Patient-Reported Utilization Patterns of Fentanyl Transdermal System and Oxycodone Hydrochloride Controlled-Release Among Patients With Chronic Nonmalignant Pain

Analysis of Medication Use Patterns: Apparent Overuse of Antibiotics and Underuse of Prescription Drugs for Asthma, Depression, and CHF

Resource Use and Patient Care Associated With Chronic Kidney Disease in a Managed Care Setting

Examination of Resource Use and Clinical Interventions Associated With Chronic Kidney Disease in a Managed Care Population

Improvements in Glycemic Control in Type 2 Diabetes Patients Switched From Sulfonylurea Coadministered With Metformin to Glyburide-Metformin Tablets

Cost and Utilization Comparisons Among Propensity Score-Matched Insulin Lispro and Regular Insulin Users

Assessment of Clinical Pharmacist Management of Lipid-Lowering Therapy in a Primary Care Setting
CONTENTS

■ ORIGINAL RESEARCH
223 Patient-Reported Utilization Patterns of Fentanyl Transdermal System and Oxycodone Hydrochloride Controlled-Release Among Patients With Chronic Nonmalignant Pain
Stacey J. Ackerman, MSE, PhD; Margaret Mordin, MS; Joseph Reblando, MPH; Xiao Xu, PhD; Jeff Schein, DRPh, MPH; Sue Vallow, MBA, MA; and Michael Brennan, MD

232 Analysis of Medication Use Patterns: Apparent Overuse of Antibiotics and Underuse of Prescription Drugs for Asthma, Depression, and CHF
Karen Gilberg, MD; Marianne Laouri, PhD; Sally Wade, MPH; and Sharon Isonaka, MD, MS

238 Resource Use and Patient Care Associated With Chronic Kidney Disease in a Managed Care Setting
James D. Robbins, MA; John J. Kim, PharmD; Gary Zdon, BA, MBA; Wing W. Chan, MS; and Jason Jones, PhD

248 Examination of Resource Use and Clinical Interventions Associated With Chronic Kidney Disease in a Managed Care Population
Roger London, MD, MBA; Amy Solis, BS; George A. Goldberg, MD, FACP; Sally Wade, MPH; and Wing W. Chan, MS

256 Improvements in Glycemic Control in Type 2 Diabetes Patients Switched From Sulfonylurea Coadministered With Metformin to Glyburide-Metformin Tablets
William Duckworth, MD; Marco Marcelli, MD; Maureen Padden, MD; Kenneth Kellick, PharmD; Teresa Duhancik, PharmD; Michelle Wilhardt, PharmD; Kevin Colgan, MA, RPh; and Alice Romie, PharmD

■ FORMULARY MANAGEMENT
263 Cost and Utilization Comparisons Among Propensity Score-Matched Insulin Lispro and Regular Insulin Users
Jennifer A. Hall, MPH; Kent H. Summers, PhD; and Robert L. Obenchain, PhD

■ CONTEMPORARY SUBJECT
269 Assessment of Clinical Pharmacist Management of Lipid-Lowering Therapy in a Primary Care Setting
L. Traywick Till, Jr., PharmD; John C. Voris, PharmD; and Julian Bourne Horst, PharmD

■ DEPARTMENTS
214 Cover Impressions
On Late Afternoon Waters (1984)
Gregory F. Harris
Sheila Macho

274 Editorial Subjects—in This Issue
• Finding the Truth About Health Care Cost Drivers—Price Versus Utilization Factors
• Real-World Research in Diabetes Care and Protocols for Patient Privacy
• JMCP Award for Excellence

278 Letters
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,
(817) 491-3593, fcurtiss@amcp.org

Managing Editor, Tamara C. Faggen,
(703) 323-0170, tfaggen@amcp.org

Peer Review Administrator, Jennifer A. Booker,
(703) 317-0725, jmcpreview@amcp.org

Graphic Designer, Laura J. Mahoney,
(703) 917-0737, laura@gilbertgordon.com

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

Contributing Editor
Sheila Macho, Minneapolis, Minnesota

EDITORIAL ADVISORY BOARD

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

Robert J. Anderson, PharmD, Mercer University, Atlanta, Georgia
John P. Barbuto, MD, Practicing Neurologist, Sandy, Utah
Diana I. Brixner, RPh, PhD, Department of Pharmacy Practice, University of Utah, Salt Lake City
Perry Cohen, PharmD, The Pharmacy Group, LLC, Glastonbury, Connecticut
Timothy Covington, PharmD, MS, McWhorter School of Pharmacy, Birmingham, Alabama
Joan Deady, MS, PharmD, Sutter Health, Sacramento, California
Leslie Fish, PharmD, Fallon Community Health Plan, Worcester, Massachusetts
Zafar Hakim, PhD, Hoffman-La Roche, Nutley, New Jersey
Alan Heaton, PharmD, BlueCross BlueShield of Minnesota
Brent C. James, MD, MStat, Institute for Healthcare Delivery Research, Intermountain Health Care, Salt Lake City, Utah
Richard A. Kipp, MAAA, Millman USA, Radnor, Pennsylvania
Katherine Knapp, PhD, Western University of Health Sciences, Pomona, California
Daniel C. Malone, RPh, PhD, College of Pharmacy, University of Arizona, Tucson

Brenda R. Motheral, RPh, MBA, PhD, Express Scripts, Inc., Maryland Heights, Missouri
Steven R. Peskin, MD, MBA, Nelson Managed Solutions, Lawrenceville, New Jersey
Cathlene Richmond, PharmD, Kaiser Permanente, California, Oakland
J. Warren Salmon, MS, PhD, University of Illinois at Chicago
Michael J. Sax, PharmD, The Pharmacy Group, LLC, Glastonbury, Connecticut
Fadia T. Shaya, PhD, MPH, University of Maryland, School of Pharmacy, Baltimore
Andy Stergachis, RPh, PhD, University of Washington and Formulary Resources, LLC, Bellevue
Sean D. Sullivan, PhD, Department of Pharmacy, University of Washington, Seattle
Robert J. Valuck, RPh, PhD, University of Colorado Health Sciences Center, School of Pharmacy, Denver
George J. Wan, PhD, MPH, Wyeth Pharmaceuticals, St. Davids, Pennsylvania
William J. Waugh, PharmD, WellPoint Pharmacy Management, West Hills, California
Bill Yates, RPh, PhD, AdvancePCS, Columbia, South Carolina

Founding Editor
Louise J. Sargent, MS, RPh

Editor-in-Chief, 1998-2001
Craig S. Stern, RPh, MBA, PharmD
Editorial Content and Peer Review

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

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

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

Original Research

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

Subject Reviews

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

Formulary Management

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

Contemporary Subjects

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

Editorials

Editorials should be relevant to managed care pharmacy and address a topic of contemporary interest; these submissions are peer reviewed.

Letters

These submissions may be peer reviewed for accuracy. If the letter addresses a previously published article, an author response may be appropriate.

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.

Advertising 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 of the Journal or 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.
More than a century after its introduction at an exhibition in Paris, the influence and popularity of Impressionism remains as strong as ever. With a firm foundation in the painting techniques of the late 19th century and early 20th century Impressionists, American Impressionist Gregory Harris has developed a style—and following—of his own. Born in California in 1953, Harris showed an interest in drawing from the age of 5, and was instructed by his mother, who was a professional artist. While in high school, he won a number of trophies and awards, and after graduation, he continued to win first-prize awards in art competitions in Southern California.

Harris attended California State University, Long Beach, in the early 1970s and continued his studies at the Art Students League in the mid-1980s in New York City. He returned to California in 1985. Since then, he has also studied at the Fechin Art Workshops in Santa Fe, New Mexico. As a freelance artist, Harris completed many art projects for motion picture studios; 11 of his paintings were purchased by Columbia Pictures for the film “Annie.”

He works in a wide variety of media—painting in oil and watercolor, drawing with pastels, sculpting in bronze, and creating ceramic pottery. Harris has been most significantly influenced by Frank Benson and Edmund Tarbell (painters of the Boston School), and European masters Claude Monet and Anders Zorn.

Through his confident brushwork and rich impasto, Harris creates a vibrant surface area in his paintings. Though his subject matter was varied in the past, he is now most comfortable and feels that he is at his best painting beautiful, sensitive women in period settings. The figures depicted in his paintings are often bathed in the light of a sun-filled beach or rendered in the warm glow of an inviting interior. Much as the artists at the turn of the century, Harris enjoys capturing these idyllic moments into which the viewer is drawn.

In a discussion of his art and the influences on it in his biography on the Hammer Galleries Web site, Harris stated, “The very reason I paint at all is because of light.”

“Alla prima” painting to me is the most challenging. Born out of plein air painting, alla prima painting involves working under ever-changing conditions forcing you to develop a clear focus early in the painting process. “Alla prima” refers to a method of painting in which the piece is completed in a single session, within just a few hours. As the paint is allowed no time to dry throughout the process, a distinctive “wet-into-wet” style results.

Harris has often asked friends to pose for his paintings—and it happens that AMCP Board member Dianne Parker, PharmD, was the model for On Late Afternoon Waters. Parker and her husband met and befriended Harris at the annual Sawdust Art Festival in Laguna Beach, California, in the mid-1980s. She posed in period attire as her husband, a professional photographer, took photos and Harris directed the shoot.

Critics have praised Harris’s professionalism, and his works have been collected widely throughout North America. A number of his paintings are in the permanent collections of regional museums, including the Zigler Museum in Louisiana and the Ella Carothers Dungan Gallery of Art in Missouri. Numerous galleries, such as the Simic New Renaissance Galleries in Carmel, La Jolla, and Rancho Santa Fe, California, and the Hammer Galleries in New York City, also represent him. On Late Afternoon Waters is currently available for acquisition through the Simic Galleries and can be viewed online at www.simic.com.

Sheila Macho
JMCP Contributing Editor

Cover credit
Gregory F. Harris, On Late Afternoon Waters, oil on canvas. Orange County, California. Copyright 1984. Image courtesy of Simic New Renaissance Galleries, Carmel, California.

Sources
Interview with Dianne Parker, PharmD.
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, a title page; an abstract of no more than 400 words; text; references; tables, figures, and graphs; and financial disclosures and conflicts of interest (see Submission Checklist for details).

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

Original Research
An abstract is required in the format of:
• Objective • Conclusion
• Methods • Keywords
• Results

Subject Reviews
An abstract is required, generally in the format of:
• Objective • Conclusion
• Summary • Keywords

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

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

Editorials
These submissions require no abstract.

Letters
These submissions require no abstract or title page.

■ Reference Style

References should be prepared following modified AMA style. Shown below are 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. Dissertation or thesis


9. Paper (or Poster) presented at a meeting

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

■ Submission of Manuscripts

A paper copy of the manuscript, including originals of figures and tables, should be submitted to the JMCP Peer Review Administrator at the Academy of Managed Care Pharmacy at 100 North Pitt Street, Suite 400, Alexandria, VA 22314. Tel: (800) 827-2627 or (703) 683-8416 or Fax: (703) 683-8417. The paper copy is necessary to ensure proper presentation and placement of text, figures, tables, and graphs. Please send an electronic version of the manuscript, either on a disk or via e-mail, to jmcp-preview@amcp.org. All text should be in a word processing program (preferably Microsoft Word). Tabular material also should be in a word processing program using the tab function to create columns, not using “tables” or “cells.” Figures should be saved in Photoshop or Illustrator and may be re-created by us. We cannot accept PowerPoint graphics. Please identify the format (PC or MAC), all programs used, and all file names.

Cover letter: the corresponding author should
• briefly describe the importance and scope of the manuscript,
• certify that the paper has not been accepted for publication or published previously and that it is not under consideration by any other publication, and
• identify the nature and extent of any financial interest or affiliation that any author has with any company, product, or service discussed in the manuscript.

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

■ Submission Checklist

Before submitting your manuscript to the Journal of Managed Care Pharmacy, please check to see that your package includes the following:

❑ Cover letter
❑ Manuscript: prepared in 10- or 12-point type, double-spaced (on disk or sent via e-mail to jmcp-preview@amcp.org), including
❑ title page with identification of all authors (with academic degrees and preferred credentials, position title, name of employer, city and state) and complete contact information for the corresponding author (mailing address, telephone and fax numbers, and e-mail address)
❑ abstract: no more than 400 words
❑ keywords: follows the abstract
❑ references: cited in numerical order as they appear in the text and prepared following modified AMA style
❑ tables and figures (generally no more than a total of 6). Submit referenced tables and figures on separate pages with titles (and captions, as necessary); match symbols in tables and figures to explanatory notes, if included.
❑ Disclosures and conflict of interest: completed and signed author attestation forms (available at www.amcp.org/jmcp/ep.pdf); clearly indicate source(s) of funding and financial support.

REFERENCE

ABSTRACT

BACKGROUND: Although use of long-acting opioid analgesics has increased for chronic nonmalignant pain management, little is known about patient-reported utilization patterns.

OBJECTIVE: To assess patient-reported utilization patterns of fentanyl transdermal system and oxycodone hydrochloride (HCl) controlled-release among patients with chronic nonmalignant pain and to compare these patterns to standard administration guidelines recommended in the manufacturers’ prescribing information (PI).

METHODS: Cross-sectional, observational, multicenter study of English-speaking patients who were seeking chronic nonmalignant pain management from 6 outpatient pain clinics. The inclusion criteria for the study were (1) diagnosis of chronic nonmalignant pain, (2) prescription for and current use of either transdermal fentanyl or oxycodone HCl controlled-release, and (3) duration of use for either transdermal fentanyl or oxycodone HCl controlled-release of at least 6 weeks. Patients completed either an oxycodone HCl controlled-release or transdermal fentanyl utilization questionnaire. A conversion table was used to standardize opioid analgesic doses from transdermal fentanyl or oxycodone HCl controlled-release to daily oral morphine equivalents. The principal outcome measures were the average interval between oxycodone HCl controlled-release administrations, the number of days the current transdermal fentanyl patch would be worn, and the percentage of oxycodone HCl controlled-release and transdermal fentanyl patients whose administration frequency exceeded the standard recommendation in the manufacturer’s PI (every 12 hours for oxycodone HCl controlled-release or every 72 hours for transdermal fentanyl). Other outcome measures included the number of oxycodone HCl controlled-release tablets per administration, the daily dose of long-acting opioid, the duration of adequate pain relief, and the difference in daily oral morphine equivalents between transdermal fentanyl and oxycodone HCl controlled-release patients, after adjusting in a multivariate regression model for demographic and clinical characteristics.

RESULTS: A total of 690 patients were enrolled in this study; 437 (63.4%) received oxycodone HCl controlled-release and 253 (36.6%) received transdermal fentanyl. Oxycodone HCl controlled-release patients reported taking a median of 1 tablet 3 times per day or a median of 3 tablets per day. A mean of 1.8 tablets per administration and 4.6 tablets per day were taken. The average interval between administrations of oxycodone HCl controlled-release was 7.8 hours, and the median daily dose was 80.0 mg (mean 155.6 mg). Among oxycodone HCl controlled-release patients, 17.5% had an average interval between administrations of 12 or more hours, whereas 1.9% reported the duration of pain relief as 12 or more hours. Transdermal fentanyl patients reported wearing the patch, on average, for 2.5 days (median 2.5), and 41.2% reported wearing the patch for at least 3 days, whereas 14.1% reported the duration of pain relief as at least 3 days. The median daily dosage strength of transdermal fentanyl was 75.0 mcg/hour. In the multivariate regression analysis, oxycodone HCl controlled-release patients had, on average, roughly 22 mg additional oral morphine equivalents per day relative to transdermal fentanyl patients (not statistically significant); the probability that oxycodone HCl controlled-release patients had higher oral morphine equivalents was 82.6%, which suggests a trend toward higher oral morphine equivalents per day in the oxycodone HCl controlled-release group.

CONCLUSION: Transdermal fentanyl and oxycodone HCl controlled-release both appear to be used by patients in a manner that is inconsistent with the standard recommendation in the manufacturers’ PI; however, the difference between patient-reported utilization and the PI recommendation is more pronounced with oxycodone HCl controlled-release.

KEYWORDS: Opioid analgesics, Fentanyl transdermal system, Oxycodone HCl controlled-release, Patient-reported utilization, Chronic nonmalignant pain

U nrelieved pain due to chronic, nonmalignant conditions affects between 8% and 30% of adults and imposes a substantial economic burden on society. Although use of opioid analgesics has increased for chronic nonmalignant pain management, little is known about patient-reported utilization patterns for long-acting opioids. To date, most studies have evaluated prescribing patterns using either health insurance claims data, pharmacy data, or medical chart review, which do not reflect actual patient consumption.

For example, a recent study by Malkin et al. used a large Medicaid claims database to describe patterns of care among patients receiving fentanyl transdermal system (Duragesic, Janssen Pharmaceutica Products, L.P., Titusville, New Jersey) or oxycodone hydrochloride (HCl) controlled-release (OxyContin, Purdue Pharma L.P., Norwalk, Connecticut) for chronic nonmalignant or malignant pain. These investigators found that if one oxycodone HCl controlled-release tablet was taken at each administration, the number of oxycodone HCl controlled-release administrations per day exceeded the manufacturers’ prescribing recommendation by 70%.

A limitation of the results reported by Malkin et al. was the inability to determine how many oxycodone HCl controlled-release tablets were taken at each administration because this information was not included in the claims database. The standard recommendation in the manufacturers’ prescribing information (PI) for oxycodone HCl controlled-release indicates that some patients may benefit from asymmetric dosing (a different dose given in the morning than in the evening), tailored to the pattern of pain. As such, a total of 3 tablets per day could still be dosed every 12 hours (for example, 1 tablet in the morning and 2 tablets in the evening). In addition, pharmacy claims databases provide information about medications dispensed, as opposed to the actual daily intake of the medications.

To address these limitations, a cross-sectional, observational, multicenter, patient-reported utilization study was conducted to assess the actual daily intake of transdermal fentanyl and oxycodone HCl controlled-release by patients with chronic nonmalignant pain. We chose these 2 long-acting opioids because they are the most commonly used long-acting opioids to treat chronic nonmalignant pain. We focused on chronic nonmalignant pain because long-acting opioids have been used with increasing frequency over the last few years for nonmalignant pain, such as chronic low back pain. Transdermal fentanyl provides continuous, controlled systemic delivery of fentanyl for up to 72 hours through a rectangular transparent patch, which is available in 4 dosage strengths: 25 mcg/hour, 50 mcg/hour, 75 mcg/hour, and 100 mcg/hour. Oxycodone HCl controlled-release is supplied...
Now please tell us at what time(s) and how many OxyContin pills you take at each time:

Example:

2 OxyContin pills at 8 PM, you would complete this question as follows:

Please fill in the number of pills in the box above the time(s) you take your pills. For example, if you take 1 OxyContin pill at 7:30 AM, and 2 OxyContin pills at 8 PM, you would complete this question as follows:

in 20 mg, 40 mg, 60 mg, and 80 mg tablet strengths for oral administration. The 160 mg dosage formulation of oxycodone HCl controlled-release was not made available until July 2000 and was later withdrawn from the market. The manufacturer's PI recommends that oxycodone HCl controlled-release tablets should be taken every 12 hours (every-12 hour) and that it is most appropriate to increase the every-12 hour dose, not the administration frequency. The standard recommendation in the manufacturer's PI for transdermal fentanyl indicates that the majority of patients are adequately maintained with transdermal fentanyl administered every 72 hours but that a small number of patients may not achieve adequate analgesia using the 72-hour administration interval and may require administration every 48 hours. The PI recommendation further indicates that an increase in the transdermal fentanyl dose should be evaluated before changing the dosing interval in order to maintain patients on a 72-hour administration regimen.6

We administered a patient-reported utilization survey to assess real-world patterns of care among patients receiving these 2 medications for chronic nonmalignant pain and compared these patterns to the standard dose administration guidelines recommended in the manufacturers' PI. We hypothesized that both oxycodone HCl controlled-release and transdermal fentanyl are used by patients in a manner that is inconsistent with the standard recommendation in the manufacturers' PI but that the difference between patient-reported utilization and the PI recommendation would be greater with oxycodone HCl controlled-release.

Methods

Study Design

A cross-sectional, observational, multicenter study was conducted of English-speaking patients who were seeking chronic nonmalignant pain management across 6 outpatient pain clinics. In order to be eligible for the study, patients must have been (1) diagnosed with chronic nonmalignant pain, (2) prescribed and currently using either transdermal fentanyl or oxycodone HCl controlled-release, and (3) on transdermal fentanyl or oxycodone HCl controlled-release for at least 6 weeks. Patients wereineligible to participate if they (1) were currently taking both transdermal fentanyl and oxycodone HCl controlled-release, (2) were currently participating or had been participating in a trial of an investigational drug within the last 30 days, or (3) would not sign informed consent to participate in this study. Institutional Review Board approval for the study was obtained for all sites. Written informed consent was obtained from all enrolled patients.

Each site was asked to enroll patients in a 2 to 1 ratio of oxycodone HCl controlled-release patients to transdermal fentanyl patients because we anticipated that this would reflect current prescription patterns.7 Trained study coordinators reported the patient's visit date, age, gender, date first prescribed oxycodone HCl controlled-release or transdermal fentanyl, and diagnosis on the inclusion/exclusion and demographic case-report form. Duration on medication was computed as the visit date minus the date first prescribed oxycodone HCl controlled-release or transdermal fentanyl. The site coordinators also completed a medication case-report form specifying the prescribed dose of oxycodone HCl controlled-release or transdermal fentanyl as well as use of supplemental prescription pain medications.

Because we collected data on patients who either were using oxycodone HCl controlled-release or transdermal fentanyl, the drugs' different routes of administration (that is, oral versus transdermal, respectively) and different standard recommendations in the manufacturers' PI (that is, every 12 hours versus every 72 hours, respectively) required that we develop separate utilization questions for each patient group. Enrolled patients, therefore,
completed either an oxycodone HCl controlled-release or transdermal fentanyl patient questionnaire during their follow-up visits once they had been established on their medications. The patient questionnaires, which required roughly 10 minutes to complete, assessed patterns of utilization from the patient's perspective, including frequency of use and duration of adequate pain relief (see Figures 1 and 2 for selected survey questions). The oxycodone HCl controlled-release utilization questions included the times when patients took their tablets on a typical day and the number of tablets taken at each time. The transdermal fentanyl utilization questions included when patients applied the patch and when they expected to change the current patch.

The principal outcome measures were the average interval between oxycodone HCl controlled-release administrations, the number of days the current transdermal fentanyl patch will be worn, and the percentage of oxycodone HCl controlled-release and transdermal fentanyl patients whose administration frequency exceeded the standard recommendation in the respective manufacturer's PI (that is, every 12 hours for oxycodone HCl controlled-release and every 72 hours for transdermal fentanyl). Other outcome measures included the number of oxycodone HCl controlled-release tablets per administration, the daily dose of long-acting opioid, the duration of adequate pain relief, and the difference in daily oral morphine equivalents between transdermal fentanyl and oxycodone HCl controlled-release patients, after adjusting in a multivariate regression model for demographic and clinical characteristics.

**Statistical Methods**

Morphine is considered the reference standard for comparing other opioid analgesics. Due to the 2 different routes of administration, we converted daily-prescribed doses of transdermal fentanyl and oxycodone HCl controlled-release to a common metric—oral morphine equivalents—given that there is a pharmacologic basis for converting fentanyl and oxycodone (a derivative of morphine) to oral morphine equivalents. The dose conversion algorithms are presented in Table 1. Because the manufacturer's PI for transdermal fentanyl provides a range of oral morphine equivalents, in the “base-case” analysis, the average of the range for each dosage strength of transdermal fentanyl was used to calculate daily oral morphine equivalents. In addition, sensitivity analyses were conducted by varying the oral morphine equivalents for each strength of transdermal fentanyl between the low and high values.

Demographic and clinical characteristics were evaluated using either t tests or Mann-Whitney U tests, as appropriate, for continuous variables and chi-square tests for categorical variables. Both means and medians were reported when the variable distributions were skewed. We also examined the duration of pain relief among transdermal fentanyl patients who expected to wear their current patches for at least 3 days and among oxycodone HCl controlled-release patients who administered every 12 or more hours. In addition, the number of oxycodone HCl controlled-release tablets per administration was calculated at the patient level. The difference between daily opioid load from transdermal fentanyl or oxycodone HCl controlled-release was examined using the Mann-Whitney U test.

Finally, in multivariate analyses using base-case (average transdermal dose) values for transdermal fentanyl, the difference in daily opioid load from oxycodone HCl controlled-release relative to transdermal fentanyl was examined, after adjusting for age, gender, and clinical characteristics that differed significantly between groups. Because the dependent variable—oral morphine equivalents—was skewed, a nonparametric “bootstrapping” approach was used to estimate the mean difference in daily oral morphine equivalents from oxycodone HCl controlled-release compared to transdermal fentanyl. Bootstrapping involves “resampling” the data many times (that is, repetitive computations) to generate an empirical estimate of the entire sampling distribution. The nonparametric bootstrapping procedure was used to develop a 95% confidence interval (CI) around the mean difference in daily oral morphine equivalents between groups. This was accomplished by drawing 1,000 random resamples of size 437 from the original oxycodone HCl controlled-release sample and size 253 from the original transdermal fentanyl sample, with replacement. In each resample, we calculated the group means and the difference and selected the 26th and 975th rank-ordered values of the observed distributions to define the 95% CI. The 95% CI contains the true value with a probability of 95%. This nonparametric approach also permitted estimation of the probability that the daily oral morphine equivalents from oxycodone HCl controlled-release exceeded the daily oral morphine equivalents from transdermal fentanyl. All statistical analyses were performed using version 8.0 of the Statistical Applications Software of the SAS Institute (Cary, North Carolina).

---

**Table 1: Dose Conversions to Oral Morphine Equivalents**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Oral Morphine Equivalents (mg)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone HCl controlled-release</td>
<td></td>
</tr>
<tr>
<td>1 mg</td>
<td>2</td>
</tr>
<tr>
<td>Fentanyl transdermal system†</td>
<td></td>
</tr>
<tr>
<td>25 mcg/hour patch</td>
<td>45, 89, 134</td>
</tr>
<tr>
<td>50 mcg/hour patch</td>
<td>135, 179, 224</td>
</tr>
<tr>
<td>75 mcg/hour patch</td>
<td>225, 269, 314</td>
</tr>
<tr>
<td>100 mcg/hour patch</td>
<td>315, 359, 404</td>
</tr>
</tbody>
</table>

* For example, a person taking 2 oxycodone HCl controlled-release 80 mg tablets daily would equal 320 mg oral morphine equivalents daily (2 tablets x 80 mg x 2). A person wearing a 25 mcg/hour patch and a 100 mcg/hour patch daily would equal 448 mg oral morphine equivalents daily (2 tablets x 80 mg x 2). The average transdermal dose tabulated above.

† The fentanyl transdermal system prescribing information provides a range of oral morphine equivalents for each dosage strength of fentanyl transdermal system. Therefore, we used the average of the range (for example, 89 mg for a 25 mcg/hour patch) in the base-case analysis and conducted sensitivity analyses using the low and high values.
### Results

Between August 2001 and January 2002, 691 patients were enrolled in the study; 438 (63.4%) were oxycodone HCl controlled-release patients and 253 (36.6%) were transdermal fentanyl patients. One oxycodone HCl controlled-release patient who was on medication for only 4 weeks was inadvertently enrolled in the study and was excluded from all analyses. Therefore, the analyses included a total of 690 patients (437 oxycodone HCl controlled-release patients and 253 transdermal fentanyl patients).

Gender, duration on medication, and use of supplemental prescription pain medications differed significantly between the transdermal fentanyl and oxycodone HCl controlled-release patient groups, whereas age and diagnosis did not differ between groups (Table 2). The average age was 46.4 years and the most common diagnosis was back and neck pain (58.1%). Among patients who received transdermal fentanyl, 34.0% were male and 87.0% used supplemental prescription pain medications; among patients who received oxycodone HCl controlled-release, 45.3% were male and 71.6% used supplemental prescription pain medication (P=0.0034 and P<0.0001, respectively). Patients in the transdermal fentanyl group were on medication for a shorter duration than patients in the oxycodone HCl controlled-release group (median 31.4 and 54.0 weeks, respectively; P<0.0001) (Table 2).

Oxycodone HCl controlled-release patients reported taking a median of 1 tablet 3 times per day or a median of 3 tablets per day (Table 3). A mean of 1.6 tablets per administration and 4.6 tablets per day were taken. The average interval between administrations of oxycodone HCl controlled-release was 7.8 hours and the median daily dose was 80.0 mg (mean 155.6 mg). Among oxycodone HCl controlled-release patients, 17.5% had an average interval between administrations of 12 or more hours and 1.9% reported the duration of pain relief as 12 or more hours. The single largest group of oxycodone HCl controlled-release patients (n=184; 42.7%) reported adequate pain relief lasting at least 4 hours but less than 6 hours; roughly 15% of patients (n=65) reported adequate pain relief lasting less than 4 hours (Table 3).

