27% of the patients had less than one half the expected LDL decrease. Analysis of 477 patients who were discharged from the hospital without lipid-lowering medication compared with 175 matched patients who were discharged on lipid-lowering medication found that 81% of the patients discharged on lipid-lowering drug therapy reported taking a lipid-lowering drug at 30 days postdischarge and 77% at 6 months. However, for the patients who started lipid-lowering therapy after hospital discharge, only 25% reported using the lipid-lowering medication after 30 days and only 13% at 6 months.

Even with patient adherence to statin therapy, the value-for-money equation shows a low return on investment for indications other than primary or secondary prophylaxis of coronary events. For example, while pravastatin and simvastatin are approved for secondary and primary prevention of stroke, respectively, the PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) trial showed no effect on stroke in high-risk elderly patients (i.e., secondary prophylaxis) after an average of 3.2 years of therapy with pravastatin 40 mg per day: 4.7% incidence of fatal or nonfatal stroke in the pravastatin group versus 4.5% in the placebo group (P = 0.81). It was only in combination with the end point of death from CHD or nonfatal myocardial infarction (MI) that the pravastatin group was favored over placebo, an absolute incidence of 10.1% versus 12.2% (P = 0.014). This absolute difference of 2.1% translates into 48, the number needed to treat to prevent 1 either fatal or nonfatal MI or stroke or coronary death. At a total discounted drug cost of $4 per day, it would cost $224,256 of pravastatin in 2004 dollars to prevent 1 fatal or nonfatal MI or stroke.

In early March 2004, the Heart Protection Study Collaborative Group authored an article that trumpeted the importance of treating patients at risk of stroke with simvastatin. The recommendation was based upon analysis of outcomes data from 3,280 adults with cerebrovascular disease and an additional 17,256 with occlusive arterial disease or diabetes. Based upon the 5-year treatment period, there was an average 39 mg/dL reduction in LDL-C. There was a 1.4% absolute reduction in the first-event rate for all stroke (fatal and nonfatal), 4.3% in the simvastatin group compared with 5.7% in the placebo group. The authors touted the "highly significant 25% proportional reduction in the first-event rate for stroke." This study involved a large number of patients; even this relatively small absolute difference (1.4%) would be statistically significant, and 25% sounds like a large proportion.

From a value-for-money perspective, the investment in simvastatin to prevent stroke does not appear to be terribly appealing. Setting aside the direct and indirect costs associated with adverse drug events in high-risk patients taking 40 mg of simvastatin per day for 5 years, the direct drug cost is large. Using discounted drug prices available in the United States at the time this study was published (March 2004), and the number needed to treat (NNT) (71.4) calculated from the Heart Protection Study, it would be necessary to spend between $520,000 and $540,000 on simvastatin to prevent 1 nonfatal stroke.

The results of the Heart Protection Study were preceded by publication in 2000 of a study of the effects of pravastatin in 9,014 high-risk patients with a history of MI or unstable angina. In that study, which was used to obtain U.S. Food and Drug Administration (FDA) approval of pravastatin for a stroke indication, there was an absolute 3.7% incidence of fatal and nonfatal stroke in the treatment groups versus 4.5% in the placebo group. This 0.8% absolute difference was touted as a 19% reduction in stroke. Translated into the NNT and the actual cost of pravastatin at discounted prices in March 2004, it would require nearly $1.1 million in drug (pravastatin) cost to prevent 1 nonfatal stroke. This cost estimate is conservative since it does not include the direct and indirect costs of adverse drug events associated with the use of pravastatin 40 mg per day for an
average of 6 years in patients with CHD. Expert observers later pointed out shortcomings in the research design, statistical analyses, and interpretation of the data that could undermine even the modest apparent favorable effect of pravastatin on the risk of stroke in CHD patients.35

In addition to considerations of drug therapy adherence, lack of attainment of target LDL-C goal and high (unfavorable) cost-effectiveness ratios for stroke and for patients at low risk of coronary events, statins are not without adverse events. Despite the high profile and oft-mentioned market recall of cerivastatin (Baycol), potential drug interactions that could cause harm similar to that reported with cerivastatin appear to go unrecognized and underappreciated. Petropoulos and Bello-Quintero in this issue of the Journal found that among 11,677 patients on simvastatin therapy, 1,231 (10.5%) were prescribed at least 1 potentially interacting medication and more than one half (57.8%) of simvastatin doses were above the maximum recommended daily dose when prescribed with potentially interacting medications.36

