RESEARCH
21 Effects on Resource Utilization of Adding Salmeterol in Combination or Separately to Inhaled Corticosteroids
James Chan, PharmD, PhD; Rita L. Hui, PharmD, MS; and Michele M. Spence, PhD

28 Adherence to Clinical Practice Guidelines for 7 Chronic Conditions in Long-term-Care Patients Who Received Pharmacist Disease Management Services Versus Traditional Drug Regimen Review
Kristin K. Horning, PharmD; James D. Hoefts, PharmD, BCPS; and William R. Doucette, PhD

FORMULARY MANAGEMENT
37 AMCP Format Dossier Requests: Manufacturer Response and Formulary Implications for One Large Health Plan
Joshua J. Spooner, PharmD, MS; Pranav K. Gandhi, BPharm, MS; and Susan Brown Connelly, PharmD, MBA

CONTEMPORARY SUBJECT
44 Descriptive Analysis of the Direct Medical Costs of Multiple Sclerosis in 2004 Using Administrative Claims in a Large Nationwide Database
Jeff D. Prescott, PharmD; Saul Factor, RPh, MBA; Michael Pill, PharmD; and Gary W. Levi, JD

BRIEF COMMUNICATIONS
53 Use of Low-Molecular-Weight Heparin During Dental Extractions in a Medicaid Population
Tracy K. Pettinger, PharmD, and Christopher T. Owens, PharmD, BCPS

59 Medicare Part D: Selected Issues for Pharmacists and Beneficiaries in 2007
Janet Killan, MPH, and JoAnn Stubbings, RPh, MHCA

DEPARTMENTS
16 Cover Impressions
Warfarin Titles (2005-2006)
Peter Whittaker, PhD
Sheila Macho
Cover Editor

66 Commentary
Bridging the Gap Between Pharmacoeconomics and the Real-World Practice of Managed Care Pharmacy
Fadia T. Shaya, PhD, MPH
Robert L. Ohsfeldt, PhD

68 Commentary
Medication Therapy Management Versus Drug Regimen Review
Kent H. Summers, RPh, PhD

70 Editorial
Peeking Inside the Statistical Black Box: How to Analyze Quantitative Information and Get It Right the First Time
Kathleen A. Fairman, MA
JMCP Associate Editor and Senior Methodology Reviewer

75 JMCP Peer Reviewers, 2006
JMCP EDITORIAL POLICY

Editorial Content and Peer Review
All articles, editorials, and commentary in JMCP undergo blinded peer review; articles undergo blinded peer review. Letters may be peer reviewed to ensure accuracy. The fundamental departments for manuscript submission are:

- Research
- Subject Reviews
- Formulary Management
- Contemporary Subjects
- Brief Communications
- Editorials/Commentary
- Letters

All submissions other than Editorials, Commentary, and Letters, should include an abstract and inform the reader at the end of the manuscript of what is already known about the subject and what the article adds to our knowledge of the subject.

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

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. The Methods section in the abstract and in the body of the manuscript should make clear to the reader the source of the material used in the review, including the criteria used for inclusion and exclusion of information.

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 are particularly timely or describe research conducted in pilot projects. Contemporary Subjects, like all articles in JMCP, must describe the hypothesis or hypotheses that guided the research, the principal methods, and results.

Brief Communications
The results of a small study or a descriptive analysis that does not fit in other JMCP departments may be submitted as a Brief Communication.

Editorials/Commentary
These submissions should be relevant to managed care pharmacy and address a topic of contemporary interest: they do not require an abstract but should include references to support statements.

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.)

Advertising Disclosure Policy
A copy of the full advertising policy for JMCP is available from AMCP headquarters and the Advertising Representative. All aspects of the advertising sales and solicitation process are completely independent of the editorial process. Advertising is positioned either at the front or back of the Journal; it is not accepted for placement opposite or near subject-related editorial copy.

Employees of advertisers may submit articles for publication in the editorial sections of JMCP, subject to the usual peer review process. Financial disclosure, conflict-of-interest statements, and author attestations are required when manuscripts are submitted, and these disclosures generally accompany the article in abstracted form if the article is published.

See “Advertising Opportunities” at www.amcp.org. Contact the Advertising Representative to receive a Media Kit.

Editorial Office
Academy of Managed Care Pharmacy
100 North Pitt St., Suite 400
Alexandria, VA 22314
Tel: (703) 683-8416
Fax: (703) 683-8417
E-mail: jmcppreview@amcp.org
tfaggen@amcp.org

Advertising Sales Office
Professional Media Group, Inc.
40 N. Woodbury Rd.,
Pitman, NJ 08071
Tel: (800) 486-5454
or (856) 589-5454
Fax: (856) 582-7611
E-mail: peter@promedgroup.net

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 that include (a) full disclosure of all sources of potential bias and conflicts of interest, nonfinancial as well as financial; (b) full disclosure of potential conflicts of interest by reviewers as well as authors; and (c) accurate attribution of each author’s contribution to the article. Aggressive bias-management methods are necessary to ensure the integrity and reliability of published work.

Editorial content is determined by the Editor-in-Chief with suggestions from the Editorial Advisory Board. The views and opinions expressed in JMCP do not necessarily reflect or represent official policy of the Academy of Managed Care Pharmacy or the authors’ institutions unless specifically stated.
EDITORIAL MISSION

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 STAFF

Editor-in-Chief
Frederic R. Curtiss, PhD, RPh, CEBS
(830) 935-4319, fcurtiss@amcp.org

Managing Editor, Tamara C. Faggen, (703) 323-0170, tafaggen@amcp.org
Associate Editor, Brian K. Crownover, MD, FAAFP, Lt. Col., USAF, MC, (850) 883-8288, brian.crownover@eglin.af.mil, bcrownover@amcp.org
Associate Editor, Kathleen A. Fairman, MA, (602) 867-1343, kathleenfairman@qwest.net
Peer Review Administrator, Jennifer A. Booker, (703) 317-0725, jmcpreview@amcp.org
Graphic Designer, Laura J. Mahoney, (703) 944-4577, lauramahoney@comcast.net
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

They and the other advisers review manuscripts and assist in the determination of the value and accuracy of information provided to readers of JMCP.

John P. Barbuto, MD, HealthSouth Rehabilitation Hospital, Sandy, Utah
Joshua Benner, PharmD, ScD, ValueMedics Research, LLC, Falls Church, Virginia
Eliot Britton, MD, School of Medicine, University of Utah, Salt Lake City
Scott A. Bull, PharmD, ALZA Corporation, Mt. View, California
Jeanne Carlson, CPA, Blue Care Network, BlueCross BlueShield of Michigan, Southfield
Norman V. Carroll, PhD, School of Pharmacy, Virginia Commonwealth University, Richmond
Tara R. Cockerham, PharmD, Clinical Pharmacy Specialist, Atlanta, Georgia
Eric J. Culley, PharmD, Highmark BlueShield, Pittsburgh, Pennsylvania
Lisa A. Edwards, PharmD, WellPoint Pharmacy Management, North Kingstown, Rhode Island
Lida R. Etemad, PharmD, MS, UnitedHealth Group, Edina, Minnesota
Patrick R. Finley, PharmD, BCPP, University of California at San Francisco
Feride Frech-Tamas, MPH, Novartis Pharmaceuticals Corp., East Hanover, New Jersey
Philip E. Greigurich, PharmD candidate, College of Pharmacy, Drake University Des Moines, Iowa
Ann S. M. Harada, PhD, MPH, Prescription Solutions, Irvine, California
Joel Hay, PhD, School of Pharmacy, University of Southern California, Los Angeles
Mark Jackson, BScPharm, BComm, RPh, Green Shield Canada, Windsor, Ontario
Joanne LaFleur, PharmD, MSPH, College of Pharmacy, University of Utah, Salt Lake City

Christina Meyer, MHS, Caremark, Hunt Valley, Maryland
Robert P. Navarro, PharmD, Campbell Alliance, Raleigh, North Carolina
Robert L. Ohsefildt, PhD, School of Rural Public Health, Texas A&M Health Science Center, College Station
Steven Pepin, PharmD, BCPS, PharmWorks, LLC, Arden Hills, Minnesota
Cathlene Richmond, PharmD, Drug Information Services, Kaiser Permanente, California Regions, Oakland
Fred L. Segol, Jr., JD, RPh, Centocor Pharmaceuticals, Poulbo, Washington
Fadia T. Shaya, PhD, MPH, School of Pharmacy, University of Maryland, Baltimore
Denise Sokos, PharmD, BCPS, School of Pharmacy, University of Pittsburgh, Pennsylvania
Brent Solseng, PharmD, BlueCross BlueShield of North Dakota, Fargo
Joshua Spooner, PharmD, MS, Advanced Concepts Institute, Philadelphia, Pennsylvania
Marilyn Stebbins, PharmD, CHW Medical Foundation, Rancho Cordova, California, University of California, San Francisco
Kent H. Summers, RPh, PhD, School of Pharmacy, Purdue University, Lafayette, Indiana
Sheryl L. Szczepanek, PhD, College of Pharmacy, Ohio State University, Columbus
Robert J. Valuck, RPh, PhD, School of Pharmacy, University of Colorado Health Sciences Center, Denver
Brian Sweet, RPh, MBA, WellPoint Pharmacy Management, Grand Island, New York (Director, AMCP Board of Directors: liaison to the JMCP Editorial Advisory Board)

Journal of Managed Care Pharmacy (ISSN 1083–4087) is published 9 times per year and is the official publication of the Academy of Managed Care Pharmacy (AMCP), 100 North Pitt St., Suite 400, Alexandria, VA 22314. (703) 683-9416; (800) TAP-AMCP, (703) 683-9417 (fax). The paper used by the Journal of Managed Care Pharmacy meets the requirements of ANSI/NISO Z39.48-1992 (Permanence of Paper) effective with Volume 7, Issue 5, 2001; prior to that issue, all paper was acid-free. Annual membership dues for AMCP include $60 allocated for the Journal of Managed Care Pharmacy. POSTMASTER: Send address changes to JMCP, 100 North Pitt St., Suite 400, Alexandria, VA 22314.
JMCP Author Guidelines

JMCP accepts for consideration manuscripts prepared according to the Uniform Requirements for the Submission of Manuscripts to Biomedical Journals.1

■ 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 carefully written narratives that contain all of the principal quantitative and qualitative findings, with the outcomes of statistical tests of comparisons where appropriate. Abstracts are required for all articles in Research, Subject Reviews, Formulary Management, Contemporary Subjects, and Brief Communications. The format for the abstract is Background, Objective, Methods, Results, Conclusion, Keywords. Editorial and Commentary do not require an abstract but should include references. Letters do not require an abstract.

For descriptions of editorial content, see “JMCP Editorial Policy” in this Journal or at www.amcp.org.

Please note:
• The JMCP Peer Review Checklist is the best guide for authors to improve the likelihood of success in the JMCP peer-review process. It is available at: www.amcp.org (Peer Reviewers tab).
• A subsection in the Discussion labeled “Limitations” is generally appropriate for all articles published in JMCP.
• 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 most articles in JMCP, 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 mention of the generic name in the article but not in the abstract.
• Many articles involve research that may pose a threat to either patient safety or privacy. It is the responsibility of the principal author to ensure that the manuscript is submitted with either the result of review by the appropriate institutional review board (IRB) or a statement of why the research is exempt from IRB review (see JMCP Policy for Protecting Patient Safety and Privacy at www.amcp.org).

■ Reference Style

References should be prepared following modified AMA style. All reference numbers in manuscript should be superscript (e.g., 1). Each unique reference should have only one reference number. If that reference is cited more than once in the manuscript, the same number should be used. Do not use ibid or op cit for JMCP references.

See the following examples of common types of references:

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. Paper (or Poster) presented at a meeting

9. Newspaper

10. Web site

■ Manuscript Submission

Please submit manuscripts electronically at jmcp.msubmit.net. All text should be in a word processing program (preferably Microsoft Word). Tables should be prepared in a word processing program using the table function. Figures should be saved in Photoshop or Illustrator and may be re-created by us. Figures may also be prepared in a word processing program (preferably Microsoft Word). We can accept PowerPoint graphics. Please identify the format (PC or MAC), all programs used, and all file names. P values should be expressed to no more than 3 decimal points in the format 0.xxxx.

Note: Please do not include author identification in the electronic manuscript document.

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 the paper copy of 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, including abstract: no more than 650 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, do not include footnotes in the manuscript
❑ 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) at the end of the manuscript; match symbols in tables and figures to explanatory notes, if included. May use 10-point font.
❑ information indicating what is known about the subject and what your article adds.
❑ 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.

Note: Please do not include author identification in the electronic manuscript document.

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

REFERENCE

Peter Whittaker, PhD, has been chosen as the cover artist for *JMCP*’s annual issue featuring an artist with a pharmaceutical, medical, or scientific background. Born in 1960 in Nottingham, England, he received his bachelor of science degree in physics from the University of Nottingham. In 1986, Whittaker earned his PhD in biophysics from the University of Western Ontario, Canada.

He then accepted a position as a research associate in the Department of Internal Medicine, Cardiology Division, at Wayne State University/Harper Hospital in Detroit, Michigan. Two years later, Whittaker became a research instructor in medicine at the University of Southern California (USC) in Los Angeles. In the early 1990s, he was promoted to assistant professor of research medicine, Department of Medicine, Section of Cardiology, USC, where he stayed until 2002. During this time, Whittaker also served as the director of microscopy and the director of laser research at Good Samaritan Hospital in Los Angeles. He is currently the director, Research Division, Department of Emergency Medicine, and an associate professor in the Departments of Anesthesiology and Emergency Medicine, University of Massachusetts Medical School, Worcester.

Whittaker said that his photographic training occurred on the job: “My PhD work, which involved microscopic assessment of the structure of cardiovascular tissue, required illustration with images, and hence I learned photomicrography.” He explained, “The methods of analyzing cardiovascular tissue that I studied exploited the optical properties of materials such as collagen and muscle, specifically their birefringent properties when viewed with polarized light. In addition to providing a considerable amount of quantitative structural information, the polarized light images of the stained tissue were aesthetically striking. I subsequently looked at anything and everything using polarized light. Thus, it was the scientific work that inspired the art; however, it is probably wrong to separate the two—the ideal (and my aim) is to combine science and art.”

Photomicrography continues to play an integral role in Whittaker’s research. He captured numerous warfarin images during 2005 and 2006 for a couple of research projects. The first was a recently published review article on the role of pharmacy-managed, in-hospital anti-coagulation services written with his colleague, Jennifer Donovan. The second was a study in which Whittaker and Donovan found that patients on long-term warfarin therapy had more tissue calcification than untreated patients. They presented this finding at an American Heart Association meeting in November 2006.

*Warfarin Tiles* is a collage that I composed, using six detailed versions of Whittaker’s photomicrographs inspired by these studies. He said, “Warfarin is a much-used, necessary, and yet potentially dangerous drug. What appealed to me about creating the warfarin images was that this was such a commonly used drug. All the physicians and pharmacists I spoke to had a picture in their minds of the various colored pills prescribed, so they were surprised that something so ‘mundane’ could look so different. My warfarin photomicrographs provided them with a new perspective on the drug. In addition, the disparity between the treatment’s potential danger and the beauty of the crystals provided an interesting and provocative contrast.”

Whittaker related that a wide range of images can be created—even from a single substance—by changing either the solvent or the concentration of the dissolved material. *Warfarin Tiles* is a splendid example of this diversity, and its vivid colors add to the appeal of the work. The upper-right tile resembles an attractive agate, while the multicolored image found in the lower-left corner looks like an upside-down rainbow. The upper-left tile is reminiscent of a patriotic fireworks display. In 2005, the full-sized version of this image earned Whittaker an honorable mention in the Olympus BioScapes International Digital Imaging Competition, and it is currently part of an Olympus BioScapes national tour. In addition, he has received two honorable mentions for entries in Nikon’s Small World Photomicrography Competition and two runner-up prizes in *Current Biology*’s Scientific Photography Competition.

Some of Whittaker’s photomicrographs of cardiac tissue have appeared on the covers of medical publications such as the *American Journal of Pathology*, and *Myocardial Laser Revascularization*, a cardiac surgery book. During the mid-1990s, he exhibited some of his remarkable photomicrographs in group shows at the Rachele Lozzi Gallery in downtown Los Angeles. At the present time, many of his photomicrographs are on display in the Department of Emergency Medicine, University of Massachusetts Medical School, Worcester.

When asked about his current projects, Whittaker discussed the use of N-acetylcysteine for the treatment of acetaminophen poisoning, “This is of particular interest to me because it is one of the most common toxicology problems that our Department of Emergency Medicine deals with,” he said. “Both the drug and the antidote make colorful crystals when viewed with polarized light. By crystallizing solutions of both on the same slide, I have been able to create some interesting images depicting ‘battles’ between poison and antidote.”

Sheila Macho
Cover Editor

**SOURCE**

Interview with the artist.

**Cover Credit**

Effects on Resource Utilization of Adding Salmeterol in Combination or Separately to Inhaled Corticosteroids

JAMES CHAN, PharmD, PhD; RITA L. HUI, PharmD, MS; and MICHELE M. SPENCE, PhD

ABSTRACT

BACKGROUND: The addition of a long-acting beta-agonist (LABA) to an inhaled corticosteroid (ICS) for patients with moderate or severe persistent asthma improves outcomes such as pulmonary function, reduces exacerbations requiring oral steroids, and reduces use of rescue beta-agonists.

OBJECTIVE: To assess the key resource utilization outcomes of adding salmeterol, a LABA, to fluticasone, an ICS, either as a fixed-combination inhaler (fluticasone-salmeterol [FSA]) or as a separate inhaler used concomitantly with the ICS beclomethasone (BSA).

METHODS: This is a retrospective, observational database study that extracted data from electronic medical and prescription records in which the prescription written was identical to the prescription dispensed. The sample included asthmatic patients aged 12 to 55 years who received a medium dose of an ICS (240-480 mcg of beclomethasone, 264-660 mcg of fluticasone, 600-1,200 mcg of budesonide, or 1,000-2,000 mcg of triamcinolone acetonide) between July 2001 and December 2002 and had salmeterol added to the regimen (index date). From this population of patients, the analytical cohort was derived to include 1,213 patients who received FSA and a matched cohort of 1,213 patients who received BSA. The primary endpoint was an asthma-related event (ARE), which was defined as (1) an emergency department (ED) visit or (2) hospital admission with a primary asthma diagnosis code (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 493.xx). The secondary endpoints were the (1) use of short-acting beta-agonist (SABA) equivalents, (2) percentage of patients who received 1 or more oral steroid prescriptions, (3) patterns of ICS use, and (4) refill rates of salmeterol. All data were collected for 6 months before and 6 months after the index date, defined as the first prescription dispensed to the patient that included salmeterol as an ingredient.

RESULTS: Outcomes were improved in both cohorts with no significant difference in the likelihood of an ARE, 60 patients (4.9%) for FSA and 90 patients (8.1%) for BSA (odds ratio [OR], 0.668; 95% confidence interval [CI], 0.443-1.008; P = 0.055). FSA was associated with a reduction in AREs of 55% (10.9%-4.9%; P < 0.001), and BSA with a reduction in AREs of 39% (13.3%-8.1%; P < 0.001). FSA compared with BSA was associated with a greater reduction in SABA use (-0.66 canister equivalents over 6 months, P < 0.001) and a lower likelihood of filling an oral steroid prescription, 35.8% of FSA patients compared with 38.0% of BSA patients (OR, 0.801; 95% CI, 0.662-0.970; P = 0.023). For the 132 FSA patients (10.9%) and 162 BSA patients (13.4%) who had an ARE in the preperiod, those who received FSA in the postperiod had a 47% lower likelihood of a subsequent ARE, 17.4% of 132 patients compared with 27.8% of 162 BSA patients (OR, 0.527; 95% CI, 0.291-0.954; P = 0.034). No ARE differences in subgroup analyses were noted for patients without an ARE in the preperiod or for patients using more than 6 canisters of SABA. More patients in the FSA group took daily doses of 400 mcg or more of ICS than those in the BSA group (32.0% compared with 10.0%, P < 0.001). The average refill rate for salmeterol was 2.71 prescriptions (SD = 1.42) over 6 months for FSA compared with 2.38 (SD = 1.49) for BSA (P < 0.001).

CONCLUSION: Overall, the addition of salmeterol as a fixed combination with fluticasone or with beclomethasone as separate inhalers was associated with a reduction in the ARE rate. Patients who received FSA were more likely to be exposed to a higher dose of ICS compared with those who received BSA. Differences in resource utilization may be attributed to how these drugs are prescribed and taken by patients in a real-practice (naturalistic) setting rather than to any inherent difference between the drugs (i.e., higher ICS dose rather than greater efficacy).

KEYWORDS: Drug therapy, Combination; Asthma; Adherence; Emergency services; Hospitalization; Fluticasone; Salmeterol; Beclomethasone

J Manag Care Pharm. 2007;13(1):21-27

Asthma is a clinical and public health problem and one of the most common chronic diseases worldwide. Asthma-related hospital admissions and emergency department (ED) visits generally suggest poor disease control and/or inadequate treatment. They are also associated with subsequent readmissions. In the United States, hospitalization with asthma as the primary diagnosis has remained relatively stable between 1980 and 2002. Hospitalization with asthma as a secondary diagnosis, however, has increased in the same time period. In 2002, asthma accounted for about 2 million annual ED visits and a half-million hospitalizations.

The inadequate management of asthma results in a significant economic burden on asthma patients as well as on society. Prescription and hospitalization costs are the largest contributors to direct health care costs, while the loss of work and productivity are the largest contributors to indirect health care costs. The estimated cost impact due to asthma in 2000 was $14 billion in medical and indirect costs, with direct medical costs accounting for an estimated $9.4 billion.

Inhaled corticosteroid (ICS) is the preferred treatment for mild, moderate, and severe persistent asthma. Use of ICS has been associated with reduced ED visits and admissions.

In patients with moderate or severe persistent asthma, the

Authors

JAMES CHAN, PharmD, PhD, is pharmacy quality and outcomes coordinator; RITA L. HUI, PharmD, MS, is a pharmacoeconomic and outcomes research pharmacist; MICHELE M. SPENCE, PhD, is a pharmacy project manager, Pharmacy Outcomes Research Group, Kaiser Permanente Medical Care Program, Oakland, California, and Downey, California.

AUTHOR CORRESPONDENCE: James Chan, PharmD, PhD, Pharmacy Quality and Outcomes Coordinator, Pharmacy Outcomes Research Group, Pharmacy Operations, Kaiser Permanente Medical Care Program, 1800 Harrison, 13th Fl., Oakland, CA 94612. Tel: (510) 625-3756; Fax: (510) 625-3307; E-mail: Jim.Chan@kp.org

Copyright © 2007, Academy of Managed Care Pharmacy. All rights reserved.
addition of an inhaled long-acting beta-agonist (LABA) to an ICS leads to improvement of pulmonary function, reduces exacerbations requiring the use of oral steroids, and reduces the use of short-acting beta-agonists (SABAs). Improved refill persistence has been reported when the combination of fluticasone and salmeterol is administered in a fixed combination (Advair, henceforth referred to as FSA) compared with use of separate inhalers. In addition to more convenient administration, the combination FSA provides possible advantages with codeposition of the drugs in the airway. FSA has been compared with a number of other dual therapies, including fluticasone (Flovent) and salmeterol (Serevent) administered separately; fluticasone and montelukast, and formoterol and budesonide. Nguyen et al. reported that in an inner-city population with a history of frequent ED visits, FSA reduced subsequent encounters (ED or hospitalization) by 33% compared with the usual care. Prior ED visits and admissions, as well as use of SABAs and oral steroids, are the strongest predictors of visits and admissions. These factors have been proposed in a risk stratification scheme for identifying patients at risk of experiencing emergency hospital care. Most studies have compared clinical outcomes such as pulmonary function and symptoms in clinical trial settings. However, the impact on health care resources, ED visits, or admissions has not been fully investigated. We sought to compare, in a real-practice (naturalistic) setting, the effects of the fixed-combination product of beclomethasone dipropionate and salmeterol on ED visits and hospitalization, as well as the subsequent use of SABAs and oral steroids. In addition, we assessed drug adherence and prescribing patterns of providers regarding these 2 drug regimens.

**Methods**

**Study Population and Design**

This was a retrospective longitudinal analysis of data from administrative databases of the Kaiser Permanente (KP) Medical Care Program, located in California. KP is a prepaid integrated health care delivery system that provides comprehensive medical care, including prescription drugs, to more than 6 million members in California and 8 million members nationwide. The study population included all patients in the 2 health plans in northern and southern California who met the following criteria: (1) aged 12 to 55 years, (2) prescribed a medium dose of an ICS between July 2001 and December 2002, and (3) had salmeterol added to the regimen. The medium daily dose was defined as a prescribed (i.e., the directions to the patients for use as documented in the electronic prescription record) dose of 240-480 mcg of beclomethasonehydrofluoroalkane (HFA), 264-660 mcg of fluticasone, 600-1,200 mcg of budesonide, or 1,000-2,000 mcg of triamcinolone acetonide. The initiation date for salmeterol was defined as the index date. Patients were excluded if they were not continuously enrolled for 6 months before and after the index date or if they had a diagnosis of chronic obstructive pulmonary disease (COPD: *International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 490.x, 491.x, 492.0, 492.8, 496, 506.4) during the 6 months before the index date. All data were collected for 6 months before and after the index date. This study was approved by the northern California and southern California Institutional Review Boards.

The study was designed as a pretest, posttest cohort analysis with 2 active groups derived from the original sample of patients who received 1 or more of 4 ICS drugs in the period prior to initiation of salmeterol (LABA). The fluticasone-salmeterol group (FSA) had salmeterol added as the combination product. The beclomethasone-salmeterol group (BSA) had salmeterol added to beclomethasone HFA and administered as separate inhalers. Only these 2 combinations of LABA and ICS were used in the analysis since beclomethasone was the plan’s preferred ICS and FSA, although a nonformulary product, was available to our prescribers without prior authorization. Patients dispensed

---

**FIGURE 1** Flowchart for Asthma Patient Selection*

- **Patients Initiated Therapy With Salmeterol and ICS in the Sampling Frame**
  - N = 22,549

- **Comorbidity Exclusions**
  - N = 3,216 (14.3%)

- **After Enrollment, Age, and Comorbidity Exclusions**
  - N = 7,902 (35.0%)

- **Medium Dose of ICS Preindex Date and Only BSA or FSA Postindex Date**
  - N = 4,852 (21.5%)

- **1:1 Matching With Propensity Scores Within ± 0.002**
  - N = 2,426 (10.8%)

- **BSA**
  - N = 1,213 (5.4%)

- **FSA**
  - N = 1,213 (5.4%)

* 6 months of continuous enrollment was required before and after initiation of combination therapy.

BSA = beclomethasone-salmeterol; COPD = chronic obstructive pulmonary disease; FSA = fluticasone-salmeterol; ICS = inhaled corticosteroid.
FSA were charged 1 copayment and those dispensed BSA were charged 2 copayments for the 2 prescriptions (salmeterol and beclomethasone). Copayment per prescription varied depending on the patient’s prescription drug coverage. However, the copayment was the same for each individual patient (e.g., $25 for FSA and 2 x $25 for BSA).

Subjects were matched using propensity scores,\textsuperscript{18} which were based on a 1-to-1 match of scores within ± 0.002. Those scores that did not match were excluded from analysis. Propensity scores were based on age, gender, unscheduled office visits, ED visits, and hospitalizations for asthma-related events (AREs), asthma medication prescribed by a specialist (allergist, pulmonologist) in addition to the primary provider, and the use of anti-inflammatory drugs and SABA. The electronic records of 22,549 patients were accessed, and 2,426 (1,213 matched pairs) met inclusion criteria and were used in the analysis (Figure 1).