Among transdermal fentanyl patients, 88.5% were wearing 1 patch, 9.5% were wearing 2 patches, and 2.0% were wearing 3 or 4 patches (Table 4). Transdermal fentanyl patients reported wearing the patch, on average, for 2.5 days (median 2.5) and 41.2% reported wearing the patch for at least 3 days, whereas 14.1% reported the duration of pain relief as at least 3 days. The single largest group of transdermal fentanyl patients (n=142; 57.3%) reported adequate pain relief lasting at least 2 days but less than 3 days. The median daily dosage strength of transdermal fentanyl was 75.0 mcg/hour (Table 4).

Table 1 provides the dose conversion algorithms for oral morphine equivalents per day from transdermal fentanyl and oxycodone HCl controlled-release. In the bivariate (unadjusted) analysis using the transdermal fentanyl base-case (average transdermal dose) values (Table 5), transdermal fentanyl patients had significantly higher oral morphine equivalents per day relative to oxycodone HCl controlled-release patients (median—transdermal fentanyl: 269 mg, oxycodone HCl controlled-release: 160 mg; P=0.0010); the inferences were similar when using the high dosage morphine equivalents for transdermal fentanyl (P<0.0001). In the sensitivity analysis using the low dosage strength of transdermal fentanyl, there was no significant difference in daily oral morphine equivalents between medications (Table 5).

In the multivariate regression analysis (Table 6), after adjusting for age, gender, duration on medication, and use of supplemental prescription pain medications, oxycodone HCl controlled-release patients had, on average, roughly 22 mg additional oral morphine equivalents per day relative to transdermal fentanyl patients.

---

**Table 2: Demographic and Clinical Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Oxycodone HCl Controlled-Release (N=437)</th>
<th>Fentanyl Transdermal System (N=253)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>0.0723</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>45.7 (11.0)</td>
<td>47.5 (10.9)</td>
<td></td>
</tr>
<tr>
<td>Gender, %</td>
<td>0.0034</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45.3</td>
<td>34.0</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>54.7</td>
<td>66.0</td>
<td></td>
</tr>
<tr>
<td>Duration on medication, ‡ weeks</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>69.0 (54.3)</td>
<td>50.9 (54.5)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>54.0</td>
<td>31.4</td>
<td></td>
</tr>
<tr>
<td>Diagnosis, %</td>
<td>0.5074</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2.8</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>Back and neck pain</td>
<td>57.9</td>
<td>58.5</td>
<td></td>
</tr>
<tr>
<td>Muscle pain</td>
<td>8.5</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td>Joint pain</td>
<td>4.1</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Arthritis pain</td>
<td>4.4</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>Generalized pain</td>
<td>5.5</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>7.8</td>
<td>8.7</td>
<td></td>
</tr>
<tr>
<td>Other§</td>
<td>9.2</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>Use of supplemental prescription pain medications, %</td>
<td>71.6</td>
<td>87.0</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Reported by site coordinators based on review of medical charts.
† T test for normally distributed continuous variables, Mann-Whitney U test for skewed continuous variables, and chi-square test for categorical variables.
‡ Oxycodone HCl controlled-release, N=434; fentanyl transdermal system, N=251.
§ Duration on medication for the remaining 5 patients exceeded 6 weeks, but the actual duration was not known.
(based on average transdermal dose values). Although this difference in daily oral morphine equivalents was not statistically significant, the results suggest a trend toward higher oral morphine equivalents per day in the oxycodone HCl controlled-release group. The probability that oxycodone HCl controlled-release patients had higher oral morphine equivalents was 82.6%, after adjusting for age, gender, duration on medication, and use of supplemental prescription pain medications, which also suggests a trend toward higher oral morphine equivalents per day in the oxycodone HCl controlled-release group. Referring to Table 6, women had significantly lower oral morphine equivalents than men (approximately 89 mg lower, on average; \(P=0.0011\)). For every month on long-acting opioid medication, patients had roughly 5 mg additional oral morphine equivalents per day (\(P<0.0001\)). With every 10 years of age, patients had 6 fewer oral morphine equivalents per day, although this trend was not significantly associated with daily oral morphine equivalents from transdermal fentanyl or oxycodone HCl controlled-release. Similarly, there was a nonsignificant trend where patients who were taking supplemental prescription pain medications were taking higher doses (50.7 mg additional oral morphine equivalents per day, on average) of these long-acting opioids (relative to patients who were not taking supplemental prescription pain medications).

**Discussion**

In this study, we administered a patient-reported utilization survey to assess actual patterns of care among patients receiving oxycodone HCl controlled-release or transdermal fentanyl for chronic nonmalignant pain. This patient-reported utilization survey demonstrated that transdermal fentanyl and oxycodone HCl controlled-release both appear to be used by patients in a manner that is inconsistent with standard recommendations in the manufacturers’ PI; however, the difference between patient-reported utilization (average interval between oxycodone HCl controlled-release administrations or number of days the current transdermal fentanyl patch will be worn) and the standard recommendations in the manufacturers’ PI is more pronounced with oxycodone HCl controlled-release.

Among oxycodone HCl controlled-release patients, 17.5% had an average interval between administrations of 12 or more hours (Table 3), whereas 41.2% of transdermal fentanyl patients reported wearing the patch for at least 3 days (Table 4). The standard recommendation in the manufacturer’s PI indicates that oxycodone HCl controlled-release tablets should be taken every 12 hours and that it is most appropriate to increase the every-12 hour dose, not the administration frequency.\(^a\) The standard recommendation in the manufacturer’s PI for transdermal fentanyl indicates that the majority of patients are adequately maintained with transdermal fentanyl administered every 72 hours, but that a small number of patients may not achieve adequate analgesia using the 72-hour administration interval and may require administration every 48 hours. The PI further indicates that an increase in the transdermal fentanyl dose should be evaluated before changing the dosing interval in order to maintain patients on a 72-hour administration regimen.\(^b\)

The results of the current study are consistent with those reported by Malkin et al.\(^c\) based on a claims database analysis using California Medicaid (Medi-Cal) data. The current survey demonstrated that the average interval between administrations of oxycodone HCl controlled-release tablets was 7.8 hours (median of 1 tablet per administration, 3 administrations per day, and 3 tablets per day; Table 3), whereas transdermal fentanyl patients reported wearing their patch an average of 2.5 days (Table 4).

In the current study, the number of oxycodone HCl controlled-release administrations per day exceeded the recommended amount by 50% (13 administrations per day—recommended use/recommended use, where recommended use equals 2 administrations per day), whereas the number of transdermal fentanyl patches applied exceeded the manufacturers’ prescribed recommendation by 17% (2.5 days patch will be worn—recommended use/recommended use, where recommended use equals 3 days). Malkin et al.\(^d\) found that nonmalignant patients in the transdermal fentanyl group were wearing their patch an average of

---

**TABLE 3** Oxycodone HCl Controlled-Release Patient-Reported Utilization

<table>
<thead>
<tr>
<th>Oxycodone HCl Controlled-Release ((N=437))</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of tablets per day* Mean (SD)</td>
<td>4.6 (4.0)</td>
</tr>
<tr>
<td>Median</td>
<td>3.0</td>
</tr>
<tr>
<td>Number of administrations per day† Mean (SD)</td>
<td>3.0 (1.0)</td>
</tr>
<tr>
<td>Median</td>
<td>3.0</td>
</tr>
<tr>
<td>Number of tablets per administration* Mean (SD)</td>
<td>1.6 (1.2)</td>
</tr>
<tr>
<td>Median</td>
<td>1.0</td>
</tr>
<tr>
<td>Average interval between administrations,‡ hours Mean (SD)</td>
<td>7.8 (2.8)</td>
</tr>
<tr>
<td>Median</td>
<td>7.0</td>
</tr>
<tr>
<td>Percent ≥12 hours</td>
<td>17.5</td>
</tr>
<tr>
<td>Daily dose, mg</td>
<td>153.6 (218.7)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>80.0</td>
</tr>
<tr>
<td>Median</td>
<td></td>
</tr>
<tr>
<td>Duration of adequate pain relief§, n (%)</td>
<td></td>
</tr>
<tr>
<td>Less than 4 hours</td>
<td>65 (15.1)</td>
</tr>
<tr>
<td>At least 4 hours but less than 6 hours</td>
<td>184 (42.7)</td>
</tr>
<tr>
<td>At least 6 hours but less than 8 hours</td>
<td>116 (26.9)</td>
</tr>
<tr>
<td>At least 8 hours but less than 10 hours</td>
<td>39 (9.1)</td>
</tr>
<tr>
<td>At least 10 hours but less than 12 hours</td>
<td>19 (4.4)</td>
</tr>
<tr>
<td>12 or more hours</td>
<td>8 (1.9)</td>
</tr>
</tbody>
</table>

\(^a\) \(N=426\). Eleven patients did not report the number of tablets per day. The number of tablets per administration was calculated as the number of tablets per day divided by the number of administrations per day.

\(^b\) \(N=432\). Five patients did not report the number of administrations per day.

\(^c\) \(N=423\). Fourteen patients did not report the average interval between administrations.

\(^d\) \(N=431\). Six patients did not report the duration of adequate pain relief.
2.2 days, whereas oxycodone HCl controlled-release patients were taking an average of 3.5 tablets per day. Using these Medi-Cal data for nonmalignant patients, we calculated that, if 1 oxycodone HCl controlled-release tablet was taken at each administration (which is consistent with the median of 1 tablet per administration in the current study), then the number of oxycodone HCl controlled-release administrations per day (3.5 administrations per day) exceeded the recommended amount by 75% (3.5–2/2), whereas the number of transdermal fentanyl patches prescribed exceeded the manufacturers’ prescribing recommendation by 27% based on 1 patch every 2.2 days (2.2–3/3).

The current patient-reported utilization study demonstrated that both oxycodone HCl controlled-release and transdermal fentanyl exceeded the manufacturers’ prescribed recommendation by less than that calculated using Medi-Cal data from Malkin et al. Nevertheless, the difference between patient-reported utilization (average interval between oxycodone HCl controlled-release administrations or number of days the current transdermal fentanyl patch will be worn) and the standard recommendations in the manufacturers’ PI remains more pronounced with oxycodone HCl controlled-release. Malkin et al. used Medicaid data from 1 state, whereas the current study included patients from 6 states without regard to insurance status, suggesting that the results reported herein may be more generalizable than those reported by Malkin et al. Further, the results of the current study reflect patient-reported consumption, whereas the results from Malkin et al. reflect medications dispensed.

We searched the PreMEDLINE, MEDLINE, HealthSTAR/OVID, Embase, Current Contents, IMS R&D Focus, and Adis R&D Insight databases (January 1994 to July 2002) using the search terms “utilization” or “prescribing patterns” or “prescriptions” or “claims analysis” or “insurance claims” coupled with “Duragesic,” “transdermal fentanyl,” “OxyContin,” “oxycodone,” “analgesia,” “analgesic,” or “opioid.” Based on this literature search, to our knowledge, this is the first cross-sectional, multicenter study describing patient-reported utilization patterns of transdermal fentanyl and oxycodone HCl controlled-release for chronic nonmalignant pain. Through this literature search, however, we identified 1 medical chart review study that compared only the initial dosage of transdermal fentanyl to the standard recommendation in the manufacturer’s PI in 32 patients hospitalized during 1993.11 We also identified 2 other patient-utilization surveys for chronic nonmalignant pain, but these studies provided no information about dosages and administration intervals for comparison with the standard recommendation in the manufacturer’s PI; the first survey identified characteristics of patients treated with various opioids versus those not treated with opioids,12 and the second survey reported the degree of pain relief and tolerance among patients using various opioids.13

The results of our survey suggest that some patients may have either inadequate pain relief or need to take their pain medication more frequently than PI administration recommendations because the duration of pain relief is not adequate with the current dosing frequency. Among oxycodone HCl controlled-release patients, 1.9% reported the duration of pain relief as 12 or more hours (Table 3). The single largest group of oxycodone HCl controlled-release patients (n=184; 42.7%) reported adequate pain relief lasting at least 4 hours but less than 6 hours and 15.1% (n=65) reported pain relief lasting less than 4 hours (Table 3). Among

### TABLE 4

<table>
<thead>
<tr>
<th>Fentanyl Transdermal System</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=253</td>
<td></td>
</tr>
<tr>
<td>Number of patches worn, n (%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>224 (88.5)</td>
</tr>
<tr>
<td>2</td>
<td>24 (9.5)</td>
</tr>
<tr>
<td>3</td>
<td>4 (1.6)</td>
</tr>
<tr>
<td>4</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Number of days current patch will be worn*</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.5 (0.6)</td>
</tr>
<tr>
<td>Median</td>
<td>2.5</td>
</tr>
<tr>
<td>Percent ≥3 days</td>
<td>41.2</td>
</tr>
<tr>
<td>Daily dose, mcg/hour</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>75.0</td>
</tr>
</tbody>
</table>

* N=228. Twenty-five patients did not report the number of days the current patch will be worn.

### TABLE 5

<table>
<thead>
<tr>
<th>Medication</th>
<th>N</th>
<th>Oral Morphine Equivalents (mg)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone HCl controlled-release</td>
<td>437</td>
<td>311.3</td>
<td>160.0</td>
</tr>
<tr>
<td>Fentanyl transdermal system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base case</td>
<td>253</td>
<td>264.9</td>
<td>269.0</td>
</tr>
<tr>
<td>Low</td>
<td>253</td>
<td>214.9</td>
<td>225.0</td>
</tr>
<tr>
<td>High</td>
<td>253</td>
<td>316.2</td>
<td>314.0</td>
</tr>
</tbody>
</table>

* P=0.001. *Fentanyl transdermal system base case, low, and high compared to oxycodone HCl controlled-release using the Mann-Whitney U test. The base-case analysis uses the average transdermal dose for fentanyl transdermal system.

† In this unadjusted analysis, fentanyl transdermal system patients had significantly higher median oral morphine equivalents per day.
transdermal fentanyl patients, 14.1% reported the duration of pain relief as at least 3 days (Table 4). The single largest group of transdermal fentanyl patients (n=142; 57.3%) reported adequate pain relief lasting at least 2 days but less than 3 days (Table 4).

Further, the standard recommendations in the manufacturers’ PI for transdermal fentanyl and oxycodone HCl controlled-release indicate that some patients may require periodic supplemental doses of short-acting analgesics for “breakthrough pain.” The current study suggests that use of supplemental prescription pain medication may be more common than previously thought. Overall, approximately 77% of patients in the current study used supplemental prescription pain medications. Similarly, Cramer et al. reported that 74.7% of 1,543 nursing home residents received adjunctive pharmacotherapy primarily for nonmalignant pain. There was a high rate of rescue medication use with both drugs—71.6% for oxycodone HCl controlled-release and 87.0% for transdermal fentanyl (Table 2)—indicating that the majority of these patients still required short-acting opioids to help control breakthrough pain, in lieu of increasing the long-acting opioid dose. Given that physicians at the 6 sites were experienced pain specialists, they may have been more aggressive in controlling pain than others, such as primary care physicians.

It is difficult to speculate why more patients on transdermal fentanyl were taking supplemental prescription pain medication; the difference in use of supplemental prescription pain medication between the 2 patient groups may not be clinically significant. Our results also suggest that patients who were taking supplemental prescription pain medications were taking higher doses of oxycodone HCl controlled-release or transdermal fentanyl, which is consistent with what one might expect, given that these were chronic pain patients who were using opioids for an extended period of time.

The current study found that with every additional month on medication, patients had, on average, roughly 5 additional oral morphine equivalents per day from transdermal fentanyl or oxycodone HCl controlled-release. The increased utilization per additional month of 5 morphine equivalents per day is of unclear clinical significance. It may represent tolerance or another mechanism. Tolerance, defined as the need for increasing doses of opioids to maintain a defined effect such as analgesia, is not unusual during chronic opioid therapy. Progressively higher dosages may be required due to disease progression or pharmacological tolerance. Other investigators have also reported dose escalation in patients being treated for chronic nonmalignant pain.

**Limitations**

Several limitations merit explanation. First, this survey was administered to patients with chronic nonmalignant pain referred to clinics that specialize in pain management. As such, the results of this study may not be generalizable to either malignant pain patients or patients who seek medical care in other settings. By definition, chronic pain patients have more intractable, difficult-to-treat pain.

![Patient-Reported Utilization Patterns of Fentanyl Transdermal System and Oxycodone Hydrochloride Controlled-Release Among Patients With Chronic Nonmalignant Pain](image-url)

The dosage of oxycodone HCl controlled-release and transdermal fentanyl, therefore, is expected to be greater in patients seen in chronic pain clinics. The number of such patients likely will grow over the next decades due to changing demographics, combined with improved medical technology, improved health care delivery, and increased patient awareness about the “right to be pain free.”

Second, we did not calculate the total daily opioid load (long-acting plus supplemental prescription pain medications) because the use of supplemental prescription pain medications was not a statistically significant confounder in the multivariate regression analysis (Table 6).

Third, we did not conduct subgroup analyses by diagnosis to assess whether patients had different administration patterns depending on their diagnosis. Nevertheless, because the distribution of diagnoses did not differ across patient groups (P=0.5074; Table 2), diagnosis would not be considered a confounding factor for the observed administration patterns. We do, however, expect that the variability in the outcome measures (for example, average interval between oxycodone HCl controlled-release administrations or number of days the current transdermal fentanyl patch will be worn) is, in part, attributable to the different etiologies and pain levels.

Fourth, the oxycodone HCl controlled-release patient questionnaire (Figure 1) was designed for patients to report administration...
times based on 2-hour intervals (rather than hourly). Similarly, the transdermal fentanyl patient questionnaire (Figure 2) was designed for patients to report when they put their patch on and expected to change the patch based on 12-hour increments (for example, put the patch on Tuesday morning and change the patch Thursday afternoon). Although the design of these particular questions introduced some imprecision, they were designed in this fashion to decrease the burden on the patients completing the surveys.

Lastly, although patient-reported data offer many advantages relative to claims data,17 patient-reported data may be subject to recall bias18; however, given that the patients in this study were reporting about medications they currently were taking, we expect that the magnitude of recall bias should have been minimal. On the other hand, the data abstracted from medical charts (for example, prescribed dose and use of supplemental prescription pain medication) may have been subject to inaccurate data abstraction; again, we anticipate that inaccurate abstraction would have been minimal because site coordinators were trained prior to data abstraction.

The current patient-reported utilization survey reported measures of utilization such as mean number of tablets per administration, interval between administrations, and percentage of patients who reported administering more frequently than is recommended in the manufacturers’ PI. On the other hand, Malkin et al. reported measures of utilization such as mean number of transdermal fentanyl patches or oxycodone HCl controlled-release tablets per day, mean cost per month, and percentage by which the administrations per day exceed the standard recommendations in the manufacturers’ PI. A recent editorial in the Journal of Managed Care Pharmacy emphasized that reporting multiple measures of utilization provides assistance to readers when interpreting the results and judging the validity of the conclusions.19 Despite the different measures of utilization used in the current study versus those reported by Malkin et al., the findings are consistent, thereby supporting the validity of the authors’ conclusions.

Conclusion

This patient-reported utilization survey demonstrated that transdermal fentanyl and oxycodone HCl controlled-release both appear to be used by patients in a manner that is inconsistent with the standard recommendations in the manufacturers’ PI. However, the difference between patient-reported utilization (that is, average interval between oxycodone HCl controlled-release administrations or number of days the current transdermal fentanyl patch will be worn) and the standard recommendations in the manufacturers’ PI (that is, every 12 hours for oxycodone HCl controlled-release and every 72 hours for transdermal fentanyl) is more pronounced with oxycodone HCl controlled-release. Among oxycodone HCl controlled-release patients, only about 18% of patients were observed to exhibit every-12-hour administration patterns (Table 3), whereas about 41% of transdermal fentanyl patients reported wearing the patch for at least 3 days (Table 4). These results underscore the need to better understand the reasons for increasing the dosing frequency for both oxycodone HCl controlled-release and transdermal fentanyl above their respective manufacturers’ PI recommendations.

Further, this study will help inform physicians and managed care organizations about the actual frequency of dosing of these long-acting opioids in a chronic nonmalignant pain setting. Lastly, these results offer insights into, and recognition of, real-world prescribing patterns and suggest that a pharmacoeconomic evaluation based solely on the PI dosing recommendations may lead to an inaccurate assessment of the true costs of these agents.

ACKNOWLEDGMENTS

Administrative, technical, and/or material support was provided by Jennifer Nordin, MS, and Ayo Inesekanor MPH, from Covance, and Julie Locklear, PharmD, and Brian Meissner, PharmD, from Janssen assisted with study implementation. Chureen Carter, PharmD, from Janssen, performed the literature search. Holly Bonello and Yu-Chen Yeh, MS, from Covance, provided administrative support. The following investigators participated as study sites: Michael Ashburn, MD, University of Utah, Salt Lake City, Utah; Michael Brennan, MD, private practice, Fairfield, Connecticut; Todd Lininger, MD, Pain Care Associates, Waterford, Michigan; Edward Michna, MD, Brigham and Women’s Hospital, Boston, Massachusetts; Douglas Pritchard, MD, Davis Regional Medical Center, Statesville, North Carolina; and Jack Rosenberg, MD, Integrated Pain Management, Concord, California.

DISCLOSURES

Funding for this research was provided by Janssen Pharmaceutica and was obtained by authors Margaret Mordin, Stacey J. Ackerman, and Jeff Schein. Janssen Pharmaceutica, the company licensed to sell fentanyl transdermal system, hired Covance Health Economics and Outcomes Services Inc. to design the study, perform the analysis, and draft the manuscript. Ackerman, Mordin, and authors Xiao Xu and Joseph Reblando are employed by Covance; Schein and author Sue Vallow are employed by Janssen Pharmaceutica; Brennan is an independent co-investigator who has received an honorarium from Covance. Ackerman served as principal author of the study. Study concept and design were contributed primarily by Ackerman, Mordin and Schein. Ackerman, Mordin, Reblando, and Xu had full access to the data and accept full responsibility for the integrity of the data and the data analysis. Ackerman, Mordin, Reblando, Xu, Schein, Vallow, and Brennan analyzed and interpreted the data, and Ackerman provided statistical expertise. Drafting of the manuscript was the work of Ackerman and its critical revision was the work of Ackerman, Mordin, Reblando, Xu, Schein, Vallow, and Brennan.

REFERENCES

3. IMS Health National Disease & Therapeutic Index (NDTI). 2002. (The majority of drug uses for OxyContin and Duragesic was for the treatment of nonmalignant pain.)
Analysis of Medication Use Patterns: Apparent Overuse of Antibiotics and Underuse of Prescription Drugs for Asthma, Depression, and CHF

KAREN GILBERG, MD; MARIANNE LAOURI, PhD; SALLY WADE, MPH; and SHARON ISONAKA, MD, MS

ABSTRACT

OBJECTIVE: To assess the appropriateness of prescription medication use based upon widely accepted treatment guidelines.

METHODS: We analyzed administrative claims for the period October 1, 1998, through September 20, 1999, supplied by 3 California health plans to determine medication use patterns for outpatient prescriptions. We compared these patterns to those expected in the presence of adherence to treatment guidelines.

RESULTS: During the study period, only 27.5% of antidepressant users received the recommended 6 months of continuous therapy, only 49.0% of diagnosed asthma patients received at least one inhaled corticosteroid prescription (compared to 67.1% who received at least one inhaled beta-agonist prescription), and only 54.5% of patients diagnosed with congestive heart failure (CHF) received an angiotensin-converting enzyme (ACE) inhibitor. Of patients who had a diagnosis of common cold or upper respiratory tract infection, 35.7% received antibiotics. Effective medications appear to be underused for patients with asthma, CHF, and depression. Antibiotics appear to be overused for the common cold and upper respiratory infections. More effective efforts must be made to address appropriate use of medications. Without these efforts, improved quality of care and decreased total health system costs are unlikely to be realized.

CONCLUSION: There is a remarkable degree of apparent overuse and underuse of prescription medications despite the existence of clinical guidelines to support appropriate use in the conditions studied. Effective medications appear to be underused for patients with asthma, CHF, and depression. Antibiotics appear to be overused for the common cold and upper respiratory infections. More effective efforts must be made to address appropriate use of medications. Without these efforts, improved quality of care and decreased total health system costs are unlikely to be realized.

KEYWORDS: Drug utilization, Delivery of health care, Managed care programs, Disease management

J Managed Care Pharm. 2003(9): 232-37

Authors

KAREN GILBERG, MD, is Senior Practice Leader, Protocare Sciences, Santa Monica, California; MARIANNE LAOURI, PhD, is Senior Program Director, California HealthCare Foundation, Oakland; SALLY WADE, MPH, is Director of Research, Zynx Health, Beverly Hills, California (At the time this work was performed, Wade was Director, Health Care Information Group, Protocare Sciences, Santa Monica, California); SHARON ISONAKA, MD, MS, is Chief Operating Officer and Practice Leader, Protocare Sciences, Santa Monica, California.

AUTHOR CORRESPONDENCE: Sharon Isonaka, MD, MS, Chief Operating Officer & Practice Leader, Protocare Sciences, 2400 Broadway, Suite 100, Santa Monica, CA 90404. Tel: (310) 264-4085; Fax: (310) 315-7432; E-mail: sisonaka@protocare.com

Copyright © 2003, Academy of Managed Care Pharmacy. All rights reserved.
Analysis of Medication Use Patterns: Apparent Overuse of Antibiotics and Underuse of Prescription Drugs for Asthma, Depression, and CHF

use that we observed within the same sample of California patients to assess the appropriateness of the current levels of drug utilization. For this part of the study, we selected medical conditions for which well-documented evidence and widely accepted treatment guidelines provide clear recommendations for appropriate drug therapy. The medications and conditions studied also represent 2 different types of medication quality concerns: underuse (inhaled corticosteroid [ICS] use in asthma, angiotensin-converting enzyme [ACE] inhibitor or angiotensin II receptor antagonist [ARB] use in congestive heart failure [CHF], and duration of antidepressant therapy for depression) and overuse (antibiotic use in the common cold and upper respiratory tract infection).

Methods

Data Sources
This study employed administrative claims data from 3 of the 10 largest health plans in California. Members were selected from large group plans to eliminate any biases inherent in benefit coverage and underwriting differences for small groups and individual coverage. Each plan submitted claims for a sample of 165,000 to 257,000 randomly selected members who had continuous medical and pharmacy coverage for the 18-month period from April 1, 1998, through September 30, 1999. These data were aggregated to form the California study population.

Study Population
The aggregated California health plan population for this study included a total of 552,748 patients (i.e., members who had benefit coverage and received services during the study period) (Table 1). The average age for this population was 47.4 years with slightly more females than males (54.6% versus 45.4%) and was considerably older than the U.S. population in 1999, which had an average age of 36.4 years. The distribution of health plan type for this study population was: health maintenance organization (HMO), 42.3%; preferred provider organization (PPO), 56.6%; point of service (POS), 1.0%; and other, 0%.

Analytic Approach
This study provides a descriptive analysis of markers of overuse and underuse of outpatient medications in 4 common therapeutic areas. Therapeutic areas for study were chosen to represent common diseases for which the available evidence can support an assessment of the clinical appropriateness of current treatment patterns. Tables 2 and 3 describe the rationale for inclusion of each of the selected therapeutic areas, the marker used to assess appropriateness, and the method used to identify patients for inclusion within each therapeutic area. The study evaluated prescription dispensing patterns for the 12-month period of October 1, 1998, through September 30, 1999.

Results
See Table 4 for a summary of study results.

Asthma. The number of patients with a diagnosis of asthma was 18,693 (3.4% of the study population). Table 5 provides an overview of the observed usage of ICSs, which guidelines recommend be used on a chronic basis as the foundation of therapy with other drugs that are commonly used in asthma but that do not treat the underlying cause of the disease.
Congestive heart failure. The number of patients with the diagnosis of congestive heart failure was 9,648 (1.7% of the study population). Of these patients, the percentage filing at least one prescription during the study period was 54.4% for ACE inhibitors, 8.4% for ARBs, and 1.8% for ACE combinations. The percentage of CHF patients who filled at least one prescription for any ACE inhibitor or ARB was 61.1%, and the average number of prescriptions filled per patient during the study period was 6.7.

Antidepressant use. The number of patients who filled at least one prescription for an antidepressant during the study period was 19,766 (3.6% of the study population), of which only a surprisingly low 27.7% received a minimum of 6 months of continuous therapy during the study period. In comparison, 59.0% of these patients received therapy for less than 3 months and 13.3% received continuous therapy for 3 to 6 months. The average number of prescriptions filled per antidepressant user was 3 during the 12-month study period.