Atorvastatin is the most prescribed statin and the number one prescription drug by sales in the United States.35,36 Clopidogrel is used increasingly in patients with acute coronary syndrome (unstable angina/non-Q-wave MI), including patients who are to be managed medically and those who are to be managed with percutaneous coronary intervention (with or without stent) or coronary artery bypass graft. Most of these patients also receive statin drug therapy; many no doubt receive atorvastatin. Atorvastatin has been reported to attenuate the antiplatelet activity of clopidogrel in a dose-dependent manner, hypothesized to be related to the metabolism of atorvastatin by the cytochrome P450 (CYP) 3A4 enzyme.37 This drug interaction was not studied by Petropoulos and Bello-Quintero in their article in this issue of the Journal.

In June 2002, the label for simvastatin was changed to warn against a potentially dangerous interaction with amiodarone.38 With this label change, approved May 6, 2002, by the FDA, simvastatin became the only statin available in the United States with a dose-related effect for myopathy and rhabdomyolysis. The previous labeling mentioned a dose-dependent relationship with myopathy, but not rhabdomyolysis, and did not cite the reported incidence. Also noteworthy in the label change in June 2002 was the fact that a labeling supplement (supplemental new drug application [sNDA]) was submitted by the manufacturer to the FDA on May 15, 2001, as part of its obligation to respond to new postmarketing adverse event signals. This occurred 3 months before the market withdrawal of cerivastatin.39

The study conducted by Petropoulos and Bello-Quintero highlights a subject that apparently warrants increased attention. Despite the label change for simvastatin in June 2002 and the well-recognized market withdrawal of cerivastatin in August 2001, the risk posed by drug interactions with statins can be overlooked, even by experts. In an article published in April 2003, the authors attributed a case of rhabdomyolysis to high-dose (40 mg per day) simvastatin and stated confidently that the “myopathy was caused by an increase in the dosage of simvastatin and not by an interaction with another medication.”40 Despite concomitant use of amiodarone (100 mg per day), the authors stated, “Our patient, however, had no concomitant use of drugs historically suspected of involvement in rhabdomyolysis, nor was he immunosuppressed secondary to organ transplantation.” In addition to missing the drug interaction, this article is likely to be picked up in electronic searches as a case report of rhabdomyolysis associated with simvastatin dose rather than the drug interaction.

Where does this information leave us with respect to the use of lipid-lowering, particularly statin, therapy? The mantra in disease management cost-effectiveness is stratification of patients by relative risk of an adverse outcome. While statin therapy may be relatively safe, there are risks.41 Setting aside the matter of drug cost, the threats to patient safety dictate that statin therapy should be restricted to patients at defined risk of an adverse cardiac or perhaps cerebrovascular outcome. The evidence at present does not support the use of statins in primary prophylaxis of cerebrovascular events, and the link between serum cholesterol and stroke has not been established.42 Lower-cost therapies (e.g., aspirin) are more effective in secondary protection, and statin therapy might be offered to younger stroke patients with a history of coronary heart disease.43 When the risk-to-benefit ratio is sufficiently low to warrant statin therapy to prevent coronary events or in secondary prevention of stroke, there is an important opportunity and a real need for pharmacists to help improve adherence to therapy44 and monitor patients for potential drug interactions and adverse effects.

Frederic R. Curtiss, PhD, RPh, CEBS
Editor-in-Chief
fcurtiss@amcp.org

REFERENCES
Letters to the Editor

JMCP welcomes letters that serve to clarify subjects published in previous issues of the Journal or regarding subject matter of interest to managed care pharmacists. Letters in JMCP are not peer reviewed but are subjected to editorial review. When a submitted letter refers to an article published in a previous issue of the Journal, the letter is sent to the authors of the subject article to allow their response to be published with the letter.

Each letter should be signed by no more than 3 authors. Submissions must include your title, affiliation, complete mailing address, telephone number, and e-mail address. Potential bias or conflicts of interest must be disclosed.

Letters should be submitted in electronic format, preferably using Microsoft Word, and may be sent by e-mail to Fred Curtiss, editor-in-chief, at fcurtiss@amcp.org or to Tamara Faggen, managing editor, at tfaggen@amcp.org.