Determination of equivalent(s) canisters of ICS and SABA was done using the method similar to that of Glauber et al.,\textsuperscript{19} which standardizes these medications on the basis of differences in potency and days supply of medication per pharmacy claim (Table 1). Patients who switched ICSs in the study period were also excluded from the analysis. However, patients who were dispensed other controllers (e.g., montelukast) were tracked and not excluded. For this analysis, the mcg equivalence was assumed for fluticasone and beclomethasone HFA based on the relative clinical effectiveness reported by Fairfax.\textsuperscript{18} Both medications appear equivalent at 400 mcg per day. At higher doses, 800 mcg of beclomethasone HFA and 1,000 mcg per day of fluticasone appear equivalent. Three subgroup analyses were done: (1) patients with prior ED visits or admissions, (2) patients without prior ED visits or admissions, and (3) patients using 6 or more canister equivalent(s) of inhaled beta-agonist. The 3 subgroups were used to determine if differences in outcomes were related to the level of asthma control.

Measurement

The primary endpoint was an ARE, which was defined as an ED visit or hospital admission for an asthma-related event (ICD-9-CM code 493.xx). The secondary endpoints were the (1) use of SABA, (2) percentage of patients with 1 or more oral steroid pharmacy claims, (3) prescribing and patient consumption patterns of ICS, and (4) refill rate of salmeterol. The data were all based on pharmacy claim records from the KP electronic prescription system.

Statistical Analysis

Patient characteristics were compared using \( t \) tests or the Wilcoxon rank sum test for continuous variables and chi-square tests or the McNemar test and Cochran’s \( Q \) test for categorical variables. Conditional logistic regression analysis was used to compare the incidence of AREs and the likelihood of filling at least 1 prescription for an oral steroid between the matched data in the 2 groups (FSA and BSA). Subgroup analyses were conducted with unconditional logistic regression because these subjects were no longer matched and analyzed as different cohorts. Change in SABA use was analyzed using analysis of covariance (ANCOVA). To adjust for differences in practice between northern and southern California regions, a dummy variable was created and used as a covariate in all the analyses. Other covariates used in the models were age, gender, prior ED visits, admissions, oral steroid use, beta-agonist use, ICS use, and medication prescribed by an allergist or pulmonologist. All \( P \) values were 2-sided. Statistical significance was defined as \( P < 0.05 \). SAS statistical software version 9.12 was used for data analysis (SAS Institute Inc., Cary, NC).

Results

Baseline characteristics of the study cohorts are summarized in Table 2. The electronic records of 22,549 subjects were screened and 2,426 met the inclusion criteria, 1,213 in each group. There were no statistical differences between the 2 groups in terms of baseline demographics or clinical characteristics. There were no statistical differences in the number of prescriptions dispensed or the estimated duration of therapy for other controllers (e.g., montelukast) between groups both preindex and postindex date (data not shown).

Changes in the primary and secondary endpoint measures,

---

**TABLE 1** Canister-Equivalent Conversion Factors

<table>
<thead>
<tr>
<th>Short-Acting Beta-Agonists</th>
<th>Quantity</th>
<th>Canister Equivalents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol 90 mcg</td>
<td>17 g</td>
<td>1</td>
</tr>
<tr>
<td>Albuterol 90 mcg HFA</td>
<td>6.7 g</td>
<td>1</td>
</tr>
<tr>
<td>Albuterol 0.083% solution</td>
<td>3 mL</td>
<td>0.02</td>
</tr>
<tr>
<td>Albuterol 0.5% solution</td>
<td>20 mL</td>
<td>0.8</td>
</tr>
<tr>
<td>Metaproterenol 0.6% solution</td>
<td>2.5 mL</td>
<td>0.02</td>
</tr>
<tr>
<td>Metaproterenol 650 mcg</td>
<td>14 g</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inhaled Corticosteroids</th>
<th>Quantity</th>
<th>Canister Equivalents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone 40 mcg</td>
<td>7.3 g</td>
<td>0.83</td>
</tr>
<tr>
<td>Beclomethasone 80 mcg</td>
<td>7.3 g</td>
<td>1.67</td>
</tr>
<tr>
<td>Fluticasone 44 mcg</td>
<td>10.6 g</td>
<td>0.8</td>
</tr>
<tr>
<td>Fluticasone 110 mcg</td>
<td>12 g</td>
<td>2</td>
</tr>
<tr>
<td>Fluticasone 220 mcg</td>
<td>12 g</td>
<td>4</td>
</tr>
<tr>
<td>Fluticasone 100 mcg (in FSA)</td>
<td>60 doses</td>
<td>1</td>
</tr>
<tr>
<td>Fluticasone 250 mcg (in FSA)</td>
<td>60 doses</td>
<td>2.5</td>
</tr>
<tr>
<td>Fluticasone 500 mcg (in FSA)</td>
<td>60 doses</td>
<td>5</td>
</tr>
<tr>
<td>Budesonide 200 mcg</td>
<td>200 doses</td>
<td>6.67</td>
</tr>
</tbody>
</table>

FSA = fluticasone and salmeterol in combination product; HFA = hydrofluoroketane.
Effects on Resource Utilization of Adding Salmeterol in Combination or Separately to Inhaled Corticosteroids

TABLE 2 Baseline Characteristics of the Study Population 6 Months Preindex* Date

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FSA N = 1,213</th>
<th>BSA N = 1,213</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>36.1 (13.8)</td>
<td>37.1 (12.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Sex (% female: % male)</td>
<td>61.39</td>
<td>59.41</td>
<td>0.349</td>
</tr>
<tr>
<td>SABA, mean (SD)</td>
<td>3.89 [4.47]</td>
<td>4.10 [4.76]</td>
<td>0.247</td>
</tr>
<tr>
<td>Anti-inflammatory (AI) equivalents†, mean (SD)</td>
<td>5.16 [6.87]</td>
<td>4.79 [6.91]</td>
<td>0.182</td>
</tr>
<tr>
<td>AI ratio‡, mean (SD)</td>
<td>0.429 [0.366]</td>
<td>0.401 [0.357]</td>
<td>0.074</td>
</tr>
<tr>
<td>ED visits with a diagnosis code for asthma (ICD-9-CM code 493.xx), mean (SD)</td>
<td>0.127 [0.471]</td>
<td>0.158 [0.522]</td>
<td>0.125</td>
</tr>
<tr>
<td>% (no.) of patients with a hospital admission with an ICD-9-CM diagnosis code of 493.xx</td>
<td>10.9 (132)</td>
<td>13.3 (162)</td>
<td>0.062</td>
</tr>
<tr>
<td>Specialist (allergist, pulmonologist) pharmacy claims, mean (SD)</td>
<td>1.56 [2.47]</td>
<td>1.52 [3.10]</td>
<td>0.674</td>
</tr>
<tr>
<td>% (no.) of patients with oral steroid prescriptions</td>
<td>41.3 (501)</td>
<td>43.1 (523)</td>
<td>0.366</td>
</tr>
</tbody>
</table>

* The index date is the first date of a pharmacy claim for salmeterol in combination (FSA) or separate inhaler.
† Anti-inflammatory (AI) equivalents is the sum of the canister equivalent(s) of inhaled corticosteroids (ICSs) in the 6-month preindex period.
‡ AI ratio is AI equivalents divided by the sum of AI equivalents and SABA canister equivalents.
BSA = beclomethasone and separate salmeterol; ED = emergency department; FSA = fluticasone and salmeterol in combination product; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; SABA = short-acting beta-agonist.

6-month postindex date, are shown in Table 3. The FSA group had a reduction in AREs of 55.0% (10.9%-4.9%; P < 0.001), and the BSA group had a reduction of 39.1% (13.3%-8.1%; P < 0.001). The adjusted odds ratio (OR) for an ARE was not statistically different for FSA compared with BSA (OR, 0.668; 95% CI, 0.443-1.008; P = 0.055). There was a 13.3% reduction in oral steroid dispensing for the FSA group (41.3%-35.8%; P = 0.002) and an 11.9% reduction (43.1%-38.0%; P = 0.002) for the BSA group. Patients treated with FSA were about 20% less likely to fill a prescription for an oral steroid. The change in the adjusted mean (least square mean) for inhaled SABA use was -1.05 canister equivalent(s) for FSA and -0.39 canister equivalent(s) for BSA. This represented a 27.0% reduction for FSA and 9.5% reduction for BSA; both were statistically significant reductions (P < 0.001). The adjusted difference between FSA and BSA was -0.66 canisters equivalent(s) (P < 0.001) in favor of FSA.

The subgroup analysis is shown in Table 4 and Table 5. No statistical difference was observed in AREs for patients with no prior AREs (OR, 0.730; 95% CI, 0.470-1.135; P = 0.163). AREs were observed in 3.4% of FSA patients and in 5.0% of BSA patients. No statistical difference was observed in the reduction of oral steroid dispensing (a relative 4.2% reduction for FSA, from 35.5% of patients to 34.0% of patients, and a relative 5.3% reduction for BSA, from 35.9% to 34.0%). Significant changes in adjusted beta-agonist use were observed for each regimen compared with baseline: -0.95 canister equivalent(s) for FSA (26% decrease) and -0.33 canister equivalent(s) for BSA (9% decrease) (P < 0.001). The adjusted difference between treatments was -0.62 canister equivalent(s) in favor of FSA over BSA (P < 0.001).

In patients who had previous AREs, a significant difference was observed (OR, 0.527; 95% CI, 0.291-0.954; P = 0.03) for FSA compared with BSA. Both regimens significantly reduced oral steroid dispensings (43.6% and 29.5%, respectively) (P < 0.001). Those treated with FSA were about 52% less likely to fill an oral steroid prescription (OR, 0.482; 95% CI, 0.293-0.793; P = 0.004). The adjusted change in inhaled SABA use was -1.76 for FSA (P < 0.01) and -0.85 for BSA (P = 0.009). An adjusted difference of -0.91 canister equivalent(s) was observed in favor of FSA but did not reach statistical significance.

In the 6-month baseline period, 665 patients used 6 or more canister equivalent(s) of SABA. The median use in each group was 9, with an interquartile range of 7-12. Both groups significantly reduced their beta-agonist use: -3.52 canister equivalent(s) for FSA and -2.71 for BSA in the post-6-month period (P < 0.001). The difference between groups in reduction of use was -0.81 canister equivalent(s) (P = 0.026) in favor of FSA.

In the postperiod, 50% of patients on BSA continued with a medium dose of inhaled steroid compared with 47% for the FSA group. Thirty-four percent of BSA subjects were prescribed a lower dose compared with 2% for the FSA group. Conversely, 33% of patients in the FSA group filled prescriptions for a higher dose compared with 2% for BSA. Thirty-two percent of patients on FSA appeared to take 400 mcg or higher compared with 10% for BSA. Twenty-six percent of patients in the BSA group adhered to the dose prescribed compared with 31% for the FSA group. Fifty-one percent of patients on BSA took a lower dose compared with 31% for FSA patients. These were all significant at P < 0.001. The mean number of equivalent prescriptions filled for salmeterol was 2.71 per 6 months for FSA compared with 2.38 for BSA (P < 0.001).

Discussion

The addition of salmeterol either to fluticasone as a combination product or individually to beclomethasone improved outcomes in asthmatic patients overall. However, the greater benefit was achieved in patients who were previously poorly controlled (i.e., had previous ED visits or hospitalizations for an asthma-related reason). After the addition of salmeterol, beclomethasone was
Effects on Resource Utilization of Adding Salmeterol in Combination or Separately to Inhaled Corticosteroids

Prescribed at a lower dose than fluticasone. The availability of the various dosage strengths may help explain the observed usage pattern. FSA is supplied commercially as 100 mcg, 250 mcg, and 500 mcg of fluticasone per diskus. These are generally dosed twice daily. In contrast, beclomethasone is supplied as 40 mcg and 80 mcg per puff. Using the 80-mcg strength, a dose of 480 mcg requires 6 puffs, and 640 mcg requires 8 puffs. Adherence was statistically better with FSA than BSA. This makes it easier for prescribers to prescribe a higher dose and for patients to adhere to a higher dose. It was not feasible to compare equipotent doses of BSA and FSA within the context of this analysis because of disproportionate distribution of doses with similar potency. Therefore, these findings, representing naturalistic or real-practice settings with attention to both the prescribers’ and patients’ perspective, suggest that patients prescribed FSA are more likely to take a higher dose and because of this, those patients with poor control may achieve greater benefit. Thus, the observed differences may be related to the way the drugs are available and used rather than to any inherent differences between them.

### Table 3

<table>
<thead>
<tr>
<th>Outcome Measures</th>
<th>FSA (N = 1,051)</th>
<th>BSA (N = 1,081)</th>
<th>Difference or Odds Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% (no.) of patients with ED visits or hospital admission with ICD-9-CM code 493.xx for asthma</td>
<td>4.9 (60)</td>
<td>8.1 (98)</td>
<td>0.668 (0.443-0.008)*</td>
<td>0.055</td>
</tr>
<tr>
<td>% (no.) of patients who received oral steroids</td>
<td>35.8 (434)</td>
<td>38.0 (461)</td>
<td>0.801 (0.662-0.970)†</td>
<td>0.023</td>
</tr>
<tr>
<td>Adjusted change in SABA</td>
<td>-1.05</td>
<td>-0.39</td>
<td>-0.66†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% (no.) of patients who consumed a daily dose of ICS of ≥400 mcg</td>
<td>32.0 (388)</td>
<td>10.0 (121)</td>
<td>N/A</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean [SD] refills for salmeterol separately or as FSA</td>
<td>2.71 [1.41]</td>
<td>2.38 [1.49]</td>
<td>N/A</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Odds ratio adjusted for baseline asthma-related event and geographic region.
† Odds ratio adjusted for baseline oral steroid use and geographic region.
‡ Least squares difference between FSA and BSA adjusted for baseline beta-agonist use and geographic region.
§ t test.
ED = emergency department; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; ICS = inhaled corticosteroid; SABA = short-acting beta-agonist.

### Table 4

<table>
<thead>
<tr>
<th>Outcome Measures</th>
<th>FSA (N = 1,081)</th>
<th>BSA (N = 1,051)</th>
<th>Difference or Odds Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% (no.) of patients with ED visits or hospital admission with ICD-9-CM code 493.xx for asthma</td>
<td>0 (0)</td>
<td>3.4 (37)</td>
<td>0 (0)</td>
<td>5.0 (53)</td>
</tr>
<tr>
<td>% (no.) of patients who received oral steroids†</td>
<td>35.5 (384)</td>
<td>34.0 (368)</td>
<td>35.9 (377)</td>
<td>34.0 (357)</td>
</tr>
<tr>
<td>SABA use‡</td>
<td>3.66</td>
<td>2.76</td>
<td>3.74</td>
<td>3.31</td>
</tr>
</tbody>
</table>

* Odds ratio adjusted for baseline asthma-related event and geographic region.
† Odds ratio adjusted for baseline oral steroid use and geographic region.
‡ No statistical difference between values at baseline.
§ Least squares mean difference between FSA and BSA adjusted for baseline beta-agonist use and geographic region.
CI = confidence interval; ED = emergency department; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; SABA = short-acting beta-agonist.
Effects on Resource Utilization of Adding Salmeterol in Combination or Separately to Inhaled Corticosteroids

Our findings suggest that higher doses of inhaled steroids may lead to a decrease in ED visits and hospital admissions. This is consistent with the findings of Schatz et al. These investigators found a trend toward decreased ED visits and admissions with increased use of inhaled canisters. This differs from the findings of Sin and Man who reported that low-dose therapy appears to be as effective as high-dose inhaled steroid therapy. The authors, however, concluded that further studies are needed to determine the optimal dosing regimen for inhaled steroids.

On the basis of the results presented, it may be cost effective to stratify patients by level of risk for ED visits or admissions similar to that described by Schatz et al. These investigators found a trend toward decreased ED visits and admissions with increased use of inhaled canisters. This differs from the findings of Sin and Man who reported that low-dose therapy appears to be as effective as high-dose inhaled steroid therapy. The authors, however, concluded that further studies are needed to determine the optimal dosing regimen for inhaled steroids.

Similarly, the 6-month preperiod may not have been adequate to define the patient’s past history. Lastly, since the 6-month period was used both preaddition and postaddition of salmeterol, seasonality may be a confounding factor. However, this factor is expected to affect both groups similarly, thus minimizing its impact.

**Limitations**

Our study is observational in nature and relies on data from administrative databases. Channeling bias or confounding by indication is an inherent problem in this type of study. We attempted to minimize this effect by matching patients using propensity scores and conditional logistic regression comparing matched pairs. However, we cannot be completely certain that we have adjusted fully for channeling bias. The baseline characteristics of the study population suggest no significant dissimilarities.

For the subgroup analysis, unconditional logistic regression was used, as the subgroups were not matched by propensity scores. In this case, potential confounders or effect modifiers were adjusted using logistic regression to minimize the influence of these factors. We may have underestimated the use of oral steroids because patients may have prefilled steroid prescriptions on hand in case of flare-ups. We did not collect asthma-related deaths as an endpoint, although this has been widely discussed in the literature; a larger study with a different design and inclusion criteria should be used to assess this endpoint. Finally, these findings are from an integrated managed care organization in California and may not be generalizable to other practice settings.

**TABLE 5** Outcome Measures After the Addition of Salmeterol to Beclomethasone (BSA) Versus the Combination Fluticasone and Salmeterol Product (FSA) in Patients With Prior ED Visits or Admissions 6 Months Postindex Date

<table>
<thead>
<tr>
<th>Outcome Measures</th>
<th>FSA (N = 132)</th>
<th>BSA (N = 162)</th>
<th>Difference or Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% (no.) of patients with ED visits or hospital admission with ICD-9-CM code 493.xx for asthma</td>
<td>100 (132)</td>
<td>17.4 (23)</td>
<td>100 (162)</td>
<td>27.8 (45)</td>
</tr>
<tr>
<td>% (no.) of patients who received oral steroids†</td>
<td>88.6 (117)</td>
<td>50.0 (66)</td>
<td>90.1 (146)</td>
<td>64.2 (104)</td>
</tr>
<tr>
<td>SABA use‡</td>
<td>5.74</td>
<td>4.17</td>
<td>6.46</td>
<td>5.29</td>
</tr>
</tbody>
</table>

* Odds ratio adjusted for asthma-related event and geographic region.
† Odds ratio adjusted for baseline oral steroid use and geographic region.
‡ No statistical difference between values at baseline.
§ Least squares mean difference between FSA and BSA adjusted for baseline beta-agonist use and geographic region.

CI= confidence interval; ED= emergency department; ICD-9-CM= International Classification of Diseases, Ninth Revision, Clinical Modification; SABA= short-acting beta agonist.
Effects on Resource Utilization of Adding Salmeterol in Combination or Separately to Inhaled Corticosteroids

Conclusion
The addition of salmeterol to either beclometasone as a separate inhaler or to fluticasone as a combination product improves clinical outcomes in asthmatic patients with no significant differences between the groups in the primary outcome of asthma-related ED visits or hospital admissions. Patients with prior ED visits or admissions for AREs showed a better primary outcome with FSA compared with BSA. For those patients with no prior ED visits or admissions (i.e., apparent lower asthma severity or better control), outcomes were not significantly different between the 2 regimens. Patients who received FSA were more likely to be exposed to a higher dose of inhaled steroid compared with those who received BSA. Differences between FSA and BSA may be attributed to the way these drugs are used in a naturalistic setting rather than to any inherent difference between drugs.

What is already known about this subject
- Previous studies on health care utilization have compared combination fluticasone (ICS) and salmeterol (LABA) with fluticasone and salmeterol separately or with fluticasone and montelukast (leukotriene inhibitor)
- Data are lacking on effects of combination fluticasone and salmeterol compared with separate inhalers of beclometasone (ICS) and salmeterol.

What this study adds
- Both combination fluticasone/salmeterol and separate inhalers of beclometasone and salmeterol reduce asthma-related ED visits and hospital admissions.
- Patients with recent ED visits or admissions (presumably with poorer control) show a greater reduction on combination fluticasone/salmeterol therapy, albeit at a higher equivalent steroid dose.

DISCLOSURES
No outside funding supported this research. The authors disclose no potential bias or conflict of interest relating to this article. Author James Chan served as principal author of the study. Study concept and design were contributed primarily by Chan, with input from authors Rita L. Hui and Michele M. Spence. Data collection was the work of Hui and Spence, with input from Chan, data interpretation was primarily the work of Chan, with input from Hui and Spence. Writing of the manuscript and its revision were primarily the work of Chan, with input from Hui and Spence.

REFERENCES
Adherence to Clinical Practice Guidelines for 7 Chronic Conditions in Long-term-Care Patients Who Received Pharmacist Disease Management Services Versus Traditional Drug Regimen Review

KRISTIN K. HORNING, PharmD; JAMES D. HOEHNS, PharmD, BCPS; and WILLIAM R. DOUCETTE, PhD

ABSTRACT

BACKGROUND: Numerous studies have shown that adherence to published clinical practice guidelines (CPGs) reduces disease morbidity and mortality. However, few benchmarks exist that demonstrate the rate of adherence to CPGs in patients in long-term-care facilities (LTCFs).

OBJECTIVE: To evaluate CPG adherence in patients in LTCFs who received consultation from pharmacists who emphasize disease state management (DSM) compared with patients in other LTCFs who received traditional drug regimen review (DRR).

METHODS: A retrospective chart review was conducted in November 2005 for 107 patients who received DSM services in 2 LTCFs and 304 patients who received DRR services in 4 LTCFs for the service period ending September 30, 2005. Chart review was conducted on all patients included in the current census as of September 1, 2005; residents were excluded from the analysis if they were discharged or deceased between September 1, 2005, and the date of chart review. CPG adherence was evaluated for the following 7 conditions: diabetes, coronary artery disease (CAD), stroke, heart failure (HF), hypertension, hyperlipidemia, and osteoporosis. In addition, the 6 most recent pharmacist recommendations for each patient were classified according to disease state.

RESULTS: Adherence to CPGs was significantly better (all P < 0.05) in patients receiving DSM services for the following performance measures for 4 of the 7 disease states: (1) diabetes: antiplatelet or warfarin use or contraindication for use (hypersensitivity or history of serious bleeding event), 89.7% for DSM services versus 71.0% for DRR services, and glycosylated hemoglobin (HbA1c) ≤ 7% (86.2% vs. 62.0%); (2) CAD: antiplatelet use (88.2% vs. 56.1%), and angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) use (82.4% vs. 40.9%); (3) HF: ACEI or ARB use (73.3% vs. 44.9%); and (4) osteoporosis: calcium use (85.0% vs. 56.3%). These observed differences in CPG adherence rates for patients receiving DSM services remained statistically significant after multivariate adjustment for likely confounders. Adherence to CPGs was not different between DSM and DRR facilities for the other 3 disease states (hypertension, hyperlipidemia, and stroke, P > 0.05). The mean number of pharmacist recommendations per patient per month was greater in DSM facilities (0.76) compared with DRR facilities (0.23, P < 0.001). Pharmacists who provided DSM consultant services were more likely to make a recommendation to improve DSM compared with DRR consultant services who provided traditional DRR services (31.7%, P < 0.001).

CONCLUSION: This self-evaluation of the provision of pharmacist consultant services that focus on disease management in addition to DRR found a higher rate of adherence to clinical practice guidelines for 4 of 7 common chronic disease states in long-term-care patients compared with patients who received only traditional DRR services.

KEYWORDS: Practice guidelines, Long-term care, Nursing homes, Geriatrics

J Manag Care Pharm. 2007;13(1):28-36

Note: A commentary on the subject of this article appears on pages 68-69 of this issue.

B y age 75, the average American has 2 or 3 chronic medical conditions.1 When patients have multiple disease states, overall management of care can be challenging and costly. Therefore, adherence to established clinical practice guidelines (CPGs) becomes extremely important. Numerous studies have shown that adherence to CPGs has benefits of reducing disease morbidity and mortality and overall treatment costs.2-5

In 2003, more than 1.3 million Americans were residents of long-term-care facilities (LTCFs).4 A 1995 report found that 28% of residents will be hospitalized at least once during an average long-term-care (LTC) stay, with heart disease as the most common discharge diagnosis in patients older than 65 years.7 In addition to having frequent hospitalizations, this patient population is commonly prescribed a large number of medications. A national survey of 878 nursing facilities conducted in 1997 found that residents received an average of 5.85 routine and 3.03 as-needed (PRN [pro re nata]) medication orders.8

Even with this sizable population with high medication use, few standards exist for determining adequacy of care in the delivery of disease state management (DSM) services, specifically in LTCFs. A 2001 report by the Institute of Medicine, Improving the Quality of Long-Term Care, concluded that few standard measurement tools exist for assessing quality of care in these LTC patients.6 In addition, an extensive literature search using the keywords “practice guidelines,” “guideline adherence,” and “long-term care” revealed only 2 published reports of adherence to recommended CPGs in this population.9,10

Authors

KRISTIN K. HORNING, PharmD, is an assistant professor (clinical), University of Iowa College of Pharmacy, Iowa City, and a clinical pharmacist, East Des Moines Family Care Center, Des Moines, Iowa (at the time of this study, she was a primary care pharmacy resident at the Northeast Iowa Family Practice Residency, Waterloo); JAMES D. HOEHNS, PharmD, BCPS, is an associate professor (clinical), University of Iowa College of Pharmacy, Iowa City, and a clinical pharmacist, Northeast Iowa Family Practice Residency, Waterloo; WILLIAM R. DOUCETTE, PhD, is an associate professor, University of Iowa College of Pharmacy, Iowa City.

AUTHOR CORRESPONDENCE: Kristin K. Horning, PharmD, Clinical Pharmacist, East Des Moines Family Care Center, 840 East University Ave., Des Moines, IA 50316. Tel: (515) 265-4211; Fax: (515) 309-5993; E-mail: HorninKK@ihs.org

Copyright © 2007, Academy of Managed Care Pharmacy. All rights reserved.
Adherence to Clinical Practice Guidelines for 7 Chronic Conditions in Long-term-Care Patients Who Received Pharmacist Disease Management Services Versus Traditional Drug Regimen Review

**TABLE 1** Clinical Practice Guidelines (CPGs) for 7 Disease States

<table>
<thead>
<tr>
<th>Disease State</th>
<th>Performance Measure</th>
<th>Reference/CPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>On antplatelet agent</td>
<td>ADA Standards of Care 2005/DQIP</td>
</tr>
<tr>
<td>A1c ≤7%</td>
<td>ADA Standards of Care 2005/DQIP</td>
<td></td>
</tr>
<tr>
<td>BP ≤130/80 mmHg</td>
<td>ADA Standards of Care 2005/DQIP</td>
<td></td>
</tr>
<tr>
<td>LDL at goal</td>
<td>ADA Standards of Care 2005/DQIP</td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>On antplatelet agent</td>
<td>ACC/AHA17</td>
</tr>
<tr>
<td>On beta-blocker</td>
<td>ACC/AHA17</td>
<td></td>
</tr>
<tr>
<td>On ACEI/ARB</td>
<td>ACC/AHA17</td>
<td></td>
</tr>
<tr>
<td>On statin</td>
<td>ACC/AHA17</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>On antplatelet therapy</td>
<td>Seventh ACCP Conference on Anti-thrombotic and Thrombolytic Therapy</td>
</tr>
<tr>
<td>Heart failure</td>
<td>On ACEI/ARB</td>
<td>ACC/AHA17</td>
</tr>
<tr>
<td>On beta-blocker</td>
<td>ACC/AHA19</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>BP ≤140/90 mmHg</td>
<td>JNC 7²⁶</td>
</tr>
<tr>
<td>Hyperlipidema</td>
<td>LDL-C at goal</td>
<td>ATP III11,12</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>On calcium</td>
<td>AACE13</td>
</tr>
<tr>
<td>On osteoporosis medication</td>
<td>AACE13</td>
<td></td>
</tr>
</tbody>
</table>


We have defined DSM as the provision of therapeutic recommendations to improve CPG adherence for common chronic medical conditions, which we have practiced since we began our LTCF pharmacist consulting service in 2001. In addition, we have delivered the traditional drug regimen review (DRR) process, which is defined in federal regulations as evaluating indications for medication use, effectiveness of therapeutic goal, medication dose, presence of monitoring and duplicate therapy, and potential for adverse drug reactions.²¹²

We previously evaluated physician acceptance and perceived value of the pharmacist consultant interventions for 155 LTCF patients during an 8-month period.¹³ Results showed that 523 of 599 recommendations (84.3%) were accepted by physicians and that 45% of recommendations were perceived as important by physicians. While 10.4% of pharmacist recommendations were made in response to federal guidelines in the DRR process, an additional 85.2% of recommendations were initiated as a result of a broader medication review, including DSM activities. These results demonstrated that our pharmacist recommendations were accepted and valued by physicians, but they did not allow us to evaluate the CPG adherence rates for the patients we served.