Common cold/upper respiratory tract infections. The number of patients with any diagnosis of respiratory tract infection was 158,553, of which 33,285 (21.0%, or 6.0% of the entire study population) had a diagnosis of either the common cold or upper respiratory tract infection (URTI). Of those patients with the diagnosis of common cold or URTI, 35.7% filled at least one prescription for antibiotics. In comparison, the use of antibiotics for the other respiratory tract infections
assessed ranged from 51.3% for the group of diagnoses pharyngitis/tonsillitis/laryngitis/tracheitis to 62.6% for the diagnosis sinusitis.

**Discussion**

This study attempts to assess real-life patterns of drug treatment against the yardstick of guidelines and clinical evidence in order to evaluate appropriateness of therapy. The results of this study suggest that a remarkable degree of overuse and underuse of prescription medications continued to exist at the time of the study despite the existence of clinical guidelines to support appropriate use in the conditions studied. Only 50% of patients with asthma received ICSs, drugs that are known to treat the underlying cause of asthma and improve mortality and morbidity; at the same time, more than three quarters of the asthma patients took at least one form of beta agonist, a class of drugs that treat the symptoms but not the underlying cause of the disease. While an administrative claims analysis cannot discern patients with persistent asthma who are candidates for ICS therapy from those with mild intermittent disease, our patient identification criteria sought patients who had significant disease (hospitalization or emergency room visit) or multiple encounters for their asthma; i.e., individuals who presumably had symptoms significant enough to actively seek health care for their asthma. Even accounting for avoidance of ICS in young children due to concerns regarding the potential impact on growth, a substantial proportion of asthmatics do not receive an important medication for their disease.

Although ACE inhibitors and angiotensin II blockers were used in 60% of patients with CHF, the very significant impact of these medications on morbidity and mortality in this condition and the wide coverage of their benefits in the medical media should have resulted in their use in a much larger percentage of patients, considering that our patient population had either hospitalizations or multiple encounters for their CHF. Slightly more than 25% of antidepressant users took antidepressants continuously for an adequate time period to prevent relapse of their disease, with the majority of patients taking these medications for less than 3 months. While some patients could have been receiving antidepressants for a nondepression indication, we still would have expected a higher rate of longer-term use. Finally, antibiotics were used in just more than one third of patients with conditions that are most likely of viral origin (e.g., the common cold and upper respiratory tract infections) and for which antibiotic treatment is not indicated, thereby increasing the avoidable risk of antibiotic resistance.

These results are particularly surprising and disturbing when we take into account the fact that 3 of the conditions studied (asthma, CHF, and depression) are known to produce high costs to the health care system. As such, they have been the subject of extensive managed care scrutiny with programs in disease management, patient education and compliance, and drug utilization review and continuing medical education for both primary care physicians and specialists. Our previous report demonstrated that there was little geographic variability in the use of these medications. Although reducing variability

### Table 3: Condition Definitions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asthma</strong></td>
<td>1. At least 1 hospitalization with asthma listed as the primary diagnosis (ICD-9 493.xx); or 2. At least 2 outpatient asthma visits (asthma diagnosis on outpatient visit claim) plus one asthma medication fill (respiratory beta agonist, mast cell stabilizers, orally inhaled corticosteroids, or xanthine); or 3. At least 2 asthma medication dispensing events (Note that 1 dispensing event is equal to a 30 day supply or less; e.g., 1 prescription fill for between 31 and 60 days would equal 2 dispensing events); or 4. At least 1 ER visit with asthma listed as the primary diagnosis.</td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td>At least one medication fill for 1. SSRI antidepressants, 2. Tricyclic antidepressants, 3. MAO inhibitors, or 4. Non-SSRI/nontricyclic new antidepressants (trazodone, maprotiline, nefazadone, venlafaxine, mirtazapine, bupropion).</td>
</tr>
<tr>
<td><strong>CHF</strong></td>
<td>1. Two or more professional or facility claims, excluding “tests,” at least 7 days apart, for CHF (ICD-9 428.x, 402.01, 402.11, 402.91, 425.4), or 2. An inpatient hospital claim with a CHF diagnosis listed as the primary diagnosis.</td>
</tr>
</tbody>
</table>
Analysis of Medication Use Patterns: Apparent Overuse of Antibiotics and Underuse of Prescription Drugs for Asthma, Depression, and CHF

has always been an important goal of quality assurance programs, these findings suggest that despite greater uniformity of practice patterns, there appears to be a need for ongoing improvement in the appropriateness of use of medications in the therapeutic areas studied.

We acknowledge the limitations inherent in the use of administrative claims as a data source for this study. Administrative claims data cannot provide clinical-record level detail (e.g., severity of disease, therapy contraindications) that would be needed to assess true appropriateness of care for specific patients. However, patient identification algorithms in this study were consistent with existing definitions for external quality assessment approaches such as those used by the National Committee on Quality Assurance. Our study was designed as an initial descriptive analysis to identify the magnitude of potential under- or over-utilization of commonly used medications across a large population of managed care patients but did not attempt to utilize more complex methodologies to assess the appropriateness of drug use at an individual patient level.

■ Conclusion

Patients are continuing to underuse and overuse important drug therapies in 4 common therapeutic areas. The underlying causes of these problems remain uncertain. Contributing factors could include prescribing practices, poor patient compliance, excessive patient demand, and inconsistent or inadequate monitoring of drug therapy use. Further study to identify the importance of these factors and predictors of potentially inappropriate utilization is needed.

What is clear is that despite the efforts of the health care system, traditional quality improvement programs continue to leave many more opportunities for optimizing care. More effective efforts must be made to address both the underuse and overuse of specific therapies. These efforts must include both studies to understand the best methods to more successfully reinforce appropriate use of medications according to accepted guidelines and innovative tools to support physician decision making and patient compliance. Without these focused efforts, it is unlikely that the opportunities of improved quality of care and decreased total health system costs through the appropriate use of pharmaceutical products can be fulfilled.

ACKNOWLEDGMENTS

The authors thank Sandra Aronberg, Jeff Kamil, Nancy Stalker, and Cheryl Tanigawa for assisting them with obtaining data and for their contributions to the Advisory Board, Robert W. Dubois and Elaine Batchlor for their contributions in designing the geographic variations study, Mary Patton and Robert Fowler for their analytic expertise; and Merle Haberman and Dorothy George for their review of and contribution to this paper.

DISCLOSURES

Funding for this research was provided by a grant from the California HealthCare Foundation. Protocare Sciences is a health care consulting company that was commissioned by the California HealthCare Foundation to design

### TABLE 4 Summary of Results

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number With Condition (% of Study Database)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>18,693 (3.4)</td>
<td>% of patients with at least 1 ICS prescription (Rx) fill: 49.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Average number of ICS Rx fills by users/12 months: 4.1</td>
</tr>
<tr>
<td>CHF</td>
<td>9,648 (1.7)</td>
<td>% of patients with at least 1 ACE/ARB Rx fill: 61.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Average number of ACE/ARB Rx fills by users/12 months: 6.7</td>
</tr>
<tr>
<td>Depression</td>
<td>19,766 (3.6)</td>
<td>% of patients with at least 6 months continuous therapy: 27.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% of patients with 3 to 6 months continuous therapy: 13.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% of patients with &lt;3 months continuous therapy: 59.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Average number of antidepressant Rx fills by users/12 months: 3.0</td>
</tr>
<tr>
<td>Common cold/URTI</td>
<td>33,285 (6.0)</td>
<td>% of patients with at least 1 antibiotic Rx fill (temporally related to common cold/URTI diagnosis): 35.7</td>
</tr>
</tbody>
</table>

### TABLE 5 Use of Selected Common Medications in Patients With the Diagnosis Asthma

<table>
<thead>
<tr>
<th>Inhaled Corticosteroids</th>
<th>Inhaled Beta Agonists*</th>
<th>Oral Beta Agonists*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number and percentage of patients who filled even 1 prescription during the 12-month study period</td>
<td>9,154 (49.0%)</td>
<td>12,534 (67.1%)</td>
</tr>
<tr>
<td>Average number of prescriptions filled during the 12-month study period</td>
<td>4.1</td>
<td>5.6</td>
</tr>
</tbody>
</table>

* 13,914 (74.4%) patients used either inhaled beta agonist alone, oral beta agonist alone, or both oral and inhaled beta agonists.

Summary of Results

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number With Condition (% of Study Database)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>18,693 (3.4)</td>
<td>% of patients with at least 1 ICS prescription (Rx) fill: 49.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Average number of ICS Rx fills by users/12 months: 4.1</td>
</tr>
<tr>
<td>CHF</td>
<td>9,648 (1.7)</td>
<td>% of patients with at least 1 ACE/ARB Rx fill: 61.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Average number of ACE/ARB Rx fills by users/12 months: 6.7</td>
</tr>
<tr>
<td>Depression</td>
<td>19,766 (3.6)</td>
<td>% of patients with at least 6 months continuous therapy: 27.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% of patients with 3 to 6 months continuous therapy: 13.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% of patients with &lt;3 months continuous therapy: 59.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Average number of antidepressant Rx fills by users/12 months: 3.0</td>
</tr>
<tr>
<td>Common cold/URTI</td>
<td>33,285 (6.0)</td>
<td>% of patients with at least 1 antibiotic Rx fill (temporally related to common cold/URTI diagnosis): 35.7</td>
</tr>
</tbody>
</table>
the study and analyze and interpret the data. Authors Karen Gilberg and Sharon Isonaka are employed by Protocare Sciences, and author Marianne Laouri is employed by the California HealthCare Foundation. Gilberg served as principal author of the study. Study concept and design were contributed by Laouri and author Sally Wade, and analysis and interpretation of data were contributed by Gilberg, Laouri, Wade, and Isonaka. Drafting of the manuscript was primarily the work of Gilberg, Wade, and its critical revision was the work of Laouri and Isonaka. Statistical expertise was contributed by Gilberg.

REFERENCES


Resource Use and Patient Care Associated With Chronic Kidney Disease in a Managed Care Setting

JAMES D. ROBBINS, MA; JOHN J. KIM, PharmD; GARY ZDON, BA, MBA; WING W. CHAN, MS; and JASON JONES, PhD

ABSTRACT

OBJECTIVE: To describe the resource utilization and care of chronic kidney disease (CKD) patients in a managed care plan.

METHODS: This was a retrospective claims analysis of a nationwide managed care medical and pharmacy database from September 1, 1998, to July 31, 2001. Twenty-seven health plans in 19 states distributed across the Northeast, Southeast, Midwest, and Southwest United States were represented in this analysis. CKD patients were identified using ICD-9 CM, CPT-4, and HCPCS codes indicative of dialysis. Patients continuously enrolled for at least 6 months before and 3 months after an initial dialysis event were included in the study. Health care charges and associated clinical information were assessed during 3 time periods: predialysis was from the sixth through the second month before initial dialysis, peri-dialysis was 30 days before and 30 days after initial dialysis, and postdialysis was the second and third month after initial dialysis. The main outcome measures were total health care charges, primary diagnoses, and diagnosis-related groups (DRGs).

RESULTS: The per-patient-per-month charges were $4,265 in the predialysis period (average for 5 months), $35,292 in the peridialysis period (average for 2 months), and $15,399 in the postdialysis period (average for 2 months). The most common primary diagnosis categories during all time periods were chronic renal failure and congestive heart failure. Similarly, the most common DRGs were related to renal and heart failure. A total of 38.2% of patients did not have an initial nephrologist visit until the first dialysis event. Treatments with nutritional supplements and medications such as angiotensin-converting enzyme inhibitors and erythropoietin were found to be suboptimal.

CONCLUSION: CKD patients generate significant medical charges during the predialysis period and after initiation of dialysis. Further investigations are warranted to assess the impact of active management of CKD patients on CKD-related health care expenditures in kidney disease.

KEYWORDS: Cost, Economic, Chronic kidney disease, CKD

J Manag Care Pharm. 2003(9)3: 238-47

Chronic kidney disease (CKD), which encompasses the entire spectrum of renal disease severity from predialysis renal insufficiency to end-stage renal disease (ESRD), is a growing health care concern. There has been a significant increase in the number of patients treated for ESRD in the United States over the past 10 years. According to recent estimates by Xue et al., the number of ESRD patients has more than doubled from 166,494 in 1990 to 372,407 in 2000. These figures are projected to exceed 650,000 by 2010. The factors associated with the increasing ESRD prevalence are unclear, but significant differences in ESRD incidence and prevalence among differing age, sex, and racial groups have been noted. As the population of ESRD patients continues to increase, so does the consumption of a considerable amount of health care resources. By 2010, the Medicare costs incurred by ESRD patients are projected to increase to $28.3 billion, from the current figure of $14 billion.

The definitive “start” of the CKD disease process had not been discreetly defined until recently. Previously, referral to a nephrologist for early CKD monitoring was recommended for patients with a serum creatinine level of 1.5 mg/dL or greater in women and 2.0 mg/dL or greater in men. However, National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) guidelines now classify patients into 5 stages of CKD, based on the presence or absence of markers of kidney disease and glomerular filtration rate (GFR) (Figure 1). Individuals are classified as having CKD if they have either (1) kidney damage (e.g., pathologic abnormalities or laboratory/imaging study markers of damage, regardless of GFR) or (2) a GFR below 60 mL/min/1.73 m² for 3 months or more (regardless of the presence or absence of kidney damage). Earlier stages of kidney disease can be detected through routine laboratory monitoring. Estimates from the Third National Health and Nutrition Examination Survey (NHANES III) indicate that the number of adults in the United States with GFR levels of ≥90, 60 to 89, 30 to 59, 15 to 29, and <15 mL/min/1.73 m² are 114.0 million, 55.3 million, 7.6 million, 0.4 million, and 0.3 million, respectively.

Recent literature has highlighted the importance of patient care in predialysis CKD. It has been suggested that the high morbidity and mortality associated with ESRD can be attributed to inadequate care prior to the initiation of dialysis therapy. Early referral of CKD patients to a nephrologist, treatment of underlying comorbidities associated with CKD (such as anemia, hypertension, and diabetes), monitoring of nutrition, early placement of vascular access, and patient education may favorably impact subsequent patient outcomes during hemodialy-
Managing this population remains a challenge, as early-stage/predialysis CKD is an underrecognized and undertreated disease entity, despite its clinical significance and prevalence.

Few economic studies have been conducted that examine the resource use associated with patient care of CKD, from predialysis through ESRD. In addition, while economic information for ESRD patients has been well documented in the United States Renal Data System (USRDS), clinical and economic information associated with predialysis CKD care has not been well documented in the current literature. Therefore, the primary aim of this study was to describe the health care resource use and patient care of CKD patients across the spectrum of disease severity, using data from a managed care setting. The rationale for these analyses is to gain a preliminary insight into the costs and patient care associated with CKD.

### Methods

A retrospective analysis of administrative claims was performed using a large managed care database. In 2001, enrollment in the plan was approximately 15 million average covered lives on any given day. Nearly one third (5 million) of these lives had medical claims that were adjudicated through one data processing system, and they represent the data that was the focus of this research. For proprietary reasons, this database is referred to as D₁. Twenty-seven health plan sites in 19 states, distributed across the Northeast, Southeast, Midwest, and Southwest United States were represented in this analysis. The 27 sites were chosen from D₁ because as a whole they had excellent completeness in terms of capturing claims and the data elements were consistent over the time period used in the analysis. The other two thirds of the initial 15 million lives had medical and pharmacy claims that were adjudicated under a separate data system (D₂). Both databases (D₁ and D₂) contained member information such as demographic and enrollment records, medical encounter services, and charges assessed for each medical service. Although the data in D₂ were available for analysis, the data were not used in this study because D₁ and D₂ were derived from 2 different business systems.

Patient care records outlining services the patient received while under care of the plan (i.e., hospitalizations, procedures, accompanying charges, etc.) are routinely captured. Each facility service record contains information on up to 9 diagnoses recorded with the International Classification of Diseases, Ninth Revision (ICD-9-CM) diagnosis codes and up to 6 procedures recorded with ICD-9-CM procedure codes, Current Procedural Terminology (CPT), or Health Care Financing Agency (HCFA) Common Procedure Coding System (HCPCS) codes. Medical claims and patient encounter data are collected from all health care settings operating within the plan for nearly every type of service provided to enrollees. Health plan providers submit claims either by mail or electronically. Claims submitted by medical facilities are reported via the HCFA Uniform Bill 82 (UB-82) or UB-92 form, while ambulatory claims are reported via the HCFA-1500 form. Claims for pharmacy services are submitted electronically by the pharmacy at the time prescriptions are filled.

### Patient Selection

To identify eligible CKD patients in the claims database, new patients initiated on dialysis therapy from September 1, 1998, through July 31, 2001, were selected using ICD-9-CM procedure codes (39.95, 54.98), ICD-9-CM diagnostic codes (996.56, 996.68, V45.1, V56, V56.1, V56.2, V56.0, V56.32, V56.8), CPT (90921, 90925, 90935, 90937, 90940, 90945, 90947, 90997, 90999), and HCPCS codes (A4690, A4820, A4900, A4901, A4905, E1510, E1590, E1592, E1594, E1632, E1635) indicative of dialysis therapy. Patients having a procedure code for new dialysis therapy were then screened for a minimum of 9 months of continuous enrollment (minimum of 6 months preceding initial dialysis event and 3 months post-dialysis) during the data analysis period. Claims prior to dialysis initiation date were evaluated to ensure that patients did not have any previous dialysis episodes. A pharmacy benefit was required for the patient’s entire enrollment period for the purpose of identifying complete medication use.

A minimum time frame of 6 months predialysis and 3 months postdialysis continuous enrollment was chosen for the following reasons. A limitation of this data source was that...
laboratory information was not available from the medical claims. Therefore, it is not clear from the medical claims when individual patients crossed the GFR threshold into CKD. Hence, a 6-month predialysis period was chosen to ensure, as much as possible, that patients had CKD, since the time period is closer to an actual dialysis event. If a longer interval for predialysis (i.e., 12 to 18 months) was chosen, there is a greater chance that we would have captured a time period when CKD was not present for some patients. A 3-month postdialysis period was chosen since there is high mortality associated with patients soon after the initiation of dialysis.8-15 Thus, a shorter postdialysis analysis period was chosen in order to account for this potential occurrence. If a longer interval for postdialysis (i.e., 12 to 18 months) was chosen, there could have been many fewer patients to analyze due to death after initiation of renal replacement therapy, and characterizing resource use may have been more difficult due to the small number of patients.

Variables of Interest

The provider billing categories were ambulatory pharmacy, facility inpatient, facility noninpatient, inpatient pharmacy, physician, and allied health (medical professionals other than physicians, e.g., dentists, chiropractors, psychologists). The primary variables of interest included charges according to billing category, primary diagnosis categories, and inpatient diagnosis-related groups (DRGs). Dollars reflect submitted (not allowed) charges by the provider and therefore do not reflect managed care negotiated rates or discounts and include the member cost-share. Allowed charges were not accessible for this analysis. The use of submitted charges presents a limitation since the allowed charges will generally be smaller in magnitude than the submitted charges, thereby creating less conservative estimates of cost. Secondary measurements included the quantification of clinical interventions such as nephrologist visits and claims for relevant prescription medications.

Statistical Analysis

Results from this study are descriptive in nature. Resource utilization was assessed during 3 time periods: the predialysis period was 5 months in length, from the sixth through the second month before the initial dialysis event; the peridialysis period was 2 months in length, 30 days before and 30 days after the initial dialysis event; and the postdialysis period was 2 months in length, the second and third month following the initial dialysis event. Note that for the peridialysis period, the “initial dialysis event” does not occur over an extended time frame; rather

### Table 2: Top 5 Primary Diagnoses With the Most Patients

<table>
<thead>
<tr>
<th>Primary ICD-9-CM Diagnosis</th>
<th>Description</th>
<th>Patients (%) (N=2,114)</th>
<th>Charges ($)†</th>
<th>PPPM ($)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Predialysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>585.0</td>
<td>Chronic renal failure</td>
<td>698 (33.0)</td>
<td>2,780,742</td>
<td>263</td>
</tr>
<tr>
<td>250.00</td>
<td>Type 2 diabetes mellitus</td>
<td>415 (19.6)</td>
<td>134,827</td>
<td>13</td>
</tr>
<tr>
<td>285.9</td>
<td>Anemia, NOS</td>
<td>371 (17.6)</td>
<td>664,260</td>
<td>63</td>
</tr>
<tr>
<td>428.0</td>
<td>Congestive heart failure</td>
<td>353 (16.7)</td>
<td>2,880,915</td>
<td>273</td>
</tr>
<tr>
<td>401.9</td>
<td>Hypertension, NOS</td>
<td>348 (16.5)</td>
<td>162,262</td>
<td>15</td>
</tr>
<tr>
<td><strong>Peridialysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>585.0</td>
<td>Chronic renal failure</td>
<td>1,523 (72.0)</td>
<td>17,303,073</td>
<td>4,092</td>
</tr>
<tr>
<td>584.9</td>
<td>Acute renal failure, NOS</td>
<td>764 (36.1)</td>
<td>8,328,484</td>
<td>1,970</td>
</tr>
<tr>
<td>586.0</td>
<td>Renal failure, NOS</td>
<td>760 (36.0)</td>
<td>1,264,947</td>
<td>299</td>
</tr>
<tr>
<td>428.0</td>
<td>Congestive heart failure</td>
<td>532 (25.2)</td>
<td>6,035,775</td>
<td>1,428</td>
</tr>
<tr>
<td>403.91</td>
<td>Renal hypertension, NOS</td>
<td>417 (19.7)</td>
<td>5,211,509</td>
<td>1,233</td>
</tr>
<tr>
<td><strong>Postdialysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>585.0</td>
<td>Chronic renal failure</td>
<td>1,312 (62.1)</td>
<td>21,880,476</td>
<td>5,175</td>
</tr>
<tr>
<td>586.0</td>
<td>Renal failure, NOS</td>
<td>336 (15.9)</td>
<td>472,380</td>
<td>112</td>
</tr>
<tr>
<td>428.0</td>
<td>Congestive heart failure</td>
<td>272 (12.9)</td>
<td>2,039,350</td>
<td>482</td>
</tr>
<tr>
<td>285.9</td>
<td>Anemia, NOS</td>
<td>231 (10.9)</td>
<td>193,232</td>
<td>46</td>
</tr>
<tr>
<td>250.00</td>
<td>Type 2 diabetes mellitus</td>
<td>206 (9.8)</td>
<td>75,747</td>
<td>18</td>
</tr>
</tbody>
</table>

* These are primary diagnoses only, not secondary or tertiary diagnoses in the medical claims.
† Provider-submitted charges.
‡ Per-patient-per-month (PPPM).
Resource Use and Patient Care Associated With Chronic Kidney Disease in a Managed Care Setting

Results

Patient Characteristics

Initially, 8,132 patients were identified as having a “first dialysis” claim, i.e., with no previous records of dialysis in the previous 6 months. Based on the inclusions of active medical and pharmacy benefits and continuous enrollment over 9 months surrounding the first dialysis, the final sample consisted of 2,114 patients. Of the 6,018 excluded patients, 181 (3.0%) had inactive medical and pharmacy benefits, while 5,837 (97.0%) had discontinuous enrollment during the initial dialysis event. Although the time periods differ and affect the calculation of PPPM costs, it is important to evaluate patients at these times to gain insight into resource use during these 3 differing clinical periods. Using the entire 9 months as the denominator for calculating PPPM, for instance, would not yield much insight into the PPPM costs before dialysis start. All statistical programming was performed using the Statistical Analysis System statistical package, version 8.2 (SAS, Cary, NC).

Primary Diagnoses

Similar primary diagnoses were noted for the 3 analysis periods. In the predialysis stage, the most common primary diagnoses were chronic renal failure (CRF), type 2 diabetes mellitus, anemia, congestive heart failure (CHF), and hypertension. In the peridialysis period, the most common diagnoses were CRF, acute renal failure, renal failure not otherwise specified, CHF, and renal hypertension. In the postdialysis period, the most common diagnoses were CRF, renal failure not otherwise specified, CHF, anemia, and type 2 diabetes mellitus (Table 2). Of note, CHF was the only primary diagnosis to appear consistently as a top common diagnosis in all time periods.

Resource Use—Total Charges

Resource use, total charges per month, and PPPM charges were determined for the 6 provider billing categories: facility inpatient, facility noninpatient, physician, ambulatory pharmacy, allied health, and inpatient pharmacy for the 3 analysis periods. Total charges increased over time, with a dramatic increase at the first dialysis event (Figure 2). During the predialysis period, health care charges totaled $45,076,115, with a PPPM of $4,265, and increased in the peridialysis period to $149,213,317, with a PPPM of $35,292. Total charges in the postdialysis period decreased from the peridialysis period ($65,106,179, with a PPPM of $15,399), but remained considerably higher than those in the predialysis period.

The top 5 billing categories by highest total charges in the predialysis period were facility inpatient, facility noninpatient, physician, ambulatory pharmacy, and allied health. In the subsequent study periods, the order of provider billing categories remained relatively consistent in order of magnitude (Table 3).

Facility Charges

During the predialysis period, facility inpatient hospitalization charges totaled $22,707,701, with a PPPM of $2,148, and accounted for 50.4% of overall charges, although only 25.9% of patients were hospitalized during this time. During the peridialysis and postdialysis periods, facility inpatient charges totaled $103,426,930 (PPPM $24,462) and $26,148,694 (PPPM $6,185) and accounted for 69.3% and 40.2% of overall charges, respectively (Table 3). In the peridialysis and postdialysis periods, a respective 64.4% and 28.1% of patients had hospitalizations. The percentage of patients requiring an inpatient admission more than doubled during the peridialysis relative to the predialysis period (25.9% to 64.4%, respectively).

According to inpatient DRGs, the most common reason for admission in the predialysis period was related to heart failure, with an average charge per admission of $12,172. During peri-dialysis, the most common reason for admission was renal failure, with an average charge per admission of $21,784. In the postdialysis period, the most common reason for admission...
was related to circulatory system diagnoses with complications, with an average charge per admission of $16,371 (Table 4). Of note, heart failure/shock appeared consistently as a common reason for admission in all 3 study periods.

Facility noninpatient charges comprised 23.2%, 14.7%, and 39.0% of total charges during predialysis, peridialysis, and postdialysis (Table 3). Interestingly, noninpatient charges did not follow the “spiking” trend at first dialysis; rather, they increased over time (charges totaled $10,437,621, $21,937,987, and $25,377,194 during the 3 respective study periods). However, the percentage of patients utilizing noninpatient facilities remained relatively unchanged over time during the predialysis, peridialysis, and postdialysis periods (79.7%, 90.5%, and 81.3%, respectively).

**Physician Visits and Costs**

In the predialysis period, total physician charges were $7,774,059, with a PPPM of $736. During the peridialysis period, total physician charges were $20,079,252, with a PPPM of $4,749. During postdialysis, total physician charges were $9,494,782, with a PPPM of $2,246. While a respective 88.9%, 96.0%, and 88.0% of patients had a recorded physician visit during the 3 study periods, 38.2% did not see a nephrologist for the first time until the month during their first dialysis event (Tables 3 and 5).

**Ambulatory Pharmacy**

In the predialysis period, ambulatory pharmacy charges were $2,180,878, with a PPPM of $206. Ambulatory pharmacy charges during the peridialysis period were $960,754, with a PPPM of $227. During postdialysis, ambulatory pharmacy charges were $940,007, with a PPPM of $222 (Table 3). In all study periods, inpatient pharmacy charges were minimal and comprised less than 1% of total charges. The top 25 prescribed medication classes, based upon utilization as measured by the value in the “days supply” field in the pharmacy claims, were assessed for the 3 study periods (Table 4).
6). Over-the-counter medications were not included. In the predialysis period, few of the expected CKD medications were among the top 25 most frequently used drugs, and only 2 different angiotensin-converting enzyme (ACE) inhibitors (11.4% of patients treated) and no phosphate binders or multivitamins/iron were listed. In the peridialysis period, only 1 type of ACE inhibitor (5.6%) and 1 type of phosphate binder (13.3%) were found among the most frequently used drugs. In the postdialysis period, 1 type of ACE inhibitor (4.5%), 2 types of phosphate binders (16.9%), and 1 type of multivitamin (8.4%) were listed. Few patients also had a recorded recombinant human erythropoietin (rHuEpo) claim in the predialysis period. The number of patients receiving rHuEpo increased every month before dialysis; during the month before first dialysis, 30.8% of patients had recorded claims for rHuEpo therapy. During postdialysis, the numbers increased slightly, ranging from 41.3% to 44.8% per month (Table 5).