The objectives of this study were to evaluate (1) the end outcome of CPG adherence and (2) the process outcome of the number of care recommendations made for patients from LTCF who received DSM pharmacy consulting services compared with patients who received traditional DRR pharmacy consulting services.

**Methods**

**Study Design**

A retrospective chart review was conducted on 411 patients at 6 LTCFs. Two facilities (107 patients) received DSM consultant pharmacist services (provided by Kristin K. Horning and James D. Hoehns) and 4 facilities (304 patients) received traditional DRR services. The 4 DRR (control) facilities constituted a convenience sample located within 30 miles of the 2 LTCFs that had consultant DSM pharmacy services. These control LTCFs had varying types of pharmacist consulting services, with 2 homes receiving corporate services (218 patients) and 2 homes receiving independent pharmacist consulting services (86 patients). While the homes receiving DSM services were both for-profit, 2 control homes were for-profit and 2 homes were nonprofit. All homes had both Medicare and Medicaid participation. The investigators believed that the control homes were a representative mix of usual pharmacist consulting services in our geographic area. Approval for the design and methodology of the study was obtained from both an institutional review board and from each LTCF administrator.

**Patient Selection and Data Collection**

All current residents admitted before September 1, 2005, were included in the analysis. Residents were excluded from the analysis if they were discharged or deceased between September 1, 2005, and the date of chart review. No patient charts were excluded because of poor documentation. A standard data collection form was used to record the following information for patient characteristics and clinical condition: patient age, gender, weight, admission date, functional status, number of scheduled and PRN medications, number of diagnoses, and presence of disease states. If a resident was diagnosed with more than 1 disease state, the subject was evaluated for all diagnoses and associated disease states. Disease state information for each resident was collected from section 11 of the full Minimum Data Set (MDS) version 2.0. Information on functional status for each resident was obtained from section G1 of the most recent quarterly MDS version 2.0. The MDS is a tool mandated by the Centers for Medicare & Medicaid Services (CMS) to record specific resident information, such as...
Adherence to Clinical Practice Guidelines for 7 Chronic Conditions in Long-term-Care Patients Who Received Pharmacist Disease Management Services Versus Traditional Drug Regimen Review

### TABLE 2 Patient Characteristics

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>DSM (N = 107)</th>
<th>Traditional DRR (N = 304)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean [SD]</td>
<td>82.0 [11.7]</td>
<td>83.7 [10.4]</td>
<td>0.163</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>31.8</td>
<td>23.1</td>
<td>0.157</td>
</tr>
<tr>
<td>Weight, kg, mean [SD]</td>
<td>164.0 [44.9]</td>
<td>156.2 [39.4]</td>
<td>0.093</td>
</tr>
<tr>
<td>Months since admission mean [SD]</td>
<td>32.7 [28.5]</td>
<td>35.2 [32.7]</td>
<td>0.489</td>
</tr>
<tr>
<td>Functional status (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poorest mobility†</td>
<td>51.4</td>
<td>53.0</td>
<td>0.822</td>
</tr>
<tr>
<td>Current diagnoses (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>27.1</td>
<td>33.1</td>
<td>0.250</td>
</tr>
<tr>
<td>CAD</td>
<td>15.9</td>
<td>21.7</td>
<td>0.197</td>
</tr>
<tr>
<td>Stroke</td>
<td>16.8†</td>
<td>28.3</td>
<td>0.019</td>
</tr>
<tr>
<td>HF</td>
<td>31.1</td>
<td>30.3</td>
<td>0.867</td>
</tr>
<tr>
<td>Hypertension</td>
<td>70.1</td>
<td>70.7</td>
<td>0.902</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>28.3</td>
<td>27.3</td>
<td>0.843</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>20.6</td>
<td>27.6</td>
<td>0.150</td>
</tr>
<tr>
<td>No. of diagnoses, mean [SD]</td>
<td>7.1 [2.8]</td>
<td>8.3 [3.3]</td>
<td>0.044</td>
</tr>
<tr>
<td>≥1 psychiatric diagnosis (%)</td>
<td>66.4</td>
<td>65.1</td>
<td>0.180</td>
</tr>
<tr>
<td>No. of scheduled medications, mean [SD]†</td>
<td>10.5 [3.5]</td>
<td>9.2 [4.0]</td>
<td>0.002</td>
</tr>
<tr>
<td>No. of PRN medications, mean [SD]</td>
<td>3.7 [1.9]</td>
<td>4.1 [1.9]</td>
<td>0.103</td>
</tr>
<tr>
<td>No. of total medications, mean [SD]</td>
<td>14.2 [4.196]</td>
<td>13.3 [4.933]</td>
<td>0.063</td>
</tr>
<tr>
<td>Monthly medication cost ($),§ mean [SD]</td>
<td>357 [216]</td>
<td>362 [264]</td>
<td>0.873</td>
</tr>
<tr>
<td>Use of antidepressants (%)</td>
<td>57.0</td>
<td>57.2</td>
<td>0.700</td>
</tr>
<tr>
<td>Use of antipsychotics (%)</td>
<td>25.2</td>
<td>23.2</td>
<td>0.695</td>
</tr>
<tr>
<td>No. of antihypertensives, mean [SD]</td>
<td>2.1 [1.3]</td>
<td>1.5 [1.2]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* All P values versus traditional DRR (2-sided t test).
† Includes bed mobility and assistance with all activities.
§ Includes oral medications and insulin.

CAD = coronary artery disease; DSM = disease-state management; DRR = drug regimen review; HF = chronic heart failure; PRN = pro re nata (as needed).

---

diagnoses and functional ability. One purpose of the MDS, which is updated at least quarterly, is to identify potential health problems. The 7 specific disease states that were analyzed were diabetes, coronary artery disease (CAD), stroke, heart failure (HF), hypertension, hyperlipidemia, and osteoporosis. These disease states were chosen because they are common in the elderly, are associated with high rates of morbidity and mortality, and have well-established CPGs.14-23

Chart abstraction was conducted during November 2005 by Horning. The most recent laboratory data that pertained to the 7 disease states and performed between April 1, 2004, and September 30, 2005, were recorded from the medical charts. A maximum of 8 blood pressure measurements performed between August 2005 and September 2005 were extracted, and the average of these readings was calculated. This timeframe was chosen to allow at least 2 months for consultant pharmacists to make recommendations and for laboratory tests to be performed on newly admitted patients. If no laboratory data or blood pressure measurements were found for patients with diagnoses of either diabetes or hypertension, the patients were considered to be not at goal. Since few patients had a documented diagnosis of hyperlipidemia, only patients with a diagnosis of either CAD and/or diabetes and with the results available for lipid laboratory panels were assessed with respect to CPG adherence for hyperlipidemia.

Assessment of CPG adherence for each disease state was based on the most recently accepted practice guideline, as summarized in Table 1. The most recent pharmacist recommendations made during previous consultations before September 1, 2005 (maximum of 6 per resident), were recorded and classified as disease state recommendations, Beers criteria,19 PRN use, or other. Estimated prescription drug costs were calculated for scheduled oral medications, insulin, inhalers, and eye drops for each LTCF resident. Drug costs were obtained from www.drugstore.com (accessed May 2006).
### Results

A total of 411 residents of 6 LTCFs were included in the analysis. Participant characteristics are summarized in Table 2. Patients were predominantly female (68% to 77%) and had resided at the facility for an average of more than 30 months. Patients receiving DSM consulting services were less likely to have a history of stroke (16.8% vs. 28.3%), had fewer medical diagnoses (7.1 vs. 8.3), and were receiving more scheduled medications (10.5 vs. 9.2) compared with patients receiving traditional DRR, respectively (all $P < 0.05$). There was no difference in the total mean medication use in DSM versus DRR facilities (14.2 vs. 13.3, $P = 0.063$) and no difference in the mean monthly medication cost per patient ($357.33 vs. $361.86$).

Adherence to CPGs was significantly higher for patients receiving DSM consultant pharmacist services for 4 of 7 disease states (Table 3). For patients with diabetes, significantly more DSM patients were receiving an antiplatelet agent, warfarin, or were recognized with a contraindication (hypo-tension or history of major bleeding event, 89.7% vs. 71.0%; $P < 0.05$). Diabetic patients on warfarin were recognized for CPG adherence because the current CPGs do not mandate that these diabetic patients also need to be on concomitant antiplatelet agents.23 More patients with diabetes receiving DSM had glycosylated hemoglobin (HbA1c) controlled to <7% than did those in traditional DRR homes (86.2% vs. 62.0%; $P < 0.05$).

In patients with CAD, significantly more patients receiving DSM were using aspirin or clopidogrel (88.2% vs. 56.1%; $P < 0.05$) and an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) (82.4% vs. 40.9%; $P < 0.05$). More patients with HF receiving DSM were prescribed an ACEI or ARB (73.3% vs. 44.9%; $P < 0.05$). Patients with osteoporosis receiving DSM were more likely to be prescribed calcium supplementation (85.0% vs. 56.3%; $P < 0.05$). CPG adherence was similar between DSM and traditional DRR groups for hypertension, hyperlipidemia, and stroke. These rates were also compared with the Health Disparities Collaboratives (HDCs), which provide goal rates of CPG adherence for specific measures in chronic care patients seen by practitioners in the primary care setting.26-27 CPG adherence rate benchmarks specifically for LTCF patients have not been addressed by the HDC. However, in our study, patients receiving DSM services met the recommended goal benchmark for 4 of 6 HDC measures and were within 6% of meeting the goal for the remaining 2 HDC measures.

A total of 349 pharmacist recommendations in DSM facilities and 445 recommendations in traditional DRR facilities were analyzed by Horning. Consultant pharmacist recommendations between DSM and DRR pharmacists are summarized in Table 4.
The mean number of pharmacist recommendations per patient per month was greater in facilities with DSM services compared with DRR facilities by a 3-to-1 ratio (0.76 vs. 0.23, P < 0.001). Pharmacists who delivered DSM services were more likely to make a recommendation to improve disease management (51.6%) than were pharmacists in comparison facilities who delivered only DRR services (31.7%, P < 0.001). Although pharmacists providing DRR services had a higher percentage of recommendations on Beers criteria and/or federal regulations, the mean number of recommendations per patient per month regarding this category was actually greater in facilities receiving DSM services (0.21 vs. 0.12, P < 0.001).

Further analysis of pharmacist recommendations showed that, for 4 of the 7 disease states, patients receiving DSM services had significantly more recommendations. Results of this analysis are summarized in Table 5. For example, 65.5% of diabetic patients receiving DSM had at least 1 of the 6 most recent consultant pharmacist recommendations pertaining to diabetes compared with 7.0% of patients receiving traditional DRR consultant services.

Logistic regression analysis was conducted for all measures, with significant differences found in CPG adherence rates between DSM and traditional DRR facilities (Table 6). Since the difference in use of antithrombotic or anticoagulation therapy in stroke patients was close to significant (P = 0.096) in the univariate analyses, this measure was also included in the multivariate analyses. The variable of DSM consulting services was significant in the following conditions: (1) diabetes patients receiving antithrombotic or warfarin or with a contraindication, and the last HbA1c <7% value; (2) CAD patients receiving aspirin or clopidogrel, and receiving ACEI or ARB; (3) HF patients receiving ACEI or ARB; and (4) osteoporosis patients receiving calcium supplementation. Overall, patients receiving DSM services were almost 4 to more than 7 times more likely to meet the criteria in CPGs than patients receiving traditional DRR. These findings further support the theory that DSM facilitates CPG adherence, even after adjusting for potential confounders. For patients with osteoporosis, adherence rates decreased significantly as the number of diagnoses increased. This finding may suggest that treatment of osteoporosis is considered a lower priority when multiple other disease states are present.

## Discussion

Our study evaluated DSM in LTCF patients based on CPGs and whether pharmacist DSM consulting services improved guideline adherence. Zarowitz et al. in an unpublished study, presented as an abstract, found results similar to our study. A pharmacist-led interventional program in more than 110,000 LTCF residents showed that patients with diabetes were more likely to adhere to diabetes management goals than benchmarks in younger (<65 years) noninstitutionalized patients: more than 85% of LTCF residents had HbA1c values of <8.0%, while the National Committee for Quality Assurance (NCQA) reported that 32.0% of younger, noninstitutionalized patients had HbA1c values >9.0%. On the basis of these data, perhaps elderly LTCF patients with diabetes are better controlled than other noninsti-
# Logistic Regression Analysis of Clinical Practice Guideline Adherence

<table>
<thead>
<tr>
<th>Variable in Model</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contraindication to antiplatelet or warfarin*</td>
<td>DSM services 5.803</td>
<td>1.464-23.004</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>Functional status† 0.559</td>
<td>0.215-1.668</td>
<td>0.327</td>
</tr>
<tr>
<td></td>
<td>Age 0.954</td>
<td>0.897-1.016</td>
<td>0.143</td>
</tr>
<tr>
<td></td>
<td>Months since admission 0.997</td>
<td>0.980-1.015</td>
<td>0.764</td>
</tr>
<tr>
<td></td>
<td>No. of diagnoses 1.092</td>
<td>0.919-1.298</td>
<td>0.315</td>
</tr>
<tr>
<td>Last A1c &lt;7%†</td>
<td>DSM services 3.881</td>
<td>1.196-12.395</td>
<td>0.024</td>
</tr>
<tr>
<td></td>
<td>Functional status† 0.774</td>
<td>0.335-1.785</td>
<td>0.548</td>
</tr>
<tr>
<td></td>
<td>Age 1.034</td>
<td>0.992-1.078</td>
<td>0.118</td>
</tr>
<tr>
<td></td>
<td>Months since admission 1.009</td>
<td>0.994-1.025</td>
<td>0.248</td>
</tr>
<tr>
<td></td>
<td>No. of diagnoses 0.960</td>
<td>0.845-1.091</td>
<td>0.533</td>
</tr>
</tbody>
</table>

**Coronary Artery Disease**

<table>
<thead>
<tr>
<th>Variable in Model</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DSM services 6.383</td>
<td>1.295-31.463</td>
<td>0.023</td>
</tr>
<tr>
<td></td>
<td>Functional status† 1.029</td>
<td>0.381-2.782</td>
<td>0.955</td>
</tr>
<tr>
<td></td>
<td>Age 1.017</td>
<td>0.954-1.083</td>
<td>0.610</td>
</tr>
<tr>
<td></td>
<td>Months since admission 0.998</td>
<td>0.984-1.013</td>
<td>0.828</td>
</tr>
<tr>
<td></td>
<td>No. of diagnoses 0.996</td>
<td>0.835-1.187</td>
<td>0.963</td>
</tr>
</tbody>
</table>

**ACEI or ARB||**

<table>
<thead>
<tr>
<th>Variable in Model</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DSM services 7.350</td>
<td>1.833-29.471</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>Functional status† 1.494</td>
<td>0.552-4.043</td>
<td>0.430</td>
</tr>
<tr>
<td></td>
<td>Age 1.001</td>
<td>0.940-1.065</td>
<td>0.987</td>
</tr>
<tr>
<td></td>
<td>Months since admission 1.002</td>
<td>0.987-1.017</td>
<td>0.787</td>
</tr>
<tr>
<td></td>
<td>No. of diagnoses 1.022</td>
<td>0.857-1.218</td>
<td>0.810</td>
</tr>
</tbody>
</table>

**Stroke**

<table>
<thead>
<tr>
<th>Variable in Model</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DSM services 5.380</td>
<td>0.975-29.684</td>
<td>0.053</td>
</tr>
<tr>
<td></td>
<td>Functional status† 0.451</td>
<td>0.154-1.319</td>
<td>0.146</td>
</tr>
<tr>
<td></td>
<td>Age 0.963</td>
<td>0.910-1.019</td>
<td>0.192</td>
</tr>
<tr>
<td></td>
<td>Months since admission 0.990</td>
<td>0.974-1.007</td>
<td>0.240</td>
</tr>
<tr>
<td></td>
<td>No. of diagnoses 1.119</td>
<td>0.965-1.298</td>
<td>0.135</td>
</tr>
</tbody>
</table>

**Heart Failure**

<table>
<thead>
<tr>
<th>Variable in Model</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DSM services 4.051</td>
<td>1.546-10.616</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>Functional status† 0.969</td>
<td>0.445-2.112</td>
<td>0.937</td>
</tr>
<tr>
<td></td>
<td>Age 1.037</td>
<td>0.988-1.088</td>
<td>0.140</td>
</tr>
<tr>
<td></td>
<td>Months since admission 0.990</td>
<td>0.977-1.003</td>
<td>0.119</td>
</tr>
<tr>
<td></td>
<td>No. of diagnoses 1.102</td>
<td>0.972-1.250</td>
<td>0.129</td>
</tr>
</tbody>
</table>

**Osteoporosis**

<table>
<thead>
<tr>
<th>Variable in Model</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DSM services 4.054</td>
<td>1.000-16.441</td>
<td>0.050</td>
</tr>
<tr>
<td></td>
<td>Functional status† 1.417</td>
<td>0.569-3.528</td>
<td>0.454</td>
</tr>
<tr>
<td></td>
<td>Age 0.972</td>
<td>0.919-1.028</td>
<td>0.317</td>
</tr>
<tr>
<td></td>
<td>Months since admission 1.008</td>
<td>0.995-1.022</td>
<td>0.219</td>
</tr>
<tr>
<td></td>
<td>No. of diagnoses 0.838</td>
<td>0.722-0.973</td>
<td>0.020</td>
</tr>
</tbody>
</table>

* Overall model significance was 0.020 and Nagelkerke R2 = 0.213.  
† Bed mobility and assistance with all activities was assigned a value of 1.  
‡ Overall model significance was 0.062 and Nagelkerke correlation coefficient R2 = 0.118.  
§ Overall model significance was 0.197 and Nagelkerke R2 = 0.119.  
|| Overall model significance was 0.045 and Nagelkerke R2 = 0.176.  
¶ Overall model significance was 0.058 and Nagelkerke R2 = 0.149.  
# Overall model significance was 0.035 and Nagelkerke R2 = 0.131.  
** Overall model significance was 0.014 and Nagelkerke R2 = 0.185.  
A1c=glycosylated hemoglobin; ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; ASA=aspirin; CI=confidence interval; DSM=disease state management.
It has also been proposed that consultant pharmacists providing DSM services in LTCFs over an 8-month period and determined that consultant pharmacists spent an average of 11.6 minutes DSM services in LTCFs over an 8-month period and determined that consultant pharmacists spent an average of 11.6 minutes DSM services in LTCFs over an 8-month period and determined that consultant pharmacists spent an average of 11.6 minutes DSM services in LTCFs over an 8-month period. In 1997, results of phase 1 of the Fleetwood Project estimated that pharmacist consultants improved therapeutic outcomes, which investigators defined as an absence of drug-related problems, by 43% and saved $3.6 billion per year in costs associated with drug morbidity and mortality from avoided drug-related problems. However, the practical use of these findings is limited since they were based on a hypothetical group of 100 LTCF patients.

Despite pharmacist intervention, adequate DSM remains a challenge, in part because of multiple comorbid conditions in the population of LTCF residents. In the current study, the DSM group had a mean of 7.1 diagnoses, two thirds of patients had at least 1 psychiatric diagnosis, 57.0% received antidepressants, 25.2% received antipsychotics, and the mean number of antihypertensive medications was 2.1.

Limitations
First and foremost among the limitations of this study was that the chart abstraction and analysis of pharmacist interventions was completed by the authors, and they could not be blinded to the source of the medical charts from DSM versus DRR facilities. Second, the primary abstraction of data from the medical charts was performed by only 1 person (Horning), who was also 1 of the 2 pharmacists who provided the DSM services.

Third, this study was a retrospective analysis of data contained in patient charts, and the extent of documentation varied among facilities. Fourth, we had been providing DSM services in the 2 facilities since 2001 and were therefore unable to measure improvement in a prepost type of 2-by-2 comparative analysis between the DSM group and the DRR group. Fifth, for some disease states, only low numbers of cases for logistic regression analysis were available. Sixth, the data available to analyze hyperlipidemia treatment were limited since fasting lipid panels are generally performed and recorded as infrequently at least once per year and many medical charts had no recorded data for lipid values.

It is also important to recognize that we measured intermediate clinical outcomes and not endpoint outcomes. While the DSM intervention influenced these process outcomes of care, we do not know if the improved process outcomes translate into measurable endpoint outcomes, including quality of life. We also did not report in the current study the physician acceptance rate of DSM or DRR recommendations.

Finally, pharmacist time spent at DRR facilities and payment for their services were not evaluated. However, we previously evaluated the time spent by consultant pharmacists providing DSM services in LTCFs over an 8-month period and determined that consultant pharmacists spent an average of 11.6 minutes per patient per month. Currently, LTCFs do not have financial or other incentives to adhere to CPGs. LTCFs pay for DRR services based solely on adherence to federal guidelines, and the focus is on inappropriate medication use. The incentive for performing adequate DRR is sizable since there are potential penalties in the form of deficiencies for poor adherence to these measures. There are no current incentives for LTCFs to pay for DSM services, and the present study did not find savings in direct drug costs associated with DSM services compared with DRR services.

Conclusions
This self-evaluation of adherence to CPGs for 7 chronic diseases...
Adherence to Clinical Practice Guidelines for 7 Chronic Conditions in Long-term-Care Patients Who Received Pharmacist Disease Management Services Versus Traditional Drug Regimen Review

found that 4 of the 7 diseases (diabetes, CAD, HF, and osteoporosis) had higher rates of CPG adherence in patients in LTCFs who received pharmacist DSM services compared with patients in LTCFs who received traditional pharmacist DRR services. For the other 3 chronic diseases (hypertension, hyperlipidemia, and stroke), there was no difference in CPG adherence for DSM services compared with DRR services. Pharmacists providing DSM services were more likely to make drug therapy recommendations for the target disease states compared with pharmacists who provided DRR services.

What is already known about this subject

- Currently, there are few measures and no benchmarks or standards to determine the adequacy of care in the delivery of DSM services to residents of LTCFs despite this sizable population with high medication use.

What this study adds

- A higher rate of adherence to clinical practice guidelines for 4 of the 7 chronic diseases was found for patients in LTCFs who received pharmacist DSM services compared with patients in LTCFs who received traditional pharmacist DRR services.
- Pharmacists providing DSM services were more likely to make drug therapy recommendations for care management of the target chronic disease states compared with pharmacists who provided DRR services.

DISCLOSURES

No outside funding supported this research. It was presented, in part, as a poster abstract at the American College of Clinical Pharmacy Spring Practice and Research Forum, April 10, 2006, Monterey, CA. The authors disclose no potential bias or conflict of interest relating to this article.

Author Kristin K. Horning served as principal author of the study. Study concept and design were contributed by Horning and author James D. Hoehns. Data collection was the work of Horning; data interpretation was the work of Hoehns and author William R. Doucette, with input from Horning. Writing of the manuscript was primarily the work of Horning, with input from Hoehns, and revision was the work of Horning and Hoehns, with input from Doucette.

REFERENCES


AMCP Format Dossier Requests: Manufacturer Response and Formulary Implications for One Large Health Plan

JOSHUA J. SPOONER, PharmD, MS; PRANAV K. GANDHI, BPharm, MS; and SUSAN BROWN CONNELLY, PharmD, MBA

ABSTRACT

BACKGROUND: The Academy of Managed Care Pharmacy (AMCP) Format for Formulary Submissions, a template for health plans to use in developing formulary submission guidelines, has been widely adopted since its initial release in 2000. Many health plans request a dossier (a standardized set of clinical and economic evidence prepared by pharmaceutical manufacturers) to provide information for consideration during the formulary decision-making process. While dossier quality has reportedly improved over time, there is no recent research examining the response rate to dossier requests and the quality of dossiers received.

OBJECTIVE: To perform an evaluation of pharmaceutical manufacturers’ response to a request for a product dossier prepared using the AMCP Format, and to determine if dossier receipt was associated with a favorable formulary placement.

METHODS: The pharmacy and therapeutics (P&T) committee of a mid-Atlantic health plan with approximately 3 million members reviewed 43 drug products from February 2004 through December 2005. A university-based clinical evaluation subcontractor requested dossiers in the AMCP Format by telephone and e-mail from the manufacturers’ drug information center about 8 weeks before the committee meeting. A retrospective evaluation of the materials received from the manufacturers was performed. A logistic regression model was developed to determine if dossier receipt increased the likelihood of second-tier copayment formulary placement for new product reviews.

RESULTS: Dossiers were requested for 43 products. We received dossiers for 25 products (58%), other drug information (e.g., journal reprints, product labeling) for 10 products (23%), a formulary kit for 4 products (9%), and no response for the remaining 4 products (9%). Of the 25 dossiers, 21 (84%) generally followed the AMCP Format. Unlocked interactive budget impact models were included in 5 dossiers (20%), and modeling reports (without an unlocked interactive model) were included in 12 dossiers (48%). Dossiers were more likely to be received when the time between U.S. Food and Drug Administration (FDA) approval and dossier request was ≥4 months (65% vs. 27% when <4 months; P < 0.05) and when requested from a large manufacturer (top 25 in sales) compared with smaller manufacturers (75% vs. 43%; P < 0.05). Dossier receipt did not improve a product’s likelihood for preferred formulary placement; none of the new products for which dossiers were received were assigned to the second copayment tier compared with 33% of the new products with no supporting dossier. The logistic regression model failed to find any correlation between dossier receipt and preferred formulary placement.

CONCLUSIONS: Manufacturers met the request for a dossier nearly three fifths of the time. The dossiers were of high quality and generally followed the AMCP Format; the models included in dossiers varied widely in their design and utility. The product manufacturer’s size and the time between FDA approval and dossier request influenced the likelihood of dossier receipt. Receipt of a dossier did not appear to influence the likelihood of a product attaining preferred formulary status.

KEYWORDS: Dossier, Formulary submission guideline, Manufacturer, Formulary, Response rate

J Manag Care Pharm. 2007;13(1):37-43

Note: A commentary on the subject of this article appears on pages 66-67 of this issue.