Discussion

Our results show that CKD patients generated significant charges to the health plan both before and after initial dialysis. In terms of responsible payers during CKD progression, it is important to note differences in the payer mix for ESRD versus predialysis CKD. Most patients receive Medicare Part A benefits automatically when they reach the age of 65. Medicare Part B is available to Part A beneficiaries aged 65 years and older, with a monthly premium required for coverage. Dialysis patients, regardless of age, have been entitled to Medicare coverage since 1972. As a result of widespread coverage, Medicare serves as primary insurance for the majority of ESRD patients after the initiation of dialysis. Most dialysis patients below age 65, however, are not eligible for Medicare benefits until the fourth month after initiating dialysis. Medicare does not cover any costs of treatment during these first 3 months of dialysis unless the patient already has primary Medicare coverage because of age or disability. The private health plan is the only payer for the first 3 months of dialysis. When a patient becomes eligible for Medicare due to ESRD in the fourth month of dialysis, there is a 30-month “coordination period” when the health plan serves as the primary payer for health care services and Medicare becomes the secondary payer. At the end of this 30-month coordination period, Medicare pays for all Medicare-covered services as a primary payer, and the health plan becomes the secondary payer. Medicare Parts A and B cover 80% of the cost of dialysis treatments or transplant once coverage begins, but coverage does not include medication coverage, with the exception of injectibles. Private insurance can also cover the entire cost of dialysis treatment and may pay for the 20% that Medicare does not cover, including prescription drugs. Medicaid may also cover the 20% of costs not covered by Medicare and part of the cost of prescription drugs.

However, private insurance and Medicaid only constitute a small proportion of dialysis coverage, and the payer mix for

### TABLE 4 Top 5 Inpatient Diagnosis-Related Groups

<table>
<thead>
<tr>
<th>Inpatient DRG</th>
<th>Description</th>
<th>Admits</th>
<th>Average Charge ($)</th>
<th>Average Length of Stay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predialysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>127</td>
<td>Heart failure and shock</td>
<td>130</td>
<td>12,172</td>
<td>5.5</td>
</tr>
<tr>
<td>316</td>
<td>Renal failure</td>
<td>73</td>
<td>10,440</td>
<td>5.6</td>
</tr>
<tr>
<td>89</td>
<td>Simple pneumonia and pleurisy, age &gt;17</td>
<td>23</td>
<td>11,433</td>
<td>4.7</td>
</tr>
<tr>
<td>294</td>
<td>Diabetes, age &gt;35</td>
<td>21</td>
<td>11,458</td>
<td>5.0</td>
</tr>
<tr>
<td>174</td>
<td>GI hemorrhage</td>
<td>20</td>
<td>16,803</td>
<td>5.8</td>
</tr>
<tr>
<td>Peridialysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>316</td>
<td>Renal failure</td>
<td>375</td>
<td>21,784</td>
<td>8.3</td>
</tr>
<tr>
<td>315</td>
<td>Other kidney and urinary tract OR procedures</td>
<td>161</td>
<td>25,240</td>
<td>7.4</td>
</tr>
<tr>
<td>127</td>
<td>Heart failure and shock</td>
<td>141</td>
<td>21,154</td>
<td>8.5</td>
</tr>
<tr>
<td>331</td>
<td>Other kidney and urinary tract diagnosis, age &gt;17</td>
<td>88</td>
<td>14,590</td>
<td>6.0</td>
</tr>
<tr>
<td>120</td>
<td>Other circulatory system OR procedures</td>
<td>60</td>
<td>36,511</td>
<td>11.6</td>
</tr>
<tr>
<td>Postdialysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>144</td>
<td>Other circulatory system diagnoses</td>
<td>66</td>
<td>16,371</td>
<td>5.8</td>
</tr>
<tr>
<td>127</td>
<td>Heart failure and shock</td>
<td>59</td>
<td>21,133</td>
<td>9.6</td>
</tr>
<tr>
<td>316</td>
<td>Renal failure</td>
<td>52</td>
<td>14,952</td>
<td>14.5</td>
</tr>
<tr>
<td>416</td>
<td>Septicemia, age &gt;17</td>
<td>33</td>
<td>23,104</td>
<td>10.2</td>
</tr>
<tr>
<td>14</td>
<td>Specific cerebrovascular disorders</td>
<td>32</td>
<td>49,907</td>
<td>20.6</td>
</tr>
</tbody>
</table>

* Provider-submitted charges.
these segments may vary depending on geographic and demographic differences across the country. As such, nationally representative numbers on the definitive payer mix in ESRD are not widely available. However, Shih18 reported from the USRDS Dialysis Morbidity and Mortality Study data that, clearly, Medicare provides the majority of primary insurance for ESRD patients, with Medicaid and other insurance types covering a much smaller proportion of patients (Figure 3).

Unlike the ESRD market, in which Medicare finances the vast majority of care, both Medicare and private payers represent a significant portion of the predialysis CKD payer mix. A recent study by Walters et al.19 estimates the proportion of predialysis CKD patients covered by Medicare/Medicare replacement and private insurance at Gambro Healthcare to be 51.7% and 29.9%, respectively (Figure 4). As with ESRD, Medicaid covered a small portion of patients, in this case 14.4% of these patients. The payer mix may again vary based on geographic and demographic differences across the country. Given the current state of coverage by the above parties, during the predialysis CKD period, much of the economic burden falls on the private payer, until the patient progresses into ESRD and initiates dialysis. However, even after dialysis starts, in many cases, the major shift of costs from private plan to Medicare does not occur until 33 months after the patient begins dialysis. As a result, the health plan is responsible for a CKD patient during much of their disease progression before and after dialysis.

CKD patients suffer from a wide variety of comorbidities, including CHF, diabetes, and hypertension. In addition to renal disease, CHF was found to be a consistently high-frequency and high-cost primary diagnosis as well as a common cause for hospitalizations. These findings suggest that appropriate management of nonrenal conditions is an important part of patient care before dialysis.

Among the complications resulting from CKD, anemia is one of the most significant that can be addressed early in the disease progression by rHuEpo.20-23 It is known that, if untreated, chronic anemia can lead to negative patient outcomes such as cardiovascular complications24 and increased morbidity and mortality. However, recent investigations of the Medicare ESRD population have shown that an increasing hematocrit level is associated with decreased risks of hospitalizations and mortality. Xia et al.15 found that compared to patients with a hematocrit of 30% to <33%, patients with a hematocrit level below 30% had a statistically significant 7% to 18% increased risk of hospitalization, while patients with a hematocrit level of 33% to <36% had a significant 7% decreased risk. In a similar study, Ma et al.25 found that compared to patients with a hematocrit of 30% to <33%, patients with a hematocrit level below 30% had a statistically significant 12% to 33% increased risk of mortality, while patients with a hematocrit level of 33% to <36% had a significant 4% decreased risk.

The number of patients in this analysis with a claim for rHuEpo was minimal, both before and after dialysis. The number of patients on rHuEpo is considered “low” when compared to literature assessing the prevalence of anemic patients beginning dialysis. An analysis by Obrador41 of 155,076 patients starting hemodialysis in the United States found that 67% of patients had a hematocrit less than 30% and 51% had a hematocrit less than 28%. This is in contrast to the 2000 NKF-K/DOQI guidelines, which recommend a target hematocrit of 33% to 36% in CKD patients.26 However, overall, only 23% received rHuEpo therapy before ESRD. These results are somewhat similar to our findings, where 30.8% of patients had a claim for rHuEpo in the month prior to dialysis.

In another study in a sample of 602 predialysis patients, a hematocrit of <30% was present in 38% of patients, and 59% of these patients received rHuEpo.7 No laboratory data were available in the claims database for our analysis. However, if the figure that 67% of patients starting dialysis have a hematocrit below 30% is representative, then the number of patients treated with rHuEpo both predialysis and postdialysis in our analysis is suboptimal. It is possible that the charge for rHuEpo was included in a physician visit and was not captured in the database. Since the rHuEpo use was captured via specific NDC codes, HCPCS Q-codes, and revenue codes, rHuEpo within a claim for a doctor visit would not have been recorded and captured. However, from the available literature it seems that treatment of anemia occurring before dialysis initiation may be not be addressed properly.

In addition to the low rHuEpo claims during predialysis, lisinopril and quinapril were the only ACE inhibitors reported in the claims for top 25 medications. Only 11.4% of patients were on either medication, although 34.8% of patients had a diagnosis for diabetes during predialysis. Similarly in the peridialysis and postdialysis periods, only 3.6% and 4.5% of patients had a claim for lisinopril, which was the only ACE inhibitor listed in the top 25 for these time periods. During these time periods, 35.1% and 30.3% of patients were diabetic, respectively, suggesting suboptimal use of ACE inhibitors in the diabetic population. Lewis27

### Table 5: First Nephrologist Visits and rHuEpo Claims

<table>
<thead>
<tr>
<th>Month</th>
<th>Number of Patients (%)</th>
<th>Number of Patients on rHuEpo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54 (2.6)</td>
<td>187 (8.8)</td>
</tr>
<tr>
<td>2</td>
<td>86 (4.1)</td>
<td>221 (10.5)</td>
</tr>
<tr>
<td>3</td>
<td>122 (5.8)</td>
<td>242 (11.4)</td>
</tr>
<tr>
<td>4</td>
<td>218 (10.3)</td>
<td>272 (12.9)</td>
</tr>
<tr>
<td>5</td>
<td>235 (11.1)</td>
<td>312 (14.8)</td>
</tr>
<tr>
<td>6*</td>
<td>807 (38.2)</td>
<td>652 (30.8)</td>
</tr>
<tr>
<td>7</td>
<td>38 (1.8)</td>
<td>948 (44.8)</td>
</tr>
<tr>
<td>8</td>
<td>10 (0.5)</td>
<td>930 (44.0)</td>
</tr>
<tr>
<td>9</td>
<td>1 (0.05)</td>
<td>873 (41.3)</td>
</tr>
</tbody>
</table>

* First dialysis occurs at end of month 6. N=2,114
† Some patients had first nephrologist visit before month 1 and after month 9.

---

244 Journal of Managed Care Pharmacy  JMCP May/June 2003 Vol. 9, No. 3 www.amcp.org
demonstrated that the ACE inhibitor captopril protected against deterioration in renal function in type 1 diabetic nephropathy and was significantly more effective than blood-pressure control alone. The treatment of diabetic predialysis CKD patients with ACE inhibitors produced a 67% reduction in relative risk of kidney disease progression. In addition, ACE inhibitors are still the medication of choice for patients with type 1 diabetes and nephropathy.28

The presence of claims for phosphate binders and multivitamins also did not appear in the top 25 drugs until the peridialysis and postdialysis periods. Control of parathyroid hormone (PTH) and calcium-phosphorus product may play an important role in the management of renal disease patients, especially in the maintenance of bone health and vascular calcification. By dialysis initiation, most patients have some form of secondary hyperparathyroidism characterized by elevated PTH, calcium, and phosphorus levels. Such alterations in these biochemical parameters can lead to cardiac and vascular calcification, parathyroid gland hyperplasia, and osteomalacia.29-32 As such, this is an area that needs to be addressed by providers in the early stages of renal disease.

Although patients may have been receiving inadequate medications during the predialysis CKD period, the study sample sought care before dialysis initiation, with 87.4% of all patients having at least one recorded physician visit. Before starting dialysis, 76.5% of patients had utilized outpatient (76.5%) and inpatient (25.5%) services. However, almost 40% did not have a first nephrologist visit until their first dialysis session.

Published literature suggests that earlier identification and focused management of predialysis CKD patients as well as early referral to a nephrologist may improve patient outcomes after the start of dialysis.4-16 While this study only describes current trends with respect to timing of nephrologist referrals and appropriate medication use, further studies are warranted to clarify the impacts of such interventions.

### Limitations

As noted earlier, a limitation of this study is that laboratory values were unavailable in the claims database. Since the selection

<table>
<thead>
<tr>
<th>Predialysis</th>
<th>Patients (%)</th>
<th>Peridialysis</th>
<th>Patients (%)</th>
<th>Postdialysis</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide</td>
<td>614 (29.1)</td>
<td>Furosemide</td>
<td>479 (22.7)</td>
<td>Amlodipine</td>
<td>269 (12.7)</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>341 (16.1)</td>
<td>Amlodipine</td>
<td>356 (16.8)</td>
<td>Furosemide</td>
<td>281 (13.3)</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>239 (11.3)</td>
<td>Calcium acetate</td>
<td>281 (13.3)</td>
<td>Calcium acetate</td>
<td>279 (13.2)</td>
</tr>
<tr>
<td>Atenolol</td>
<td>174 (8.2)</td>
<td>Atorvastatin</td>
<td>192 (9.1)</td>
<td>Amlodipine</td>
<td>188 (8.9)</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>175 (8.3)</td>
<td>Clonidine</td>
<td>179 (8.3)</td>
<td>Multivitamin</td>
<td>177 (8.4)</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>159 (7.5)</td>
<td>Atenolol</td>
<td>159 (7.5)</td>
<td>Metoprolol</td>
<td>159 (7.5)</td>
</tr>
<tr>
<td>Clonidine</td>
<td>172 (8.1)</td>
<td>Metoprolol</td>
<td>159 (7.5)</td>
<td>Lansoprazole</td>
<td>158 (7.5)</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>142 (6.7)</td>
<td>Lansoprazole</td>
<td>148 (7.0)</td>
<td>Levothyroxine</td>
<td>110 (5.2)</td>
</tr>
<tr>
<td>Levothyroxine</td>
<td>127 (6.0)</td>
<td>Levothyroxine</td>
<td>121 (5.7)</td>
<td>Clonidine</td>
<td>142 (6.7)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>137 (6.5)</td>
<td>Multivitamin</td>
<td>153 (7.2)</td>
<td>Atenolol</td>
<td>122 (5.8)</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>142 (6.7)</td>
<td>Doxazosin</td>
<td>117 (5.5)</td>
<td>Warfarin</td>
<td>103 (4.9)</td>
</tr>
<tr>
<td>Metolazone</td>
<td>161 (7.6)</td>
<td>Lisinopril</td>
<td>119 (5.6)</td>
<td>Lisinopril</td>
<td>101 (4.8)</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>139 (6.6)</td>
<td>Isosorbide mononitrate</td>
<td>113 (5.4)</td>
<td>Isosorbide mononitrate</td>
<td>95 (4.5)</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>113 (5.3)</td>
<td>Warfarin</td>
<td>102 (4.8)</td>
<td>Droxigoxin</td>
<td>100 (4.7)</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>131 (6.2)</td>
<td>Metolazone</td>
<td>127 (6.0)</td>
<td>Ranitidine</td>
<td>95 (4.5)</td>
</tr>
<tr>
<td>Insulin syringe</td>
<td>180 (8.5)</td>
<td>Prednisone</td>
<td>135 (6.4)</td>
<td>Insulin syringe</td>
<td>115 (5.4)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>104 (4.9)</td>
<td>Ranitidine</td>
<td>111 (5.3)</td>
<td>Calcitriol</td>
<td>80 (3.8)</td>
</tr>
<tr>
<td>Glyburide</td>
<td>81 (3.8)</td>
<td>Calcitriol</td>
<td>113 (5.4)</td>
<td>Prednisone</td>
<td>109 (5.2)</td>
</tr>
<tr>
<td>Prednisone</td>
<td>155 (7.3)</td>
<td>Droxigoxin</td>
<td>107 (5.1)</td>
<td>Droxazosin</td>
<td>77 (3.6)</td>
</tr>
<tr>
<td>Isosorbide mononitrate</td>
<td>100 (4.7)</td>
<td>Insulin syringe</td>
<td>119 (5.6)</td>
<td>Metoprolol ext. release</td>
<td>70 (3.3)</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>78 (3.7)</td>
<td>Allopurinol</td>
<td>78 (3.7)</td>
<td>Allopurinol</td>
<td>74 (3.5)</td>
</tr>
<tr>
<td>Insulin 70/30</td>
<td>121 (5.7)</td>
<td>Hydralazine</td>
<td>90 (4.3)</td>
<td>Temazepam</td>
<td>80 (3.8)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>78 (3.7)</td>
<td>Potassium chloride</td>
<td>92 (4.4)</td>
<td>Omeprazole</td>
<td>88 (4.2)</td>
</tr>
<tr>
<td>Quinapril</td>
<td>82 (3.8)</td>
<td>Famotidine</td>
<td>93 (4.4)</td>
<td>Sevelamer</td>
<td>79 (3.8)</td>
</tr>
<tr>
<td>Calcitriol</td>
<td>99 (4.7)</td>
<td>Metoclopramide</td>
<td>97 (4.6)</td>
<td>Warfarin generic</td>
<td>61 (2.9)</td>
</tr>
</tbody>
</table>
of patients was not based on GFR levels, the time point during the predialysis period at which patients crossed the threshold for CKD is not known. However, given the limited 6-month time frame before dialysis and the presence of dialysis itself, it is likely that patients had progressive kidney disease. No hemoglobin or hematocrit laboratory data were available, so it is not known how many patients were considered to be anemic. A second limitation is that submitted charges were used in the analysis and not allowed charges. Net health plan costs may be lower, particularly after provider discounts and after subtraction of member cost-share responsibility from allowed charges. These submitted charges may overstate the actual financial burden for the managed care plan. Third, while we could measure claims for medications, we could not assess the impact of these medications on patient outcomes such as mortality, hospitalizations, and delay of disease progression. Such impacts may only be demonstrated through a clinical trial or disease management program. Fourth, it is unclear how much of the charges were billed to Medicare before and after the start of dialysis. However, since most patients 65 years and above would have Medicare as a primary payer before and after dialysis start and those below 65 years would not have Medicare as a primary payer until 33 months after dialysis start, Medicare charges may not have had a great effect on the charge totals. Finally, the strict inclusion of 9 months of continuous enrollment may have excluded other CKD patients from the analysis. As such, the costs incurred by all CKD patients covered in the health plans were not captured due to these patient exclusions. Interestingly, considering that only 2,114 patients from 27 health plans generated such significant charges in this study, one need only consider the number of CKD patients estimated in NHANES III to comprehend the magnitude of financial burden to other health plans across the country.

**Conclusion**

The results of this study showed increasing costs as CKD patients approached dialysis, with a considerably high average submitted charge PPPM. In addition, the data suggest that patients may not be seeing nephrologists early in their disease progression or receiving the expected medications before initiation of dialysis. Additional research is warranted to determine if increased patient monitoring and physician education about the importance of predialysis care have the potential to decrease resource utilization. In addition, opportunities exist to improve patient care in predialysis through close management of anemia, administration of appropriate medications and nutritional supplements, and better management of comorbid conditions. Our results may be of interest to health care payers and providers to use as a basis for future studies to assess the impact of active interventions in CKD or as a baseline to assess the impact of future changes in nephrology practice.

**DISCLOSURES**

Funding for this research was provided by Amgen Inc. and was obtained by author John J. Kim. Kim and author Wing W. Chan are employed by Amgen. Amgen manufactures/markets products for the treatment of anemia associated with chronic renal failure, including patients either on or not on dialysis. Author James D. Robbins served as principal author of the study. Study concept and design and analysis and interpretation of data were contributed by Robbins and Kim. Drafting of the manuscript was primarily the work of Robbins and Kim and its critical revision was the work of Robbins, Kim, Zdon, Chan, and author Jason Jones. Statistical expertise was contributed by Zdon, Chan, and Jones.

**REFERENCES**

Resource Use and Patient Care Associated With Chronic Kidney Disease in a Managed Care Setting


5. Eadlington DW. Delayed referral for dialysis: higher morbidity and higher costs. Semin Dial. 1995;8:258-60.


ABSTRACT

BACKGROUND: The management of chronic kidney disease (CKD) is multifaceted, including monitoring, early diagnosis, and treatment of comorbidities such as diabetes, hyperalbuminemia, and anemia, and initiating timely procedures in preparation for dialysis such as vascular access placement. Presumably, optimal care provided to patients during the predialysis phase will produce a significant impact on morbidity and mortality outcomes.

OBJECTIVE: A retrospective analysis was conducted to assess specific factors that may be associated with optimal quality of care for CKD patients during the predialysis phase.

METHODS: Health care resource utilization and the occurrence of interventions associated with optimal predialysis care were evaluated with claims data. Predialysis erythropoietin (EPO) therapy, nephrology referrals, and nutritional supplementation administration were all examined during the 12 months prior to dialysis.

RESULTS: Medical and pharmacy claims from a managed care database were analyzed for 1,936 incident dialysis patients. Of these, 48.7% did not have any interventions associated with optimal care. Only a minority of patients received prescription iron preparations (6.8%), vitamin D (4.0%), and phosphate binders (7.7%). A total of 20.8% patients had a vascular access placement, and 29.8% were in the care of a nephrologist during this same time period. Only 10.5% received predialysis EPO, yet more than 40% were diagnosed with anemia. Of the EPO users, however, 72.4% were also receiving other interventions to appropriately manage CKD.

CONCLUSION: These claims-documented results suggest that the lack of EPO use in predialysis patients in a managed care plan may predict overall suboptimal treatment of these patients. There is an apparent need for the proactive management of CKD in a managed care plan to potentially redistribute or reduce health care resource utilization while improving patient outcomes.

KEYWORDS: CKD, Erythropoietin alpha, Predialysis care

J Managed Care Pharm. 2003(9)3: 248-55

A number of underlying diseases, such as diabetes mellitus and hypertension, can contribute to the incidence of chronic kidney disease (CKD), which in 1996 accounted for 43% and 23% of incident cases of end-stage renal disease (ESRD), respectively (Table 1). Simultaneous with the proactive management of these underlying diseases, these patients should also undergo comprehensive preparatory treatment for entry into ESRD. According to The National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative Guidelines (NKF–K/DOQI) recently released for CKD, the evaluation and treatment of patients with CKD requires understanding of separate but related concepts of diagnosis, comorbid conditions, severity of disease, complications of disease, and risks for loss of kidney function and cardiovascular disease. Among CKD patients, the disease stages are defined based on the level of kidney function, thus the rate at which patients approach ESRD varies. Defining the stages of CKD is crucial to the effective management of these patients and requires “categorization” of continuous measures of kidney function. Presumably, the staging of CKD will facilitate application of clinical practice guidelines, clinical performance measures, and quality improvement efforts to the evaluation and management of CKD.

Optimal standards of predialysis care should encompass early interventions focused on delaying the progression of chronic renal failure, implementation of educational programs targeted at maximum rehabilitation, timely initiation of kidney function replacement, and judicious management and correction of anemia. Severe anemia of chronic renal failure is associated with left ventricular dilation, left ventricular hypertrophy, and high output cardiac failure, all of which are important predictors of mortality and cardiac complications in patients with renal failure. Several studies have shown that the correction of anemia with erythropoietin (EPO) therapy in patients with renal failure is associated with significant improvements in quality of life, immune function, and energy level. For this reason, EPO use was selected as an index of optimal quality of predialysis care.

Optimal predialysis care should also include the timely placement of dialysis access. This is the site where blood will be removed and returned during dialysis, allowing for easier and more efficient removal of blood with fewer complications. The presence of a functioning vascular access site represents a critical factor in the well-being of these patients. Ideally, vascular access should be placed at least 6 months prior to the start of dialysis. The well-timed administration of nutritional supplements such as iron, vitamin D, and phosphate binders is also crucial in ongoing predialysis treatment because previous...
studies have shown a strong association between increased risk of death in dialysis patients and malnutrition and nonrenal comorbidity.21-24

Referral to a nephrologist is another expected intervention that should occur during the time between the diagnosis of CKD and dialysis initiation. Data from multiple international studies have shown that delayed referral to a nephrologist is a significant problem and is associated with a higher prevalence of uremic complications at the initiation of dialysis, with increased hospitalization and higher cost of care.21-24 In addition, Arora and colleagues demonstrated that incident dialysis patients who were referred late (defined as the first encounter with a nephropathologist occurring within 4 months of dialysis initiation) were significantly more likely to have hypoalbuminemia and hypocalcemia and less likely to have received EPO and a permanent vascular access before the first hemodialysis. Late referrals to a nephrologist were also associated with lower levels of renal function at dialysis initiation, as documented by higher serum creatinine and a higher proportion of patients with predicted glomerular filtration rate <5 mL/min per 1.73 m².25

As soon as a diagnosis of CKD has been established, screening for complications of CKD and disease management planning should commence. There is a growing consensus that the timing and quality of predialysis care may be pivotal to improved patient outcomes. Optimal predialysis care in CKD patients begins early and, as documented above, should include an aggressive treatment strategy that incorporates interventions that protect existing renal function, delay disease progression, prevent or attenuate comorbid conditions, correct anemia, and prepare patients for kidney function replacement so that it can be initiated in a timely manner.26-29 The lack of interventions during the predialysis period may have an enormous effect on the outcomes of mortality, cost of care, illness, and disability at the time of dialysis,30 and improved treatment for ESRD could have a substantial impact on national resource expenditures for ESRD, estimated at $14.55 billion across all payers in 1996.31

The primary aim of this study was to examine factors that may be associated with optimal quality of care for CKD patients during the predialysis phase in order to determine if opportunities exist in a managed care population to improve management of these patients by initiating clinically important interventions during the year prior to initiation of dialysis.

**Methods**

**Data Source**

This study consisted of a retrospective administrative claims-based analysis using a large, proprietary managed care database with annual membership of 3 million enrollees. The integrated claims database contains facility, professional, and outpatient pharmacy services and associated billed amounts for each service, as well as demographic and enrollment records.

Representing a wide geographic distribution, members reside in 22 states, with concentration in the South, Southwest, and Midwest. Approximately 72% of the managed care database members belong to health maintenance organization (HMO) or preferred provider organization (PPO) plans. Over the past decade, the database has been used by researchers as a data resource for a variety of analyses, including cost of illness and postmarketing drug surveillance studies.32-34

The database contains all diagnosis and procedure codes submitted with each professional and facility claim. Coding schemes used in the database include the International Classification of Diseases (ICD-9-CM) diagnosis and procedure codes, Common Procedural Technology (CPT-4) procedure codes, and Health Care Financing Administration Common Procedure Coding System (HCPCS) procedure codes.

Within health plans, managed care capitation arrangements and provider contractual agreements produce different billed charges for the same services. Although complete utilization data are available in this database, cost data for patients receiving services under these specific arrangements may not be reflected in the actual billed amounts. To adjust for the differences in charge data, a proprietary resource-based relative value scale fee schedule based on the standard Medicare RBRVS fee schedule was applied for all study patients. Costs were then standardized to 1999 health care Consumer Price Index (CPI) levels. Total pharmacy charges were the drug ingredient cost plus dispensing fee plus sales tax (i.e., including the member cost-share) for each claim.

**Study Selection and Data Extraction**

During the study time period, the prevalence of chronic renal disease in the entire managed care database was 60,475 patients (3.3%) and incidence was 52,333 patients (2.9%). Patients were enrolled in the study population if they had at least one ICD-9-CM diagnosis code (V45.1, V56, V56.0, V56.1, V56.2, V56.8), CPT-4 code (90935, 90937, 90945, 90947), HCPCS code (A4690, A4820, A4900, A4901, A4905, E1510, E1590, E1592, E1594, E1632, E1635), or ICD-9-CM procedure code (39.95,
54.98) indicating renal dialysis at any time during the 24-month time period of January 1, 1998, through December 31, 1999 (n=7,049). Patients receiving dialysis prior to their first dialysis date during the defined time period (index date) were excluded (n=4,833). In addition to evidence of initial renal dialysis, all patients were aged 99 years or younger, had continuous medical eligibility and pharmacy benefits for at least 12 months prior to their index date, had at least one claim of any type in the 12 months prior to their index date, and were not enrolled in a Medicare supplement plan (n=2,359). All patients received dialysis in response to chronic renal failure. Patients receiving dialysis in response to an acute catastrophic event only, e.g., an accident, were also excluded (n=1,936).

According to federal regulations, if ESRD patients have any insurance (i.e., HMO, PPO, or fee-for-service [FFS]) through their employer, then Medicare coordination of benefits becomes primary at 33 months for hemodialysis and 30 months for peritoneal dialysis. Medicare+Choice plans will accept patients already receiving dialysis if the patient has existing coverage through an HMO, PPO, or FFS plan. Uninsured hemodialysis patients are eligible for Medicare 3 months after initiating dialysis, and uninsured peritoneal dialysis patients are eligible immediately upon dialysis initiation. Since all patients included in this analysis were covered under a commercial health plan and the claims for these patients were analyzed prior to dialysis initiation, the regulations outlined above did not directly apply in this study.

### Data Synthesis

Aggregated comorbidities were defined by the 18 fundamental categories of ICD-9-CM diagnosis coding. In order to accurately define each condition explicitly analyzed, a comprehensive evaluation was performed to select all diagnosis codes that correctly describe each condition. Diagnoses recorded during the entire predialysis year were assessed, and an overall aggregated comorbidity score was calculated for each patient. The Charlson Comorbidity Index (CCI) was also used to quantify the comorbidity level of each study patient.35,36 The CCI used is consistent with published versions, with necessary modifications to account for the use of administrative claims instead of medical records as the data source. CCI was chosen to adjust for comorbidities because it focuses on chronic conditions, typically the principal drivers for health care resources consumed among this population.

Resource use and total costs were calculated for facility, professional, and outpatient pharmacy services during the 12 months prior to initiating dialysis. Facility resource use was further classified as inpatient hospital, outpatient hospital, and emergency room (ER) visits.