The pharmacy and therapeutics (P&T) committees of health plans have traditionally requested drug information from pharmaceutical manufacturers to assist them in the formulary review process. Until the turn of the century, manufacturers often responded to this request by providing information regarding potential price rebates and sending formulary kits containing marketing materials and clinical trial reprints. Concerns pertaining to the comprehensiveness and veracity of information provided by manufacturers led to the development of formulary submission guidelines, which served to formalize, standardize, and expand the information required for formulary review. In 2000, the Academy of Managed Care Pharmacy (AMCP) developed its Format for Formulary Submissions, a template for health plans to use to develop their own formulary submission guidelines. The Format has since been modified several times, most recently in April 2005. While the use of formulary submission guidelines has slowed to evolve, they have come into widespread use, with more than 50 health plans, pharmacy benefit managers, hospitals, state Medicaid programs, or other public agencies (covering more than 100 million people) adopting the AMCP Format or a Format-like process.

The centerpiece of the formulary submission process is the dossier, a standardized set of clinical and economic evidence prepared by pharmaceutical manufacturers and presented to health plans in response to unsolicited requests, for the plans’ consideration during the formulary decision-making process. Many health plans questioned the quality of the first sets of dossiers they received, citing what they perceived to be poorly constructed dossiers containing incomplete or unreliable data. While the quality and completeness of dossiers have reportedly improved over time, recent research examining the response rate...
The purpose of this study was to perform an evaluation of pharmaceutical manufacturers’ responses to a request for a product dossier prepared using the AMCP Format for Formulary Submissions.

Methods

The university-based unit of the authors (Advanced Concepts Institute [ACI] of the University of the Sciences in Philadelphia) was contracted by a health plan to develop and present detailed product reviews (written and oral presentations) to their P&T committee in 2004 and 2005. This multistate health plan is located in the mid-Atlantic region of the United States, provides medical and pharmacy benefit coverage for approximately 3 million members, and offers a pharmacy benefit with a 3-tier copayment design. The health plan’s P&T committee meets semimonthly to conduct both new product reviews and class reviews.

To support the development of the detailed product reviews, ACI requested AMCP Format dossiers by telephone or e-mail from the product manufacturers’ drug information center about 8 weeks before the committee meeting. If notified that a dossier was not available, ACI requested other drug information materials to support monograph development. If no materials were received within 4 weeks of the committee meeting, a follow-up request for a dossier or other drug information was made. The P&T committee did not delay a product review if materials were not received from the manufacturer; in such instances, a detailed product review was prepared using information obtained by ACI through other sources.

A retrospective analysis of the manufacturers’ responses to the dossier request was performed. All materials received during the 6-week period starting on the initial dossier request date and ending 2 weeks before the P&T committee meeting (the submission date of review materials to the health plan) were catalogued. The materials were classified into 1 of 3 categories: (1) dossier (materials titled or identified as such; or materials not titled or identified as a dossier that clearly followed the AMCP Format or another submission format); (2) formulary kit (materials titled or identified as such); or (3) other drug information (including product labeling, reprints of key publications, meeting abstracts and posters, and economic analyses).

Each dossier was examined by 1 of 2 clinical pharmacists to determine if it included the information requested for each subject heading in version 2.0 of the AMCP Format (the current version of the AMCP Format for the majority of the study period): Product Description, Place of Product in Therapy, Summaries of Key Clinical and Economic Studies, Spreadsheet of All Clinical Studies, Product Value and Overall Cost, Reprints of All Key Trials, Summaries of Outcomes Studies and Economic Evaluation Supporting Data, A Review of Clinical and Disease Management Intervention Strategies, Formulary Submission.

<table>
<thead>
<tr>
<th>Characteristics of the Products for Which AMCP Format Dossiers Were Requested</th>
<th>New Product Reviews n = 31</th>
<th>Class Reviews n = 12</th>
<th>Total n = 43 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic area</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular agents</td>
<td>4</td>
<td>6</td>
<td>9 (21)</td>
</tr>
<tr>
<td>Central nervous system agents</td>
<td>6</td>
<td>3</td>
<td>9 (21)</td>
</tr>
<tr>
<td>Endocrine/metabolic agents</td>
<td>7</td>
<td>0</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Anti-infective agents</td>
<td>6</td>
<td>0</td>
<td>6 (14)</td>
</tr>
<tr>
<td>Gastrointestinal agents</td>
<td>1</td>
<td>4</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Renal/genitourinary agents</td>
<td>5</td>
<td>0</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Respiratory agent</td>
<td>1</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Antineoplastic agent</td>
<td>1</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Time between FDA approval and dossier request—mean [SD]</td>
<td>5.2 [2.9] months</td>
<td>9.0 [4.4] years</td>
<td>–</td>
</tr>
<tr>
<td>Manufacturer size (in pharmaceutical sales)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-10</td>
<td>8</td>
<td>8</td>
<td>16 (37)</td>
</tr>
<tr>
<td>11-25</td>
<td>6</td>
<td>2</td>
<td>8 (19)</td>
</tr>
<tr>
<td>26-50</td>
<td>4</td>
<td>1</td>
<td>5 (12)</td>
</tr>
<tr>
<td>≥51</td>
<td>13</td>
<td>1</td>
<td>14 (33)</td>
</tr>
<tr>
<td>FDA chemical type and review classification†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New molecular entity, standard review (1s)</td>
<td>12</td>
<td>8</td>
<td>20 (47)</td>
</tr>
<tr>
<td>New molecular entity, priority review (1p)</td>
<td>4</td>
<td>1</td>
<td>5 (12)</td>
</tr>
<tr>
<td>New ester, salt, or other covalent derivative, standard review (2s)</td>
<td>1</td>
<td>1</td>
<td>2 (5)</td>
</tr>
<tr>
<td>New formulation, standard review (3s)</td>
<td>7</td>
<td>2</td>
<td>9 (21)</td>
</tr>
<tr>
<td>New combination, standard review (4s)</td>
<td>4</td>
<td>0</td>
<td>4 (9)</td>
</tr>
<tr>
<td>New combination, priority review (4p)</td>
<td>2</td>
<td>0</td>
<td>2 (5)</td>
</tr>
<tr>
<td>New indication, standard review (6s)</td>
<td>1</td>
<td>0</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

* Manufacturer size (in descending order) by total pharmaceutical sales in the calendar year preceding the dossier request.
† Alphanumeric code indicates the U.S. Food and Drug Administration (FDA) designation for chemical type (number) and review classification (letter). AMCP = Academy of Managed Care Pharmacy.
Checklist, and Model. If included in the dossier, the pharmacoeconomic or disease impact-model was classified as a working model (a spreadsheet or other model allowing for baseline variable manipulation and calculation review) or a model report (the results of a model were presented, but a working model was not included). Lastly, the reviewer's subjective determination on whether the dossier followed the AMCP Format was recorded; dossiers exhibiting general accordance with the Format's prescribed layout and content without any evidence of omission of requested information were considered to have followed the AMCP Format.

For comparison purposes, dossier requests were classified as new product reviews (requested to aid a committee review of a recently approved single product) or a class review (requested to aid a committee review of all the products within the class). For each dossier request, the request lag time (equal to the time difference between the U.S. Food and Drug Administration [FDA] approval date of each agent and the date of the dossier request) was calculated, and the size of the product manufacturer (based on the preceding year's sales data) was determined. The FDA chemical type and review classification of all products were also noted.

Tests of significance were performed on continuous and categorical data (t test and chi-square, respectively) to determine if any statistically significant differences existed between groups (new product reviews vs. class reviews, groupings for manufacturer size, dossier request lag time, and FDA chemical type/review classification). Following the P&T committee review, the committee's decision on the product's formulary placement was noted. All new products received a full formulary review. For new product reviews, a logistic regression model was developed to determine if dossier receipt was associated with a favorable (second-tier copayment) formulary placement. In addition to dossier receipt, variables accounted for in the regression model included (at the time of formulary review) manufacturer size, number of competing in-class agents, number of competing in-class agents on formulary, presence of in-class generic formulary agents, and cost comparison (average wholesale price) to competing in-class formulary agents.

## Results

The P&T committee selected 43 drug products for review at 10 committee meetings occurring during the evaluation period (a mean number of 4.3 [±3.8] per committee meeting; range: 2-13). The characteristics of these products are reviewed in Table 1. A majority of the products (72%) were new product reviews. Eight therapeutic areas were covered by dossier requests; products in the cardiovascular and central nervous system therapeutic areas were most commonly requested. The mean length of time between FDA product approval and the dossier request was 5.2 ± 2.9 months for products covered by new product reviews and 9.0 ± 4.4 years for products covered by class reviews. Thirty-seven percent of all dossier requests went to the 10 largest pharmaceutical manufacturers (by U.S. sales figures), and more than half of all requests went to the top 25 manufacturers. Fifty-eight percent of the products were classified by the FDA as new molecular entities, followed by new formulation (21%) and new combination (14%); a majority of the products (84%) underwent a standard FDA review.

Dossier receipt was more likely to be received when the lag time between FDA approval and dossier request was ≥4 months (65% [13/20] when ≥4 months vs. 27% when <4 months; P <0.05) (Table 2). The receipt of dossiers tended to be higher when requested for products covered by class reviews (75%) than those for new product reviews (52%), although this difference did not achieve statistical significance. The size of the manufacturer of the requested product played a role in dossier receipt; receipt of dossiers was more likely when requested from a larger manufacturer than from a smaller one (75% for top 25 manufacturers vs. 43% for all others; P <0.05). Dossier receipt was also more likely for new molecular entities compared with new formulations (76% vs. 22%; P <0.01).
The size of the dossiers received ranged from 39 to 210 pages of content, excluding clinical trial reprints. The majority of the dossiers that were received (84%) were judged by the authors to have generally followed the AMCP Format. Three of the 4 dossiers that were judged to have not followed the AMCP Format excluded numerous studies (with positive and negative results) from the dossier, while the fourth failed to provide succinct study summaries for the key clinical studies. None of the dossiers followed any other recognized dossier format such as the Regence BlueShield or Ontario guidelines. Dossier sections that were included or addressed in less than 70% of submissions were (1) a pharmacoeconomic or disease management impact model (included in 68% [48% + 20%] of dossiers), (2) reprints of all key trials (68%), (3) summaries of outcomes studies and economic evaluation supporting data (64%), (4) a review of clinical and disease management intervention strategies (40%), and (5) the formulary submission checklist (0%) (Table 3). There were no statistically significant differences between new product reviews and class reviews with regard to likelihood of inclusion in any one section of a dossier. Additional information (information not requested in the AMCP Format) was included in 36% of the dossiers; executive summaries, and a section titled “answers to frequently asked questions” accounted for most of the additional content.

Pharmacoeconomic or disease-impact models were included in 17 of the 25 dossiers received. Of these, only 5 (20% of all dossiers, 29% of all dossiers with models) included unlocked interactive economic or budget-impact models in which the user could alter key variables and enter health plan-specific data. All 5 of these models were budget-impact models. The remaining 12 models (48% of all dossiers, 71% of all dossiers with models) provided only reports describing the economic analyses performed in varying length and detail. Overall, products evaluated as part of a new product review were assigned preferred formulary placement (second copayment tier) 16.1% (5/31) of the time. Receipt of a product dossier to support the development of the detailed product review did not improve a product's likelihood for preferred formulary placement; none of the 16 new product reviews for which dossiers were received were assigned to the second copayment tier of the formulary, compared with 5 of the 15 new product reviews (33%) for which dossiers were not received. The logistic regression model failed to find any correlation, positive or negative, between dossier receipt and preferred formulary placement for new product reviews.

### Discussion

In October 2006, the AMCP executive director announced that the Academy would begin the process of evaluating the utility of dossiers in the formulary decision process. While a few studies have evaluated the quality of responses received in response to a dossier request, to our knowledge there have been no publications describing the response rate to dossier requests and no evaluations about how dossiers might affect the formulary decision-making process. While we do not know the methodology or extent to which this forthcoming research will address those questions, our analysis represents the first attempt at answering some of these important questions.

In this analysis, manufacturers supplied a dossier in response to a request for an AMCP Format dossier 58% of the time. This percentage is lower than anticipated, especially given the large-scale adoption of the AMCP Format by health care management organizations. While some manufacturers stated that they believed dossier production inflicted a great expense

### Table 2

<table>
<thead>
<tr>
<th>Dossiers Received, Stratified by Review Type, Manufacturer Size, FDA Chemical Type/Review Classification, and Time between FDA Approval and Dossier Request</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Requested</strong></td>
</tr>
<tr>
<td>Class reviews</td>
</tr>
<tr>
<td>New product reviews</td>
</tr>
<tr>
<td><strong>By manufacturer size</strong> (sales rank in preceding year)</td>
</tr>
<tr>
<td>≥26</td>
</tr>
<tr>
<td><strong>By FDA chemical type</strong></td>
</tr>
<tr>
<td>New molecular entity</td>
</tr>
<tr>
<td>New ester, salt, or other covalent derivative</td>
</tr>
<tr>
<td>New formulation</td>
</tr>
<tr>
<td>New combination</td>
</tr>
<tr>
<td>New indication</td>
</tr>
<tr>
<td><strong>By FDA review classification</strong></td>
</tr>
<tr>
<td>Standard review</td>
</tr>
<tr>
<td>Priority review</td>
</tr>
<tr>
<td><strong>New product reviews: stratified by length of time between FDA approval and dossier request</strong></td>
</tr>
<tr>
<td>&lt;4.0 months</td>
</tr>
<tr>
<td>4.0-7.9 months</td>
</tr>
<tr>
<td>8.0 months</td>
</tr>
</tbody>
</table>

* P <0.05 for comparison of manufacturer size by sales in previous year, 1-25 vs. 26, chi-square test.
† P <0.01 for comparison of new molecular entity vs. new formulation, chi-square test.
‡ P <0.05 for comparison of ≤4.0 months vs. 4.0-7.9 months and ≥8.0 months, chi-square test.
FDA = U.S. Food and Drug Administration.
on their organization, no recent complaints have been noted. As evidence suggests that adoption of a systematic formulary review process may lead to an increase in pharmaceutical spending in health programs, manufacturers should strive to develop dossiers for those organizations that have adopted such evidence-based formulary reviews.

Factors that influenced the likelihood of dossier receipt included the length of time between FDA approval and the dossier request, and product manufacturer size. A period of at least 4 months between FDA approval of a product and request of a dossier increased the likelihood of dossier receipt by 140% for new product reviews. The AMCP Format recommends that manufacturers should have dossiers completed by the time of the product launch to avoid any delays in responding to unsolicited dossier requests; our findings indicate that many manufacturers may not be meeting this recommendation. The higher likelihood of dossier receipt for products covered by class reviews (75%) over new product reviews (52%) may be a result of the difference in lag time between the 2 types of reviews. Large manufacturers (top 25 in sales) were able to meet requests for dossiers more frequently (75%) than were small manufacturers (43%), this difference remained once the dossier requests with a lag time <4 months were eliminated (8/10 [80%] for large manufacturers vs. 5/10 for small manufacturers [50%]). Large manufacturers are likely to have more internal resources or financial resources available for developing dossiers, which may contribute to the different rates of dossier receipt.

While the likelihood of dossier receipt appeared to be greater for requests made in 2005 (64%) compared with 2004 (52%), this is skewed by the fact that 2005 had all 12 product requests pertaining to class reviews. With a focus only on new product reviews, the likelihood of dossier receipt fell to 50% for 2005, indicating a flat rate of dossier receipt over the 2-year evaluation period.

“Other drug information” and formulary kits were received in response to 33% of requests. While formulary kits have essentially been replaced by dossiers as the information package of choice for health care decision makers, manufacturers continue to produce and distribute them. Several manufacturers offered to provide them in addition to the dossier if we so desired. However, we did not receive any formulary kits that were labeled as dossiers, an experience described by others.

Despite repeated attempts, no response of any kind was received in response to 9% of the requests. We found this result surprising; at the very least a minimal response (such as study reprints) should have been received. Notably, all 4 of the “no responses” came from smaller manufacturers.

The majority of the dossiers that were received generally followed the AMCP Format. Three of the 4 dossiers that did not follow the AMCP Format failed to include summaries of all the trials that included the product. While we judged some dossiers to have followed the AMCP Format even if they had failed to include 1 or 2 studies in the spreadsheet of all clinical/outcomes/economic studies, these 3 dossiers were missing a large number of trials from their spreadsheets, and 2 of the 3 dossiers appeared to include only those trials that provided

<table>
<thead>
<tr>
<th>TABLE 3 Characteristics of Submitted Dossiers According to AMCP Format Version 2.0 Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMCP Format Version 2.0</td>
</tr>
<tr>
<td>Section Number</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Product description</td>
</tr>
<tr>
<td>Place of product in therapy</td>
</tr>
<tr>
<td>Summaries of key clinical and economic studies</td>
</tr>
<tr>
<td>Spreadsheet of all clinical studies</td>
</tr>
<tr>
<td>Product value and overall cost</td>
</tr>
<tr>
<td>Reprints of all key trials</td>
</tr>
<tr>
<td>Summaries of outcomes studies and economic evaluation supporting data</td>
</tr>
<tr>
<td>A review of clinical and disease management intervention strategies</td>
</tr>
<tr>
<td>Formulary submission checklist</td>
</tr>
<tr>
<td>Model</td>
</tr>
<tr>
<td>A model report (but no working model)</td>
</tr>
<tr>
<td>A working model (spreadsheet or other model for data input)</td>
</tr>
<tr>
<td>No model</td>
</tr>
</tbody>
</table>
the most favorable data for the product under consideration. While we have observed that it is common practice for manufacturers to choose the most favorable trials when selecting the trials that receive the detailed study summaries in the dossier, it is unacceptable (and against Format guidelines) to exclude any trials from the spreadsheet, regardless of the trial’s results. Models were included in 68% of the dossiers we received, somewhat higher than the 45% observed in a larger study of 115 dossiers. While the smaller sample size of our study may account for some of this difference, the different time frames of these studies (2004-2005 for our study compared with 2002-2005 for the comparator study) was not a factor because the percentage of dossiers containing models in the comparator study was actually lower in 2004-2005 (37%) compared with 2002-2003 (51%).

Products evaluated as a new product review received preferred formulary placement 16.1% of the time. By itself, receipt of a dossier did not influence the formulary decision. Our finding that none of the products with dossiers received preferred formulary status was far less than the 54% reported by Fullerton and Atherly for another health plan, although the requirements for formulary acceptance and level of formulary placement were not clearly delineated in their report. Our results are also inconsistent with the recent case report from Watkins et al. Nevertheless, in the current study, products for which dossiers were received fared worse than those products for which dossiers were not received, as 33% of those products without dossiers were assigned preferred formulary status. While we would not suggest that submission of a dossier actually lessens a product’s chances for preferred formulary placement, it is clear that preparation of a dossier provides no guarantee that a product will be looked on favorably by a P&T committee. A logistic regression model accounting for several other factors that influence formulary decision making failed to find any correlation between dossier receipt and preferred formulary product placement.

**Limitations**

While the logistic regression model employed in the current study accounted for many factors that could potentially influence formulary placement (e.g., number of competing in-class agents, number of competing in-class agents on formulary, presence of in-class generic formulary agents, and cost comparison (average wholesale price) to competing in-class formulary agents), 2 of the most significant variables that influence formulary decision making, the safety and efficacy of the product, were not included in the model. To do so would have required development of comparative measures for safety and efficacy that would have to be validated and would certainly generate considerable controversy. Nonetheless, we believe that this model represents a useful first step in analyzing the influence of dossiers in the formulary decision-making process.

In addition to the limitations in the logistic regression model, several other limitations in our analysis merit mention. First, a change in the AMCP Format criteria occurred with the release of Format version 2.1 in April 2005. While Format version 2.1 requested some additional information to be supplied in dossiers, all the information requested in Format version 2.0 was carried over into the new version (albeit streamlined in places). As such, a quantitative evaluation using the Format version 2.0 criteria for dossiers received throughout the entire evaluation period is acceptable because it did not result in any differences in evaluating the dossiers received throughout the analysis period.

Second, one manufacturer of a single product under review claimed to have a product dossier but refused to send it to us, stating it would only send a dossier to the health plan directly. Since we were prohibited from revealing the identity of the health plan we were working with, we had to accept the manufacturer’s offer to send “other drug information” (product labeling and study reprints) in place of the dossier. While the possibility exists that other manufacturers did not send dossiers because (1) we were not a health plan and (2) we did not identify the health plan we were working with, no other manufacturer explicitly stated that these factors would prevent us from receiving a dossier.

Third, we utilized the FDA approval date as one benchmark for assessing the likelihood of dossier receipt. The product launch date may be a better index for dossier availability than the FDA approval date since not all FDA-approved products have been launched by their manufacturer. Three of the products under evaluation in this study had received FDA approval but had not been launched by their manufacturer prior to the date of the initial dossier request. However, this did not affect our findings, as removal of these 3 products from the analysis did not alter the statistical significance of any of the results.

**Conclusions**

In summary, manufacturers provided a dossier in response to a specific request for an AMCP Format dossier nearly 60% of the time. These dossiers generally followed the AMCP Format and addressed most of the information requested in the Format. While the models included in dossiers varied widely, most were not unlocked interactive economic or budget-impact models that allowed the user to alter key variables and enter health plan-specific data, thereby limiting the model’s utility. Factors such as the size of the manufacturer of the product and the length of time between the product’s FDA approval date and the dossier request can predict the likelihood of receiving a dossier. While we did not find that the receipt of a dossier improved a product’s likelihood for preferred formulary placement, manufacturers should continue to provide dossiers in response to unsolicited requests for product information. Additional research in this field can help further determine the influence that dossiers play in the formulary decision-making process.
What is already known about this subject

- The majority of U.S. health plans or their pharmacy benefit managers request product dossiers from manufacturers according to the AMCP Format.
- The information contained in dossiers can influence drug formulary decisions and product placement in copayment tiers.

What this study adds

- The university-based clinical evaluation subcontractor for a large health plan of approximately 3 million members received product dossiers for 58% of requests made in 2004 and 2005.
- The size of the product manufacturer (based on sales data) and the length of time between FDA approval of the product and the request for a dossier are directly related to the likelihood of receiving a product dossier.
- Receipt of a dossier was not influential in the formulary placement of the product for this large health plan.

DISCLOSURES

No outside funding supported this research. The preliminary results of this analysis were presented, in part, as a poster at the AMCP Annual Meeting, April 20-23, 2005, in Denver, CO. The authors disclose no potential bias or conflict of interest relating to this article.

Author Joshua J. Spooner served as principal author of the study. Study concept and design were contributed primarily by Spooner, with input from author Susan Brown Connelly. Data collection was the work of Spooner; data interpretation was primarily the work of Spooner, with input from Connelly and author Pranav K. Gandhi. Writing of the manuscript was the work of Spooner; its revision was the work of all authors.

REFERENCES

10. Neumann PJ. Quality of dossiers submitted under the AMCP Format. Presented at: Academy of Managed Care Pharmacy 17th Annual Meeting and Showcase; April 22, 2005, Denver, CO.
13. Cahill J. Welcoming address. Presented at: Academy of Managed Care Pharmacy 2006 Educational Conference; October 6, 2006, Chicago, IL.
Descriptive Analysis of the Direct Medical Costs of Multiple Sclerosis in 2004 Using Administrative Claims in a Large Nationwide Database

JEFF D. PRESCOTT, PharmD; SAUL FACTOR, RPh, MBA; MICHAEL PILL, PharmD; and GARY W. LEVI, JD

ABSTRACT

BACKGROUND: Multiple sclerosis (MS) is chronic and debilitating, affects patients in the prime of their lives, and requires costly, decades-long disease management. MS prevalence is increasing, and treatment with new drug therapies is expensive.

OBJECTIVES: The objectives of this analysis were to (1) determine the average total and component direct medical costs incurred in the treatment of MS patients in 2004, and (2) compare MS treatment costs and cost factors in 2004 with 1995.

METHODS: The data for this analysis were abstracted from the PharMetrics Integrated Patient-centric Database, which contains administrative claims data from more than 80 private and public health plans in the United States, representing more than 9.6 million unique patients in 2004. To be included in this analysis, each patient had to have at least 1 medical claim with a diagnosis of MS (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 340) in the date of service period from January 1, 2004, through December 31, 2004. Patients were segmented according to patient age and sex, comorbid conditions, payer type, and use of specific types of disease-modifying drugs (DMDs). Episode Treatment Group (ETG) software (ETG numbers 149 or 150) was used to aggregate medical claims related to MS since not all MS-related medical claims have the ICD-9-CM code 340. ETGs are commonly used to aggregate administrative claims data and to define discrete periods of care (episodes); this study used ETGs only to aggregate administrative claims. Statistical comparisons were subsequently performed using analysis of variance and chi-square analyses. The source of the data for the aggregate MS treatment costs in 1995 was the Medstat MarketScan database.

RESULTS: In calendar year 2004, a total of 13,420 patients were identified with a medical or hospital claim with ICD-9-CM code 340, a prevalence of approximately 14.0 per 10,000. The final study population was reduced to 10,099 patients (75.3%) after applying the criterion of 12 full months of available claims data. The total average annual cost for the 10,099 patients in 2004 was $12,879 (standard deviation, $18,582), 64.8% of which was attributable to the cost of prescription drugs and 61.4% to the cost of DMDs in particular, 26.2% to outpatient care, 7.8% to inpatient care, and 1.1% to emergency room visits. There was no difference in total average annual medical costs for males compared with females, but costs did differ among age categories and by insurance type and payer. A total of 5,810 patients (57.5% of the study population) reported at least 1 pharmacy claim for a DMD, and these patients had average annual costs of $18,944 compared with $4,662 total annual costs for MS patients who did not receive DMDs. Pharmacy costs represented 75.3% of annual medical costs for the patients who reported at least 1 pharmacy claim for a DMD but only 7.4% for patients who did not receive DMDs. A comparison of 2004 costs with 1995 costs (adjusted for 2004 based on the Consumer Price Index; CPI-U [All Urban Consumers, All Items]; 1982-84 = 100) demonstrated that total annual MS-related treatment costs increased by 35%, from $9,515 in 1995 to $12,879 in 2004. There was some difference in total annual MS-related treatment costs in 2004 among the 4 DMD therapy groups—$16,928 for glatiramer, $17,987 for IFN beta-1a (intramuscular), $19,616 for IFN beta-1b, and $22,557 for IFN beta-1a (subcutaneous), P <0.001.

CONCLUSION: Pharmacy costs accounted for 65% of total MS-related medical costs in 2004 and 75% of total costs for the subset of MS patients (58%) who received at least 1 DMD.

KEYWORDS: Multiple sclerosis, Benchmarking, Managed care

J Manag Care Pharm. 2007;13(1):44-52

Multiple sclerosis (MS) is a chronic debilitating disease characterized by inflammatory demyelination (loss of myelin) within the central nervous system (CNS). Loss of myelin disrupts the nerves’ ability to conduct electrical impulses to and from the brain, triggering a variety of symptoms, including fatigue, visual disturbances secondary to optic neuritis, and sensory disturbances such as paresthesias or hypoesthesia (numbness). Spasticity of the limbs and bladder, impotence, fatigue, depression, and mild emotional or intellectual changes may also develop over time.

MS affects approximately 350,000 people in the United States, with approximately 12,000 new cases diagnosed each year. The majority of MS cases (approximately two thirds) occur in young adults between the ages of 20 and 40, with incidence peaking between the ages of 30 and 35. Females are 2 to 3 times more likely to develop MS than males, and whites are more likely to develop MS than persons of Asian or African descent.