Clinically important interventions associated with the optimal care of CKD patients and preparation for dialysis initiation, such as predialysis EPO therapy, nephrology visits, vascular access placement, and nutritional supplement administration, were quantified. The number of patients who sought services from a nephrologist and the number of patients who underwent a vascular access placement during the 12 months prior to initiating dialysis were examined. Also examined was the administration of specific prescription nutritional supplements and other medications during the year prior to initiating dialysis. The number of patients administered vitamin D and iron preparations (injectable and oral) as well as the administration of phosphate binders over the course of the year prior to dialysis.
Examination of Resource Use and Clinical Interventions Associated With Chronic Kidney Disease in a Managed Care Population

initiation was quantified. The number of patients who received more than one type of intervention during the 12 months prior to initiating dialysis was quantified as well.

Because EPO use was selected as an indicator for optimal predialysis care (see introduction), all interventions described above were further stratified by whether or not patients were also receiving EPO therapy to determine if patients receiving predialysis EPO were more likely to receive optimal care than patients not receiving EPO.

Statistical Analysis

Baseline characteristics such as age, gender, and comorbid conditions as well as clinically important interventions (i.e., vascular access placement) were described using descriptive statistics. Whenever comparisons were made between EPO and non-EPO events, the groups were assessed and compared using chi-square and t tests.

Results

Demographics

The average age of the 1,936 patients was 66.8 years and 54.0% were male (Table 2). Prior to dialysis initiation, 203 (10.5%) patients received supportive EPO therapy and 1,733 (89.5%) were not receiving EPO. The average age of the EPO treatment group was 64.2 years, younger than the untreated group (67.1 years). The gender mix of the 2 comparison groups differed as well, although this difference did not achieve statistical significance. For the purposes of this analysis, the pediatric population (i.e., patients under the age of 18 years) was retained; it represented less than 2% of the overall population.

Comorbid Conditions

Patients, overall, had an average of 8±3 aggregated comorbidities during the 12 months prior to initiating dialysis. EPO patients had 9±3 comorbidities, and non-EPO patients had 8±3 aggregated comorbidities during the 12 months prior to dialysis. The average CCI was 4.9 for the EPO group compared to 4.1 for the untreated group (P=0.0001). Hypertension (79.4%), renal failure (74.6%), other forms of kidney disease (55.1%), and diabetes (53.2%) were the most common comorbidities (Figure 1). When stratified by EPO use, 60.1% of all EPO patients and 52.3% of all nonusers had a diabetes diagnosis during the year prior to dialysis (P=0.0360).

Cost and Resource Utilization

Economic Burden

Total annual charges for the entire CKD population were $72,270,920, with a mean overall charge per utilizing patient of $37,330. Total annual facility charges were $50,730,701, accounting for 70.2% of the total annual charges. Total annual professional charges were $18,630,114, which was 25.8% of the total annual charges. Total annual pharmacy charges were $2,910,105, or 4% of the total annual charges (Table 3). The detailed financial profile of health care service use (total and average charges per utilizing member per month) were previously reported by London et al.37; this paper focuses on patterns of care from the clinical perspective.

Inpatient Hospitalization and Emergency Room Visits

Of all patients, 62.6% were hospitalized at least once during the year prior to dialysis, with an average length of stay of 7.82 days. Congestive heart failure was the most frequently occurring discharge diagnosis, followed by hypertensive renal disease with renal failure and acute renal failure. A total of 60.3% of all patients visited the ER at least once during the 12 months prior to initiating dialysis. The average number of ER visits per patient was 2.

Professional Services

Of all patients, 92.8% had at least one office visit in the year prior to initiating dialysis, which was the most frequently occurring service during the predialysis period (Figure 2). The average number of office visits per patient was 12.

Medication Use

In the predialysis period, loop diuretics, angiotensin-converting
enzyme inhibitors, and nitrate coronary vasodilators were the most commonly prescribed medications (Figure 3).

**Clinically Important Interventions**

Clinical interventions, defined as vascular access placement, nephrology visits, the administration of vitamin D, iron preparations, phosphate binders, and EPO therapy, were examined during the year prior to initiating dialysis (Figure 4). Of the total population, 942 patients (48.7%) did not have any of these expected interventions within 12 months of initiating dialysis.

**Vascular Access Placement**

There were 403 patients (20.8%) who established access during the 12 months before initiating dialysis. Of these patients, 260 (64.5%) received at least one other intervention in the predialysis period in addition to vascular access placement.

Patients who were also on EPO therapy were almost twice as likely as patients who did not receive EPO to have an access procedure performed in the predialysis period (35.5% and 19%, respectively, P<0.01) and also more likely to have the access placed more than 60 days before initiating dialysis than patients not receiving EPO (15.76% and 6.12%, respectively).

**Nephrology Visits**

A total of 576 patients (29.8%) had at least one outpatient nephrology visit during the 12 months prior to dialysis. Of these patients, 151 (26.2%) were seen by a nephrologist for the first time within 30 days preceding dialysis initiation. Of the 576 patients, 267 (46.4%) also received at least one other intervention in the predialysis period. Further examination of nephrology practice patterns revealed that, of the 576 patients, 282 (49.0%, which is 14.6% of all predialysis CKD patients) were actually “in the care” of a nephrologist, as defined by the occurrence of ≥3 nephrology visits, with at least 30 days between the first and last visit. EPO patients (n=50, 24.6%) were significantly more likely to be in the care of a nephrologist than non-EPO patients (n=232, 13.4%; P<0.0001).

**Nutritional Supplement Administration**

**Iron preparations.** A total of 131 (6.8%) patients received iron preparations. Of the 131, 85 (64.9%) received iron preparations in combination with at least one other intervention during the year prior to dialysis. For those patients who also received EPO, 17.2% were administered iron preparations, while only 5.9% of patients non-EPO users received iron preparations during the year prior to dialysis (P<0.00005).

**Vitamin D.** Of the 78 (4.0%) total patients on vitamin D therapy, 65 patients (83.3%) were administered vitamin D in combination with at least one other intervention during the year prior to dialysis. For those patients who were also on EPO therapy, 10.1% filled at least one prescription for vitamin D, and 3.5% of patients who were not on EPO therapy received vitamin D during the year prior to dialysis (P<0.00005).

**Phosphate binders.** A total of 149 (7.7%) patients were administered phosphate binders during the year prior to initiating dialysis. Of these patients, 118 (79.2%) were administered phosphate binders in combination with at least one other
intervention during the year prior to dialysis. For those patients who were also on EPO therapy, 14.1% filled at least one prescription for phosphate binders, and 7.3% of those who were not on EPO therapy (P=0.0008) received phosphate binders during the year prior to dialysis.

Erythropoietin Therapy

Although 46% of all patients were diagnosed with deficiency anemia, only 10.5% (n=203) received EPO therapy during the 12 months prior to dialysis. Of the 203 patients, 147 (72.4%) received EPO in combination with at least one other intervention. That is, the majority of patients receiving EPO also received additional predialysis interventions to manage CKD, such as a vascular access placement (Table 4). In contrast, of the 1,733 non-EPO patients, 794 (45.8%) received at least one intervention to manage CKD.

Management of Clinical Interventions

A small percentage of the study population (0.05%) received all interventions concurrently within the year prior to initiating dialysis. When interventions were examined one by one, of those patients who underwent vascular access placement, 143 (35.5%) did not have any other interventions; 31 (20.8%) who received phosphate binders, 13 (16.7%) who received vitamin D, and 46 (35.1%) who received iron preparations did not receive any other interventions during the predialysis period; and 56 patients (27.6%) who received EPO therapy did not receive any other interventions. Of the 576 patients who saw a nephrologist, 306 (53.1%) did not have any of the interventions during the year prior to dialysis.

Patients were more likely to receive their first intervention in the months closer to dialysis initiation. Specifically, of those who underwent a vascular access procedure, 73.7% did so within the 90 days preceding dialysis initiation; 39.4% seen by a nephrologist had their first nephrology consultation within 90 days preceding dialysis; and 29.0% who filled their first prescription for iron preparations, 32.0% who filled their first prescription for vitamin D, and 45.6% who filled their first prescription for phosphate binders did so within 90 days of initiating dialysis. Of those patients who were receiving EPO, 35.5% began treatment within 90 days of initiating dialysis.

Discussion

Clinically Important Interventions

Optimal standards of care for progressive renal disease include identification and treatment of renal disease progression, adequate blood pressure control, proper nutritional support, good glycemic control, and anemia correction with EPO as well as administration of vitamin D, phosphate binders, and calcium. If dialysis is chosen for renal replacement therapy, vascular access needs to be placed prior to dialysis.

In the current study, nearly half of all study patients from a managed care population did not receive any of the interventions associated with the proactive management of CKD and preparation for renal dialysis. Results also suggested suboptimal use of EPO among patients entering dialysis in a managed care plan.

A minority of the study population received nutritional supplements such as iron preparations, vitamin D, and phosphate binders, all of which are associated with appropriate management of CKD. Interestingly, even though 92.8% of all patients had at least one office visit, only one third of the eligible population was actually seen by a nephrologist during the year prior to initiating dialysis, with many of the initial consultations occurring within 90 days of dialysis.

Although it is recognized that not all patients are appropriate candidates for all of the interventions studied, results revealed evidence of underutilization and delayed utilization of expected resources and interventions associated with CKD during the critical period prior to initiating dialysis, when CKD should be diagnosed and suitable management should begin. When interventions occurred, they were typically first introduced during the late predialysis stages of the disease (as defined by the number of months prior to initiating dialysis), suggesting opportunities to employ clinical strategies for early detection and diagnosis, followed by treatment and management of CKD and underlying conditions.

Factors Associated With Optimal Predialysis Care

In a recent study, Revicki and colleagues concluded that the correction of anemia using EPO therapy in renal failure patients produced improvements with health-related quality of life, significant cardiovascular benefits, and improved renal function. Despite these documented strong clinical advantages, only 10.5% of the eligible population in the current study received EPO, even though nearly half of the study population was diagnosed with deficiency anemia, thus underscoring the need to maintain specific programs to facilitate the management of CKD and comorbidities.

It is remarkable that of the subpopulation that received supportive predialysis EPO therapy, the majority of these patients...
were also receiving other interventions associated with the management of CKD. For example, only 1 in 5 study patients underwent a vascular access placement to prepare for dialysis. However, receiving EPO raised the likelihood of this procedure, as EPO patients in the current study were almost twice as likely to have the access procedure performed and even more likely to have the access placed greater than 60 days before initiating dialysis. In another illustration, patients on supportive EPO therapy were statistically significantly more likely to receive nutritional supplements such as iron preparations, vitamin D, and phosphate binders than those patients not receiving EPO.

The results from the current study suggest both triumph and challenge for the managed care pharmacist. Results stress that aggressively approaching the management of CKD and comorbidities with pharmacologic therapies in the earlier stages of their disease may redistribute health care resources, while improving patient outcomes. This provides support and validation to the managed care pharmacist that the concept of a well-designed, appropriate drug-use program or disease management program to focus on correction through pharmacologic therapies to ultimately reduce health care costs and improve outcomes is crucial. The challenge for the managed care pharmacist is complex and begins with designing a benefit and managing a formulary that will provide the patient with the most effective treatments to manage CKD at the most appropriate time, while controlling cost. Managing compliance of these patients will be a great hurdle, yet key to the success of their outcomes, requiring careful monitoring of disease progression, early detection and diagnosis, followed by the treatment of CKD and underlying conditions.

**Limitations**

The financial profile presented in this analysis is not a reflection of managed care organization financial statistics, allowed charges, or net health plan costs after subtraction of member cost-sharing responsibilities from the allowed charges. Rather, estimated charges reported in this analysis were calculated from a Medicare-based fee schedule. Although the occurrence of a procedure or laboratory or other test was evident via the CPT-4 and HCPCS code(s) identified on claims, the results of these services (e.g., laboratory values) were not available. Prescription medications and supplements were quantified in this analysis. Utilization of these products may be underestimated because data for the over-the-counter medications and supplements (e.g., iron preparations) were not available.

**Conclusion**

In this managed care plan, nearly half of all study patients were not receiving interventions for the management of CKD or preparation for dialysis initiation despite published standards of care and the complexity of these patients, as evidenced by the number of comorbidities per patient. Noteworthy is the fact that predialysis EPO use indicated a significantly higher quality of care, as measured by the presence of other appropriate services received by EPO patients in comparison to patients not receiving EPO. These results underscore the suitability of implementing specific guidelines to effectively manage the care of these patients. Guidelines should specify early detection based on disease staging, appropriate and timely utilization of pharmacologic therapies, and the employment of a multidisciplinary approach to managing these patients, including timely specialist referrals, administration of nutritional supplements, and vascular access placement. Many opportunities exist to further explore the timing of each of the interventions and whether the implementation of guidelines, earlier detection, and aggressive treatment can reduce the total health care resource utilization and cost burden in the CKD managed care population as well as improve the clinical outcomes.

**ACKNOWLEDGMENT**

The views expressed in this article are those of authors and do not necessarily reflect those of Oxford Health Plans.

**DISCLOSURES**

Funding for this research was provided by Amgen Inc. and was obtained by author Sally Wade and project manager Amy Solis. Author Wing W. Chan is an employee of Amgen, and author Roger London has a consultant agreement with and has received honoraria from Amgen. London served as principal author of the study. Study concept and design were contributed by author George A. Goldberg and London, Solis, and Wade. Analysis and interpretation of data were contributed by Goldberg, Solis, and Wade. Drafting of the manuscript was primarily the work of Goldberg and Solis and its critical revision was the work of Goldberg, London, Solis, and Chan. Statistical expertise was contributed by Chan, Solis, and Wade. Administrative, technical, and/or material support was provided by Protocare Sciences.

**REFERENCES**

Examination of Resource Use and Clinical Interventions Associated With Chronic Kidney Disease in a Managed Care Population


15. National Institutes of Health/NIDDK. Healthy People 2010 Objectives: Chronic Kidney Disease [proposed chapter].


Improvements in Glycemic Control in Type 2 Diabetes Patients Switched From Sulfonylurea Coadministered With Metformin to Glyburide-Metformin Tablets

WILLIAM DUCKWORTH, MD; MARCO MARCELLI, MD; MAUREEN PADDEN, MD; KENNETH KELLICK, PharmD; TERESA DUHANCICK, PharmD; MICHELLE WILHARDT, PharmD; KEVIN COLGAN, MA, RPh; and ALICE ROMIE, PharmD

OBJECTIVE: To evaluate the change in hemoglobin A1C (A1C) in patients with type 2 diabetes who switched from coadministration of a sulfonylurea (SU), glyburide or glipizide, and metformin (SU+Met) to a single glyburide-metformin tablet.

METHODS: A retrospective cohort study design of patients with type 2 diabetes treated at 3 Veterans Affairs Medical Centers and 1 Department of Defense Medical Center was utilized. One hundred percent of patients receiving glyburide-metformin tablets were screened for inclusion. Patients with at least 6 months of prior SU+Met combination therapy and a baseline A1C measured within 35 days prior to or 3 days after switch to glyburide-metformin tablets were included. At least one documented follow-up A1C at ≥90 days after the switch to glyburide-metformin was required for inclusion. Glycemic control, complications, lipid parameters, concomitant medications, and weight were analyzed prior to and following the switch to glyburide-metformin.

RESULTS: Seventy-two patient records were included after the disqualification criteria excluded 488 prospective patients. The mean age of the 72 patients was 62 years; average body mass index was 32.9 kg/m², and average baseline A1C was ≥8.3%, and the average time since diagnosis was 7.6 years. The mean reduction in A1C was 0.6% (P=0.002) at a mean follow-up of 196 days after the switch to glyburide-metformin tablets. Improvement in glycemic control was predominantly seen in patients with a baseline A1C ≥8% in whom a 1.3% mean reduction in A1C (P=0.0002) was achieved despite a lower mean final dose of glyburide.

CONCLUSION: The results of this study suggest that in type 2 diabetic patients with an A1C ≥8%, switching from coadministration of a sulfonylurea plus metformin to combination glyburide-metformin tablets may provide an improvement in glycemic control in the range of 1.2 to 1.4 absolute percentage point decrease in A1C. A randomized, prospective trial comparing these 2 methods of treatment is needed, however, to determine the precise effect provided by the unique formulation of glyburide in the glyburide-metformin tablet.

KEYWORDS: Type 2 diabetes, Glycovance, Glycosylated hemoglobin, A1C

J Managed Care Pharm. 2003(9)3: 256-62

Authors

WILLIAM DUCKWORTH, MD, is Director, Diabetes Research, TERESA DUHANCICK, PharmD, is a Clinical Pharmacist, and MICHELLE WILHARDT, PharmD, is a Clinical Pharmacist, Pharmacoeconomics, Carl T Hayden VA Medical Center, Phoenix, Arizona; MARCO MARCELLI, MD, is an Associate Professor, Dept. of Medicine, Baylor College of Medicine, and a Staff Physician, Houston VA Medical Center, Texas; MAUREEN PADDEN, MD, is Faculty Development Fellow, Family Practice, Madigan Army Medical Center, Tacoma, Washington, KENNETH KELLICK, PharmD, is Clinical Pharmacy Coordinator, VA Western New York Health Care System, Buffalo, New York; KEVIN COLGAN, MA, RPh, is Vice President, Outcomes and Pharmacoeconomic Research, and ALICE ROMIE, PharmD, is a Clinical Pharmacist, EPI-Q, Inc., Oakbrook Terrace, Illinois.

AUTHOR CORRESPONDENCE: Kevin Colgan, MA, RPh; Vice President, Outcomes and Pharmacoeconomic Research, EPI-Q, Inc., 17W727 Batterfield Rd., Suite F & G, Oakbrook Terrace, IL 60181. Tel: (630) 889-1280, Fax: (630) 889-1284; E-mail: kevin.colgan@epi-q.com

Copyright© 2003, Academy of Managed Care Pharmacy. All rights reserved.
therapy in patients failing diet and exercise. In addition, we have observed anecdotally significant reductions in A1C in patients switched from coadministration of a sulfonylurea and metformin to glyburide-metformin tablets in our respective practice settings. These anecdotal observations and the fact that no data were available differentiating glyburide-metformin tablets from combination therapy with a sulfonylurea plus metformin (SU+Met) delivered independently formed the impetus for this study.

The objective of our study was to investigate the change in the glycemic control achieved by switching from treatment with coadministered SU+Met tablets to glyburide-metformin tablets. This was achieved using a retrospective cohort study design and an analysis of the change in glycosylated hemoglobin before and after the switch to glyburide-metformin tablets.

Methods

A retrospective, medical record review was conducted for patients initiated on glyburide-metformin tablets between September 2000 and December 2001. The study included patients from 3 Veterans Affairs Medical Centers (VAMCs) and 1 Department of Defense Medical Center. All patients who had a prescription for glyburide-metformin tablets (n=560) had their medical records examined for inclusion and exclusion criteria.

Patients aged ≥18 years or ≥80 years with type 2 diabetes were eligible if they had received glyburide-metformin therapy for at least 90 days, had been treated with glipizide or glyburide plus metformin at least 6 months prior to switching to glyburide-metformin tablets, and did not exceed the maximum daily dose of 20 mg of glyburide, 40 mg of glipizide, 2,000 mg of metformin (preswitch), or 20 mg/2,000 mg of glyburide-metformin tablets (postswitch). A1C values must have been measured within 35 days prior to or 3 days after initiation of glyburide-metformin and at least 90 days after the switch. Patients were excluded if they had any of the following: diabetic ketoacidosis; congestive heart failure (ejection fraction <40%); requiring pharmacologic treatment (diuretics, digoxin, angiotensin-converting enzyme inhibitors, positive inotropes); acute or chronic metabolic acidosis; renal dysfunction (serum creatinine ≥1.5 mg/dL for males and ≥1.4 mg/dL for females) or hemodialysis; pregnancy; hypersensitivity to glyburide or metformin prior to initiation of glyburide-metformin tablets; concomitant use of either glyburide or metformin with glyburide-metformin tablets; or type 1 diabetes.

The inclusion and exclusion criteria were applied in an attempt to allow a critical time period for A1C to have stabilized preswitch and postswitch to glyburide-metformin tablets and to include only those who received treatment that was not contraindicated and at doses approved within each medication’s package insert. Institutional Review Board approval was obtained from the responsible IRB at each participating site.

Seventy-two patients were identified who qualified by meeting the inclusion criteria at the Carl T. Hayden VA, Phoenix, Arizona (n=29); Houston VA (n=14); Buffalo VA (n=21); and Madigan Army Medical Center, Tacoma, Washington (n=8). These patients had their medical and pharmacy prescription records reviewed by nurses and pharmacists trained in outcomes research from an independent research organization and pharmacists and physicians at the study sites using a standard data collection form and data dictionary to assure standardized collection of data.

Data collected for analysis included baseline characteristics: age, sex, height, weight, ethnic origin, family history of diabetes, tobacco use, alcohol use, and history of stroke, hypertension, coronary artery disease, hypercholesterolemia, peripheral neuropathy, retinopathy, diabetic foot disease, and proteinuria. Laboratory findings collected during the treatment period included glycosylated hemoglobin A1C, fasting plasma glucose, blood glucose, serum creatinine, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, blood urea nitrogen, aspartate aminotransferase, and C-peptide, if available. Baseline and follow-up laboratory testing was performed for each patient in the same laboratory at each specific site. Complications, the date of each complication, and the treatment for the complication were collected. A complication was defined as any event attributable to diabetes or its treatment, such as hypoglycemia or diabetic foot disease.

Medication dose, route, frequency, start date, and stop date were collected for the study medications from both the medical record and the pharmacy computer records at each site. Prescription data for coadministered sulfonylurea and metformin tablets were included for the 30-month period prior to the switch. Prescription data were included for glyburide-metformin tablets for a period of up to 19 months after the switch. This 19-month period represents the date between the first commercial use of a glyburide-metformin combination tablet and the date data collection was completed. Adherence was defined as the ratio of days of therapy supplied to the total days in the treatment period. The treatment period for the measurement of adherence was defined as the period from the index prescription fill date to run-out of days supplied in the last refilled prescription for the index drug. Other prescribed medications were recorded, including antilipemias and medications that can affect blood glucose levels.

Statistical Analysis

Analyses were conducted to compare the effects of the switch from SU+Met to glyburide-metformin tablets on A1C, body weight, lipid profile, patient adherence to the prescribed drug regimen, and concomitant medical conditions. Changes in baseline from A1C, lipid parameters, and weight were analyzed using a paired t test. A1C change was also analyzed using paired t tests for the following subgroups: patients not receiving insulin, patients not receiving additional adjunctive oral anti-diabetic therapy, patients whose daily metformin dose did not increase after the switch, and patients not having any of the
Improvements in Glycemic Control in Type 2 Diabetes Patients Switched From Sulfonylurea Coadministered With Metformin to Glyburide-Metformin Tablets

Table 1: Disqualified Glyburide-Metformin Patient Records

<table>
<thead>
<tr>
<th>Reason for Exclusion</th>
<th>n=488 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 diabetes</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Age &gt;80 years</td>
<td>11 (2.3)</td>
</tr>
<tr>
<td>History of hypersensitivity to glyburide or metformin</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Not receiving SU+Met prior to initiation of glyburide-metformin tablets</td>
<td>145 (29.7)</td>
</tr>
<tr>
<td>Not receiving SU+Met combination for 6 months prior to switch to glyburide-metformin</td>
<td>64 (13.1)</td>
</tr>
<tr>
<td>Dose of glyburide &gt;20mg, glipizide &gt;40mg, or metformin &gt;2,000 mg</td>
<td>50 (10.2)</td>
</tr>
<tr>
<td>Receiving concomitant sulfonylurea or metformin with glyburide-metformin tablets</td>
<td>9 (1.8)</td>
</tr>
<tr>
<td>Receiving glyburide-metformin tablets &lt;90 days</td>
<td>38 (7.8)</td>
</tr>
<tr>
<td>No baseline A1C within 35 days prior to or 3 days after switch to glyburide-metformin</td>
<td>66 (13.5)</td>
</tr>
<tr>
<td>No follow-up ≥ 90 days after start of glyburide-metformin tablets</td>
<td>73 (15.0)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>7 (1.4)</td>
</tr>
<tr>
<td>Diagnosis of congestive heart failure</td>
<td>18 (3.7)</td>
</tr>
<tr>
<td>Restricted access to medical record</td>
<td>2 (0.4)</td>
</tr>
</tbody>
</table>

Table 2: Diabetic Patient Demographics at Baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>70 (97.2)</td>
</tr>
<tr>
<td>Female</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>72 (100)</td>
</tr>
<tr>
<td>Ethnicity:</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>52 (72.2)</td>
</tr>
<tr>
<td>African/American</td>
<td>8 (11.1)</td>
</tr>
<tr>
<td>Latino/Hispanic</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>9 (12.5)</td>
</tr>
<tr>
<td>Glyburide+metformin</td>
<td>69 (95.8)</td>
</tr>
<tr>
<td>Glipizide+metformin</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>Mean glyburide dose</td>
<td>69 (17.2mg)</td>
</tr>
<tr>
<td>Mean glipizide dose</td>
<td>3 (5.0mg)</td>
</tr>
<tr>
<td>Mean body mass index</td>
<td>63 (32.9 kg/m²)</td>
</tr>
<tr>
<td>Mean number of years diagnosed with diabetes</td>
<td>72 (7.6 years)</td>
</tr>
</tbody>
</table>

Of the 560 patients screened at 3 VAMCs and 1 Department of Defense Medical Center, 72 patient records met inclusion criteria. The most common reasons for exclusion were patients not receiving SU+Met prior to the initiation of glyburide-metformin and no baseline or follow-up hemoglobin A1C measurement within the limits of the inclusion criteria (Table 1).

Those patients included in the study were predominantly white (72.2%), male (97.2%), with an average age of 61.9 years. Subjects were obese, on average, with a mean body mass index (BMI) of 32.9 kg/m². Patients had been diagnosed with diabetes, on average, 7.6 years prior to inclusion in the study (Table 2). Five patients received insulin at baseline (6.9%), and 6 patients (8.3%) were on an additional oral antidiabetes medication (Table 3).

Results

Of the 560 patients screened at 3 VAMCs and 1 Department of Defense Medical Center, 72 patient records met inclusion criteria. The most common reasons for exclusion were patients not receiving SU+Met prior to the initiation of glyburide-metformin and no baseline or follow-up hemoglobin A1C measurement within the limits of the inclusion criteria (Table 1).

Those patients included in the study were predominantly white (72.2%), male (97.2%), with an average age of 61.9 years. Subjects were obese, on average, with a mean body mass index (BMI) of 32.9 kg/m². Patients had been diagnosed with diabetes, on average, 7.6 years prior to inclusion in the study (Table 2). Five patients received insulin at baseline (6.9%), and 6 patients (8.3%) were on an additional oral antidiabetes medication (Table 3).

Patients served as their own controls, having received SU+Met coadministration for at least 6 months prior to switch to glyburide-metformin tablets. The mean baseline A1C in the total population (n=72) was 8.3% (±SD 1.7). The mean reduction in A1C was 0.6% (P=0.002) with a mean follow-up of 196 days after initiation of glyburide-metformin. Mean daily doses of glyburide and metformin at baseline and at final follow-up were 17.2 mg and 1,607 mg and 14.7 mg and 1,750 mg,
The greatest reduction in A1C was seen in those with a baseline A1C ≥8% (n=37). This cohort experienced a mean reduction in A1C of 1.3% (P=0.0002) with similar doses of glyburide (14.7 mg versus 16.9 mg, P=0.077) and metformin (1,743 mg versus 1,624 mg, P=0.11) in both treatment periods (Figure 1).

To examine the effects of confounding variables, subset analyses were performed on patients receiving additional oral antidiabetic agents or insulin and those with an increased dose of metformin. Fifteen patients received an additional oral antidiabetic agent (i.e., thiazolidinediones, α-glucosidase inhibitors) either before or after the switch to glyburide-metformin. When these patients were excluded, the reductions in A1C were similar to the entire patient population regardless of baseline A1C levels (0.5% versus 0.6%, respectively). Separate subset analyses also revealed similar mean A1C responses after exclusion of the 19 patients receiving insulin at any time during the observation period (change in A1C of 0.5%) or after exclusion of the 16 patients whose metformin dose was increased after the switch (change in A1C of 0.5%) (Figure 2).

Some patients had overlapping confounders (i.e., an increased metformin dose and insulin). A separate no-confounder subset analysis using paired t tests was performed including only those patients who did not receive an additional oral antidiabetic agent, did not receive insulin, and did not have an increased dose of metformin after the switch to glyburide-metformin tablets. The mean baseline A1C in this cohort (n=42) was 7.9% (±SD 1.7), and the mean reduction in A1C was 0.4% (P=0.35). Those with a baseline A1C ≥8% (n=16) had a mean baseline A1C of 9.7% (±SD 0.7) and a mean A1C reduction of 1.4% (P=0.026). After the switch to glyburide-metformin tablets, the mean daily doses of glyburide and metformin were less than during the SU+Met coadministration period (14 mg versus 17 mg glyburide, P=0.003 and 1,578 mg versus 1,650 mg metformin, P=0.07). Those with a baseline A1C <8% (n=26) had a mean baseline A1C of 6.8% (±SD 1.7) and a mean A1C increase of 0.2% (P=0.14). This analysis reveals that the removal of confounding factors did not affect the results.