Because MS is chronic and disabling—and because, despite their disability, most people with MS have a normal life span—MS imposes considerable cost on individuals, families, the health care system, and society. In 1998, it was estimated that the total annual economic burden of MS in the United States

Authors

JEFF D. PRESCOTT, PharmD, is vice president, science and technology, and GARY W. LEVI, JD, is senior vice president, The MCM Group, Marlton, NJ; MICHAEL PILL, PharmD, is an independent consultant (at the time of this study, he was vice president, client services, The MCM Group); SAUL FACTOR, RPh, MBA, is vice president, specialty pharmaceuticals, McKesson, San Francisco, California (at the time of this study, he was vice president, clinical services, and chief operating officer, RxAmerica LLC, Salt Lake City, Utah).

AUTHOR CORRESPONDENCE: Jeff D. Prescott, PharmD, Vice President, Science and Technology, The MCM Group, 1081 Centre Blvd., Marlton NJ, 08053. Tel: (856) 596-6995; Fax: (856) 596-8996; E-mail: jprescott@theMCMgroup.com

Copyright© 2007, Academy of Managed Care Pharmacy. All rights reserved.
 exceed $6.8 billion, with a lifetime cost (direct and indirect) of $2.2 million per patient. Since MS patients are typically affected in the prime of life, most of the total costs (57%) are related to indirect costs such as lost income, equipment and alterations, and formal (paid) and informal (unpaid) care. MS is, in fact, more costly than other debilitating diseases, such as stroke or Alzheimer's disease, that generally occur later in life. Moreover, as the prevalence of MS increases, and new, more expensive drugs are launched, MS-related costs are becoming more closely scrutinized by payers in the managed care arena.

This background underscores the need for managed care professionals to understand how MS is treated and managed system-wide. However, little current information is available because much of the available research was conducted before the emergence of contemporary disease-modifying drugs (DMDs) or immunomodulators, such as the interferons and glatiramer. For example, the first of these agents (interferon beta-1b, Betaseron) was approved by the U.S. Food and Drug Administration for use in the United States in 1993, and the most recently approved product (interferon beta-1a, Rebif) entered the market in 2002 (Table 1).

This is a descriptive analysis of the results of aggregating administrative claims for more than 10,000 MS patients in 2004. The direct medical costs are reported by component cost categories and arrayed by other variables of interest that may be useful to managed care clinicians and administrators.

## Methods

### Source Data

Patient-level administrative claims data were obtained from the PharMetrics Integrated Patient-centric Database, a large data warehouse of administrative claims. At the time of this analysis, the database contained data from more than 80 private and public (Medicare and Medicaid) health care plans across the United States, representing more than 9.6 million unique patients in 2004. Medical and facility claims have diagnosis codes in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) format, and procedure codes are in Current Procedural Terminology version 4 (CPT-4) and Health Care Procedure Coding System formats. National Drug Code (NDC) numbers are used to identify drugs in pharmacy claim records from both community and mail-service pharmacies. Additional data elements from the database used in this analysis include patient characteristics such as geographic region, age and gender, insurance type (e.g., health maintenance organizations [HMOs], preferred provider organizations [PPOs]), and payer type (e.g., commercial, self-insured, Medicare risk).

### Cost-Aggregating Software

The source data for this analysis were organized and grouped using Episode Treatment Group (ETG) software from Symmetry Health Data Systems, a widely used illness-classification and episode-building software application. The ETG methodology...
Descriptive Analysis of the Direct Medical Costs of Multiple Sclerosis in 2004 Using Administrative Claims in a Large Nationwide Database

### TABLE 3
Total Average Annual MS Cost per Patient by Region (2004)

<table>
<thead>
<tr>
<th>Region</th>
<th>N</th>
<th>% of Total</th>
<th>Average Cost per Year ($) [SD]</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midwest</td>
<td>4,817</td>
<td>47.7</td>
<td>13,228 [19,301]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Northeast</td>
<td>1,821</td>
<td>18.0</td>
<td>12,471 [13,809]</td>
<td></td>
</tr>
<tr>
<td>Southcentral</td>
<td>650</td>
<td>6.4</td>
<td>8,418 [9,907]</td>
<td></td>
</tr>
<tr>
<td>Southeast</td>
<td>2,099</td>
<td>20.8</td>
<td>12,912 [22,459]</td>
<td></td>
</tr>
<tr>
<td>West</td>
<td>712</td>
<td>7.1</td>
<td>15,533 [16,990]</td>
<td></td>
</tr>
<tr>
<td>Overall (all regions)</td>
<td>10,099</td>
<td>100.0</td>
<td>12,879 [18,583]</td>
<td>–</td>
</tr>
</tbody>
</table>

* Calculated using analysis of variance. MS = multiple sclerosis.

matches medical claims and pharmacy claims data to specific diagnoses through a series of temporal and clinical-association algorithms. ETG-based episodes of care are longitudinal packages of disease-specific claims data and provide a consistent method for reporting health care economics spanning the entire continuum of care and for relating these measures to independent variables such as patient demographics, clinical markers, and pharmacotherapy. For purposes of this analysis, only the aggregation feature of ETGs was employed; i.e., ETGs were used to aggregate medical costs and not to define discrete episodes of care.

The ETGs used in this analysis, ETG 149 (inflammation of the CNS, with surgery) and ETG 150 (inflammation of the CNS, without surgery), are based on ICD-9-CM codes that include MS (340) and other neurological conditions such as 336 (spinal cord disease not elsewhere classified), 337 (autonomic nerve disorder), 341 (other CNS demyelination), and 344 (other paralytic syndromes). ETG-based episodes are typically built using a variety of similar ICD-9-CM codes to compensate for variations or errors in provider coding practices; however, as noted in the patient selection criteria sections of this analysis, only ETGs built upon ICD-9-CM code 340 were used in this analysis. The ETG methodology was used to identify and aggregate claims data for economic measurements and, as mentioned, captures claims that are not only directly identified by ICD-9-CM code 340 for the treatment of MS but also other, less specific ICD-9-CM codes that are associated with procedures and services identified as being specific and relevant to the treatment of MS, compensating for coding variations or errors.

**Patient Selection**

Patient data comprising the primary MS study population were selected from the source database for January 1, 2004, through December 31, 2004. Patients were selected on the basis of the presence of ETGs 149 or 150 and at least 1 medical claim with a diagnosis of MS (ICD-9-CM code 340). This ICD-9-CM code is specific to ETGs 149 and 150 and is a primary marker used by the ETG software methodology to define the MS episodes for this analysis. The ETG codes were used to capture MS-related costs.

**Reporting Metrics**

Cost information related to use of medical and pharmacy services was captured using ETG-defined aggregation for dates of service over an interval of 365 days (representing the 2004 calendar year); thus, each patient contributed only 1 episode to the analysis. The cost fields from the administrative claims data used in this analysis are submitted charges (i.e., charges submitted by providers) and do not represent actual payer costs. The cost data were then broken down into the following categories and, where applicable, subcategories, thereby identifying the point along the patient care continuum at which MS-specific service was received:

- **Inpatient**
  - Ancillary: diagnostic or treatment-related procedures
  - Facility: room and board charges
  - Management: clinician inpatient visit
  - Surgical: surgical procedures

- **Outpatient**
  - Ancillary: diagnostic or treatment-related procedures
  - Management: office visit charges for usual care
  - Surgical: surgical procedures

- **Pharmacy.** All prescription drug claims (provided by in-office administration, community, or mail-order pharmacies) defined by an NDC code and/or a J code. J codes used in this analysis for the identification of DMDs were J1825 (injection beta-1a, 33 mcg), J1830 (injection interferon beta-1b, 0.25 mg), and J1595 (injection, glatiramer acetate, 20 mg).

- **Emergency room.** Any medical claim containing procedure codes (CPT-4) 99281-99288 or revenue codes 450-452, 456, 459, or 981.

**Cost Aggregation by Drug**

Costs were also aggregated by DMD for the 3 interferons and glatiramer. Each DMD patient had to have at least 1 pharmacy claim with an NDC code for a DMD or at least 1 medical claim with a J code for a DMD in 2004. A subanalysis was also performed for patients who received only 1 DMD (i.e., monotherapy).

**Statistical Analysis**

Analysis of univariate means was performed using analysis of variance, and proportions were compared with chi-square testing. All statistics were generated using SPSS version 13.0 software (SPSS Inc., Chicago, IL).

### Results

**Population Characteristics**

The MS population in this analysis consisted of 10,099 patients (Table 2). This was a national-level sample, with nearly half...
Descriptive Analysis of the Direct Medical Costs of Multiple Sclerosis in 2004 Using Administrative Claims in a Large Nationwide Database

(48%) of the patients from the Midwest, and a total of 40% from the Northeast and Southeast (Table 3). These percentages do not reflect the prevalence of MS in those regions but only the composition of the database. With respect to line of business, the analyzed patient population was primarily derived from commercial insurance plans (89%) and from HMOs and PPOs (49% and 33%, respectively) (Table 4).

The average age of a patient with MS was 47 years (standard deviation [SD], 11.2 years); nearly 63% of patients were between the ages of 36 and 55 years. Female patients outnumbered male patients by more than 3 to 1 (Table 5). Of the concurrent conditions (selected conditions of interest) in the MS population in this study, the most commonly reported in medical claims were malaise and fatigue (ICD-9-CM codes 780.7, 780.71, or 780.79, in 21.6% of patients), depression (ETGs 95 or 96 [which are based on ICD-9-CM codes 296, 298, 300, 301, 309, 311 and 313], reported in 19.8% of patients), and burning/numbness/tingling sensations (ICD-9-CM code 782.0, reported in 17.2% of patients). Reported less frequently were some of the more severe complications of the disease, such as ataxia (ICD-9-CM code 781.3, reported in 3.1% of patients) and optic neuritis (ICD-9-CM code 341.0, reported in 0.4% of patients) (Table 6).

**Annual Costs**

The total cost for the average MS patient in calendar year 2004 (representing total direct MS costs over the 365-day period for inpatient, outpatient, emergency room, and pharmacy services) was $12,879 (Table 7). Average outpatient costs were $3,380 per patient (26% of total costs), attributable to 14.5 outpatient services (units of use), which included 4.4 physician office visits (outpatient management) and 10 diagnostic procedures (Table 7). Per patient, approximately 8.8 MS-specific prescriptions including DMDs were dispensed during the year 2004, representing $8,351 in costs (64.8% of total annual costs) (Table 7).

There were significant differences in total annual costs for all demographic subgroups, except for gender. Region, line of business, payer, and patient age were associated with statistically significant variation (P <0.001). There was no significant difference in total annual costs by gender (P = 0.396) (Tables 3, 4, and 5).

Average annual costs per patient were often significantly higher when certain conditions were present (compared with episodes that reported no evidence of those conditions). When aggregated by clinical condition, patients with medical claims with 1 or more diagnosis codes for abnormality of gait had average costs of $20,871, and patients with diagnosis codes for spasms had average costs of $20,376, both about 60% higher than the cost of the average MS episode ($12,879) (Table 6).

**Annual Costs by DMD**

Use of a single drug in the interferon class was observed in 36.0% of MS patients (combined n = 3,640) with sole use of IFN beta-1a (intramuscular [IM]) the most frequent (n = 2,023, 21.0% of all MS patients), followed by glatiramer (n = 1,837, 20.2%), IFN beta 1-b (n = 952, 8.6%), and IFN beta-1a (subcutaneous [SC]) (n = 665, 6.7%) (Table 8). Among the patient groups analyzed, the group treated with IFN beta-1a (SC) was slightly younger (average of about 44 years old), but the absolute difference among the 4 DMDs was small (Table 9).

<table>
<thead>
<tr>
<th>TABLE 4</th>
<th>Total Average Annual MS Cost by Insurance Type and Payer (2004)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insurance Type</td>
<td>N</td>
</tr>
<tr>
<td>Health maintenance organization</td>
<td>4,941</td>
</tr>
<tr>
<td>Indemnity plan</td>
<td>657</td>
</tr>
<tr>
<td>Point of service</td>
<td>958</td>
</tr>
<tr>
<td>Preferred provider organization</td>
<td>3,377</td>
</tr>
<tr>
<td>Payer</td>
<td></td>
</tr>
<tr>
<td>Commercial plan</td>
<td>8,982</td>
</tr>
<tr>
<td>Medicaid</td>
<td>190</td>
</tr>
<tr>
<td>Medicare cost</td>
<td>63</td>
</tr>
<tr>
<td>Medicare risk</td>
<td>253</td>
</tr>
<tr>
<td>Self-insured</td>
<td>476</td>
</tr>
</tbody>
</table>

* Calculated using analysis of variance. MS = multiple sclerosis.

<table>
<thead>
<tr>
<th>TABLE 5</th>
<th>Total Average Annual MS Cost by Patient Age and Sex (2004)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Age</td>
<td>Mean</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>N</td>
</tr>
<tr>
<td>0-17</td>
<td>74</td>
</tr>
<tr>
<td>18-25</td>
<td>257</td>
</tr>
<tr>
<td>26-35</td>
<td>1,249</td>
</tr>
<tr>
<td>36-45</td>
<td>2,684</td>
</tr>
<tr>
<td>46-55</td>
<td>3,651</td>
</tr>
<tr>
<td>56-64</td>
<td>1,744</td>
</tr>
<tr>
<td>65+</td>
<td>440</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7,749</td>
</tr>
<tr>
<td>Male</td>
<td>2,350</td>
</tr>
</tbody>
</table>

* Calculated using analysis of variance. MS = multiple sclerosis.
Descriptive Analysis of the Direct Medical Costs of Multiple Sclerosis in 2004 Using Administrative Claims in a Large Nationwide Database

There was no difference in the ratio of females to males, about 75% to 79% for the 4 DMDs. There were small differences in the rates of selected conditions of interest among patients who received the 4 DMDs, including abnormality of gait ($P<0.001$); ataxia ($P=0.004$); burning, numbness, and tingling sensations ($P<0.001$); depression ($P<0.001$) and malaise and fatigue ($P=0.002$); and fibromyalgia, myalgia, and myositis ($P=0.015$) (Table 10).

Total average annual MS-related treatment costs appeared to be slightly lower (about 6%) for the patient group treated with glatiramer ($\$16,928$) compared with IFN beta-1a (IM) ($\$17,987$), about 14% lower compared with IFN beta-1b ($\$19,616$), and 25% less than the group treated with IFN beta-1a (SC) ($\$22,557$) (Table 11). The glatiramer group had the lowest number of pharmacy claims for the DMD (average 8.14), and the IFN beta-1a (IM) group had the highest number of DMD claims (average 10.41).

**Discussion**

MS disease treatment costs are affected by both clinical and nonclinical factors. The nonclinical factors include patient demographics, region of the country, type of insurance, and payer type. This study provides a description of the distribution of direct costs related to MS treatment within U.S. managed care organizations and indemnity health insurance plans. On average, the total annual cost in 2004 for MS-related medical care was

**Table 6** Total Average Annual MS Cost by Presence of Selected Comorbid Conditions (2004)

<table>
<thead>
<tr>
<th>Condition</th>
<th>N</th>
<th>% of Total</th>
<th>Average Annual Cost ($ SD)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormality of gait (781.2)</td>
<td>744</td>
<td>7.4</td>
<td>20,871 [37,948]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ataxia (781.3)</td>
<td>311</td>
<td>3.1</td>
<td>16,168 [19,317]</td>
<td>0.002</td>
</tr>
<tr>
<td>Burning, numbness, tingling sensations (782.0)</td>
<td>1,738</td>
<td>17.2</td>
<td>12,504 [14,913]</td>
<td>0.356</td>
</tr>
<tr>
<td>Convulsions (780.3)*</td>
<td>349</td>
<td>3.5</td>
<td>15,664 [20,381]</td>
<td>0.004</td>
</tr>
<tr>
<td>Depression (ETGs 95 or 96)</td>
<td>2,001</td>
<td>19.8</td>
<td>13,928 [14,757]</td>
<td>0.005</td>
</tr>
<tr>
<td>Fecal incontinence (787.6)</td>
<td>40</td>
<td>0.4</td>
<td>18,694 [14,101]</td>
<td>0.047</td>
</tr>
<tr>
<td>Fibromyalgia/myalgia and myositis (729.1)</td>
<td>744</td>
<td>7.4</td>
<td>11,478 [12,574]</td>
<td>0.033</td>
</tr>
<tr>
<td>Malaise and fatigue (780.7*)</td>
<td>2,177</td>
<td>21.6</td>
<td>14,604 [17,630]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Optic neuritis (341.0)</td>
<td>37</td>
<td>0.4</td>
<td>39,247 [138,557]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spasms (781.0)</td>
<td>333</td>
<td>3.3</td>
<td>20,376 [26,652]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Trigeminal neuralgia (350.1)</td>
<td>92</td>
<td>0.9</td>
<td>12,467 [17,494]</td>
<td>0.831</td>
</tr>
<tr>
<td>Urinary incontinence (788.3*)</td>
<td>558</td>
<td>5.5</td>
<td>16,898 [19,118]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Voice disturbances (784 4*, 784.5)</td>
<td>165</td>
<td>1.6</td>
<td>16,463 [25,537]</td>
<td>0.012</td>
</tr>
</tbody>
</table>

* The prevalence of selected conditions was based on the presence of listed ETGs or 1 or more ICD-9-CM codes present on medical claims any time during the study period.
† Calculated using analysis of variance.
MS = multiple sclerosis.

**Table 7** MS Component Costs—Overall Population (2004)

<table>
<thead>
<tr>
<th>Service Category</th>
<th>Units of Use* per Year</th>
<th>Costs per Year ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean [SD]</td>
<td>Mean (% of Total) [SD]</td>
</tr>
<tr>
<td>Inpatient ancillary</td>
<td>0.80 [5.76]</td>
<td>543 (4.2) [4,592]</td>
</tr>
<tr>
<td>Inpatient facility</td>
<td>0.06 [0.48]</td>
<td>414 (3.2) [8,716]</td>
</tr>
<tr>
<td>Inpatient management</td>
<td>0.24 [1.85]</td>
<td>39 (0.3) [277]</td>
</tr>
<tr>
<td>Inpatient surgical</td>
<td>0.01 [0.15]</td>
<td>7 (&lt;0.1) [165]</td>
</tr>
<tr>
<td>Inpatient total</td>
<td>1.11 [7.36]</td>
<td>1,004 (7.8) [10,866]</td>
</tr>
<tr>
<td>Outpatient ancillary</td>
<td>9.96 [18.77]</td>
<td>2,777 (21.6) [9,108]</td>
</tr>
<tr>
<td>Outpatient management</td>
<td>4.36 [8.23]</td>
<td>546 (4.2) [1,171]</td>
</tr>
<tr>
<td>Outpatient surgical</td>
<td>0.15 [0.71]</td>
<td>57 (0.4) [368]</td>
</tr>
<tr>
<td>Outpatient total</td>
<td>14.47 [22.47]</td>
<td>3,380 (26.2) [5,527]</td>
</tr>
<tr>
<td>Emergency room</td>
<td>0.64 [3.61]</td>
<td>145 (1.1) [9,212]</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>8.79 [10.4]</td>
<td>8,351 (64.8) [13,513]</td>
</tr>
<tr>
<td>Disease-modifying drugs</td>
<td>5.29 [6.37]</td>
<td>7,901 (61.4) [13,336]</td>
</tr>
<tr>
<td>Total annual costs</td>
<td>–</td>
<td>12,879 (100.0) [18,583]</td>
</tr>
</tbody>
</table>

* Units of use refers to the number of claims submitted that fall under each service category or subcategory.
MS = multiple sclerosis.
$12,879 per patient/episode, with 64.8% of the total charges attributable to prescription drugs. A comparison of these data with research performed before the emergence of DMDs indicates that, over time, the cost structure for treating MS has changed notably. In particular, in a 1995 analysis of 6,412 MS patients from a privately insured population Pope et al. reported annual costs per patient (in 1995 dollars) of $7,677—equivalent to $9,515 in 2004 dollars—with 18% attributable to prescription drugs. The analysis by Pope et al. used allowed charges (i.e., net health plan cost plus member cost share) rather than the provider-submitted charges used in the present analysis, thereby understating the cost basis data for 1994-1995. With this caveat, the comparison reflects that 2004 pharmacy costs were higher and constituted a higher percentage of the total annual costs. Yet, 2004 costs for medical services were—after adjusting for inflation—actually lower than those reported in the 1995 study: $4,529 in 2004 compared with $7,802 in 1995 (Table 12). This trend may be related to the effectiveness of DMD therapy in managing MS severity and reducing functional disability, which has been correlated with lower costs.8,9

Exacerbations of MS symptoms, referred to as relapses, also substantially increase the cost of medical care.10 Although the limitations of this analysis preclude links between clinical severity and costs, we have observed how the presence of certain concurrent conditions related to the progression of MS,11 used as surrogates of disease severity, can influence costs. In the present study, the medical claim diagnoses associated with higher costs include abnormality of gait, optic neuritis, and spasms.

The present study was limited to direct medical costs in 2004. Kobelt et al. estimated that direct medical and nonmedical costs represented 53% of the total cost of MS.8 Almost half of the total societal cost of MS is attributable to production losses (37%) and informal care (10%). In their cross-sectional postal survey, Kobelt et al. also found considerable interpatient variability in disease severity and 29% of MS patients reporting a relapse in the past 3 months.

Using administrative claims data for approximately 9.6 million patients covered by public payers (Medicare or Medicaid) and private health plans, we found a prevalence of 14.0 patients per 10,000. This is considerably lower than the prevalence of 24 per 10,000 found by Pope et al. in the privately insured population in 1994 and 1995, of 36 per 10,000 in the Medicare population (1996 and 1997), and of 71 per 10,000 in the disabled subpopulation of Medicaid recipients in 6 states (1991-1996).7

In the present study, use of the 4 DMDs was associated with different total MS-related treatment costs. This descriptive analysis cannot be used to ascertain the reasons for the variance in total treatment costs, which could be explained by the effect

---

**TABLE 8** Utilization of Disease-Modifying Drugs in MS Patients (2004)

<table>
<thead>
<tr>
<th></th>
<th>IFN Beta-1a (IM)</th>
<th>IFN Beta-1a (SC)</th>
<th>IFN Beta-1b</th>
<th>Glatiramer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any DMD use</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Patients with DMD monotherapy†</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
</tbody>
</table>
| IFN= interferon; IM= intramuscular; SC= subcutaneous.

* %= the ratio of DMD (disease-modifying drug) use in the total sample of 10,099 MS patients.
† Monotherapy refers to the sole use of the DMD listed in the column heading during the study year, with no evidence of other DMDs.

**TABLE 9** Average Patient Age and Sex by Specific Disease-Modifying Drug (2004)

<table>
<thead>
<tr>
<th>Average age</th>
<th>Gender</th>
<th>IFN Beta-1a (IM)</th>
<th>IFN Beta-1a (SC)</th>
<th>IFN Beta-1b</th>
<th>Glatiramer</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>46.7</td>
<td>Female</td>
<td>1,548</td>
<td>498</td>
<td>729</td>
<td>1,453</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>43.7</td>
<td>Male</td>
<td>475</td>
<td>167</td>
<td>223</td>
<td>384</td>
<td>0.089†</td>
</tr>
</tbody>
</table>

* Calculated using analysis of variance.
† Calculated using chi-square analysis.
IFN= interferon.
of disease severity. The United Kingdom’s National Institute for Health and Clinical Excellence (NICE) released an unfavorable evaluation of available DMDs in 2002, but these agents are commonly used for treating MS in the United States. A 5th DMD, natalizumab (Tysabri), was withdrawn from the U.S. market in February 2005 because of an association between that drug and the development of progressive multifocal leukoencephalopathy. However, natalizumab was reintroduced to the U.S. market in June 2006, evidence of the demand and need for alternative therapies for MS, particularly for those patients with relapsing MS.

There are gaps in information about MS-related health care costs. Our results were similar to those of a 2002 study designed to measure cost-effectiveness among the DMDs, including slightly lower costs associated with use of glatiramer compared with use of interferons. However, at the time of the 2002 analysis, only 2 of the 3 interferons were available: interferon beta-1a (IM) and interferon beta-1b.

**Limitations**

Foremost among the limitations of this study is the method of data aggregation and follow-up for MS patients. For example, drug utilization was quite different among the 4 DMDs, an average of 10.4 DMD pharmacy claims for IFN beta-1a (IM) versus 8.7 each for IFN beta-1a (SC) and IFN beta-1b, and 8.1 for glatiramer in calendar year 2004. Second, administrative claims data do not include clinical information, such as laboratory values, or other measures, such as disease severity, and this study could not aggregate data by MS disease type (e.g., primary progressive vs. relapsing-remitting or secondary progressive disease). There is large variation in the cost measures in the present study, as evidenced from the large standard deviation values.

Third, this is a descriptive analysis that cannot inform about cause-and-effect relationships. While we were curious about the aggregate costs by DMD, it is not possible to determine how economic outcomes are related to clinical status or the effect of patient severity on economic outcomes in this study. Fourth, the cost data in the present study were provider-submitted charges, which may, because of variable reimbursement rates, overstate actual payer costs.

Fifth, this study relied on third-party software (i.e., the ETGs) to aggregate administrative claims data since MS-related medical claims may not have the specific 340 ICD-9-CM diagnosis code for MS. This method has 2 implications. First, the ETG software is commercially available and widely used tool such as ETGs enables others to perform an analysis similar to this study in their own environments and to use the data from the present study for comparison. On the other hand, the ETG software is

### Table 10: Prevalence* of Selected Conditions by Disease-Modifying Drug Therapy (2004)

<table>
<thead>
<tr>
<th>Condition</th>
<th>IFN Beta-1a (IM)</th>
<th>IFN Beta-1a (SC)</th>
<th>IFN Beta-1b</th>
<th>Glatiramer</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>% of Total</td>
<td>N</td>
<td>% of Total</td>
<td>N</td>
<td>% of Total</td>
</tr>
<tr>
<td>Abnormality of gait (781.2)</td>
<td>100</td>
<td>4.9</td>
<td>57</td>
<td>8.6</td>
<td>96</td>
</tr>
<tr>
<td>Ataxia (781.3)</td>
<td>49</td>
<td>2.4</td>
<td>28</td>
<td>4.2</td>
<td>30</td>
</tr>
<tr>
<td>Burning, numbness, tingling sensations (782.0)</td>
<td>244</td>
<td>12.1</td>
<td>132</td>
<td>19.8</td>
<td>90</td>
</tr>
<tr>
<td>Convulsions (780.3*)</td>
<td>35</td>
<td>1.7</td>
<td>22</td>
<td>3.3</td>
<td>22</td>
</tr>
<tr>
<td>Depression (ETGs 95 or 96)</td>
<td>344</td>
<td>17.0</td>
<td>132</td>
<td>19.8</td>
<td>174</td>
</tr>
<tr>
<td>Fecal incontinence (787.6)</td>
<td>5</td>
<td>0.2</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Fibromyalgia/myalgia and myositis (729.1)</td>
<td>104</td>
<td>5.1</td>
<td>42</td>
<td>6.3</td>
<td>52</td>
</tr>
<tr>
<td>Malaise and fatigue (780.7*)</td>
<td>357</td>
<td>17.6</td>
<td>154</td>
<td>23.2</td>
<td>172</td>
</tr>
<tr>
<td>Optic neuritis (341.0)</td>
<td>3</td>
<td>0.1</td>
<td>3</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Spasms (781.0)</td>
<td>47</td>
<td>2.3</td>
<td>19</td>
<td>2.9</td>
<td>34</td>
</tr>
<tr>
<td>Trigeminal neuralgia (350.1)</td>
<td>16</td>
<td>0.8</td>
<td>4</td>
<td>0.6</td>
<td>3</td>
</tr>
<tr>
<td>Urinary incontinence (788.3*)</td>
<td>88</td>
<td>4.3</td>
<td>38</td>
<td>5.7</td>
<td>44</td>
</tr>
<tr>
<td>Voice disturbances (784.4*, 784.5)</td>
<td>19</td>
<td>0.9</td>
<td>8</td>
<td>1.2</td>
<td>16</td>
</tr>
</tbody>
</table>

* The prevalence of selected conditions was based on the presence of listed ETGs or 1 or more ICD-9-CM codes present on medical claims any time during the study period.

IFN = interferon; IM = intramuscular; SC = subcutaneous.
not free, and other methods to group administrative claims data may produce different results.

Conclusions

Pharmacy costs represented 65% of total MS-related treatment costs in 2004, and 57.5% of all MS patients received at least 1 DMD. For the patients who used DMDs, pharmacy costs represented an average 75% of total MS-related medical care costs. While there were differences in the total MS-related treatment costs among the 4 DMDs, the reasons for these differences could not be ascertained in the present study.

Descriptive Analysis of the Direct Medical Costs of Multiple Sclerosis in 2004 Using Administrative Claims in a Large Nationwide Database

**TABLE 11** Average Total Annual MS Cost by Disease-Modifying Drug Utilization (2004)

<table>
<thead>
<tr>
<th>Service Category</th>
<th>IFN Beta-1a (IM) [N = 2,023]</th>
<th>IFN Beta-1a (SC) [N = 665]</th>
<th>IFN Beta-1b [N = 952]</th>
<th>Glatiramer [N = 1,837]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ($) [SD]</td>
<td>% of Total</td>
<td>Mean ($) [SD]</td>
<td>% of Total</td>
</tr>
<tr>
<td>Inpatient</td>
<td>744 [7,297]</td>
<td>4.1</td>
<td>1,204 [6,811]</td>
<td>5.3</td>
</tr>
<tr>
<td>Outpatient</td>
<td>2,834 [52]</td>
<td>15.8</td>
<td>5,157 [6,722]</td>
<td>22.9</td>
</tr>
<tr>
<td>Emergency room</td>
<td>91 [6]</td>
<td>0.5</td>
<td>265 [1,527]</td>
<td>1.2</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>14,318 [73]</td>
<td>79.6</td>
<td>15,930 [9,258]</td>
<td>70.6</td>
</tr>
<tr>
<td>Total charges</td>
<td>17,987 [11,714]</td>
<td>100.0</td>
<td>22,557 [12,566]</td>
<td>100.0</td>
</tr>
<tr>
<td>DMD costs*</td>
<td>13,860 [7,066]</td>
<td>77.1</td>
<td>15,278 [8,890]</td>
<td>67.7</td>
</tr>
<tr>
<td>All other pharmacy costs</td>
<td>457 [1,759]</td>
<td>2.5</td>
<td>653 [2,172]</td>
<td>2.9</td>
</tr>
</tbody>
</table>

* Refers to only the disease-modifying drug named in the respective column heading.
† Calculated using analysis of variance.
IFN = interferon; IM = intramuscular; MS = multiple sclerosis; NA = not applicable; SC = subcutaneous.

**TABLE 12** Comparison of MS Costs for 1995 and 2004

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Medical</td>
<td>6,329</td>
<td>7,802</td>
<td>4,529</td>
<td>-42%</td>
</tr>
<tr>
<td></td>
<td>Pharmacy</td>
<td>1,348</td>
<td>1,713</td>
<td>8,351</td>
<td>388%</td>
</tr>
<tr>
<td></td>
<td>Total Annual Costs</td>
<td>7,677</td>
<td>9,515</td>
<td>12,879</td>
<td>35%</td>
</tr>
</tbody>
</table>

* Adjusted for inflation using the U.S. Consumer Price Index. MS = multiple sclerosis.

What is already known about this subject

- Multiple sclerosis is a chronic and debilitating medical condition with a growing patient population that requires long-term treatment. The economic burden imposed by MS is substantial, consisting of direct and indirect costs. The indirect costs are, by definition, largely outside the control of managed care, but managed care can influence the direct costs of treating MS.

What this study adds

- This study promotes better understanding of the factors that influence direct costs. This study presents direct medical claims data that managed care decision makers can use as benchmarks to evaluate their own cost and utilization data.

DISCLOSURES

Funding for this study was provided, in part, by a grant from Biogen Idec, manufacturer of interferon beta-1a (IM), and was obtained by author Michael Pill. Pill and authors Jeff D. Prescott, Saul Factor, and Gary W. Levi disclose that they do not have a financial interest or affiliation with Biogen Idec and have not participated in Biogen Idec advisory boards, consulting, or speakers bureaus. Prescott served as principal author of the study. Study concept and design, data collection and interpretation, and writing of the manuscript and its revision were the work of all authors.

REFERENCES


Use of Low-Molecular-Weight Heparin During Dental Extractions in a Medicaid Population

TRACY K. PETTINGER, PharmD, and CHRISTOPHER T. OWENS, PharmD, BCPS

ABSTRACT

BACKGROUND: Evidence-based guidelines recommend against discontinuation of oral anticoagulation therapy during most dental procedures because severe bleeding complications are rare and there is an increased risk for thromboembolic events in patients for whom warfarin therapy is interrupted. Although interruption of oral anticoagulation and bridge therapy with low-molecular-weight heparin (LMWH) may be indicated for high-risk individuals undergoing certain procedures, the use of LMWH in tooth extractions is expensive and often unnecessary.

OBJECTIVE: The purpose of this review was to identify and characterize procedural use of LMWH for dental extractions with respect to current consensus recommendations.

METHODS: The Idaho Medicaid pharmacy and medical claims database was queried to identify patients with a tooth extraction procedure between February 1, 1998, and January 31, 2005. Patients on warfarin therapy for 2 months before tooth extraction were identified as were claims for LMWH within 30 days before the procedure or 5 days after. Patient profiles were reviewed to determine number of extractions, rate of LMWH use, indication for anticoagulation, and associated drug costs.

RESULTS: Of 55,260 Medicaid patients who had a tooth extraction, 518 (0.9%) had received warfarin for at least 2 consecutive months before the tooth extraction procedure. Of these, 31 patients (6%) received LMWH therapy at the time of extraction for a total of 35 procedures. All procedures selected for review carried a low bleeding risk, with an average of 1.3 teeth extracted per procedure. The indications for anticoagulation included 16 procedures (45.7%) involving patients with a history of a thromboembolic event more than 90 days before the procedure, 10 procedures (28.5%) involving patients with a prosthetic valve, 4 procedures (11.4%) involving anticoagulated patients with atrial fibrillation, and 5 procedures (14.2%) involving patients with a history of thromboembolism fewer than 3 months before the procedure. LMWH costs for these 35 extractions totaled $22,294, or an average of $637 per procedure or $474 per extracted tooth. Enoxaparin was used in all but 1 of the procedures, with an average 5-day supply (average 8 enoxaparin units) dispensed per procedure. The costs associated with the required additional drug monitoring, e.g., INR monitoring, were not included in this analysis.

CONCLUSION: Although the overall number of dental procedures in anticoagulated patients using LMWH was small in our review, this inappropriate use resulted in avoidable costs to this Medicaid program.

KEYWORDS: Anticoagulation, Warfarin, Low-molecular-weight heparin, Dental extraction

J Manag Care Pharm. 2007;13(1):53-58

A therapeutic dilemma exists when it comes to the appropriate management of anticoagulated patients who are required to undergo certain medical or dental procedures. Particularly in the case of uncomplicated dental procedures such as tooth extractions, evidence-based guidelines advise against discontinuation of oral anticoagulation therapy. A review of more than 700 case reports indicates few severe bleeding complications but severe thromboembolic complications in patients for whom therapy is interrupted. Although interruption of oral anticoagulation and “bridge therapy” with low-molecular-weight heparin (LMWH) may be indicated for high-risk individuals undergoing certain procedures (e.g., patients with mechanical valves or those who experienced a recent thromboembolic event), LMWH use in tooth extractions is expensive, often unnecessary, and not generally recommended.

A perceived risk of serious bleeding is the most often cited reason for discontinuing or modifying the warfarin therapy of continuously anticoagulated patients undergoing dental procedures, even though a review of the literature yields evidence to the contrary. While severe bleeding has been reported, reviews indicate that this occurs in less than 2% of cases. Many clinicians and dentists often associate experiences in general surgical procedures with those in tooth extractions, therefore magnifying the risk of complications, primarily bleeding. Another motive behind discontinuation of oral anticoagulation is the decreased amount of blood in the surgical field, allowing improved visual evaluation of the procedure.

In reality, the more prevalent concern with discontinuation of anticoagulant therapy is the risk of thrombosis. Rates of thrombosis in patients whose anticoagulation therapy is...
interrupted are difficult to determine due to lack of conclusive evidence; however, patients with mechanical valves and those who experienced a thromboembolic event within 3 months before the discontinuation of anticoagulation are considered to be at high risk for new or recurrent thromboembolism. In contrast, patients who are anticoagulated for indications such as atrial fibrillation are at much lower risk.¹

Current guidelines from the American College of Chest Physicians recommend against warfarin discontinuation during both routine dental procedures (i.e., cleanings, fillings, and crowns) as well as during more invasive surgical procedures (i.e., tooth extractions and gingival surgery) on the basis of few reported bleeding complications and an increased risk for thromboembolic events.¹²³ Control of local bleeding with tranexamic acid mouthwash or epsilon amino caproic acid mouthwash is also often recommended since studies have shown that these mouthwashes have allowed the patient to continue to use anticoagulation therapy successfully during dental procedures.¹¹²⁶

Anticoagulated patients should receive regular monitoring of the international normalized ratio (INR). However, the importance of the INR in anticoagulated patients undergoing dental procedures is not clear. A 2001 study involving 249 patients who underwent 543 dental procedures showed that the incidence of postoperative bleeding in anticoagulated patients was not significantly influenced by the INR value. Patients were divided into 5 groups, based on the INR taken on the day of the dental procedure. Groups 1-4 included patients with INR values of 1.5-1.99, 2.0-2.49, 2.5-2.99, and 3.0-3.49, respectively. Group 5 included patients with an INR greater than 3.5. The group included 23 patients and 43 extractions. Three patients (13%) experienced postoperative bleeding. This was not a statistically significant increase in postoperative bleeding compared with the other 4 groups analyzed, and the author concluded that dental procedures could be conducted without alteration in anticoagulation therapy.⁷

LMWH is an important option to consider in patients whose oral anticoagulation must be interrupted because of the potential for procedure-related bleeding complications but whose risk level necessitates continued protection from thromboembolism. The use of this so-called bridge therapy is indicated for high-risk individuals (i.e., patients with prosthetic valves) undergoing invasive procedures (i.e., knee/hip replacement or abdominal surgery). Because the majority of dental surgeries are not considered invasive, the use of LMWH bridge therapy in patients undergoing such procedures is unnecessary.¹

In the cases in which bridge therapy is appropriate, proper dosage of LMWH therapy is imperative for appropriate anticoagulation. Treatment guidelines recommend full-dose LMWH therapy for those patients with high thromboembolic risk, while prophylactic doses of LMWH are used in patients considered to have intermediate thromboembolic risk (patients not considered low or high risk).¹ Though more convenient than unfractionated heparin from a monitoring and administration standpoint, LMWH requires once- or twice-daily painful abdominal injections, which are also expensive (approximately $20 to $98 per day, based on dosage and number of daily injections).⁹ Despite the high cost of LMWH, its appropriate use has been associated with economic savings in preventing thromboembolic events.⁹

With the available evidence discouraging both the interruption of oral anticoagulation or the use of LMWH bridge therapy in patients undergoing minimally invasive dental procedures (e.g., 1 or more tooth extractions), and the high cost of LMWH treatment, our review focused on the inappropriate management of anticoagulated patients in a Medicaid population and the potential cost savings when guidelines are observed.

### Methods

A retrospective analysis of the Idaho Medicaid pharmacy and medical claims database was conducted for the 7-year period from February 1, 1998, through January 31, 2005. Over this time period, prescribers were not constrained by formulary restrictions or prior authorization criteria, and Medicaid recipients had no copayments or other drug-related costs. The first LMWH, enoxaparin (Lovenox), became available on the U.S. market in 1998, and others in the class (e.g., dalteparin [Fraxiparin], fondaparinux [Arixtra], and tinzaparin [Innohep]) were likewise available to Medicaid patients without restriction or copayment throughout the review period. In addition, consensus guidelines regarding appropriate management of anticoagulated patients remained consistent during the study period.

The database was queried to identify patients with 1 or more tooth extraction procedures based on Current Dental Terminology coding (Table 1). Dental procedure codes were limited to those representing extractions, including those surgical in nature, to ensure that only procedures with a low risk of bleeding were reviewed. More complicated surgical procedures, such as those involving the sinuses, were not included in the analysis because recommendations for anticoagulation and bridge therapy differ, depending on risk factors.

From the population identified, patients who had monthly claims for warfarin sodium in the 2 consecutive months preceding the dental procedure were identified (Figure 1). The database was queried to detect at least 1 claim for LMWH within 30 days before the procedure to 5 days after the procedure for these patients. Up to 30 days before the procedure was selected to permit inclusion of LMWH prescriptions written in anticipation of the tooth extraction, and 5 days after the procedure was selected to permit inclusion of LMWH used to stabilize INR as a result of interruption of oral anticoagulation. To help identify patients who were at risk for a thromboembolic event, we stratified individuals by likely indication for anticoagulation therapy. These indications were based on International Classification of Diseases, Ninth Revision, Clinical Modification
### TABLE 1: Codes Used to Extract Data, Including the Current Dental Terminology, Tooth Extraction Codes, International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) Codes, and Drug Codes

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>ICD-9-CM Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>D7111</td>
<td>Extraction, coronal remnants – deciduous tooth</td>
<td>673.20</td>
</tr>
<tr>
<td>D7140</td>
<td>Extraction, erupted tooth or exposed root (elevation and/or forceps removal)</td>
<td>673.21</td>
</tr>
<tr>
<td>D7210</td>
<td>Surgical removal of erupted tooth requiring elevation of mucoperiosteal flap and removal of bone and/or section of tooth</td>
<td>673.22</td>
</tr>
<tr>
<td>D7220</td>
<td>Removal of impacted tooth – soft tissue</td>
<td>673.23</td>
</tr>
<tr>
<td>D7230</td>
<td>Removal of impacted tooth – partially bony</td>
<td>673.24</td>
</tr>
<tr>
<td>D7240</td>
<td>Removal of impacted tooth – completely bony</td>
<td>673.25</td>
</tr>
<tr>
<td>D7241</td>
<td>Removal of impacted tooth – completely bony, with unusual surgical complications</td>
<td>673.26</td>
</tr>
<tr>
<td>D7250</td>
<td>Surgical removal of residual tooth roots (cutting procedure)</td>
<td>673.27</td>
</tr>
<tr>
<td>427.3</td>
<td>Atrial fibrillation and flutter</td>
<td>95075</td>
</tr>
<tr>
<td>427.31</td>
<td>Atrial fibrillation</td>
<td>95776</td>
</tr>
<tr>
<td>427.32</td>
<td>Atrial flutter</td>
<td>95777</td>
</tr>
<tr>
<td>996.02</td>
<td>Mechanical complication due to heart valve prosthesis</td>
<td>95778</td>
</tr>
<tr>
<td>996.71</td>
<td>Complications due to heart valve prosthesis</td>
<td>95779</td>
</tr>
<tr>
<td>V42.2</td>
<td>Transplant of heart valve</td>
<td>95780</td>
</tr>
<tr>
<td>V43.3</td>
<td>Replacement by other means – heart valve</td>
<td>95781</td>
</tr>
<tr>
<td>415.1</td>
<td>Pulmonary embolism and infarction</td>
<td>95782</td>
</tr>
<tr>
<td>415.11</td>
<td>Iatrogenic pulmonary embolism/infarction</td>
<td>95783</td>
</tr>
<tr>
<td>415.19</td>
<td>Pulmonary embolism and infarction – other</td>
<td>95784</td>
</tr>
<tr>
<td>444.21</td>
<td>Upper extremity embolism</td>
<td>96334</td>
</tr>
<tr>
<td>444.22</td>
<td>Lower extremity embolism</td>
<td>15494</td>
</tr>
<tr>
<td>453.0</td>
<td>Other venous embolism and thrombosis</td>
<td>23775</td>
</tr>
<tr>
<td>453.2</td>
<td>Venous embolism and thrombosis of vena cava</td>
<td>23776</td>
</tr>
<tr>
<td>453.3</td>
<td>Venous embolism and thrombosis of renal vein</td>
<td>23777</td>
</tr>
<tr>
<td>453.40</td>
<td>Venous embolism and thrombosis of unspecified deep vessels of lower extremity</td>
<td>23778</td>
</tr>
<tr>
<td>453.41</td>
<td>Venous embolism and thrombosis of deep vessels of the proximal lower extremity</td>
<td>25790</td>
</tr>
<tr>
<td>453.42</td>
<td>Venous embolism and thrombosis of deep vessels of distal lower extremity</td>
<td>25791</td>
</tr>
<tr>
<td>453.43</td>
<td>Venous embolism and thrombosis of other specified veins</td>
<td>25792</td>
</tr>
<tr>
<td>453.9</td>
<td>Embolism of vein – thrombosis (vein)</td>
<td>25793</td>
</tr>
<tr>
<td>639.6</td>
<td>Embolism</td>
<td>25794</td>
</tr>
<tr>
<td>673.0</td>
<td>Obstetrical pulmonary embolism</td>
<td>25795</td>
</tr>
<tr>
<td>673.2</td>
<td>Obstetrical blood clot embolism</td>
<td>25796</td>
</tr>
</tbody>
</table>

*The 5-digit numbers for drugs are First DataBank generic code numbers. NOS = not otherwise specified, U = unit.
Use of Low-Molecular-Weight Heparin During Dental Extractions in a Medicaid Population

At the time of a tooth extraction procedure, 518 patients were anticoagulated with warfarin sodium. Of these, 31 patients (6%), for a total of 35 procedures, appeared to have had their oral anticoagulation therapy interrupted at the time of the procedure and subsequently received LMWH bridge therapy.

The average age of the 31 patients was 49.6 years, with 41.9% of them male. Enoxaparin was the primary LMWH used, prescribed in 97.1% of the tooth extractions with LMWH bridge therapy. Procedures were relatively low risk for bleeding, with an average of 1.3 teeth extracted per procedure.

The primary diagnosis for anticoagulation therapy in the patient procedures included those with a thromboembolic event more than 90 days before the dental extraction (45.7%, \( N = 16 \) extractions). Other diagnoses included mechanical valves (28.5%, \( N = 10 \)), lone atrial fibrillation (11.4%, \( N = 4 \)), and a thromboembolic event fewer than 90 days before the dental extraction (14.2%, \( N = 5 \)). Evaluation of the LMWH dose prescribed for each procedure indicated the majority of patients received the full dose of LMWH. Patients considered at low risk for thromboembolism (e.g., patients with atrial fibrillation and those with a thromboembolic event greater than 90 days) received full-dose LMWH during 75% and 62.5% of procedures, respectively. Conversely, higher-risk patients (e.g., those with mechanical valves or patients with a history of a recent thromboembolic event) received full-dose LMWH during 40% and 20% of procedures, respectively (Figure 2).

The use of LMWH in this patient population resulted in average drug costs of $637 per procedure or $22,294 for these 31 patients, or an average drug cost of $474 per extracted tooth. Enoxaparin was used in all but 1 of the procedures, with an average 5-day supply dispensed per procedure; an average of 8 enoxaparin units were dispensed per procedure. Any costs incurred in additional drug monitoring (e.g., INR) were not determined in this analysis.

Discussion

Although the concern for bleeding complications in anticoagulated patients undergoing dental procedures is shared by patients and dentists alike, most clinical experience, as well as reports from the literature, does not support this concern.\(^{23,31,12}\) A review of the literature shows that the severity of embolic complications is greater than that of bleeding complications in patients who have undergone a dental procedure. One review showed that of 774 patients on continued anticoagulation in 2,014 dental procedures, 12 (1.6%) experienced bleeding that could not be controlled by local means, and the majority

---

(1) Jan/Febr 2007 Vol. 13, No. 1 www.amcp.org

---

Results

At the time of a tooth extraction procedure, 518 patients were anticoagulated with warfarin sodium. Of these, 31 patients (6%), for a total of 35 procedures, appeared to have had their oral anticoagulation therapy interrupted at the time of the procedure and subsequently received LMWH bridge therapy.

The average age of the 31 patients was 49.6 years, with 41.9% of them male. Enoxaparin was the primary LMWH used, prescribed in 97.1% of the tooth extractions with LMWH bridge therapy. Procedures were relatively low risk for bleeding, with an average of 1.3 teeth extracted per procedure.

The primary diagnosis for anticoagulation therapy in the patient procedures included those with a thromboembolic event more than 90 days before the dental extraction (45.7%, \( N = 16 \) extractions). Other diagnoses included mechanical valves (28.5%, \( N = 10 \)), lone atrial fibrillation (11.4%, \( N = 4 \)), and a thromboembolic event fewer than 90 days before the dental extraction (14.2%, \( N = 5 \)). Evaluation of the LMWH dose prescribed for each procedure indicated the majority of patients received the full dose of LMWH. Patients considered at low risk for thromboembolism (e.g., patients with atrial fibrillation and those with a thromboembolic event greater than 90 days) received full-dose LMWH during 75% and 62.5% of procedures, respectively. Conversely, higher-risk patients (e.g., those with mechanical valves or patients with a history of a recent thromboembolic event) received full-dose LMWH during 40% and 20% of procedures, respectively (Figure 2).

The use of LMWH in this patient population resulted in average drug costs of $637 per procedure or $22,294 for these 31 patients, or an average drug cost of $474 per extracted tooth. Enoxaparin was used in all but 1 of the procedures, with an average 5-day supply dispensed per procedure; an average of 8 enoxaparin units were dispensed per procedure. Any costs incurred in additional drug monitoring (e.g., INR) were not determined in this analysis.
of the patients who experienced a bleed had an INR above therapeutic range. In the relative risk analysis of continuous versus interrupted anticoagulation, 5 of 493 patients (1%) who discontinued anticoagulation for 542 dental procedures experienced a thromboembolic event, which was fatal in 4 cases.

Because only patients undergoing minimally invasive procedures were included in our review and the bleeding risk associated with such procedures is low, all these patients could have likely remained on continuous warfarin therapy without risk of significant bleeding complications. Noncompliance with current guidelines in this population resulted in small but avoidable drug costs. However, we did not assess INR monitoring costs that would presumably be increased in patients stopping and restarting oral anticoagulation therapy, thereby adding to the avoidable drug costs that were estimated in the present study. Therefore, the total cost savings to be realized from continuous versus interrupted oral anticoagulation therapy in this population of Medicaid recipients are likely greater than were calculated in the current study.

This analysis also revealed improper dosing of LMWH during bridge therapy, with the majority of atrial fibrillation patients receiving full doses of LMWH. On the other hand, those at highest risk for a thromboembolic event (e.g., patients with mechanical valves) received the appropriate full LMWH dose only 30% of the time. Although dentists took precautions with the bleeding risk, this analysis shows they disregarded the more likely and more life-threatening complication of thromboembolism. In addition, the use of higher than necessary doses in patients with atrial fibrillation also contributed to excessive LMWH costs.

Controversy regarding the appropriate management of anticoagulated patients undergoing medical and dental procedures has existed for decades, with little objective data to help guide clinicians. Current recommendations state that chronically anticoagulated patients should not have their therapy interrupted for most minor dental procedures, such as tooth extraction. Additionally, bridge therapy with LMWH is likewise not indicated for such patients and is associated with unnecessary economic costs.

To our knowledge, this is the first review of its kind and suggests the potential cost savings and opportunity for quality improvement that might be realized from adherence to consensus recommendations for continuous oral anticoagulation in patients at risk of thrombosis who undergo minor dental procedures. Further education on this issue for prescribers and a better understanding of the high cost, proper dosage, and specific place in therapy for LMWH are important for optimum care management of these patients.

**Limitations**

There were some limitations associated with this review. First, laboratory values were unavailable and it was impossible to determine if an INR was obtained before the procedure and, if so, what that INR level was. Such information could have influenced the decision to use LMWH. Second, as with all administrative claims analyses, we relied on appropriate coding by providers to select study patients, which may have resulted in underestimation or misclassification of potential cases.

Third, patient weight, disease severity, and renal function were not assessed, and these factors could have influenced the decision to consider LMWH therapy as well as to select the LMWH dose.

Fourth, this review included Idaho Medicaid recipients only and, as such, may not have represented the population as a whole. Fifth, there was no evaluation of the clinical outcomes for these patients who received bridge therapy with LMWH, and there was no comparison of clinical outcomes for bridge therapy with those of the patients who continued oral anticoagulation and did not receive LMWH therapy. Examining these additional data may have permitted us to determine if LMWH might have been appropriate in some cases, although given the patient and procedure-selection criteria employed in the current study, we thought this was unlikely.

**Conclusion**

In this review of Medicaid patients anticoagulated with warfarin and undergoing dental extractions, LMWH bridge therapy was employed in approximately 6% of procedures. Despite the overall
infrequent use of LMWH bridge therapy, such therapy was likely unnecessary in all the cases reviewed. This inappropriate drug use resulted in avoidable costs of more than $600 per extraction procedure in this Medicaid population.

What is already known about this subject

- Current guidelines from the American College of Chest Physicians (ACCP) recommend against warfarin discontinuation during both routine dental procedures (i.e., cleanings, fillings, and crowns) as well as during more invasive surgical procedures (i.e., tooth extractions and gingival surgery), based on a lack of reported bleeding complications and an increased risk for thromboembolic events.

What this study adds

- Less than 1% of Medicaid patients who had a tooth extraction received warfarin for at least 2 consecutive months prior to the tooth extraction procedure. Six percent of these patients received therapy with low-molecular-weight heparin (LMWH) coincident to the tooth extraction procedure, at an average LMWH cost of $637 per procedure.

DISCLOSURES

This research was funded under a cooperative interagency agreement between the College of Pharmacy at Idaho State University and the Idaho Department of Health and Welfare and was obtained from the Idaho Drug Utilization Review Program, Idaho State University, by authors Tracy K. Pettinger and Christopher T. Owens, who are employed by Idaho State University. They disclose no potential bias or conflict of interest relating to this article.

Pettinger served as principal author of the study. Study concept and design were contributed primarily by Pettinger, with input from Owens. Data collection and interpretation was the work of both authors. Writing of the manuscript was primarily the work of Pettinger, with input from Owens, its revision was primarily the work of Owens, with input from Pettinger.

REFERENCES


 Medicare Part D: 
Selected Issues for Pharmacists and Beneficiaries in 2007

JANET KILIAN, MPH, and JOANN STUBBINGS, RPh, MHCA

ABSTRACT

BACKGROUND: Upon signing the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) on December 8, 2003, President Bush set in motion the greatest change in the Medicare program since its inception in 1965. MMA was implemented on January 1, 2006, and established the Medicare prescription drug benefit, also known as Medicare Part D. Community and managed care pharmacists were essential to the success in 2006 of this new benefit program with 33 million beneficiaries. Pharmacists will continue to be an essential and integral part of the continued success of the Medicare prescription drug benefit in 2007, in part by being informed about the policies and regulations.

OBJECTIVE: To review policy statements released by the Centers for Medicare & Medicaid Services (CMS) for the Medicare prescription drug benefit in 2006 and to compile an abridged version of the highlights from the policy statements that may affect pharmacists and their interaction with Medicare beneficiaries.