There were no significant changes in total cholesterol (185 mg/dL before versus 178 mg/dL after, n=49), HDL cholesterol (38 mg/dL before versus 39 mg/dL after, n=49), LDL cholesterol (107 mg/dL before versus 96 mg/dL after, n=45) or triglyceride (236 mg/dL before versus 235 mg/dL after, n=49). There were also no significant differences in patient adherence to the prescribed drug regimen (92.4% before versus 90.9% after, n=72), or body weight (104.3 kg before versus 104 kg after, n=64). The concurrence of prescriptions for medications that may cause glucose intolerance (nicotinic acid, thiazide diuretics, or β-blockers) increased from 17 before the switch to 32 after.

Six patients experienced complications related to diabetes or its treatment prior to switch, and 11 patients experienced complications after the switch to glyburide-metformin. The primary complication observed during each treatment phase was hypoglycemia. During the SU+Met treatment period, 3 patients experienced hypoglycemia in comparison to 8 patients during the glyburide-metformin treatment period. Three of 8 patients with hypoglycemia after the switch to glyburide-metformin were also receiving concomitant insulin, and the treatment for the hypoglycemia was documented as reduction in insulin dose. No patient meeting the inclusion criteria had glyburide-metformin therapy discontinued secondary to hypoglycemia.

During the SU+Met treatment period, 1 patient had a coronary artery bypass graft and 2 patients experienced diabetic foot disease. During the glyburide-metformin treatment period, 2 patients experienced chest pain and 1 patient had diabetic foot disease.

**Discussion**

This study found important differences between coadministered SU+Met and glyburide-metformin tablets. In patients switched to glyburide-metformin, a mean A1C reduction of 0.6% was realized in the total population. The improvement in glycemic control was significant predominantly in patients with an A1C ≥8% who experienced a mean 1.3% decrease in A1C. ADA practice recommendations indicate that an average A1C ≥8% requires a change in treatment.15 The present study indicates that a significant reduction in A1C (on average 1.3%) may be
achieved in patients needing a change in therapy by switching patients from a SU+Met treatment regimen to glyburide-metformin tablets.

Given epidemiological findings showing that 42.2% of type 2 diabetics taking oral agents have an A1C >8%,11 the clinical implications of these results become more important and worth studying in a prospective manner. In addition, the UKPDS of 5,102 type 2 diabetic patients showed that reducing A1C by 1% decreased the risk of any diabetes-related complication by 21%, death related to diabetes by 21%, myocardial infarction by 14%, and microvascular complications, including retinopathy, nephropathy, and neuropathy, by 37%. Therefore, a reduction in A1C of at least 1 percentage point, as seen in patients with a baseline A1C ≥8% in this study, would be anticipated to impart a meaningful reduction in both cardiovascular and microvascular complications.

In a retrospective cohort study design, it is important in analysis of the findings to examine all treatment variables that may influence the study results. For example, it is necessary to consider whether changes in the doses of the components of glyburide-metformin tablets may explain, weight, or lipid levels. The greater A1C reduction also could not be attributed to increased use of concomitant insulin or other oral antidiabetes drugs or to any increase in the daily dose of metformin (0.5% for each subset versus 0.6% study population). In addition, there were no significant changes in other potentially confounding factors, including medication refill rate, body weight, or lipid levels. The greater A1C reduction also could not be attributed to decreased use of medications that may increase glucose intolerance, such as nicoitin acid, thiazide diuretics, and beta adrenergic blocking agents; instead, use of these medications increased after the switch. Thus, the variable most likely to account for the reduction in A1C was the actual change in treatment from coadministration of a sulfonylurea plus metformin to the glyburide-metformin tablets.

In interpreting these data, one must be aware of the potential phenomenon of regression to the mean in A1C measurement. Correlation between the pre-glyburide-metformin and post-glyburide-metformin readings was significant (Pearson’s r=0.5, P=0.000009), suggesting that regression to the mean could only account for a portion of the difference seen. However, without a control group, it is difficult to assess the true effect of regression to the mean.

Improved glycemic control attained by switching from coadministration of the individual agents to the glyburide-metformin tablets may be attributable, at least in part, to the unique glyburide formulation of the glyburide-metformin tablets. Glyburide-metformin tablets are engineered to contain a spectrum of glyburide particle sizes. Theoretically, the smaller particles would dissolve faster and be absorbed more quickly than the larger particles. In a recent study of type 2 diabetic patients, glyburide-metformin tablets were compared to coadministration of glyburide and metformin. Results indicate that twice as many glyburide-metformin tablets were compared to coadministration of a sulfonylurea plus metformin tablet (AUC0-3 47 ng.hr/mL versus 95 ng.hr/mL), while the metformin pharmacokinetic profiles were indistinguishable. Because glyburide-metformin tablets are routinely dosed with a meal, one may expect that the early rise in glyburide concentrations would deliver the highest


insulin levels during the time of peak postprandial hyperglycemia. Therefore, the unique glyburide pharmacokinetic profile of the glyburide-metformin tablet may explain, in part, its improved control of hyperglycemia in the postprandial state when compared to monotherapy with glyburide or metformin. 

Although not powered on this specific endpoint, adherence to drug regimens before and after switch in therapy was not significantly different (92.4% versus 90.9%) and was not related to mean reductions in A1C. In the VA and Department of Defense settings, as well as in the private sector, beneficiaries are charged a copayment per prescription filled, typically $7 per 30-day supply in the VAMC setting and $8 to $35 per 30-day supply in the private sector, depending on the copay tier in the managed care plan. With the switch to glyburide-metformin combination, only 1 prescription copayment would be required, saving the patient an additional copayment. In addition, another published study has shown that reducing the tablet number for each dosing interval improves adherence in the diabetic patient.

The VAMCs and Department of Defense Medical Center provided an ideal setting for this retrospective study of type 2 diabetes. Diabetes care is provided longitudinally in a closed setting. Patients are seen by the same physicians and prescriptions are filled by the same pharmacy, allowing easy tracking of the effect of each treatment on the outcome of the patient. A retrospective study does not approach the rigor of a controlled, randomized trial but does provide insight into real-world outcomes in actual clinical practice.

Improved glycemic control is often achieved by stricter adherence to diet, increased exercise, medication titration, or a blend of these methods. Switching from single-dose tablets to a combination product may not be the customary course used to improve glycemic control when a patient is at the take-action threshold (A1C ≥8%) published in 2000 ADA standards. 

Upward titration of one or both medications or the addition of another agent is often chosen until the patient achieves that targeted response. The results of this study suggest that the use of glyburide-metformin combination tablets can be an effective alternative to traditional medication titration in type 2 diabetic patients.

**Limitations**

The primary limitation of this study is the relatively small sample size. The number of cases excluded due to the absence of a baseline A1C (66 of 560 cases screened, or 11.5%) or the use of a glyburide or metformin dose that was greater than the recommended package insert dose (50 of 560 cases screened, or 8.9%) were major factors limiting our sample size. The sample size may have been insufficient in each subset to determine a difference in the preswitch and postswitch doses of glyburide and metformin.

The retrospective design of our study and the inclusion/exclusion criteria did not allow for control of all confounding variables, such as the daily dose of glyburide-metformin and the utilization of insulin or other oral antidiabetic agents. The predominant glyburide-metformin effect was found in patients with a baseline A1C ≥8%. Of those with no confounders, only 16 patients had a baseline A1C ≥8%, although their outcome was similar to the study population (A1C reduction of 1.4% in the no-confounder population versus 1.3% in the study population). Further research could focus on patients whose A1C is ≥8% to evaluate the glyburide-metformin effect in a larger sample.

Due to the study being performed in the VA and Department of Defense medical centers, it is difficult to determine if the results of this study can be generalized to a more diverse population. The study population was predominantly male (97.2%). The sample size was also not large enough to evaluate the affect of age or disease duration on outcome.

**Conclusion**

Patients switched from coadministered SU+Met to combination glyburide-metformin tablets experienced an overall mean decrease of 0.6% in hemoglobin A1C (P=0.002) and a mean reduction of 1.3% (P=0.0002) in those patients with baseline A1C >8%. Based on the recent demonstration that the glyburide-metformin tablet delivers twice as much glyburide during the first 3 hours than does glyburide coadministered with metformin, the unique tablet design may explain, in part, the greater decrease in A1C observed in this study. Although a randomized, prospective trial is needed for verification, the present findings suggest that switching from a sulfonylurea coadministered with metformin to the glyburide-metformin tablet may improve glycemic control in patients with type 2 diabetes and an A1C >8%.

**ACKNOWLEDGMENTS**

The authors acknowledge Farid Roman, MD, who worked with Dr. Marco Marcelli, MD, at the VA Hospital in Houston; Larry Greene, PharmD, CDE, for providing assistance with data collection at Madigan Army Medical Center; and Alicia Shillington, RN, MPH, and Mark Jewell, PhD, for providing assistance with statistical analyses.

**DISCLOSURES**

Funding for this research was provided by a grant from Bristol-Myers Squibb that was obtained by author Kevin Colgan. Author Alice Romie was the project manager of this research project, and author William Duckworth served as principal author of this study. Duckworth is an advisor to Bristol-Myers Squibb. Study concept and design were contributed by Duckworth, Colgan, Romie, authors Marco Marcelli, Maureen Padden, Kenneth Kellick, Teresa Duhancik, and Michelle Wilhardt and Farid Roman. Analysis and interpretation of data and drafting of the manuscript were primarily the work of Colgan and Romie. Critical revision of the manuscript was the work of Duckworth, Marcelli, Roman, Padden, Kellick, Duhancik, and Wilhardt.

The opinions or assertions contained in this article are the private views of the authors and are not to be construed as official or reflecting the view of the Department of the Army or the Department of Defense.

**REFERENCES**

Improvements in Glycemic Control in Type 2 Diabetes Patients Switched From Sulfonylurea Coadministered With Metformin to Glyburide-Metformin Tablets

Cost and Utilization Comparisons Among Propensity Score-Matched Insulin Lispro and Regular Insulin Users

JENNIFER A. HALL, MPH; KENT H. SUMMERS, PhD; and ROBERT L. OBENCHAIN, PhD

ABSTRACT

OBJECTIVE: To compare cost and utilization among users of insulin lispro and regular (human) insulin.

METHODS: This was a retrospective analysis using administrative claims data for continuously enrolled subjects using insulin lispro or regular insulin between January 1, 1998, and December 31, 1999. Subjects were matched 1 to 1 on the propensity to receive lispro versus regular insulin using a score estimated from baseline characteristics such as age, gender, comorbidities, and oral hypoglycemic use. Once matched, 12 months of follow-up pharmacy and medical cost and utilization data (e.g., prescriptions, office visits, hospitalizations) from July 1, 1997, through December 31, 2000, were analyzed using univariate statistics.

RESULTS: Of 11,443 subjects, 3,341 (29.2%) had received a prescription for insulin lispro, while 8,102 (70.8%) had received a prescription for regular insulin. At baseline, lispro subjects tended to be younger, more often had type 1 diabetes and a history of insulin use, had fewer comorbidities, visited endocrinologists more often than family practice physicians, and had lower total costs. After matching on propensity score to within ±0.01, 1,832 subject pairs were retained. On average, lispro subjects had significantly more office visits (P=0.0022) and pharmacy prescriptions (P=0.0165) but fewer inpatient hospital visits (P=0.0028) compared to regular insulin subjects. Cost results were similar, with insulin lispro subjects having significantly higher average office visit costs (P=0.0237) and pharmacy costs (P=0.0001) but lower inpatient hospital costs (P=0.0227). Total costs were not significantly different between treatment groups (P=0.5266).

CONCLUSION: Total direct health care costs were not different between insulin lispro and regular insulin users. An association was observed between higher direct drug product cost and more intensive ambulatory care for insulin lispro users and lower inpatient hospital cost in the short-term.

KEYWORDS: Insulin, Lispro, Cost

J Managed Care Pharm. 2003;9(3): 263-68

T he average total charge for treating U.S. patients hospitalized for diabetes with complications increased from $10,271 in 1993 to $14,779 in 2000. The total number of patients hospitalized increased from 373,666 to 455,027 during that time period. With diabetes treatment expenses and lost productivity reaching $98 billion in the United States annually, the urgency for timely diagnosis, treatment, and better glycemic control continues.

Advancements in the treatment of diabetes mellitus have long focused on improving glucose control. One such improvement has been the market availability of insulin lispro. Insulin lispro is a rapid-acting human insulin analog with a faster onset and shorter duration of action compared to regular human insulin. The shorter time to peak serum insulin level more closely mimics physiologic secretion of insulin, which results in greater relative reductions of postprandial blood glucose concentrations. Better clinical outcomes (superior postprandial glycemic control without an increase in the risk of severe hypoglycemia) with insulin lispro have been demonstrated in numerous clinical trials. There are, however, few economic studies of insulin lispro use. While these studies demonstrated that consumers perceive the benefits of insulin lispro therapy to justify its additional cost relative to regular (human) insulin, no studies have been published that examine whether insulin lispro’s higher drug cost is offset by direct medical cost savings in areas of the health care system outside of pharmacy.

The objective of this study was to assess potential economic benefits of insulin lispro use compared to regular insulin in a population of managed care enrollees with diabetes. This study was designed to address questions from the perspective of the employer, who has the option to choose among a variety of benefit designs, i.e., which drugs to cover at a preferred status versus a nonpreferred status. An analysis that considers both third-party payer payments and patient copayments is relevant when considering the true cost of insulin. This study addressed the question of whether the higher total product cost of insulin lispro compared to regular insulin therapy is offset by health care cost savings in nonpharmacy areas.

Methods

Study Site and Data Source

This study was conducted using enrollment, medical, and pharmacy claims data from 14 UnitedHealthcare affiliated health plans located throughout the southeastern, northeastern, midwestern, and western United States. These health plans are independent practice association model plans that employed the discounted, fee-for-service method for provider reimbursement.
Cost and Utilization Comparisons Among Propensity Score-Matched Insulin Lispro and Regular Insulin Users

Study Period
All prevalent users of insulin from January 1, 1998, through December 31, 1999, were identified in the claims database. For each subject, the fill date of the first insulin prescription during that 24-month period was considered the study index date. Each subject’s health services utilization patterns were examined for a period from 6 months prior through 12 months following this study index date. Thus, the study included pharmacy and medical claims data from July 1, 1997, through December 31, 2000.

Inclusion Criteria
Health plan enrollees meeting all of the following inclusion criteria were selected as study subjects: (1) at least 1 pharmacy claim for insulin lispro or regular insulin between January 1, 1998, and December 31, 1999; (2) continuous enrollment for at least 6 months prior to and 12 months following the study index date; and (3) drug benefit coverage during the entire 18-month continuous enrollment period.

Treatment Groups
If a subject filled a prescription for insulin lispro between January 1, 1998, and December 31, 1999, the subject was included in the lispro group. If a regular insulin prescription was filled and no insulin lispro prescription was filled in this time frame, the subject was included in the regular insulin group.

Propensity Score Matching
Subjects were matched on the propensity to receive lispro insulin versus regular insulin. Matching subjects on propensity scores is one method of controlling for confounding when numerous characteristics are related to the outcome of interest or when 2 populations are known to differ due to selection bias. This method serves to balance the treatment groups at baseline.11 While standard regression modeling can handle several regressor variables, results can be misleading because small differences in numerous covariates can accumulate into a substantial overall difference. Two treatment groups may differ in a multivariate direction to an extent that cannot be discerned in the separate analyses of each covariate.12 For this reason, propensity score methodology is a reasonable alternative. In this study, baseline characteristics were used as independent predictors in a multivariate logistic regression model. The model was constructed to predict the probability (score) of receiving lispro versus regular insulin. Subjects were subsequently matched (1 to 1) on propensity scores within ±0.01. Subjects who could not be matched were removed from further analysis. Baseline characteristics were compared before and after matching to insure that all significant differences between the treatment groups had become nonsignificant. The independent variables used in the logistic regression model are defined in Appendix A. Due to the large number of comparison tests (N=21), the alpha level for all comparison tests was adjusted using a Bonferroni correction procedure, which resulted in

APPENDIX A Baseline Variables Used in Logistic Model to Derive Propensity Scores

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Continuous, as of 12/31/00</td>
</tr>
<tr>
<td>Gender</td>
<td>Male=1</td>
</tr>
<tr>
<td>Physician specialty</td>
<td>A categorical variable indicating dominant provider (family practice/internist or Ob/Gyn, endocrinologist, pediatrician, other)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>One continuous variable indicating total number of comorbidities based on chapters of the ICD-9-CM codebook</td>
</tr>
<tr>
<td>Related comorbidities</td>
<td>Eight (0,1) variables indicating presence or absence of cardiovascular disease, hypertension, lower extremity infections, other metabolic diseases, nephropathy, neuropathy, obesity, and retinopathy (details appear in Appendix B)</td>
</tr>
<tr>
<td>HbA1c tests</td>
<td>Continuous variable indicating total number of HbA1c tests on medical claims</td>
</tr>
<tr>
<td>Oral hypoglycemic use</td>
<td>Continuous variable indicating total number of oral hypoglycemic prescriptions filled</td>
</tr>
<tr>
<td>Insulin prescriptions</td>
<td>Continuous variable indicating total number of insulin prescriptions filled</td>
</tr>
<tr>
<td>Basal insulin use</td>
<td>A (0,1) variable indicating any prescriptions for basal insulin</td>
</tr>
<tr>
<td>Eye exams</td>
<td>A (0,1) variable indicating an eye exam on a medical claim</td>
</tr>
<tr>
<td>Diabetes education</td>
<td>A (0,1) variable indicating diabetes education on a medical claim</td>
</tr>
<tr>
<td>Benzodiazepine use</td>
<td>A (0,1) variable indicating any prescriptions for benzodiazepines</td>
</tr>
<tr>
<td>Plan</td>
<td>A categorical variable of plan by region (SW, NE, MW, W)</td>
</tr>
<tr>
<td>Total costs</td>
<td>A continuous variable, all-cause medical and pharmacy costs, including member cost-share as well as net health plan cost</td>
</tr>
</tbody>
</table>
Cost and Utilization Comparisons Among Propensity Score-Matched Insulin Lispro and Regular Insulin Users

TABLE 1
Bivariate Tests Before and After Matching Lispro and Regular Insulin Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>P Value Before Matching</th>
<th>P Value After Matching</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lispro N=4,318</td>
<td>Regular N=11,155</td>
</tr>
<tr>
<td></td>
<td>Lispro N=1,832</td>
<td>Regular N=1,832</td>
</tr>
<tr>
<td>Basal insulin use</td>
<td>&lt;0.0001</td>
<td>0.7121</td>
</tr>
<tr>
<td>Diabetes education</td>
<td>0.0068</td>
<td>0.8268</td>
</tr>
<tr>
<td>Eye exam</td>
<td>&lt;0.0001</td>
<td>0.2445</td>
</tr>
<tr>
<td>Benzodiazepine use</td>
<td>&lt;0.0001</td>
<td>0.6746</td>
</tr>
<tr>
<td>Age (in years)</td>
<td>&lt;0.0001</td>
<td>0.3902</td>
</tr>
<tr>
<td>Dominant physician specialty</td>
<td>&lt;0.0001</td>
<td>0.7764</td>
</tr>
<tr>
<td>Number of baseline HbA1c tests</td>
<td>&lt;0.0001</td>
<td>0.8866</td>
</tr>
<tr>
<td>Number of baseline insulin presc</td>
<td>&lt;0.0001</td>
<td>0.9399</td>
</tr>
<tr>
<td>Health plan location</td>
<td>0.6352</td>
<td>0.3467</td>
</tr>
<tr>
<td>Number of baseline comorbidities</td>
<td>&lt;0.0001</td>
<td>0.6957</td>
</tr>
<tr>
<td>Cardiovascular disease in baseline</td>
<td>&lt;0.0001</td>
<td>0.8919</td>
</tr>
<tr>
<td>Hypertension in baseline</td>
<td>&lt;0.0001</td>
<td>0.5032</td>
</tr>
<tr>
<td>Infection in baseline</td>
<td>&lt;0.0001</td>
<td>0.4431</td>
</tr>
<tr>
<td>Metabolic disease in baseline</td>
<td>0.0708</td>
<td>0.8645</td>
</tr>
<tr>
<td>Nephropathy in baseline</td>
<td>0.1107</td>
<td>0.7189</td>
</tr>
<tr>
<td>Neuropathy in baseline</td>
<td>0.9233</td>
<td>0.7350</td>
</tr>
<tr>
<td>Obesity in baseline</td>
<td>&lt;0.0001</td>
<td>0.4127</td>
</tr>
<tr>
<td>Retinopathy in baseline</td>
<td>0.0011</td>
<td>0.3221</td>
</tr>
<tr>
<td>Gender (male=1)</td>
<td>0.0436</td>
<td>0.3903</td>
</tr>
<tr>
<td>Total baseline costs</td>
<td>&lt;0.0001</td>
<td>0.8554</td>
</tr>
<tr>
<td>Oral hypoglycemic use</td>
<td>&lt;0.0001</td>
<td>0.3949</td>
</tr>
</tbody>
</table>

* Based on an algorithm combining diagnosis codes and presence/absence of oral hypoglycemics, 14.9% of lispro and 8.8% of regular insulin subjects appeared to have type 1 diabetes prior to matching compared to 11% and 10.4% after matching, respectively.

Summary of Matching Procedure
Prior to matching subjects by their propensity scores (predicted value of receiving insulin lispro versus regular insulin based on baseline characteristics), 21 different baseline characteristics were compared across the 2 treatment groups. For 15 of the 21 (71.4%) baseline characteristics, the 2 treatment groups differed significantly. Insulin lispro subjects tended to be younger, used fewer oral hypoglycemics, had fewer comorbidities, visited endocrinologists more often than family practitioners, and had lower total costs compared to subjects who received regular insulin (Table 1). Of 3,341 insulin lispro subjects, 1,832 (54.8%) subjects were matched to a regular insulin-using subject within ±0.01. All subsequent analyses were limited to this matched sample (N=3,664 subjects [1,832 subject pairs]). After matching, none of the 21 baseline comparison tests remained significantly different. Characteristics of subjects lost during the matching procedure are summarized below.

The lispro subjects who were not matched were more often type 1 diabetics (based on an algorithm combining ICD-9-CM diagnosis codes [250.xx, Appendix B] and presence or absence of prescriptions for oral hypoglycemic agents) who were younger; prevalent users of insulin; treated by specialists; had less circulatory disease, cardiovascular disease, hypertension, or obesity; filled more insulin prescriptions; and had more HbA1c tests compared to the lispro subjects who were matched. The regular insulin subjects for whom no match existed were more often older; were treated by general practitioners; had more neoplasms and circulatory, digestive, cardiovascular and musculoskeletal disease, hypertension, ill-defined conditions, lower extremity infections, and obesity; had fewer pregnancy complications, HbA1c tests, and insulin prescriptions; had more oral hypoglycemic prescriptions; and had higher baseline pharmacy and total costs.

Follow-up Cost and Utilization Analysis
Health services utilization during the 12-month follow-up period was compared across the 2 treatment groups (Table 2). While average rates of outpatient hospital visits, emergency room visits, or lab tests did not differ significantly between the 2 treatment groups, there were significant differences detected in numbers of office visits, prescriptions filled, and inpatient hospitalizations. On average, insulin lispro subjects had significa-
Significantly more office visits ($P=0.0022$) and filled significantly more prescriptions (diabetes-related and nondiabetes-related prescriptions, $P=0.0165$) compared to regular insulin subjects. In contrast, insulin lispro subjects had, on average, significantly fewer inpatient hospitalizations compared to regular insulin subjects ($P=0.0028$). Among subjects who received at least one diagnosis of hypoglycemia in the follow-up period, insulin lispro subjects had a significantly lower average number of hypoglycemia-related hospitalizations ($P=0.0014$).

Cost during the 12-month follow-up period was compared across the 2 treatment groups (Table 3). Insulin lispro subjects had significantly higher average office visit costs and pharmacy costs compared to regular insulin subjects ($P=0.0237$ and $P<0.0001$, respectively) as well as significantly lower average inpatient hospital costs compared to regular insulin subjects ($P=0.0227$); there was no significant difference in average emergency room, outpatient, laboratory, or total costs. It is important to note that although lispro subjects did have significantly higher average office visit costs and pharmacy costs ($+$106 and $+$447, respectively) relative to regular insulin subjects, these higher costs were offset by lower average inpatient hospital cost ($-$769), a cost savings for insulin lispro (albeit not statistically significant) of $216 during the 12-month follow-up period.

### Discussion

With its faster onset and shorter duration of action compared to regular insulin, insulin lispro has demonstrated a decreased risk of severe hypoglycemia compared to regular insulin. Type 1 patients taking insulin lispro also report improved satisfaction with their treatment and its flexibility. This study sought to determine whether the use of insulin lispro would result in no additional health care costs (cost neutral) as compared to regular insulin therapy.

As anticipated, subjects at baseline who were treated with insulin lispro differed significantly from those treated with regular insulin. Insulin lispro subjects tended to be younger, use fewer oral hypoglycemics, were less likely to be a new insulin user, were more likely to be treated by an endocrinologist or pediatrician, had fewer comorbidities, received more preventive care (e.g. eye exams, diabetes education, HbA1c tests), and had fewer inpatient visits, pharmacy prescriptions, or laboratory tests during the 6 months prior to the study period as compared...
Cost and Utilization Comparisons Among Propensity Score-Matched Insulin Lispro and Regular Insulin Users

TABLE 3 Univariate Comparison of All-Cause Cost in Follow-up Period on Propensity Score-Matched Subjects

<table>
<thead>
<tr>
<th>Type of Cost</th>
<th>Lispro</th>
<th>Regular</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office visit</td>
<td>$822</td>
<td>$716</td>
<td>0.0237</td>
</tr>
<tr>
<td>Emergency visit</td>
<td>$185</td>
<td>$177</td>
<td>0.6433</td>
</tr>
<tr>
<td>Outpatient hospital</td>
<td>$1,008</td>
<td>$1,062</td>
<td>0.7077</td>
</tr>
<tr>
<td>Inpatient hospital</td>
<td>$1,741</td>
<td>$2,510</td>
<td>0.0277</td>
</tr>
<tr>
<td>Laboratory</td>
<td>$233</td>
<td>$251</td>
<td>0.4200</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>$2,244</td>
<td>$1,797</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total</td>
<td>$6,231</td>
<td>$6,511</td>
<td>0.5266</td>
</tr>
<tr>
<td>Total PPPM†</td>
<td>$519</td>
<td>$543</td>
<td>0.5266</td>
</tr>
</tbody>
</table>

* T test comparing lispro versus regular insulin for 1,832 subject-pairs. † Per-patient-per-month.

To an employer in an administrative services-only arrangement with health maintenance or preferred provider organization plans. Further research is necessary to determine whether the result of fewer hospitalizations would be corroborated over a longer follow-up period.

Limitations

While this study faced some limitations, we believe these limitations did not compromise the overall study findings. The following limitations should be observed when interpreting the study results. First, subjects were categorized as “insulin lispro” users if they had at least 1 lispro prescription during the subject identification period. Therefore, a subject could have switched therapy during the study period. However, <1% of regular insulin users filled a lispro prescription during the follow-up period, suggesting that alternative therapy did not attribute to outcomes observed during the follow-up period. Second, compliance with therapy was not measured and could account for some of the differences in outcomes. Third, because the 2 populations of subjects were quite different at baseline, the matching technique likely resulted in the pairing of a “sicker” lispro subject and a “healthier” regular insulin subject at baseline. However, this method also had the advantage of taking away much of the “noise” that would cloud true associations when starting with 2 populations that were very different. Fourth, the study design included prevalent insulin users. While prior insulin use was controlled for in the propensity score-matching procedure, it may be preferable to include only new users of insulin in future studies. Due to the relatively small number of lispro insulin subjects, both prevalent and incident insulin users were retained for study as a way to preserve sample size. Fifth, while propensity score matching can control for selection bias, it can only control for known or measurable confounders. As with many statistical techniques, residual confounding was still a possibility. Finally, this study used only 12 months of follow-up data and claims through December 31, 2000. It would be beneficial to repeat this study with more current data and also allow for a longer period of follow-up time. Studies such as the United Kingdom Prospective Diabetes Study and the Diabetes Control and Complications Trial determined patient outcomes for an average of 10 and 7 years, respectively.20,21

Future Research

Based on the study results, there are several possibilities for future research. First, further studies could examine only diabetes-related costs and utilization, as opposed to all-cause costs and utilization studied here, to determine whether the above relationships remain similar. Second, results could be examined separately for pediatric and adult populations. Differences in utilization patterns by treatment type may vary even within the pediatric population; the benefit of insulin lispro’s flexibility with regard to dosing and timing of meals may be far more beneficial in teenagers, a population prone to forgotten or otherwise
missed doses, as compared to children under 6 whose dosing may be closely supervised by a parent. Third, results could be stratified according to type 1 or type 2 diabetes status because of the differences in comorbidities and demographic characteristics, qualities that may influence their health-seeking behavior and treatment outcomes. Fourth, a longer follow-up period may better illuminate treatment differences particularly with regard to hospitalization. Continuous enrollment requirements for retrospective database studies often limit sample size. However, results could be reported for each subset of subjects enrolled 12 months, 24 months, 36 months, etc. Finally, the addition of laboratory data, such as HbA1c tests, may better explain why insulin lispro users had significantly less hospital utilization as compared to regular insulin users.

Conclusion

This study aimed to show that despite its higher total product cost, use of insulin lispro would be associated with total direct medical care costs similar to regular (human) insulin therapy. Findings from this study supported this supposition. We observed lower inpatient hospital expenditures during the 12-month study period, which appeared to offset the higher cost attributable to more intensive ambulatory patient care and the higher direct drug cost of lispro insulin. These results should be weighed by managed care organizations in the context of prior evidence from clinical trials of lower risk of severe hypoglycemia and dosing flexibility for patients who use insulin lispro.

ACKNOWLEDGMENTS

The authors would like to thank Pam Erickson, MS; John Holcombe, MD; and Scott Jacober, DO, CDE, for their helpful reviews of this paper.

DISCLOSURES

Funding for this study was provided by Eli Lilly & Company and was obtained by author Kent H. Summers, who is employed by Lilly. Author Robert L. Obenchain is also a Lilly employee and author of papers proposing and comparing alternative methods of propensity scoring. Author Jennifer A. Hall is an employee of Ingenix, which was contracted by Eli Lilly & Company to complete the research. Hall served as principal author of the study and was responsible for the analysis and interpretation of data and drafting of the manuscript. Study concept and design and critical revision of the manuscript were the work of Summers and Obenchain. Statistical expertise was contributed by Obenchain.

An abstract of this research was printed in Value in Health following a poster presentation at the May 2002 Annual International ISPOR meeting.

REFERENCES

Assessment of Clinical Pharmacist Management of Lipid-Lowering Therapy in a Primary Care Setting

L. TRAYWICK TILL, JR., PharmD; JOHN C. VORIS, PharmD; and JULIAN BOURNE HORST, PharmD

ABSTRACT

BACKGROUND: Pharmacists have been shown to positively impact the outcomes of care for treatment of many different kinds of disease states. In particular, pharmacist-run lipid clinics have enjoyed varying degrees of success, depending on the outcome assessed. At our hospital, when a patient is transferred to the pharmacist-coordinated lipid clinic, the primary care pharmacist is responsible for ordering and interpreting labs and prescribing and monitoring lipid-altering therapy.

OBJECTIVE: This study was designed to assess if there is a statistically significant difference between the magnitude of serum cholesterol reduction for patients receiving lipid-altering pharmacotherapy when clinically trained pharmacists are actively prescribing and adjusting the drug therapy compared to other health care practitioners (usual care).

METHODS: Patient records from the hospital computer databases were retrospectively and randomly selected for inclusion. Following evaluation for inclusions and exclusions, 41 patient records remained for statistical analysis for the cohort group, and 47 records remained from the group of patients managed by a clinical pharmacist.

RESULTS: Management of dyslipidemia by a clinical pharmacist was associated with a significant reduction in overall mean low-density lipoprotein (LDL, 18.5%) compared to the cohort that did not have a clinical pharmacist as the primary manager of dyslipidemia (6.5%, P=0.049). This suggests improved clinical outcomes, defined as greater LDL reduction, when clinical pharmacists participate in lipid management, including drug prescribing. The magnitude reduction in LDL was found to be related to the number of clinical pharmacy visits (11.4% for 1 visit, 23.2% for 2 visits, and 23.7% for >3 visits), compared to the usual care group (-11.0%, 18.0%, and 7.4%; statistically significant, P=0.038, for >3 visits only). These results occurred even though the group of dyslipidemic patients managed primarily by a clinical pharmacist contained a statistically greater number of patients with 2 or more risk factors and high-density lipoprotein (HDL) levels less than 40 mg/dL.

CONCLUSION: Interdisciplinary medical teams that include clinical pharmacists who are actively prescribing and adjusting lipid drug therapy may achieve greater reductions in LDL for patients who have been assessed with multiple risk factors compared to patients managed without clinical pharmacists. Active participation of clinical pharmacists in lipid management for patients with elevated LDL resulted in improved treatment success as measured by the magnitude reduction in LDL. The reduction in LDL was between 5% and 22% per visit greater for patients being treated by clinical pharmacists versus usual care, even in a patient population with more risk factors. These intermediate outcomes may translate into long-term outcomes in fewer cardiovascular events, improved quality of life for patients with dyslipidemia, and lower costs associated with sequelae of dyslipemias.

KEYWORDS: Pharmacist, Primary care, Lipid therapy, Dyslipidemia

Assessment of Clinical Pharmacist Management of Lipid-Lowering Therapy in a Primary Care Setting

L. TRAYWICK TILL, JR., PharmD; JOHN C. VORIS, PharmD; and JULIAN BOURNE HORST, PharmD

ABSTRACT

BACKGROUND: Pharmacists have been shown to positively impact the outcomes of care for treatment of many different kinds of disease states. In particular, pharmacist-run lipid clinics have enjoyed varying degrees of success, depending on the outcome assessed. At our hospital, when a patient is transferred to the pharmacist-coordinated lipid clinic, the primary care pharmacist is responsible for ordering and interpreting labs and prescribing and monitoring lipid-altering therapy.

OBJECTIVE: This study was designed to assess if there is a statistically significant difference between the magnitude of serum cholesterol reduction for patients receiving lipid-altering pharmacotherapy when clinically trained pharmacists are actively prescribing and adjusting the drug therapy compared to other health care practitioners (usual care).

METHODS: Patient records from the hospital computer databases were retrospectively and randomly selected for inclusion. Following evaluation for inclusions and exclusions, 41 patient records remained for statistical analysis for the cohort group, and 47 records remained from the group of patients managed by a clinical pharmacist.

RESULTS: Management of dyslipidemia by a clinical pharmacist was associated with a significant reduction in overall mean low-density lipoprotein (LDL, 18.5%) compared to the cohort that did not have a clinical pharmacist as the primary manager of dyslipidemia (6.5%, P=0.049). This suggests improved clinical outcomes, defined as greater LDL reduction, when clinical pharmacists participate in lipid management, including drug prescribing. The magnitude reduction in LDL was found to be related to the number of clinical pharmacy visits (11.4% for 1 visit, 23.2% for 2 visits, and 23.7% for >3 visits), compared to the usual care group (-11.0%, 18.0%, and 7.4%; statistically significant, P=0.038, for >3 visits only). These results occurred even though the group of dyslipidemic patients managed primarily by a clinical pharmacist contained a statistically greater number of patients with 2 or more risk factors and high-density lipoprotein (HDL) levels less than 40 mg/dL.

CONCLUSION: Interdisciplinary medical teams that include clinical pharmacists who are actively prescribing and adjusting lipid drug therapy may achieve greater reductions in LDL for patients who have been assessed with multiple risk factors compared to patients managed without clinical pharmacists. Active participation of clinical pharmacists in lipid management for patients with elevated LDL resulted in improved treatment success as measured by the magnitude reduction in LDL. The reduction in LDL was between 5% and 22% per visit greater for patients being treated by clinical pharmacists versus usual care, even in a patient population with more risk factors. These intermediate outcomes may translate into long-term outcomes in fewer cardiovascular events, improved quality of life for patients with dyslipidemia, and lower costs associated with sequelae of dyslipemias.

KEYWORDS: Pharmacist, Primary care, Lipid therapy, Dyslipidemia

A relationship between serum cholesterol and the pathogenesis of arteriosclerosis has been supported in many animal, genetic, and epidemiological studies as well as in clinical trials. Additionally, clinical trials that have evaluated the effect of cholesterol-reducing pharmacotherapy on coronary heart disease (CHD) have confirmed a causal relationship between cholesterol and CHD. Patients treated with lipid-lowering medications have increased from 5% in 1997 to 8% in 1999. The Framingham Study demonstrated the increasing risk of developing cardiovascular disease as related to low-density lipoprotein (LDL) elevation. The combined effects of elevated LDL with other nonlipid risk factors (cigarette smoking, hypertension, diabetes, low high-density lipoprotein [HDL] levels) are additive in their contribution to the development of CHD. Thus, it is essential that health care professionals effectively assess their patients for the presence of risk factors, especially LDL, and recommend treatments to reduce or eliminate these risk factors. Recommendations of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III) may be used as an evaluation and treatment guide by which health care professionals may assess and provide pharmacotherapeutic treatment for dyslipidemia, thereby reducing the patient’s potential of developing CHD.

Pharmacist-run lipid clinics are one way a health care organization can address the health needs of patients, and pharmacist intervention in the treatment of lipid disorders is an area of active research. A study by Simpson et al. showed that the 10-year risk of cardiovascular disease decreased from 17.3% to 16.4% during the 4 months patients were enrolled in a pharmacist intervention program. Bozovich et al. reported that greater numbers of patients seen in a pharmacist-managed lipid clinic (in conjunction with a cardiologist) achieved their LDL goal as compared to a cardiologist alone. Nola et al. showed that patients in a pharmacist-directed lipid management clinic achieved their cholesterol goals 32% of the time versus 15% of control patients. O'Donnell et al. found that 28 of 60 patients, not at LDL goal when referred to their pharmacist-coordinated lipid clinic, achieved the desired LDL goal after the intervention. The Primary Care Clinics of the William Jennings Bryan Dorn Veterans Administration Medical Center (WJBV) have attempted to build on the successful experiences of others with pharmacist-coordinated lipid clinics. The WJBV clinics provide care for approximately 35,000 veterans. An interdisciplinary medical team consisting of primary care physicians, nurse practitioners, physician assistants, and clinical pharmacists provide and direct care for this patient population. Clinical pharmacists at this facility have had prescriptive authority for more than 20 years.
When a patient is diagnosed with dyslipidemia, the health care providers of this team may use NCEP/ATP III recommendations to address lipid management (there is no mechanism to enforce adherence to a protocol). In most cases, recommendations for lifestyle modification (diet and exercise) are rendered unless immediate lipid-altering pharmacotherapy is indicated. When diet and exercise fail to reduce lipid levels to those recommended by NCEP/ATP III, patients are prescribed lipid-altering pharmacotherapy from a list of formulary approved lipid-altering medications.

This study was designed to assess the hypothesis that there is no statistically significant difference between the mean percentages in LDL reduction for patients receiving lipid-altering pharmacotherapy when clinically trained pharmacists are actively prescribing medications as compared to other health care practitioners.

Methods

Patients seen in the pharmacist-coordinated lipid clinic had their lipid-oriented care transferred to the clinical pharmacist. The pharmacist was responsible for ordering and interpreting laboratory values and for prescribing and monitoring lipid-altering pharmacotherapy: the “Clinical Pharmacist Management” cohort in this study. When a pharmacist was not involved, a physician, nurse practitioner, or physician’s assistant provided the patient’s lipid care: the “Usual Care” cohort in this study.

Patient records from the WJBD patient computer databases were retrospectively and randomly selected for analysis in this study. The patient information was extracted from these databases using data extraction protocols designed with the Fileman program. The first data extraction identified all primary care patients, regardless of the provider type, who received refill prescriptions for lipid-altering medications (HMG-CoA reductase inhibitors, niacin, fibrates, or bile acid sequestrants) during the 6-month period from July 1, 2001, through December 31, 2001. The results of this search included the patient’s name, social security number, name of the lipid medication, and service date of the refill prescription.

Following the removal of duplicate patient entries, 9,521 records remained for randomization. The patient records in this file were then randomly selected until 50 records were identified according to the following inclusion criteria for the Usual Care group: (a) patient <80 years and (b) patient’s record contains at least one progress note from a physician, nurse practitioner, or physician assistant that addressed lipid management in the SOAP (Subjective, Objective, Analysis, Plan) note format. The same inclusion criteria were used to identify 50 patient records for the Clinical Pharmacist group, except the medical record must have contained a pharmacy progress note addressing lipid management during the time period from July 31, 2001, to December 31, 2001, and had no clinical pharmacy

### Table 1: Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total Number of Patients for Both Samples</th>
<th>Number of Patients With</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Usual Care</td>
<td>Clinical Pharmacist Management</td>
</tr>
<tr>
<td>Number of charts evaluated</td>
<td></td>
<td>41</td>
<td>47</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>84 (95%)</td>
<td>40 (98%)</td>
<td>44 (94%)</td>
</tr>
<tr>
<td>Female</td>
<td>4 (5%)</td>
<td>1 (2%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 years old</td>
<td>7 (8%)</td>
<td>3 (7%)</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>≥50 years old</td>
<td>81 (92%)</td>
<td>38 (93%)</td>
<td>43 (91%)</td>
</tr>
<tr>
<td>Risk Factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 risk factors</td>
<td>2 (2%)</td>
<td>1 (3%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>1 risk factor</td>
<td>6 (7%)</td>
<td>5 (12%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>2+ risk factors</td>
<td>80 (91%)</td>
<td>35 (85%)</td>
<td>45 (96%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>74 (84%)</td>
<td>32 (78%)</td>
<td>42 (89%)</td>
</tr>
<tr>
<td>Age</td>
<td>83 (93%)</td>
<td>38 (93%)</td>
<td>45 (96%)</td>
</tr>
<tr>
<td>HDL&lt;40 mg/dL</td>
<td>48 (55%)</td>
<td>18 (44%)</td>
<td>30 (64%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>15 (17%)</td>
<td>6 (15%)</td>
<td>9 (19%)</td>
</tr>
<tr>
<td>Comorbid factors</td>
<td>Diabetes</td>
<td>35 (40%)</td>
<td>15 (37%)</td>
</tr>
<tr>
<td>Framingham</td>
<td></td>
<td></td>
<td>20 (43%)</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>16 (18%)</td>
<td>9 (22%)</td>
<td>7 (15%)</td>
</tr>
<tr>
<td>10%-20%</td>
<td>42 (48%)</td>
<td>18 (44%)</td>
<td>24 (51%)</td>
</tr>
<tr>
<td>For CHD</td>
<td>&gt;20%</td>
<td>30 (34%)</td>
<td>14 (34%)</td>
</tr>
<tr>
<td>Average levels at time of hyperlipidemia diagnosis</td>
<td>LDL (mg/dL)</td>
<td>128.7</td>
<td>137.8</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>48.0</td>
<td>43.4</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>211.3</td>
<td>224.0</td>
<td></td>
</tr>
</tbody>
</table>

* Statistically significant (z test), P < 0.05.
consult prior to the hyperlipidemia diagnosis. According to the research protocol at our institution, a code was assigned to each patient's record to ensure patient confidentiality by blinding researchers to actual patient names. (The VA policy on identifying patients is based on the U.S. Code of Federal Regulations [45CFR46.101(b)(4)], that says: “(4)...the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.”) For each patient record, the information in Table 1 was collected.

The data were then transferred into Microsoft Excel files for analysis. The numeric components of the data were collected at 2 points: at the time of the hyperlipidemia diagnosis and “most recent.” The data in both groups were reviewed for completeness. Because this information is essential for statistical analysis and comparison between the groups, incomplete patient records were excluded from statistical analysis. Following evaluation for numerical completeness, 41 patients records from the Usual Care group and 47 records from the Clinical Pharmacist group remained for statistical analysis (88 total records). The null hypothesis of this study was statistically evaluated to a confidence interval of 95% utilizing the \(z\) test. The data in which patients were divided into “Number of Consults” subgroups were analyzed via the \(t\) test. The 2-sample \(z\) test and its associated confidence interval is employed for inferences concerning the difference between 2 population means and should only be used when both \(n_1 \geq 30\) and \(n_2 \geq 30\). If one or both of the sample sizes is smaller than 30, then inferences are based on a \(t\) statistic. Small samples require more assumptions than large samples.

### Results

The data were analyzed to provide demographic descriptive information and statistical comparison of the patient groups (Table 1). For all patients in the Clinical Pharmacist group, the average decrease in LDL levels was 30.1 mg/dL, an average reduction of 18.5%. The average LDL reduction in the Usual Care group was 16.8 mg/dL, or 6.5%. Both of the decreases in the Clinical Pharmacist group (absolute and percent) as compared to the Usual Care group were statistically significant (\(P<0.05\), Table 2).

### Table 2: Lipid Values After Intervention

<table>
<thead>
<tr>
<th>Lipid Goals Achieved</th>
<th>Number of Patients</th>
<th>Total Number of Patients</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL at goal</td>
<td>24 (59%)</td>
<td>50 (57%)</td>
<td>NS</td>
</tr>
<tr>
<td>HDL &gt;40 mg/dL</td>
<td>23 (56%)</td>
<td>40 (46%)</td>
<td>0.037*</td>
</tr>
<tr>
<td>Triglycerides &lt;200 mg/dL</td>
<td>28 (68%)</td>
<td>65 (74%)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean LDL (mg/dL)</td>
<td>41 (111.9)</td>
<td>47 (107.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean HDL (mg/dL)</td>
<td>41 (43.4)</td>
<td>47 (37.7)</td>
<td>0.019†</td>
</tr>
<tr>
<td>Mean total cholesterol (mg/dL)</td>
<td>41 (192.2)</td>
<td>47 (175.0)</td>
<td>0.021†</td>
</tr>
<tr>
<td>Mean % reduction in LDL</td>
<td>41 (6.5%)</td>
<td>47 (18.5%)</td>
<td>0.049†</td>
</tr>
<tr>
<td>Mean absolute LDL reduction (mg/dL)</td>
<td>41 (16.8)</td>
<td>47 (30.1)</td>
<td>0.048†</td>
</tr>
</tbody>
</table>

* Statistically significant \((z\) test); \(P<0.05\)
† Statistically significant \((t\) test); \(P<0.05\)

### Table 3: Change in Lipid Values After Clinical Pharmacist Intervention

<table>
<thead>
<tr>
<th>Number of Consults</th>
<th>Usual Care [Number of Patients]</th>
<th>Clinical Pharmacist Management [Number of Patients]</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute LDL reduction</td>
<td>4.6 (52.5) [9]</td>
<td>18.2 (27.6) [19]</td>
<td>NS</td>
</tr>
<tr>
<td>in mg/dL (SD)</td>
<td>28.6 (28.4) [12]</td>
<td>37.7 (35.9) [17]</td>
<td>NS</td>
</tr>
<tr>
<td>≥3</td>
<td>15.3 (34.2) [20]</td>
<td>39.5 (33.2) [11]</td>
<td>0.021</td>
</tr>
<tr>
<td>% LDL reduction (SD)</td>
<td>-11.0 (68.6) [9]</td>
<td>11.4 (23.3) [19]</td>
<td>NS</td>
</tr>
<tr>
<td>≥2</td>
<td>18.0 (24.4) [12]</td>
<td>23.2 (22.3) [17]</td>
<td>NS</td>
</tr>
<tr>
<td>≥3</td>
<td>7.4 (25.1) [20]</td>
<td>23.7 (19.0) [11]</td>
<td>0.038</td>
</tr>
</tbody>
</table>

*Statistically significant \((z\) test); \(P<0.05\)
tion was significantly lower ($P=0.021$) for the Clinical Pharmacist group even though the Usual Care group started with a lower absolute serum level of total cholesterol; the relative medical complexity of the patients in the Clinical Pharmacist sample was higher compared to the Usual Care sample. In the Clinical Pharmacist group, there was a significantly greater percentage of patients with 2 or more major risk factors ($P=0.046$) and patients with $<40$ mg/dL HDL levels ($P=0.031$). The Clinical Pharmacist group had a greater prevalence of other risk factors: age (3%), hypertension (11%), smoking (4%), and diabetes (6%).

Table 3 and Figures 1 and 2 show the data for each group as a function of the number of consults. When the data were subdivided into “number of consults,” statistical significance was only achieved between the $>3$ consult groups. The 1 and 2 consult groups did not achieve statistical significance due to low patient numbers and large standard deviations. In general, LDL serum levels were decreased between 5.2% and 22.4% per visit as compared to the group with no clinical pharmacist involvement.

Although the achievement of the NCEP/ATP III LDL goal appeared slightly less common when clinical pharmacists are involved in lipid management—55% versus 59% of patients—this difference in LDL goal achievement was not statistically significant ($P=0.38$). Postintervention HDL levels were significantly lower ($P=0.019$) in the Clinical Pharmacist group although each group's HDL levels decreased about 5 mg/dL.

The null hypothesis that there is no statistically significant difference between the LDL reductions for patients receiving lipid-altering pharmacotherapy when clinically trained pharmacists are actively prescribing medications as compared to other health care practitioners was rejected. This result demonstrated that a significant difference exists between the mean LDL reductions of the Clinical Pharmacist and Usual Care patient groups. This suggests improved results, defined as greater LDL reductions, when clinical pharmacists participate in lipid management.

**Discussion**

Pharmacist involvement in a variety of primary care clinics is increasing in frequency. Studies have shown pharmacists to be successful in several aspects of lowering a patient's cholesterol. Gee et al. found that splitting tablets of HMG-CoA reductase inhibitors was an effective way to reduce costs while having a favorable effect on clinical and service (satisfaction) outcomes. Gerber et al. found 85% of patients in a pharmacist-managed clinic achieved an LDL value of less than 105 mg/dL. Bozovich et al. reported that 69% of patients achieved LDL goals in their pharmacist-run clinics (in conjunction with a cardiologist), and Cording et al. showed that 77% of pharmacist-managed patients achieved LDL goal. Our study complements this previous work, with a somewhat lower overall achievement of LDL goal: 55% of patients in the intervention group. However, there was a statistically significant difference in the absolute and percent reduction of LDL and total cholesterol levels after intervention between the group managed by clinical pharmacists and the control group that did not involve clinical pharmacists in primary management of dyslipidemia.

Our study confirms the favorable impact on LDL reduction when clinical pharmacists are active participants in the interdisciplinary medical team. The patients in the Clinical Pharmacist group had a higher level of disease complexity (i.e., more patients with 2 or more risk factors and $<40$ mg/dL HDL) compared to the Usual Care group. The reason for the more complex patient being referred to the lipid clinic and clinical pharmacists is unknown, but it may be related to provider confidence in the ability of clinical pharmacists to have a favorable effect in lipid management of higher-risk patients.
Assessment of Clinical Pharmacist Management of Lipid-Lowering Therapy in a Primary Care Setting

Limitations

This was a retrospective analysis that did not have an equal number of patients in the 2 comparison groups. If we had replaced patients not fulfilling the numerical completeness criteria, we would have increased the power of our study. Instead of 100 evaluable patients, we had 88. Additionally, when patients were divided into groups based on number of visits, the number of study subjects was reduced further. We only evaluated lipid profiles at 2 points: at the time of the hyperlipidemia diagnosis and the “most recent” point and, therefore, could not show incremental changes for each patient. We did not record the amount of clinic time spent by the pharmacist versus nonpharmacist on each patient visit. Perhaps the LDL reductions were due to a patient perception of a more caring experience by virtue of the number of minutes spent in the health professional’s office, causing them to try harder to lower their cholesterol. We did not conduct cost studies to evaluate dollars per visit or dollars per percent of LDL reduction. Lastly, we did not assess if the LDL reduction was due to factors other than the profession of the individual providing care, such as compliance, patient knowledge of diet, or drug selection.

Conclusion

There is significant potential for clinical pharmacists to contribute to improvement in the efficiency and effectiveness of pharmacotherapy in patients with dyslipidemia. As demonstrated in this study, interdisciplinary medical teams that include clinical pharmacists in lipid management realize greater reductions in LDL for patients who have been assessed with multiple risk factors compared to patients without clinical pharmacist management of dyslipidemia. Active participation (including prescribing) by clinical pharmacists in lipid management for all patients with elevated LDL results in improved intermediate outcomes in the achievement of NCEP/ATP III lipid goals. These intermediate outcomes may result ultimately in reduced long-term cardiovascular events and an improved quality of life for patients with dyslipidemia as well as reduced long-term costs associated with sequelae of dyslipidemia. Increased treatment efficiency in the management of dyslipidemia by clinical pharmacists may permit providers to address and manage other aspects of their patients’ health.

References


Acknowledgments

References and tables were provided by all authors.

Disclosure

No outside funding supported this study. Authors L Traywick Till, Jr., John C. Voris, and Julian Bourne Horst were employed by the federal government at the time this work was prepared. Till served as principal author of the study and contributed statistical expertise. Study concept and design, analysis and interpretation of data, and drafting and critical revision of the manuscript were provided by all authors.
The Blue Cross and Blue Shield Association sponsored a 400-page report released in October 2002 that concluded that 19% of the increase in hospital costs between 1998 and 2001 was attributable to medical technology and 18% to hospital consolidation. The Federation of American Hospitals, which represents 1,700 for-profit hospitals, responded by planning its own study of health care cost drivers, with a specific focus on insurance premiums. No doubt that both organizations will produce credible data. Observers will be left to interpret the data to find the truth.

A report released in July 2000 by the National Institute for Health Care Management (NIHCM) Research and Education Foundation found that the average patent life of new drug approvals in the middle 1980s until the present was effectively 13 to 15 years as a result of 6 laws enacted between 1983 and 1997 that strengthened the patents of brand drugs, extended their period of exclusivity, or eased the transfer of government discoveries to pharmaceutical companies. The report was critical of these federal protections that reduced generic drug competition, increased consumer prices, and helped make the drug industry the most profitable industry in the United States. NIHCM also found that 64% of “new” drug approvals were actually reformulations of existing drugs or combinations of existing drugs. The NIHCM study in 2000 was followed by a study released in May 2002 that found only 361 (35%) of 1,035 new drugs approved by the U.S. Food and Drug Administration from 1989 through 2000 to be new molecular entities. The other 674 “new” drugs were existing drugs or modified versions of existing drugs. Only 153 drugs (15%) were designated as “highly innovative drugs.” Both studies were shots across the bow of the branded name pharmaceutical industry, represented by the National Pharmaceutical Council (NPC) and the Pharmaceutical Research and Manufacturers of America (PhRMA). NIHCM is funded largely by Blue Cross and Blue Shield health plans.

NIHCM has needled PhRMA and NPC in other ways. NIHCM reports in 1999 and 2002 attributed more of the large cost trend in prescription drug spending by health plans to “price” rather than to utilization. The July 9, 1999, report, “Factors Affecting the Growth of Prescription Drug Expenditures,” prepared by Barents Group LLC for NIHCM, found that total spending on prescription drugs increased by an average annual 11% in the 5-year period from 1992 to 1997, twice the 5.5% average annual increase for total health care spending. There was also acceleration in the increase in prescription drug spending, rising 8.7% in 1993, 9.0% in 1994, 10.6% in 1995, 13.2% in 1997, and 18.4% in 1998. This report pointed the finger at the drugs most heavily advertised to consumers as a major source of the increase in drug spending. The 1999 report from NIHCM was followed by the May 2001 report, “Prescription Drug Expenditures in 2000: The Upward Trend Continues,” in which the 18.8% increase in outpatient prescription drug spending was attributed 42% to “an increase in the number of prescriptions dispensed,” in other words, utilization, and 58% to increase in “price,” distributed 22% (about one third) to the “price of individual drugs” and 36% to “the shift in the mix of drugs dispensed.” The May 2002 report from NIHCM, “Prescription Drug Expenditures in 2001: Another Year of Escalating Costs,” attributed the 17.1% increase in drug spending in 2001 to a 39% “increase in the number of prescriptions,” 37% to “price increases,” and 24% to a “shift to higher-cost drugs.” So, NIHCM attributed 58% of the 18.8% cost trend for prescription drugs in 2000 to price and 61% of the 17.1% cost trend in 2001 to price.

In this issue of the Journal, Gilberg, Laouri, Wade, and Tsonaka examined drug utilization as determined from dispensing records (drug claims) in patients with medical claim diagnoses for asthma, congestive heart failure, depression, or common cold/upper respiratory tract infection. Along the way, the authors claim that “utilization” is the major driver for drug cost trends and, hence, the need for more examination of drug utilization patterns in the United States. Readers should note that this study was funded by the National Pharmaceutical Council, a champion of policy and interests of brand-name prescription drug manufacturers.