METHODS: We reviewed all policy statements that were released publicly via the CMS Web site (www.cms.gov) policy guidance section between January 1, 2006, and September 30, 2006. We read through approximately 100 guidance statements and summarized approximately 50 that were determined to be relevant to beneficiaries and pharmacists in various practice settings.

RESULTS: Policy statements that may impact beneficiaries of the Medicare prescription drug benefit in 2007 include the timeline for the annual coordination election period, managed care open enrollment period, and distribution of annual notices of change to beneficiaries. Changes have also occurred in the standard benefit and cost sharing for low-income subsidy (LIS) or extra help that some beneficiaries are eligible to receive based on their current financial status. Discontinuation of coverage of erectile dysfunction drugs is a noteworthy coverage change. For all health care providers, the National Provider Identification (NPI) number will be used beginning May 23, 2007. Once the system using NPI numbers is required, no other provider identification number will be valid for billing Medicare and Medicaid.

CONCLUSION: Important policy updates to the Medicare prescription drug benefit in 2007 include the subject areas of: (1) beneficiary enrollment, (2) transition medication fills, (3) standard benefit, (4) cost sharing, particularly for those who qualify for LIS, (5) enhancement of the Medicare Prescription Drug Plan Finder, (6) beneficiary complaints, (7) discontinuation of coverage for erectile dysfunction drugs, (8) vaccine coverage by the Medicare Prescription Drug Plan Finder, (9) syringes in long-term care (LTC), donation of unused medications by beneficiaries, (10) implementation of the NPI, and (12) preventive services covered by the Medicare program.

KEYWORDS: Medicare Part D, Pharmacist intervention, Medicare policy

J Manag Care Pharm. 2007;13(1):59-65

For the Medicare & Medicaid Services (CMS) Administrator Mark McClellan, MD, PhD, recognized pharmacists upon implementation of the Medicare prescription drug benefit in January 2006. He stated, “Pharmacy perspectives are now an essential and integral part of our agency, just as prescription drugs are an absolutely essential part of modern medicine and now, for the first time, an integral part of Medicare.... The implementation of the drug benefit was a once-in-a-lifetime challenge for all of us, but the heightened level of interaction between CMS and our nation’s pharmacists is here to stay.”

In September 2006, CMS made available Medicare & You 2007, a handbook of new developments and considerations for Medicare beneficiaries. This is a valuable source of information for pharmacists about issues related to beneficiary enrollment, transition medication fills, standard benefit, cost sharing (particularly for those who qualify for low-income subsidy [LIS] for a beneficiary who has annual income below $14,700 [or $19,800 if married and living with a spouse], otherwise known as “extra help”), Medicare Prescription Drug Plan Finder, beneficiary complaints, erectile dysfunction (ED) drugs and other drugs such as heparin flushes that are not classified as a part D drug, vaccine coverage by the Medicare prescription drug benefit, syringes in long-term-care (LTC), donation of unused medications by beneficiaries, National Provider Identification (NPI) numbers, and the preventive services offered by the Medicare program.

Authors

JANET KILIAN, MPH, is a doctor of pharmacy candidate, 2007, University of Illinois at Chicago College of Pharmacy, and JOANN STUBBINGS, RPh, MHCA, is manager, research and public policy, Ambulatory Care Pharmacy Department, and clinical assistant professor, Department of Pharmacy Practice, Center for Pharmacoeconomic Research, University of Illinois at Chicago College of Pharmacy.

AUTHOR CORRESPONDENCE: Janet Kilian, MPH, in care of JoAnn Stubbings, RPh, MHCA, Manager, Research and Public Policy, Ambulatory Care Pharmacy Department, Clinical Assistant Professor, Department of Pharmacy Practice, Center for Pharmacoeconomic Research, University of Illinois at Chicago College of Pharmacy, 833 South Wood St., MC 886, Chicago, IL 60612. Tel: (312) 996-3098; Fax: (312) 355-1916; E-mail: jstubbin@uic.edu

Copyright© 2007, Academy of Managed Care Pharmacy. All rights reserved.
When Can a Beneficiary Join or Change a Medicare Prescription Drug Plan (PDP)?

Medicare beneficiaries can join, switch, or drop coverage from a Medicare prescription drug plan (PDP) during the annual coordinated election period (AEP). For the contract year 2007, the AEP was from November 15 through December 31, 2006. This is an important date span to remember each year because, every year, the AEP for the following contract year will be from November 15 through December 31 of the previous year. The AEP is the only time when all individuals eligible for Medicare prescription drug coverage can join a Medicare PDP, add additional coverage, or leave a Medicare PDP or a portion of the coverage. A beneficiary may also switch PDPs during the same time period. For example, a beneficiary may decide to switch from one PDP to another PDP during the AEP. If an eligible beneficiary drops Medicare prescription drug coverage entirely or misses the enrollment deadline, that beneficiary may not be eligible to enroll in the Medicare prescription drug benefit until November 15 of the following year, which may cause the beneficiary to incur a penalty for late enrollment.

How Does the Open Enrollment Period (OEP) Differ From the Annual Coordinated Election Period (AEP)?

The open enrollment period (OEP) takes place between January 1, 2007, and March 31, 2007, and is scheduled to occur during the same time period in subsequent years. The OEP is the opportunity for beneficiaries to add or change enrollment in a Medicare Advantage (MA) plan. For example, a beneficiary already enrolled in a Medicare Advantage-Prescription Drug plan (MA-PD) may change enrollment to a different MA-PD plan or to the traditional Medicare plan with a PDP (Table 1). The beneficiary cannot use the OEP to add or drop Medicare prescription drug coverage—any new enrollment or disenrollment in prescription drug coverage must occur during the AEP.

At year-end 2006, Congress passed the Tax Relief and Health Care Act of 2006, which President Bush signed on December 20, 2006. This legislation (a) relaxed the rigid lock-in/lock-out feature of the MA program and (b) allows eligible beneficiaries to enroll in a separate MA-only plan. Prior to the Tax Relief and Health Care Act of 2006, beneficiaries unhappy with the choice they made during the annual open enrollment had only 3 months, from January through March each calendar year, to move in or out of an MA plan. Beginning in 2007, the OEP for MA-only plans extends for the entire year in both 2007 and 2008. For example, if a beneficiary has original Medicare coverage, he/she may join an MA-only plan at any time during 2007 or 2008. These changes are indicated with an asterisk (*) in Table 1.

How Will Beneficiaries Know What Changes to Current Coverage Occur in 2007?

During October 2006, all beneficiaries received an annual notice of change (ANOC) from the plan in which they were enrolled, and ANOCs will be sent to beneficiaries each year. ANOCs include notice of the monthly premium amount cost-sharing requirements and a summary of the benefits provided by the plan, including the drug formulary.

What If a Beneficiary Changes Plans and a Drug Is Not Included in the Formulary?

A beneficiary who changed prescription drug plans in the AEP period may find, upon refilling usual prescriptions, that the drugs are not on the formulary of the new plan. A transition period applies in 2007, as it did in 2006, during which the nonformulary drug is covered for the first 30 days supply even if the prescription is for a drug that is not on the new plan’s drug list (or is a step-therapy drug). This gives the beneficiary and the physician time to find another drug on the plan’s drug list that would work as well or time for the physician to request an exception due to any special medical needs. In addition, those individuals who reside in an LTC setting are eligible for transition fills up to 90 days supply. The same appeals process for exceptions exists in 2007 as did in 2006.

### Table 1: Medicare Advantage Open Enrollment Period Limits

<table>
<thead>
<tr>
<th>If coverage is</th>
<th>Can use OEP to get</th>
<th>Cannot use OEP to get</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicare Advantage with prescription drug coverage (MA-PD)</td>
<td>• a different MA-PD • original Medicare with PDP</td>
<td>• MA-only • original Medicare only</td>
</tr>
<tr>
<td>Medicare Advantage with no prescription drug coverage (MA-only)</td>
<td>• a different MA-only • original Medicare only</td>
<td>• MA-PD • original Medicare with PDP</td>
</tr>
<tr>
<td>Original Medicare with a prescription drug plan (PDP)</td>
<td>• MA-PD</td>
<td>• a different PDP to use with original Medicare</td>
</tr>
</tbody>
</table>
| Original Medicare only                                  | • MA-only (entire year)* | • MA-PD  
| * Entire year = calendar year.                          |                     | • original Medicare with PDP |

OEP = open enrollment period.
What If a Formulary Brand Drug Becomes Available as a Generic Drug?

If a plan changes the formulary status of a medication in the middle of a contract year, a beneficiary who had received the medication affected by the midyear formulary change can continue to receive the brand formulary medication for the same cost-share amount for the remainder of the contract year. For example, if a generic version of a single-source medication is released to the pharmaceutical market midyear and a plan adds the generic version to the formulary at tier-1 copayment and moves the original version of the drug, now a multiple-source brand drug, to tier-3 copayment from tier-2 copayment, the beneficiary who had received the brand medication in the contract year would be permitted to continue to receive the drug at the tier-2 cost-share amount for the remainder of the contract year.  

How Will the Change in the National Average Premium Affect the Penalty Payment?

The national average premium in 2006 was $32.20. The Part D base beneficiary premium for 2007 has been reduced to $27.35. Beneficiaries who have incurred the late-enrollment penalty are most affected by the decrease in the national average base premium because the penalty amount is based on the national average Part D base beneficiary premium. “The late-enrollment penalty amount is at least 1% of the “base beneficiary premium” (the national average premium) for each full uncovered month that someone was eligible to but did not join a Medicare prescription drug plan.” For example, if a beneficiary must pay a 7% penalty because the beneficiary missed the May deadline for enrollment in 2006, the beneficiary will pay a penalty of $27.35 X 0.07 = $1.91/month in addition to their normal monthly premium. Pharmacists need to be aware that the penalty is based on the national average premium, not the premium of the beneficiary, and affected beneficiaries will always pay the penalty but the penalty amount will change from year to year as the national average premium changes each year. 

Will the Standard Benefit Change in 2007?

Changes will occur in the standard benefit (defined as the standard deductible, initial coverage limit, no coverage ["donut hole"], catastrophic coverage threshold, and other related factors) which is required to be updated every year by CMS as directed in the Medicare Prescription Drug, Improvement, and Modernization Act of 2003. These changes are outlined in Table 2. In fact, most beneficiaries do not have the standard coverage because beneficiaries can enroll in a plan with enhanced coverage that may charge a higher premium. Many beneficiaries have plans that require no deductibles or include coverage for drugs that are not Part D-covered drugs, such as benzodiazepines or barbiturates. For 2007, beneficiaries may enroll in plans offering enhanced coverage that includes ED drugs. Individuals who qualify for certain levels of extra help will not be affected by the changes to the standard benefit because they qualify for premium assistance provided by the federal government.

If a beneficiary enrolls in a plan with the standard coverage, the deductible will increase to $265 and the initial coverage limit will increase to $2,400. The true out-of-pocket (TrOOP) threshold will increase to $3,850, thereby creating a coverage gap between $2,400 and $5,451 in CY 2007. TrOOP costs are defined by CMS as “the expenses that count toward the annual Medicare drug plan threshold for the year. These annual expenses determine the start of a beneficiary’s catastrophic coverage. The drug plan will keep track of each person’s TrOOP costs. For every month that a beneficiary buys covered prescriptions, an explanation of benefits will be mailed that shows the beneficiary’s TrOOP costs to date.”

What Changes Apply to Those Who Are Qualified for “Extra Help”?

The income points for qualification for the LIS, or “extra help,” in 2007 are annual incomes below $14,700 if single or $19,800 if married and living with a spouse. The subsidy and copayments are based on a sliding scale according to income and assets. The prescription copayment for institutionalized beneficiaries will remain at $0 in 2007. The copayments for noninstitutionalized LIS beneficiaries will increase in 2007. For those beneficiaries whose copayments were $1 (generic)/$3 (brand) in 2006, the copayments in 2007 will increase to $1/$3.10. For those whose copayments were $2 (generic)/$5 (brand) in 2006, the copayments in 2007 will increase to $2.15/$5.35. Therefore, beneficiaries who are not institutionalized and who qualified for extra help in 2006 will experience this (small) increase in their copayments in 2007.

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>2007 Changes to the Standard Benefit ($)</th>
<th>11,14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefit Parameters</td>
<td>2006</td>
<td>2007</td>
</tr>
<tr>
<td>Deductible</td>
<td>250</td>
<td>265</td>
</tr>
<tr>
<td>Initial coverage limit</td>
<td>2,250</td>
<td>2,400</td>
</tr>
<tr>
<td>Out-of-pocket threshold</td>
<td>3,600</td>
<td>3,850</td>
</tr>
<tr>
<td>Total covered drug expenses at out-of-pocket threshold (start of catastrophic coverage)</td>
<td>5,100</td>
<td>5,451</td>
</tr>
<tr>
<td>LIS Copayments</td>
<td>2006</td>
<td>2007</td>
</tr>
<tr>
<td>Institutionalized</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Up to or at 100% FPL</td>
<td>1/3</td>
<td>1/3.10</td>
</tr>
<tr>
<td>Other LIS</td>
<td>2/5</td>
<td>2.15/5.35</td>
</tr>
</tbody>
</table>

FPL=federal poverty level; LIS=low-income subsidy.
Where Can a Beneficiary Find Help Choosing a Medicare Prescription Drug Plan?

The Medicare Prescription Drug Plan Finder (www.medicare.gov) is useful in finding options within the Medicare prescription drug benefit. Beneficiaries can enter into the Medicare Prescription Drug Plan Finder their maintenance medications, location of residence, and preferred pharmacy, and the finder will provide them with plan options that fit their individual needs. Changes have been made to the finder to enhance its use and understanding, allow for the results to be more specific to the beneficiary, view and compare plans, and allow the beneficiary to determine what each plan will cost monthly.

What If a Beneficiary Has a Complaint?

Assisting a beneficiary with a complaint can be a demanding but rewarding endeavor. The complaints process can be reviewed at: The Tip Sheet: Information Partners Can Use On: Handling Medicare Part D Prescription Drug Complaints, released in August 2006; it is located on the CMS Web site.

If the complaint refers to the drug formulary of a prescription drug plan, the appeals process is the first option. Once the plan renders a decision through the appeals process, the complaint process is the second step if the beneficiary believes that the plan has not acted in accordance with the policy of the Medicare Drug Benefit.

What Is the Coverage Policy for Erectile Dysfunction Drugs Under Medicare Part D in 2007?

One major change in the coverage provided by the Medicare prescription drug benefit beginning in 2007 is the exclusion of ED drugs when prescribed for the treatment of sexual dysfunction or ED; the coverage exclusion for ED drugs does not apply, however, when prescribed for a U.S. Food and Drug Administration-approved indication other than ED, such as pulmonary hypertension. Also a beneficiary may be enrolled in an enhanced coverage plan that extends coverage for certain drugs that are not mandated to be covered by law, such as ED drugs for ED. Additional information on Part D drug coverage was issued in February 2006. This important guidance can be located on the CMS Web site at Part D Drugs/Part D Excluded Drugs (Table 3).

What Is the Difference Between Part B and Part D for Vaccines?

The only vaccines currently covered under Medicare Part B are the “preventive vaccines” for influenza, pneumonia, and hepatitis B (for intermediate- to high-risk beneficiaries), along with “medically necessary” vaccines to treat illness or injury. When a Part B-covered vaccine is administered, the health care professional who administers the vaccine may bill an administration fee to Part B in addition to the vaccine fee. Newer vaccines, such as the herpes zoster vaccine, are covered by Part D. When a Part D-covered vaccine is administered, Part D will pay for the vaccine. According to the Tax Relief and Health Care Act of 2006, the health care professional who administers the vaccine may bill an administration fee to Part B in 2007 for the Part D-covered vaccine. In 2008, both the administration fee and the vaccine fee for a Part D-covered vaccine may be billed to Part D.

There are a small number of inexpensive vaccines, such as those for tetanus, that are not covered by Part B. Part D plans are required to provide access to vaccines not covered under Part B. During rule-making, CMS described use of standard out-of-network requirements to ensure adequate access to the small number of inexpensive vaccines covered under Part D, when the vaccines must be administered in a physician’s office. “The beneficiary would pay the physician and then submit a paper claim to their Part D plan for reimbursement up to the plan’s allowable charge, possibly leaving a differential amount for which the beneficiary is solely responsible for paying.”

When Are Syringes Covered Under Part D for Long-term Care?

CMS issued guidance for the coverage of syringes used to administer insulin in the LTC setting versus coverage of syringes used to administer other drugs covered by the Medicare prescription drug benefit. CMS went on to define insulin syringes equipped with a safe needle device as Part D drugs. “Syringes,
when used for the administration of insulin, meet the definition of Part D drugs. Preexisting 2006 regulations from the Occupational Safety & Health Administration require employers whose employees are exposed to self-injected needles, such as in nursing homes, to provide ‘safe needle devices.’ We view the sharps injury prevention feature involved with these specific types of syringes as ‘special packaging’ required for the administration of insulin in LTC facilities.”

“Part D sponsors are required to contract with LTC pharmacies that provide safe needle devices (and who meet all other applicable minimum performance and service criteria), and we expect the availability of these safety-capable syringes to be incorporated into the Part D sponsor’s standard network contract. As a reminder, payment to LTC pharmacies under Part D may only cover drug ingredient costs and dispensing fees as defined in the final regulations. These safe needle devices would be legitimate costs reflected in the dispensing fee. “This does not extend Part D reimbursement to any other types of syringes used in the administration of other Part D drugs in the LTC facility.”

“While we continue to maintain that the syringes, associated with the administration of insulin dispensed in the long-term care setting, must maintain a safety device, based upon comments from the public, we believe these are better described in accordance with 1860D-2(e) of the Act, which defines ‘medical supplies associated with the injection of insulin’ as covered Part D drugs. Therefore, we are correcting our previous Q&A to define insulin syringes equipped with a safe needle device, in their entirety (syringe and device), as Part D drugs and subsequently they should be managed like any other Part D drug the plan places on their formulary.” LTC pharmacies may continue to seek Part D coverage for the appropriate insulin syringes used in administering insulin to patients residing in LTC facilities. Pharmacies that supply services to nursing homes, hospices, and home health services must follow the appropriate guidance for the appropriate setting.

### Under What Circumstances Can Beneficiaries Return or Donate Unused Medications?

CMS issued guidance for the handling of Part D-covered unused medications, which may commonly occur in the LTC setting. “If a beneficiary, typically residing in a nursing home, finds that they have an unused prescription medication, paid for by the Medicare prescription drug benefit, they can donate this medication, to the extent allowable under federal and state law and regulation, to state agencies and charitable organizations. Once the beneficiary has taken possession of, and insurance has paid for, the medication, the beneficiary is the owner of such medication and can dispose of the medication as they deem necessary. In certain circumstances, specially packaged unused drugs could be returned to long-term care pharmacies (LTCPs) and resold, provided such returns and resales are consistent with provisions of federal and state law. However, LTCP administrative costs to inspect, document, reverse claims, reimburse any beneficiary cost sharing, and reinventory of any such returned medications cannot be included in either the Part D ingredient cost or a corresponding dispensing fee. Consequently, these associated restocking fees cannot be billed as Part D drug costs. Further, while facilitating returns is discretionary, for those plans and pharmacies that process returns for resale, they must adjust the prescription drug expense and TrOOP accordingly.” In order to adjust the prescription drug expense and TrOOP expenses, a plan must follow the current policies of the plan that are based on the guidance issued by CMS for that contract year.

### What Is the NPI and Why Do I Need One?

“The NPI is the first opportunity for pharmacists to have an individual provider number with which to bill third parties. This includes billing PDPs for medication therapy management services (MTMS) under the Medicare Part D drug benefit. Pharmacists are encouraged to obtain an individual NPI. This is a new opportunity for pharmacists. Use of an NPI number is a
Importantly, health care professionals are in a key position to inform Medicare beneficiaries about the new preventive services that are covered by Medicare. For example, a beneficiary is eligible for a “Welcome to Medicare” medical office visit that includes a comprehensive physical examination during the first 6 months that a beneficiary first becomes eligible for Medicare Part B. The entry physical examination is the gateway to the Medicare health system and an opportunity for an individual to be diagnosed and receive care before the disease state has advanced and requires more care. The early diagnosis is beneficial to the individual because the beneficiary receives earlier care, resulting in better outcomes. When beneficiaries see their physician for the “Welcome to Medicare” physical examination, they should receive any needed referrals for other preventive services or treatment to be covered by Medicare. Beneficiaries need to utilize this benefit within the first 6 months of enrollment in Medicare Part B if their Medicare coverage begins on or after January 1, 2005.

A beneficiary may also receive other preventive services such as:

- influenza, pneumococcal or hepatitis B vaccination;
- mammography screening and Pap test and pelvic examination;
- screening for colorectal cancer, prostate cancer, cardiovascular disease, diabetes, glaucoma;
- bone-mass measurement;
- diabetes self-management, supplies, and services;
- medical nutrition therapy; and
- smoking cessation.

Many health care professionals may not be aware of these benefits available to Medicare beneficiaries, and CMS has been working to promote awareness of the available preventive services. CMS recognizes the crucial role that health care professionals play in promoting, providing, and educating Medicare patients about these potentially life-saving preventive services and screenings. Because of this understanding, we are taking significant steps to reach out and educate the provider community as well as Medicare beneficiaries about the array of preventive services and screenings covered by Medicare. However, we need your help to get the word out to your Medicare patients and their caregivers about the many preventive services and screenings covered by Medicare. Health care providers can find additional information and links to materials for educating patients at: http://www.cms.hhs.gov/MLNProducts/35_PreventiveServices.asp#TopOfPage on the CMS Web site.

**Did You Know That Medicare Covers All of the Preventive Services Listed Below?**

Pharmacists are the health care providers most accessible to Medicare beneficiaries and are in a key position to inform beneficiaries about the new preventive services that are covered by Medicare. Many health care professionals may not be aware of these benefits available to Medicare beneficiaries, and CMS has been working to promote awareness of the available preventive services. CMS recognizes the crucial role that health care professionals play in promoting, providing, and educating Medicare patients about these potentially life-saving preventive services and screenings. Because of this understanding, we are taking significant steps to reach out and educate the provider community as well as Medicare beneficiaries about the array of preventive services and screenings covered by Medicare.

**Important Dates**

- October 1, 2006: Plans begin marketing for 2007 plan year
- Mid-October 2006: 2007 plan data and enhanced plan finder available
- October 31, 2006: Annual notice of change and Medicare & You 2007 handbook must be in the mail to beneficiaries
- November 15, 2006: Annual enrollment begins for 2007 plan year
- December 8, 2006: Optimum date for early enrollment to ensure timely processing
- December 31, 2006: Annual enrollment ends for 2007 plan year
- January 1, 2007: Open enrollment for managed care plans begins
- March 31, 2007: Open enrollment for managed care plans ends

**A Pharmacist Can Find More Assistance At:**

- Call 1-800-MEDICARE: 1 (800) 633-4227
- TTY users should call 1 (877) 486-2048
- Visit www.medicare.gov and select “Frequently Asked Questions”
- Visit www.medicare.gov/contacts/static/allStateContacts.asp for a list of local senior health insurance program (SHIP) organizations
- Web sites provided in Tables 3 and 4.

**ACKNOWLEDGMENTS**

The authors acknowledge Magdalena Zasadzki, BS, doctor of pharmacy candidate, 2008, University of Illinois at Chicago College of Pharmacy, for assistance with the manuscript.

**DISCLOSURES**

No outside funding supported this study. The authors disclose no potential bias or conflict of interest relating to this article. Author Janet Kilian served as principal author of the study. Study concept and design were contributed by Kilian and author JoAnn Stubbings. Data collection was the work of both authors; data interpretation was primarily the work of Kilian, with input from Stubbings. Writing of the manuscript was primarily the work of Kilian, with input from Stubbings; its revision was the work of both authors.

**REFERENCES**


Bridging the Gap Between Pharmacoeconomics and the Real-World Practice of Managed Care Pharmacy

Drug coverage decisions made by managed care payers have the potential to influence millions of lives at a time. The importance of making “evidence-based” coverage decisions has never been greater, particularly since the implementation of Medicare Part D in January 2006. For the first time since the inception of Medicare in 1965, all Medicare beneficiaries have access to drug coverage, albeit in different coverage schemes with some variation in out-of-pocket expense.

The influx of about 50 million managed care members from Medicare Part D into the overall managed care pharmacy market further amplifies the significance of any coverage decision. Currently about 250 million Americans obtain their medications through managed care plans.1 While medication therapy management has emerged as a framework to streamline the determination of optimal treatment options at the individual level, there remains a need for a universally accepted framework for the clinical and economic evaluation of therapies at the population level for drug coverage policies. In addition to examining the safety and cost-effectiveness of drugs, plans need to consider the implications of copayments, deductibles, and prior authorization requirements for access to new drugs.

Within an increasingly competitive landscape, there is a delicate balance between the access and cost implications of coverage decisions because patients, as imperfectly informed consumers, will be concerned about what they pay for coverage and what benefits they receive as a result. At no other time have the questions of drug benefit design and formulary decisions been so critical for managed care plans and their enrollees. Indeed, this new Medicare benefit has arguably made the relationship between premiums and out-of-pocket costs for prescription drugs more visible to millions of Americans.

Optimal coverage decisions require evidence that is timely, relevant, and adaptable to the specific population characteristics of the health plan. Perhaps most importantly, the evidence should be transparent to all stakeholders, particularly the members of the pharmacy and therapeutics (P&T) committee. The goal of transparency is sometimes difficult to achieve, especially with respect to the economic evaluation of innovative therapies for complex, multifaceted chronic conditions such as diabetes. Such economic evaluations often rely on pharmacoeconomic models that project the likely costs and outcomes of new therapies over time, based on safety and efficacy data from phase 3 trials and data from numerous secondary sources, through a complex set of mathematical relationships among model variables. These complex models employ many interrelated assumptions, making it difficult to identify the precise process through which any particular assumption affects model projections.

In the current issue of JMCP, Spooner et al. found that 25% of manufacturer dossiers received by a large health plan did not contain a pharmacoeconomic model for a new product, and 45% of class review dossiers did not contain a pharmacoeconomic model.2 Receipt of a dossier, with or without a pharmacoeconomic model, did not appear to influence the outcome of the drug formulary decision by the P&T committee for the health plan.3 In contrast, in the previous issue of JMCP, Watkins and colleagues provide a case study of a complex Markov model—the CORE diabetes model—that was employed to inform formulary decisions relating to the prevention and control of diabetes in a managed care plan. This case study from Watkins et al. provides a good example of how information can be organized, analyzed, and presented to guide decision making. However, the question of how to raise the level of fluency with such models in managed care still remains to be answered.

This example also serves to underscore the numerous caveats that result from model assumptions required in such analyses. The authors acknowledge, for example, the design weakness of using a 30-year projection, given the irrelevance of this time frame to managed care, but more importantly, the lack of safety data on such cumulative exposure, if it were plausible. They also admit that they may have overestimated the benefit of weight loss, based on the first-year estimate alone. Attrition bias inherent in the numbers from the intent-to-treat analyses appears to be another source of possible error.4

An increasing share of health budgets is being consumed by chronic disease, and this is only expected to increase, given the demographics of Medicare beneficiaries and the epidemiology of these diseases. For instance, more than 10 million Americans are diagnosed with type 2 diabetes, with an additional 5.5 million estimated to have the disease but who have not yet been diagnosed.5 Diabetes has been identified as a significant risk factor for the development of heart failure, a disease with major public health implications.6 Clearly, the potential impact of an efficient clinical and economic evaluation framework can have major budget implications for managed care plans.

As Watkins et al. note, “Many health plans now use the AMCP Format as a tool to improve efficiency in gathering clinical information, but relatively few decision makers give serious consideration to the [pharmacoeconomic] models offered with product dossiers,” often due to the fact that the majority of plans still do not know what to do with this information. In some cases, the problem is that pharmacoeconomic models are not considered credible because of the use of implausible or unsubstantiated model assumptions. In other cases, the model results are not considered informative because of the selection of an irrelevant comparator for the new treatment. Lack of transparency also contributes to the lack of credibility—many pharmacoeconomic models resemble a “black box” where model assumptions are fed into one end, “magic” happens, and results emerge from the other end. In the absence of transparency, health plans are likely to suspect that the results produced by models reflect some form of hidden bias, which impairs credibility.
We have seen the need for “translational research” in clinical medicine, and perhaps this is what is needed now in managed care pharmacy. We need to bridge the gap between pharmacoeconomics and actual pharmacy management practice. The “number needed to treat” measure for example can be intuitive to managed care due to its focus on population care management. Similarly, pharmacoeconomic models using “cost per disease-event avoided” as a cost-effectiveness metric may be more intuitive for managed care when making coverage decisions among alternative treatments for a particular condition than the metric of “costs per quality-adjusted life-year gained” preferred by methodological purists.

An alternative to using economic evaluations in product dossiers based on industry-sponsored pharmacoeconomic models is to use economic evaluations produced by third parties, such as the United Kingdom’s National Institute for Health and Clinical Excellence (NICE). This approach may alleviate some of the inherent limitations—such as in the example presented by Watkins et al.—of a model application developed by industry, presumably for a commercial purpose. However, such third-party evaluations for new products may not be available within the necessary time frame for a particular health plan’s formulary decision. Further, results of third-party evaluations often must be adapted for the specific populations or clinical issues relevant for a formulary decision within a particular managed care plan.

In the absence of timely economic evaluation from independent third parties, managed care plans could, of course, develop their own pharmacoeconomic models, but in many cases, this option will be prohibitively expensive, time consuming, and require expertise not readily available to the health plan. Thus, communication between managed care plans and pharmaceutical companies to generate pharmacoeconomic information regarded as credible and relevant can, under the right circumstances, enable health plans to make more informed and timely formulary decisions.

In the example presented by Watkins et al., a proactive effort by a pharmaceutical company to understand a payer’s modeling needs resulted in the development of pharmacoeconomic information that the payer regarded as credible and meaningful for its population. However, a practical limitation of this example is that different managed care organizations will have different concepts of what specific model characteristics contribute to credible or useful pharmacoeconomic information. Therefore, the diversity of managed care organizations, pharmacoeconomic models provided by pharmaceutical companies must be flexible, particularly in the definition of relevant population characteristics and in selection of the specific treatment comparators.

Unfortunately, the modeling framework used in the example presented by Watkins et al. is relatively inflexible. In addition, many fixed data inputs are speculative and perhaps erroneous, and some assumptions employed by the researchers impractical. The impact of these potentially erroneous assumptions on model results is not adequately illustrated or made explicit using sensitivity analyses. The description of the model is not sufficiently transparent to enable a reader to assess the implications of these assumptions. Further, although this modeling effort was regarded as useful by the health plan in this example, the ultimate formulary decision was to impose almost none of the criteria for use of the drug suggested by the pharmacoeconomic model. Finally, the lack of transparency and flexibility in the modeling approach in this example limits the potential for its immediate use for formulary decisions by other health plans.

**DISCLOSURES**

The authors disclose no potential bias or conflict of interest relating to this article.

**REFERENCES**


Fadia T. Shaya, PhD, MPH
Associate Professor, Associate Director
Center on Drugs and Public Policy
University of Maryland School of Pharmacy
Pharmaceutical Health Services Research
220 Arch St., 12th Fl.
Baltimore, MD 21201
fshaya@rx.umaryland.edu

Robert L. Ohsfeldt, PhD
Professor, Health Policy & Management
School of Rural Public Health
Texas A&M Health Science Center
College Station, TX
rohsfeldt@srph.tamhsc.edu
Medication Therapy Management
Versus Drug Regimen Review

The article by Horning, Hoehns, and Doucette in this issue of *JMCP* provides important information that should be of much interest to pharmacists and policy decision makers. The authors evaluate the quality of care under different forms of pharmacist services in long-term-care facilities (LTCFs). The federally mandated requirement for drug regimen reviews (DRRs) by pharmacists in LTCFs has long represented a good opportunity to broaden pharmacy’s role to ensure safe drug use, the cost-efficient use of resources, and optimum health outcomes. However, there remains a need for direct funding for the provision of pharmacists’ services in LTCFs, as well as changes in other factors, to facilitate pharmacists’ ability to optimize pharmaceutical care for LTCF residents.

The Medicare Modernization Act (MMA) of 2003 included a requirement that Medicare Part D sponsors provide a medication therapy management (MTM) program as part of their Medicare drug benefit program offered to Medicare beneficiaries. Recently, the promise of MTM programs has received much attention as an evolution in pharmacy services. MTM programs are designed to enhance enrollee understanding of medications and compliance with medication therapy as well as to detect adverse drug events and patterns of overuse or underuse of medications.

From a clinical perspective, there is a great deal of overlap between MTM services and DRR. A DRR is required for all LTCF residents monthly. The DRR conducted by the pharmacist in the facility setting is the financial responsibility of the nursing facility. On the other hand, MTM services apply only to targeted beneficiaries, the definition of which will be different from one prescription drug plan (PDP) to another. MTM services under Medicare Part D are the financial responsibility of the PDP, which receives compensation for these services as part of the administrative overhead provided by the Center for Medicare & Medicaid Services (CMS). It is likely that a majority of nursing facility residents will meet the criteria for a targeted beneficiary. However, many of the clinical services provided by pharmacists in the LTCF as part of DRR could be considered MTM services in the ambulatory setting. The primary factors to consider in distinguishing between MTM services and DRR are the facility setting and payment.

CMS provided no specific guidelines on the frequency or intensity of MTM services, and various PDPs may take a variety of approaches to providing them. A pharmacy service paid for by one PDP might not be covered by another PDP. Or, a pharmacist may have an agreement with one PDP to provide MTM services but may not have an agreement with another PDP in the same region, leading to a confusing variety of services for Medicare beneficiaries residing in the same LTCF. In addition, some PDPs may use their own staff pharmacists or nurses to provide remote services for targeted LTCF residents. However, LTCF residents are different from ambulatory Medicare beneficiaries in terms of regulatory and operational differences in the environment of care and prevalence of comorbid conditions and cognitive impairment.

Therefore, the American Society of Consultant Pharmacists believes that face-to-face interaction between a pharmacist with geriatric expertise and the LTCF staff, as well as with residents and caregivers, would be expected to provide the best outcomes. Further, a joint document from AARP, the Academy of Managed Care Pharmacy, American College of Clinical Pharmacy, American Geriatrics Society, American Pharmacists Association, American Society of Consultant Pharmacists, Case Management Society of America, College of Psychiatric and Neurologic Pharmacists, and Department of Veterans Affairs calls for the measurement of outcomes to document the quality and value of the pharmacist services provided. These organizations declare that MTM programs will need to identify and perform a variety of measurements and document program results to determine overall program effectiveness and achievement of desired treatment outcomes (economic, clinical, or humanistic).

Few standards exist for determining the quality of pharmacy services, specifically in LTCFs. Horning, Hoehns, and Doucette evaluated the quality of care by looking at various process measures from LTCFs in which the residents received intensive consulting services from pharmacists compared with LTCFs receiving traditional DRR pharmacy services. They made comparisons with various clinical practice guidelines as the basis for evaluating care quality. Under Medicare Part D and MTM, we can expect to see more studies of this nature in the future.

Section 109(b) of MMA amended Section 1154(a) of the Social Security Act to give quality improvement organizations (QIOs) authority to provide quality improvement assistance pertaining to prescription drug therapy to Medicare Advantage plans and to prescription drug sponsors offering PDPs. QIOs are independent, mostly nonprofit health care organizations that employ physicians from a wide range of specialties, statisticians, epidemiologists, health information technology experts, nurses, communications professionals, pharmacists, and other health care specialists who serve as a resource for local health care professionals and consumers.

Under the direction of CMS, the QIO program consists of a national network of 53 QIOs responsible for each U.S. state, territory, and the District of Columbia. The main goal of QIOs is to accelerate the diffusion of evidence-based medicine into everyday clinical practice. With implementation by QIOs, Section 646 demonstration projects test system changes to improve the quality of care while increasing efficiency across the whole system. According to the Quality Improvement Organization Support Center for Pharmacy, there are 5 projects under way focused on pharmacotherapy in LTCF settings. CMS intends to use these demonstration projects to identify, develop,
and disseminate major multifaceted improvements to the entire health care system. In addition, CMS believes that these efforts will identify best practices that will evolve into industry practice standards and could eventually be adopted as federal standards. For additional information on QIO efforts in pharmacy, those interested should contact their own state’s QIO.13

This work by Horning, Hoehns, and Doucette is laudable. The interpretation of this work is limited because it is a self-assessment, leaving the potential for bias. Perhaps in the future, Medicare QIOs will provide an independent source of data collection and evaluation of such projects so that CMS can obtain unbiased estimates of the outcomes of more intensive pharmacists’ services in LTCFs. Pharmacists and policymakers alike should pay close attention to this and other research on pharmacotherapy in LTCFs as health care delivery continues to evolve to improve the care for those most in need of pharmacists’ clinical services.

Kent H. Summers, RPh, PhD
Associate Professor
Purdue University School of Pharmacy
R. Heine Pharmacy Bldg., Rm. 502
575 Stadium Mall Dr.
West Lafayette, IN 47907-2091
ksummers@pharmacy.purdue.edu

DISCLOSURES
The author discloses that he serves as pharmacy consultant for the LTCF pharmacy collaborative project by the Medicare QIOs in Indiana (Health Care Excel), Kentucky (Health Care Excel), and Ohio (KePRO).

REFERENCES
Peeking Inside the Statistical Black Box: How to Analyze Quantitative Information and Get It Right the First Time

The Problem: We’re Vulnerable
What do sociologist Lenore Weitzman, the state of Arizona’s Independent Redistricting Commission, and the National Aeronautics and Space Administration (NASA) Mars Polar Explorer have in common? All were the subject of considerable media attention in their day. All were carrying out important work. All employed bright and talented people dedicated to getting the job done, yet each fell victim to the same problem: work delegated to others was either inadequately communicated or mismanaged, with disastrous consequences.

Published in 1985, Weitzman’s study of no-fault divorce in California—“The Divorce Revolution”—was heralded as a groundbreaking indictment of the legal system’s victimization of women.1 Following a divorce, Weitzman reported, females’ standard of living dropped 73%, while males’ increased by 42%.2 Weitzman’s finding captured remarkable public attention despite its inconsistency with other published work. In the decade that followed, Weitzman’s book was cited by 175 newspaper and magazine stories, 348 social science articles, 250 law review articles, 24 legal appeals, Supreme Court cases, and President Clinton’s 1996 budget. “There’s only one problem,” reported an Associated Press news story in 1996. “Her figures are wrong.”3 Investigation revealed that Weitzman had turned her calculations over to a research assistant, who had apparently made 1 or more error(s) in data analysis or processing. Another researcher, given access to the data in 1996, found not only discrepancies in the calculations themselves but also paper data collection records that did not match to Weitzman’s computer files.4

Charged with the controversial task of redrawing Arizona’s legislative boundaries, the state’s Independent Redistricting Commission encountered serious trouble in April of 2002. Testimony given in a legal deposition revealed that a serious miscommunication between the commission and a consulting firm had taken place months before. Active and inactive voters had inappropriately been combined in tallying district populations. “The mistake means further chaos for the state’s election system,” a local newspaper reported. “As filing deadlines approach, candidates don’t know where to collect the signatures and donations they need to run for office.”5

The Mars Polar Explorer was launched in January 1999 to find evidence of precipitation on Mars, but it crashed into the planet’s surface upon arriving on December 3, 1999. Investigation revealed that the 2 teams working on the project had used different measurement units, one metric (e.g., kilometers, kilograms), the other English (e.g., miles, pounds). Neither team knew how the other was carrying out its work, resulting in the failure to place the spacecraft into proper orbit. A NASA administrator assessed the situation: “People sometimes make errors. The problem here was not the error; it was the failure of NASA’s systems engineering and the checks and balances in our processes to detect the error. That’s why we lost the spacecraft.”6

While few of us working in managed care pharmacy are likely ever to be responsible for writing Supreme Court legal opinions, planning an election, or navigating a spacecraft, many of us routinely use quantitative analyses to inform decisions that affect the lives and health care of thousands and even millions of members of health plans. This makes us vulnerable to errors that can diminish the quality of the information we provide to others, affecting benefit management or possibly even patient care. And the more emotionally or financially attached we are to the results of our analyses, the more vulnerable we are to mistakes. Personal investment in our own results, a habit that most of us are guilty of at one time or another, tempts us to ignore the only reliable method to prevent small mistakes from becoming big problems: data quality control (DQC).

Data Quality Control Principles
Most of us confront DQC with little or no inherent interest. Results are much more intriguing than the “nuts and bolts” methodology that generated them. However, DQC can and should be incorporated into organizational culture as an essential precursor to information release and utilization. The idea is not to prevent every error, which is impossible given human fallibility; instead, the point is to keep errors from causing avoidable damage. Implemented properly, good DQC provides the assurance that all disseminated work has been appropriately verified for accuracy. DQC also facilitates easy responses to information requests and produces a net time savings from a relatively small time investment. Built on the fundamental principle that everyone makes mistakes, DQC relies on procedures instead of on individuals. People have bad days; procedures do not.

A good DQC program is composed of 3 components: (1) verification of what is received from others; (2) verification of what is provided to others, including documentation standards; and (3) internal quality control peer review procedures that are never overlooked, no matter how urgent the need for information (Table 1).

Verification of What Is Received From Others
In performing quantitative analyses, it is common to receive data (e.g., claims files, eligibility records, questionnaires) from others. Data received according to request should always be verified against stated criteria. For example, assume a researcher has requested a file of all pharmacy claims for the year 2005 for health plan members who were continuously enrolled throughout 2005 and had at least 1 diagnosis of rheumatoid arthritis (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] 714.xx) during the year’s first quarter. Upon receipt of the file, each requirement of the request (all pharmacy claims, continuously enrolled, diagnosis of rheuma-
toid arthritis) should be verified against specifications. When receiving data from a colleague, it is helpful to ask him or her for a few key calculations (e.g., descriptive information for several of the most important variables of interest) and replicate them. Similarly, when modifying previous work (e.g., a previously published analysis or model), the researcher should first replicate the previous work, then modify it.

This procedure detects numerous issues that threaten integrity of work: data transmission problems, miscommunication about what the dataset does and does not contain or about how previous work was performed, and misunderstanding about project specifications, specifically how key outcomes are defined. This last point is worthy of particular attention because it comes up often in managed care pharmacy. Key concepts, such as compliance, termination of treatment, cost, and “washout,” are often understood very differently by different people. A verification procedure helps refine the methodology by addressing important but sometimes ignored questions: How much of a gap between refills constitutes noncompliance? If a patient stops taking medication for 4 months and then resumes, is that a treatment termination? Does “cost” refer to billed charge, paid amount, payer cost after subtraction of member cost share, or patient out-of-pocket cost? For how many months should a patient be naive to drug therapy prior to an index date to be considered a “new start”? When possible, key outcomes should be characterized using definitions similar to those in previously published literature in the same field or based on well-considered departures from previously published research. Utilizing common terminology or classifications allows ready comparison of multiple studies.

- **Special Verification Considerations for Administrative Claims**

When the source data are administrative claims, a thoughtful assessment of whether the codes in the dataset actually represent what the researcher wants to study is essential. Claims data are generated for billing purposes. From the payer’s and provider’s perspectives, if a claim is good enough to make a payment, it is good enough. This means that some codes are likely to be more accurate than others. For example, the “quantity dispensed” field on a drug claim is usually reliable because it is (a) typically tied to a pharmacy’s billing and inventory system, (b) essential for payment to take place, and (c) often edited real time in claims transaction processing systems. The “days supply” field, which is entered in the claim transaction by the pharmacist or pharmacy technician at the point of service and potentially affects patients’ out-of-pocket cost (e.g., when a pharmacy benefit plan calls for a 30-day supply maximum but the physician has prescribed a 35-day supply), is less reliable.

Diagnosis codes pose a particular challenge, especially when the patient’s condition is socially stigmatized or in any way linked to payment. For example, in a 1994 survey, 50% of primary care providers reported that they had deliberately miscoded major depression as a different diagnosis at least once during the prior 2 weeks, most commonly because of uncertainty about the diagnosis or concerns about obtaining reimbursement for a mental health diagnosis. In a 2004 letter to *JMCP*, Dr. John Barbuto told a similar story: because “tension headache” was once considered a psychiatric diagnosis and therefore payable at a lower rate, physicians would avoid using that diagnosis and “miraculously, everyone seemed to have migraine.”

One type of analysis common to managed care pharmacy, assessment of the effect of a benefit design change, requires special verification procedures. Copayments, deductibles, and other benefit design features (e.g., coinsurance or mandatory payment of the brand-generic cost differential for multiple-source brand drugs) should be verified before analysis. Typically, it is necessary to remove the lowest-cost medications from these verifications because of policies that limit out-of-pocket outlays to the lesser of the expected copayment or the medication cost. For example, for evaluation of a 3-tier structure of $10/$20/$30, the analyst should select generic drugs, with an ingredient cost >$10; preferred brand drugs, with an ingredient cost >$20; and nonpreferred brand drugs with an ingredient cost >$30 and verify that copayment amounts are as expected for each copayment tier. If the copayment amounts on the claims do not fall into the expected pattern ($10/$20/$30 in this example), additional analyses will be necessary to detect the source of the discrepancy. The analyst should examine copayments by month (did the copayment distribution inexplicably change over time?) and by therapy class or drugs (do the copayment distributions look accurate for some classes or drugs but not others?). Common sources of copayment discrepancies are: (1) “grandfathering” (i.e., charging the tier-2 copayment for the first month after a medication’s status changes to non-formulary [tier-3 copayment]), (2) mid-year changes in tier status, and (3) charging the generic copayment amount for certain drugs, e.g., maintenance drugs. Decision rules are needed to handle each of these situations. This verification process, though somewhat tedious, helps the analyst to make conscious a priori choices about how to handle special, potentially important factors affecting the integrity of the work.

Claims processing time and payment cycles should be considered as well. So that results are not affected by possibly irregular payment cycles, date of service, not paid date, should be used to define time periods whenever possible. Analysts should also be aware of the sources of the claims data being used for a project. Paper claims, which must be submitted and manually keyed before processing into a data file, introduce both delay and possible inaccuracy into the claims data. Analysts working on longitudinal studies should be especially aware that claims with dates of service 10 or 15 years ago might have been processed very differently than today, when much processing is carried out with “real time” verification. Claims submitted by members are subject to the so-called “shoebox
### TABLE 1 Checklist for Data Quality Control

**Documentation**
1. Documents are stored in location(s) accessible to all members of the team
2. Documentation is clear even to persons unfamiliar with the work
3. Written specifications indicate work to be performed and clear definitions of terms (e.g., washout, termination, cost)
4. Computer printouts include annotation at the start of the printout indicating the program name, date created, where stored, and identity of analyst
5. Computer printouts include annotations throughout explaining each major step

**Internal Peer Reviewer Verifies the Following:**
11. Previously published or known results are replicated before using file
10. File is as specified (e.g., patient demographics and utilization, dates, N)
9. File names match what the files are (e.g., claims, eligibility)
8. For work submitted for publication, internal documentation includes a summary table indicating source(s) of all data tables in the manuscript
7. Sample tracking document shows N at each stage of sampling process
6. Each step in analysis includes a verification of accuracy
5. Computer printouts include annotations throughout explaining each major step
4. Computer printouts include annotation at the start of the printout indicating the program name, date created, where stored, and identity of analyst
3. Written specifications indicate work to be performed and clear definitions of terms (e.g., washout, termination, cost)
2. Each step in analysis includes a verification of accuracy
1. Documentation is complete and adequate to verify results

**Receipt of File/Start of Project**
10. File is as specified (e.g., patient demographics and utilization, dates, N)
11. Previously published or known results are replicated before using file
12. Benefit design features (e.g., copayments, deductibles) are verified before beginning analysis
13. “Claims completion” is verified for entire analysis period

**Effect,” in which claims can be stored for months before being submitted to the payer for reimbursement. “Claims completion,” i.e., whether all claims for a given time period have been received and processed through to the administrative data files, should be verified by examining claim counts for each month of the time period of interest.

### Verification of What Is Provided to Others
A fundamental factor in providing accurate information to others is to have well-defined roles for data analysts and study decision makers, particularly principal investigators (PIs). This does not imply that rigid roles are necessary. The appropriate roles might vary from one organization to another; a reasonable structure is shown in Table 2. The goal is to ensure a comprehensive approach to quality, which prevents gaps caused by each party assuming that the other was responsible for a piece of the process. In implementing policies of this type, it should be emphasized that roles are minimum guidelines, not excuses to shift responsibility for accuracy to someone else.

**TABLE 2 Suggested Principal Investigator (PI)-Analyst Responsibilities for Data Quality Control**

**Principal Investigator**
1. Specifies clearly project objectives and methods, in writing whenever possible
2. Obtains Institutional Review Board approval or waiver before beginning work
3. Documents any changes necessary, the date made, and the reason for the decision
4. Verifies that the analysts’ work products meet specification(s)
5. Verifies that written reports (e.g., papers, presentations) match the procedures actually performed by the analyst
6. Permits information release only after internal peer review verification is performed

**Analyst**
1. Ensures that work performed matches project specifications provided by PI
2. Ensures accuracy of quantitative analysis before providing PI with results
3. Ensures that project documentation contains sufficient information for PI or other objective third party to verify quality of work
4. Maintains easily accessible records
5. Safeguards any protected health information, per HIPAA guidelines
6. Discloses results of quantitative analysis only after PI has completed review and authorized release

*HIPAA = Health Insurance Portability and Accountability Act.*

When writing analytic code, analysts should begin each program with a comment line explaining what the program does, where it is located, the date that it was last modified, and the analyst’s name. At each step in the program, a comment line should explain in simple terms what the statistical code does so that someone reading it at a later date can easily understand the procedures and how they were applied. A sample annotation at the start of the program should provide a brief explanation of what the program does (e.g., “This job calculates treatment termination rates for each age group.”) along with the name and location of the program file, the identity of the programmer,
and the date that the program was created. A sample annotation at the start of a section of code should explain what steps the code is taking and why (e.g., "Identify claim date; this will be used to identify the earliest and latest use dates for the target medication.").

It is also strongly recommended that analysts complete each major step of a computer program with a visible verification that the step was successful. This verification is a check not only on the coding process used but also on the source data. For example, an analysis of cost data should include basic descriptive measures, such as minimum, maximum, median, mean, and interquartile range, so that the analyst and PI can verify that the calculations used (e.g., mean cost) are appropriate for the data. A classification of patients by age group should be verified using a check of descriptive measures on age for each group (e.g., verifying that patients in an “18-to-24-year-old” age group have minimum and maximum ages of 18 and 24 years, respectively). A matching of claims to eligibility data should include verification that every person with a claim has an eligibility record and that a reasonable proportion of eligible members has at least 1 claim. The appropriate form of verification varies depending on the situation. For example, a reclassification of one variable’s discrete categories into another variable can be verified with a simple cross tabulation of the 2 variables. A “list cases” command can be used to verify some types of code. A good “rule of thumb” for the analyst to follow is that output should include all the information necessary for a reasonable person to verify, based on the job output alone and with no other knowledge of the project procedures, that the work performed matches specifications.

The tracking of sample size from the beginning to end of the sampling process is both a critical component of verification of study procedures and very strongly recommended for articles published in JMCP. A summary table (see Figure 1 for an example) should track the effect of each inclusion or exclusion criterion on sample size. For each step in the process, numbers in the table should match exactly to the job output available to the PI. Counts that do not match are a sign of a coding error, methodology that mistakenly excluded certain subgroups, or an incompatibility between code and data; these occurrences require further investigation.

One particularly helpful step for work intended for publication or presentation is to document the source of each finding in the internal study files. Analysts should keep copies of each data table included in a publication or presentation, along with an annotation indicating the name of the computer program that produced the finding. (Example annotation: “Source: Job name is ‘demographics.sps’ in the XYZ subdirectory on the ABC computer, run date 9-22-06”). The annotation enables the PI to locate and respond to questions easily even when the analyst is not available because the findings table can quickly be tracked back to the source code. Following receipt of peer-review comments, returning to the initial study files to perform any necessary reanalysis becomes a relatively easy task. Reanalysis is not uncommon, given the need by journal editors to ensure that results provide useful information for readers.

Internal Quality Control Peer Review

No quantitative results should be released until they are verified by a second person, an “internal peer reviewer” (IPR) who compares the work performed with the project specifications, checks the integrity of the figures produced, and looks for problems affecting interpretation. The IPR process should not be seen as an excuse to transfer all responsibility for quality to a second person; instead, both the original producers of the findings and the IPR share in responsibility for the final work product.

Having a relatively standard package of materials to provide to an IPR facilitates his/her work. The package should include: (1) written specifications for the project, such as a study plan or proposal document; (2) printouts (or links to electronic versions) of all programs relevant to the final study work product, such as computer jobs that create new data files from source files, pull a sample, or perform calculations; (3) a guide to the order in which steps were undertaken, such as the sequence of computer jobs; (4) the sample tracking document; and (5) any other information necessary for the IPR to understand how the work was performed and why.

The IPR should compare all steps in sampling, processing, and calculation with the initial written specifications for the project. Deviations from the plan should be reasonable and, preferably, documented. For example, if the study’s original plan was to analyze results separately for different clinics but one...
The IPR should also ensure that counts of cases are consistent throughout all calculations and match the sample tracking document. For example, if there were 1,000 cases in the dataset at the end of the first step in sampling, both the tracking document and all computer printouts should indicate 1,000 cases not only at the end of the first step but also at the start of the second step. Cases should never just “disappear;” a change in case counts should be both explainable and visible in the documentation. Finally, calculations and processing steps should be verified. For example, if a grouped-age variable was to be created from date of birth, the IPR should verify that the grouping was accurate and consistent with the data. Was the coding performed correctly? Did any cases have missing or out-of-range values for age, and, if so, how did the grouping handle them? The IPR should note where the documentation does not contain sufficient information to answer these questions.

A key element of success is the authority of the IPR to request additional information when necessary. An IPR who is charged with “signing off” on a project but not given access to all the necessary information will become, at best, frustrated and, at worst, a “rubber stamp.” It should be clearly understood by all analysts and PIs that internal peer review is in their best interest and that they are obligated to cooperate fully with the process. An organizational culture that embraces peer review is ultimately necessary to ensure high-quality administrative claims research.

Conclusion

As the cases of Lenore Weitzman, the Arizona redistricting project, and the Mars Polar Explorer demonstrate, catastrophic errors are often the result of simple and avoidable mistakes. DQC procedures greatly reduce the possibility of these unfortunate events. When DQC is consistently applied, the ubiquitous problems of human error and miscommunication can be reduced to measurable and largely controllable impediments to producing high-quality, reliable quantitative information. The lives of health plan members will be affected by our attention to DQC.

Kathleen A. Fairman, MA
Outcomes Research Consultant
JMCP Associate Editor and Senior Methodology Reviewer
kathleenfairman@qwest.net

DISCLOSURES

The author discloses no potential bias or conflict of interest relating to this article.

REFERENCES