This battle between PhRMA/NPC and NIHCM regarding price versus utilization as the drivers of the prescription drug expenditure trend is no small matter, with barrages from both sides. Some of the back-and-forth can be reviewed at www.nihcm.org, including “The NIHCM Foundation Responds to PhRMA’s Criticisms of the Report, ‘Changing Patterns of Pharmaceutical Innovation.’” One line of thinking appears to assume that prescription drug utilization is de facto medically necessary. If one makes this assumption, then the next argument is that any effort to reduce drug spending could have adverse health consequences, if utilization is, in fact, a sufficiently large percentage of the increase in drug spending. The third argument in this line of thinking is that price controls will not have much influence on total drug spending if price is a relatively small portion of the trend in drug spending. But NIHCM attributed 58% of the 18.8% cost trend for prescription drugs in 2000 to price and 61% of the 17.1% cost trend in 2001 to price. These findings have been supported by the work of others, including pharmacy benefit manager Express Scripts, which found 63% of the 16.9% cost trend in prescription drugs in 2001 to be attributable to price. Therefore, these 2 data sources showed utilization to account for 37% to 39% of the approximate 17% increase in prescription drug spending in 2001.

It is also important to take a temporal perspective of the price versus utilization debate in total prescription drug spending. In the trenches of drug benefit management in 2001-2003, price appears to be maintaining its prominent and dominant position, compared to utilization. Based on data in the IMS Health summary report released in February 2003, prescription drug sales in the United States in 2002 rose by 11.7%, from $172.0 billion in...
2001 to $192.2 billion.\textsuperscript{11} Drug price inflation for existing drugs was 4% in 2002, twice the inflation rate in the general economy and more than one third of the total 11.7% increase in drug spending. Utilization as measured by the volume of prescriptions accounted for less than 40% of the increase in total sales. Drug “mix,” defined as the use of newer, higher-cost drugs, accounted for the balance of the drug cost trend in 2002. In other words, inflation in prices of existing drugs, utilization, and the drug “mix” each accounted for about one third of the total increase in prescription drug spending in 2002.

Data from Verispan Scott-Levin for community pharmacy sales in calendar year 2002 show a more remarkable influence of price versus utilization in prescription drug sales. These data, based on prescriptions dispensed in 36,000 chain and independent pharmacies, mass-merchandisers, deep-discounters, and food stores, showed a 10% increase in prescription drug sales in 2002 to $166.66 billion, contributed 95% by price and about 5% by utilization.\textsuperscript{12} The average prescription price increased by 9.5% to $54.57 in 2002, and volume increased 0.4% to 3.054 billion prescriptions.

Yet, the commonly accepted measure of utilization of prescription drugs, the prescription dispensed, has flaws, and the drug industry position, as presented by NPC and PhRMA, has merit in this regard. Unreported in the summary data for community pharmacy is the “size” of the average prescription as measured in days of therapy. Second, the relative growth in mail-order pharmacy is the “size” of the average prescription as measured in days of therapy. The customary mail-order prescription is nearly 3 times the size of the average prescription dispensed by community pharmacy, and a more precise measure of “utilization” would appear to be number of days of therapy rather than the number of prescriptions. At the least, this alternate measure of days of therapy would provide additional information about the trend of increased utilization of prescription drugs.\textsuperscript{13} Mail-order pharmacy accounted for about 120 million prescriptions and $8.5 billion in sales in 1995, or about 10% of the total pharmaceutical market.\textsuperscript{14} Mail-order pharmacy had an average annual growth rate of 20% over the 8-year period ended June 30, 2001, accounting for 16% of all prescription drug dollars in 2001.\textsuperscript{15} Data from IMS Health showed that mail-order pharmacy accounted for 17% of the prescription drug market in calendar year 2001 as measured by “retail” pharmacy sales (versus manufacturer sales).\textsuperscript{16} This growth in mail-order pharmacy as a percentage of total “retail” pharmacy sales would cause the prescription as a measure of utilization to understate the actual increase in utilization of prescription drugs and as a percentage of the total increase in prescription drug spending in the United States.

The proliferation of generic drug alternatives in the treatment of depression, heartburn, hypertension, and other important therapeutic categories increases the opportunities for managed care pharmacy to blunt the cost trend in prescription drugs. Overall, much of the opportunity appears to be unfulfilled. For example, the top 2 drugs by total spending in 2002 were atorvastatin at $6.1 billion and simvastatin at $4.2 billion, up 19% and 16% from 2001, respectively. Both are brand drugs for treating dyslipidemia, a condition treated effectively in most patients by generic lovastatin at about 75% to 85% discount to the cost of the brand drug alternatives. Two of the other top 10 drugs in 2002 were sertraline at $2.5 billion and paroxetine at $2.3 billion, up 14% and 11% from 2001, respectively. These 2 drugs are therapeutic alternatives to generic fluoxetine, which has a managed care price about 90% less than sertraline or paroxetine. Stated in terms of population health, generic fluoxetine can treat about 10 patients with depression for the same managed care cost as treating 1 patient with either sertraline or paroxetine. Generic lovastatin can treat about 5 patients with dyslipidemia for the same managed care cost as 1 patient treated with simvastatin and about 4 patients with dyslipidemia for each patient treated with atorvastatin.

\textbf{Real-World Research in Diabetes Care and Protocols for Patient Privacy}

Two articles in this issue of the \textit{Journal} derive from research in Veteran Affairs (VA) medical centers. Aside from the obvious predominance of males in these study populations, readers might also note the possibility of alternate explanations for the study findings in the effectiveness research in diabetes care by Duckworth, Marcelli, Padden, et al., using combination glyburide-metformin versus separate formulations of metformin and sulfonylurea.\textsuperscript{17} In this pre/post study of patients switched from separate sulfonylurea and metformin to combination glyburide-metformin, there was a significant increase in (a) the number of patients who received insulin (on separate sulfonylurea and metformin), from 5 (6.9%) in the preperiod to 19 (26.4%; \textit{P}=0.0001) in the postperiod; (b) the number of patients who received additional oral antidiabetic agents, from 6 (8.3%) in the preperiod to 15 (20.8%; \textit{P}=0.04) in the postperiod; and (c) the mean dose of metformin, from 1,607 mg in the preperiod to 1,750 mg in the post period (\textit{P}=0.02). These factors create alternative explanations for the 0.6% improvement in hemoglobin A1C (\textit{P}=0.002) at a mean follow-up of 196 days after the switch to combination glyburide-metformin tablets.

This study of combination glyburide-metformin suggests that there may be some synergy in the formulation of the combination product that is not explained by the simple addition of the 2 products, noting the possible alternate explanations for the findings. Also, there was a remarkable increase in the number of patients who experienced clinically significant hypoglycemia in the postswitch period, on the combination glyburide-metformin product. Eight patients experienced clinically significant hypoglycemia in the postperiod on the combination product versus 3 patients who experienced hypoglycemia in the preswitch period. This outcome may be related more to the significant increase in the number of patients who received concomitant insulin in the postswitch period rather than being attributable to the combination glyburide-metformin product.
These 2 studies in VA medical centers, the study by Till, Voris, and Traywick and the study by Duckworth, Marcelli, Padden, et al., are published at a time when the VA is undergoing a thorough review of its medical research protocols. Results released in mid-March 2003 of investigations performed by the VA inspector general showed that “one or more patients” died due to falsified data at one VA research site, another patient received an overdose of a drug under study at a separate site, and there were 2 instances in 2 other VA medical centers in which a researcher did not have proper credentials and another in which an ethics board did not meet “even minimal standards” for safeguarding patients.19 The VA conducts more than 15,000 research studies involving about 150,000 patients in a program that will cost $1.3 billion in fiscal year 2003. The VA was conducting a 90-day review of its clinical research practices at the 115 VA medical centers throughout the United States, a review process that was expected to be completed by early June 2003. The 90-day review was ordered by a memo signed by 2 deputy undersecretaries for health that was dated March 6, 2003, and warned that principal researchers at the VA centers “will be held responsible for ethical breaches in the conduct of their research.”19

Till, Voris, and Traywick noted in their article in this issue of the Journal that according to the research protocol at their VA institution, a code was assigned to each patient’s record to ensure patient confidentiality by blinding researchers to actual patient names. The VA policy on identifying patients is based on the U.S. Code of Federal Regulations (CFR) 46.101(b)(4), that says: “(4) ...the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.” This language is consistent with the “final rule” published February 20, 2003, to implement the patient privacy and security standards of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).20 Patient records that are de-identified are no longer protected health information. HIPAA rules regarding the approval of research by a review board and confidentiality and privacy rights for access to medical records are covered in the Privacy Rule.21

Also in this issue of the Journal, Hall, Summers, and Obenchain argue that the higher drug product cost for human insulin lispro (Humalog, Lilly), similar to human insulin aspart (Novolog, Novo Nordisk), is offset by apparent savings in other medical costs. This is a worthwhile debate, and the argument is of great interest to managed care pharmacists even if the extent study findings do not seem to be compelling to some observers; i.e., are short-term savings in hospital costs predictable from the use of human insulin lispro versus regular human insulin? Human insulin lispro commands a higher price (direct drug cost) of more than 2 times the price of regular human insulin because it provides additional benefits to users in the form of greater flexibility in dosing associated with its very rapid onset of action, making it possible to be injected immediately before meals. To noninsulin users, this may seem a minor point, but the faster onset of action reduces some of the demand made on patients with type 1 diabetes mellitus, and those with type 2 disease who require insulin, that stem from the incessant need for careful meal planning and timing of insulin administration. Numerous clinical studies have shown significant improvements in postprandial glycemic control and some evidence of reduced rates of severe or nocturnal hypoglycemia compared to conventional human insulin.21 Quality-of-life studies show consistent preferences by patients for and increased treatment satisfaction with insulin lispro over regular human insulin, as measured by the disease-specific Diabetes Treatment Satisfaction Questionnaire22 and the more general health-related quality-of-life instruments.23 Readers may find additional guidance regarding effective methods for managing diabetes care and avoiding adverse events in the supplement to this issue of the Journal.23

JMCP Award for Excellence

The JMCP Award for Excellence was created in 2002 to recognize the best article published each year in JMCP according to criteria that included originality, scientific merit, timeliness of the topic, relevance to managed care pharmacy, quality of the writing, and the potential impact on the profession or knowledge of managed care pharmacists.24 The inaugural award was presented in April 2003 to Doctors Michael Gee, Noelle Hasson, Terri Hahn, and Russell Ryono for their research in the management of dyslipidemia among patients at a Veterans Affairs medical center in northern California.25 The article by Gee, Hasson, Hahn, and Ryono reported research that measured clinical, service, and cost outcomes of pharmacist interventions with managed care patients. Conducted prior to the market introduction of generic lovastatin, the researchers found that tablet splitting of hydroxymethylglutaryl-CoA reductase inhibitor (HMG) drugs was associated with favorable clinical (laboratory) outcomes (i.e., a statistically significant, but perhaps not practically significant, decrease in low-density lipoprotein [LDL] after tablet splitting and favorable compliance with tablet splitting) and humanistic-service outcomes (patient satisfaction) while creating the opportunity to treat nearly twice as many patients for the same cost.

Frederic R. Curtiss, PhD, RPh, CEBS
Editor-in-Chief

REFERENCES


Dear Editor,

We read with interest the article by Fivenson and colleagues1 on the total burden of illness associated with atopic dermatitis. The study is important in that it provides a perspective from payer costs to individual productivity. We agree with their conclusion that atopic dermatitis “imposes a financial burden on the health care system.”

Using a claims-based approach that included comorbidities associated with atopic dermatitis and eczema, we estimated direct payer costs within a managed care population to average $580 per patient per year (n=35,000),2 significantly higher than the $167 per patient per year (n=298) found by Fivenson et al.

The difference in annual direct payer cost per patient appears mainly to be the result of different cost-accounting methods. We incorporated costs for comorbid conditions; the validity and accuracy of our use of expert opinion to incorporate disease comorbidities were confirmed in a separate report.3 It appears that Fivenson et al. included direct costs only if they could be tied directly to atopic dermatitis. Although data in the 2 studies are not directly comparable, direct costs in Fivenson et al. are in the range of those in our study if costs for comorbid conditions that we examined are excluded.

Other factors might also explain the disparate results. First, we included patients with eczemas as well as atopic dermatitis; however, we would surmise that the average annual direct payer cost would be even higher than $580 if we restricted our study to patients with atopic dermatitis, which is often chronic and difficult to treat. Second, Fivenson et al. report that 7% to 12% of their patients had severe disease. Yet, a recent report estimates the prevalence of severe disease in atopic dermatitis to be 16% of patients.4 Therefore, average annual direct costs likely would have been higher if more severe patients were included.

Regardless, the study by Fivenson et al. is particularly valuable because it quantified various costs associated with atopic dermatitis including out-of-pocket expenses and productivity. Those costs were obtained by survey of patients and families who, although asked about “eczema,” may not ascribe their time and expenses so specifically; therefore, those costs may, in fact, include the effects of at least some comorbidities. Thus, an annual cost burden of $1,022 per patient with atopic dermatitis may be a conservative total (using our total of $580 for payer direct costs plus the Fivenson et al. total of $442 for out-of-pocket expenses and productivity). In addition, neither study attributes a cost to patients’ decreased quality of life. Thus, we still have not captured completely the financial burden of having atopic dermatitis, which is indeed substantial. Further research will be required to fully understand the burden of illness as well as the cost-effectiveness of patient management and intervention programs.

Charles N. Ellis, MD, Professor of Dermatology University of Michigan Medical School, Ann Arbor

The Authors Respond

We thank JMCP for the opportunity to comment on the letter by Ellis and colleagues in response to the recent publication of our study.1 We concur that it is difficult for patients to specifically ascribe their out-of-pocket costs to atopic dermatitis (AD). However, since our study showed that approximately 50% of the total burden of illness associated with AD resulted from days lost from work, it is most important that the patient’s perception of his or her illness, in addition to the health care provider’s perception, be taken into consideration. We admire Ellis et al.’s examination of 35,000 claims and understand their use of comorbidities in their evaluation, especially since one of the most common comorbidities in our population (occurring in approximately 8% of our prospective cohort) was “dermatitis not otherwise specified.” However, we, too, examined the population over a 3-year period (n=6,609) and found mean annual per-patient direct expenditures ranging from $123 (in 1995) to $128 (in 1997). Therefore, the $167 per-patient-per-year direct expenditure we found would not appear to be an artifact of our relatively smaller sample size. Certainly, as we have found, it is important to directly query a representative sample of the dataset to gain an understanding of the error inherent in claims analyses.2

Moreover, we used different insurance systems and not stan-

Mary M. Prendergast, MBA
Fujisawa Healthcare, Inc., Deerfield, Illinois
Michael Tokar, MS
Quorum Consulting, Inc., San Francisco, California
Kuo Tong, MS
Quorum Consulting, Inc., San Francisco, California
E-mail: cellis@med.umich.edu

REFERENCES
dard costs applied to health care resource use. The Ellis manu-
script is not very transparent on how costs were attributed
except that a panel determined it. They may have attributed
costs to AD/E based on ICD-9 codes other than those we used.
Furthermore, we most probably used a different method of
assessing severity than the method used in the international
study cited. Also, we included individuals with private insurance
in our study; thus, our study population probably had different
characteristics from the sample used in the ISAAC study. Therefore, it is
difficult to compare our findings to those of Ellis et al.

Lastly, our previous analyses did attempt to quantify the
effects of this illness on quality of life.\textsuperscript{1,4} Indeed, using Pearson
correlation coefficients, we found that visit count correlated
moderately well with the results of the Dermatology Life
Quality Index ($r=0.33$; $P=0.0006$).

Taken together, all of our results, in concert with those of Ellis
and colleagues, would indeed indicate that AD might impose a
significant financial and humanistic burden on society.

David Fivenson, MD
Joel L. Cohen, MD
Department of Dermatology,
Henry Ford Hospital, Detroit, Michigan

Renee J. Goldberg Arnold, PharmD
Diana J. Kaniecki, PharmD
Pharmacon International, New York, New York

Email: rarnold@pharmacon.com

REFERENCES

1. Fivenson D, Arnold RJG, Kaniecki DJ, Cohen JL, Frech F, Finlay A. The
effect of atopic dermatitis on total burden of illness and quality of life on
adults and children in a large managed care organization. J Managed Care

2. Arnold RJG, Kotsanos JG. Proceedings of the Advisory Panel Meeting and
Conference on Pharmacoeconomic Issues: Panel 3: methodological issues in
conducting pharmacoeconomic evaluations—retrospective and claims data-

Relationship between quality of life, disease severity and physician visits
1998;1:45.

4. Finlay AY, Cohen J, Pettit K, Fivenson D. Quality of life in atopic dermati-
tis. Presented at: American Academy of Dermatology 57th Annual Meeting;
March 19-24, 1999, New Orleans, LA.
are now recognized as the most important clinical and pharmacoeconomic endpoints.9

Neither of these endpoints has been consistently reported in the clinical-trial literature.5,9 Two recent meta-analyses have attempted to evaluate them. In a meta-analysis of 24-hour sustained relief,5 only 3 of the currently marketed triptans (rizatriptan 10 mg, sumatriptan 50 mg and 100 mg, and zolmitriptan 5 mg) were included. At the time this meta-analysis was performed, the other triptans did not have published data available on sustained relief. In a separate meta-analysis that evaluated 24-hour sustained pain-free response, all but one of the triptans (frovatriptan) were included.6 However this endpoint could only be calculated for some of the 53 trials that were identified for the primary meta-analysis; the actual number of trials included is not reported. Therefore it would not be appropriate to make comparisons across the entire triptan class based on either of these meta-analyses.

It is currently not reasonable to undertake a single endpoint meta-analysis in order to determine relative cost-effectiveness of the triptans. In addition, the cost of adverse events should be included. Some triptans have higher adverse-event rates than others.7 A sensible approach to cost-effective migraine treatment requires stratification based on the patient’s migraine history and particular attack characteristics. Patients with short-duration migraine do well using triptans that deliver freedom from pain within 2 hours. Patients who are more susceptible to recurrence and adverse events might find it more cost effective to use triptans with less recurrence and fewer adverse events.

Stephan D. Silberstein, MD, FACP
Professor of Neurology, Jefferson Medical College of Thomas Jefferson University
Director, Jefferson Headache Center, Philadelphia, Pennsylvania
Email: Stephen.Silberstein@mail.tju.edu

REFERENCES


The Authors Respond

We thank Dr. Silberstein for his carefully constructed comments regarding our article on the relative cost-effectiveness of triptans.1 His criticism of the piece offers some interesting notes concerning the methodology of cost-effectiveness analyses.

Silberstein writes that our paper is “misleading” due to “an oversimplified analysis of cost-effectiveness.” His argument rests on 3 pivots: (a) the choosing of an inappropriate endpoint, (b) the excluding of recurrence rates, and (c) the ignoring of adverse events. Responding to these points will allow us to clarify our methodological motivations.

Silberstein criticizes the choice of the 2-hour pain-free endpoint, the industry standard. It does not take into account recurrence, the return of a moderate or severe headache within 24 hours.2 Recurrence, as Silberstein points out, is a persistent problem from the perspective of effectiveness of treatment as well as cost.

Recurrence data derived from randomized controlled trials should be used with caution. Although comparing recurrence rates appears to offer clinically useful information, the lack of a consistently used definition of recurrence invalidates such comparisons. Recurrence figures also tend to be derived from a selected subset of patients—those who initially responded to treatment—rather than the entire intention-to-treat population.3 The resultant corruption of randomization means that any conclusions will be prone to significant bias.4

Silberstein suggests using the “24-hour sustained pain-free-domain” endpoint instead of 2-hour pain free. We agree that the 24-hour data is a quality gauge of sustained migraine relief. We explained in the original paper, “The endpoint of ‘24-hour sustained pain free’ could also have been used in this meta-analysis. It would have produced data similar to the ‘pain-free’ data presented.”1 We based this statement on the strong correlation (R2=0.89 for Ferrari’s meta-analysis6 between the 2 endpoints.

Unfortunately, sustained response only constitutes a primary outcome measure in a very small number of triptan studies. Estimates of these rates found in the literature generally relate to post hoc analyses of previously published data rather than results derived from primary data gathering.7 The potential for bias is therefore considerable.4 Although Ferrari’s analysis confirms a strong concordance between these 2 outcomes, when examining older studies, the 2-hour response offers the more statistically rigorous results.

Recently, Reeder conducted a cost-effectiveness study based on the 24-hour sustained pain-free endpoint, which confirmed our prediction of parallel cost-effectiveness for the 2 endpoints.6 In both studies, almotriptan and rizatRIPTAN were the most cost effective, while naratriptan was the least cost effective (among the triptans included in both; frovatriptan did not have published 24-hour sustained pain-free data).

Reeder’s analysis indicates that sustained pain-free status depends more heavily on response than on recurrence. Lack of initial effect, therefore, would be expected to cause more multi-
ple dosing than would recurrence. Pascual’s triptan per-attack study verifies this idea. His results indicate that rizatriptan, with its large response rates, has a significantly lower incidence of attacks treated with multiple tablets than does sumatriptan, zolmitriptan, and naratriptan in spite of relatively high recurrence rates.

Simply, recurrence is a poor endpoint. We would recommend that studies not report recurrence rates; instead, they should use 24-hour sustained pain relief or 24-hour sustained pain free to indicate the long-term efficacy of acute medications.

Like recurrence, adverse events were not included in the original analysis because they do not clarify or alter the cost-effectiveness of the medications. In addition, it would not have been statistically valid to include the measure in our analysis. No published triptan study has measured adverse events as a primary outcome. Although it is certainly possible to pool such data as exists in order to define a “number needed to harm,”4 inconsistent recording of adverse events and very wide confidence intervals mean that these findings are of limited value when comparing alternative treatments.

Triptans are consistently well tolerated.8 Most adverse effects are mild and have no related costs. Even the once-feared side effects of neck and chest tightness do not trigger cardiac evaluation as they once did. These side effects are not thought to be related to cardiac events.

There seems to be no correlation between the adverse effects and safety of triptans, nor is there any evidence of safety differences among triptans. The impact of side effects on cost is inconsequential compared to migraine disability considerations.

To conclude, we chose the 2-hour pain-free data because it was the industry standard,10 matched the desires of patients,11,12 mirrored 24-hour sustained pain-free results,9 and minimized the risk of introducing bias into our conclusions.5 Including recurrence rates and adverse events in the analysis would not have significantly altered the results, only added complicating factors. Again, we thank Dr. Silberstein for his comments.

James U. Adelman, MD
Jonathan Belsey, MBBS
Leon C. Adelman, BA
Headache Wellness Center,
Greensboro, North Carolina
Email: jadelman@triad.rr.com

REFERENCES

---

Provider Perspective on HIPAA

Dear Editor,

I had some thoughts about the Health Insurance Portability and Accountability Act of 1996 (HIPAA) subsequent to the recent article1 and editorial1 in the Journal. There are real and presumably unintended consequences of the HIPAA statute and regulations.

I was looking for a new car. I decided to be patriotic and avoid German cars—the Russians and French long ago sinking into the oblivion of instant lemons—due to the antiwar stances being taken by our former enemies/charity recipients/allies. However, before I could leave the office, I had an inch-thick pile of HIPAA compliance policies and forms to review and frantic administrators calling in panic and fear about the impending invasion of trial lawyers and bureaucrats looking for HIPAA compliance gotchas over which to sue. Also, in the local paper, Los Angeles County announced it was closing a dozen or more primary care clinics to save money, while, in another article in a trade rag, there was mention of the fact that L.A. County had just announced it had signed agreements with consultants totaling $16 million to prepare the county for HIPAA. The more I thought, the more angry I became over the fed’s heavy-handed, dogmatic, and ignorant approach to confidentiality.

Here we are with literally hundreds of years of experience with the doctor-patient relationship and its spillover, and relatively stringent laws in almost every state governing the use and release of patient information, panicked over HIPAA. We have a government of know-nothing technocrats who are blindly marching to the drum of regulations that ignore the reality of medical practice, with providers left to wonder about the costs and aftereffects of the federal mandates. Suddenly, I had a little empathy for the Germans. While I agree with our stance toward Iraq, I can’t help thinking that the Europeans’ complaints about Bush’s foreign policy sound all too familiar when walking the
hospital and health plan hallways. Unfortunately, we providers don't have veto power over HIPAA at the United Nations.

While we chafe at the dictatorial approach of HIPAA, try to put HIPAA in perspective. In most states, HIPAA changes are bothersome, but they don't need to be the huge and expensive problem some consultants are making it out to be. All HIPAA does is formalize what is being done, hopefully, in practice. Yes, it adds some costs and bureaucratic and unnecessary steps to the health care process, but common sense should still prevail.

I think HIPAA really only requires a written notice of privacy practices that is available to patients, on the Web and in the facility or office or store; some kind of acknowledgment from the patient in writing, like signing a log book; care in the use of medical information and tracking its disclosure outside regular health care operations (meaning sending a bill to a payer is not trackable); and patient access to his or her record, with the right to request the ability to alter or comment on the record, which the provider doesn't have to agree to.

There are stupid sides to HIPAA, like requiring a provider to obtain written privacy agreements from vendors who obtain protected information. They are already required to keep the information confidential, but we will waste millions of dollars nationwide in legal, printing, and postage costs just to comply with this make-work, unnecessary requirement. I guess I should get over it and feel sorry for the thousands of people in Los Angeles who have lost access to primary care while the county fattens the pockets of consultants and feels that it has somehow done something to protect patients' privacy. I am sure that the sick who show up at shuttered clinics will suddenly be cured knowing that if they can find a provider, their information will be protected.

Michael Tichon, Esq.
Executive Vice President and General Counsel
Healthsmart Corp., Long Beach, California
E-mail: mtichon@healthsmartcorp.com

REFERENCES
1. Walden DC, Craig RP. The Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the pharmacy benefit: implications for health plans, PBMs, and providers. J Managed Care Pharm. 2003;9(1):66-71
2. Curtiss FR. HIPAA effects on health research and PBM functions in drug UR. J Managed Care Pharm. 2003;9(1):95-97

Dear Editor,

My job takes me to many different types of health care settings. I have been painfully watching the HIPAA evolution in the places I visit. It spurs me to share a few stories.

Last month, I was in a local hospital. The hospital was challenged to figure out how to dispose of their used IV bags. Each IV bag is labeled with the patient's name. Evidently, the local hospital association sent this hospital a news-flash informing them that they would be in violation of HIPAA if they simply threw the empty IV bag in the patient's waste paper basket—a practice that has been done forever. Emptying the trash 3 times a day is simply not adequate anymore—absolute paradise for a HIPAA consultant!

Last week, one of my friends told me of a heated battle he observed in the academic medical center. Legal counsel had informed the medical staff that all specialists, unless they were the admitting physician, could not look at a patient's chart until the patient had given informed consent. Yes, another potential HIPAA violation. Can you imagine a teaching hospital full of specialists who can't look at a chart until the patient provides informed consent? HIPAA on the edge!

Closer to home, I am coordinating a 40-site, 4,000-patient benchmarking study. It involves a retrospective review of the patient's medical record and data collection by a clinician who works in the study site. No patient-identifying information is transferred to me to perform the benchmarking—no name; no geographic subdivision of the patient's address smaller than a state; no elements of date (birth, admission, discharge, initiation of therapy, etc.); and no identifying numbers (social security, medical record, prescriber number, etc.).

I coordinated a conference call earlier this week, and one site (and I am thankful it was only one) inquired about locating patients who had previously been discharged from the hospital to obtain informed consent to retrospectively review their medical record. The reason cited—HIPAA. Eeeeks, I quietly thought, HIPAA on the edge again—it has finally happened to me!

Quickly, though, I discovered the valuable HIPAA consultants—those other pharmacists on the conference call. They profoundly dismissed the notion that this practice would constitute a HIPAA violation. Their logic was as simple as one...two...three: (1) no patient identifying information, (2) the hospital's own staff collecting the data, (3) therefore, no need for informed consent. Patient privacy can be a good thing—but not on the edge!

Kevin Colgan, RPh, MA
Vice President, Pharmacoeconomic & Outcomes Research
EPI-Q, Inc., Oakbrook Terrace, Illinois
E-mail: kevin.colgan@epi-q.com
### Member Information

<table>
<thead>
<tr>
<th>Role</th>
<th>First Name</th>
<th>Last Name</th>
<th>Title</th>
<th>Organization Name</th>
<th>Organization Address</th>
<th>City</th>
<th>State</th>
<th>Zip Code</th>
<th>Home Address</th>
<th>City</th>
<th>State</th>
<th>Zip Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mr.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ms.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mrs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Address all mailings to my:  
- [ ] Company Address  
- [ ] Home Address

**Work Telephone**

**Home Telephone**

**E-mail Address (Primary)**

**E-mail Address (Secondary)**

Send all e-mail messages to my:  
- [ ] Primary E-mail  
- [ ] Secondary E-mail

**Referred By**

---

### Demographic Information

Please tell us:

I. Are you a pharmacist?  
- [ ] Yes  
- [ ] No

II. What degrees/designations do you hold?  
- [ ] B.S. Pharmacy  
- [ ] Pharm.D.  
- [ ] M.P.A.  
- [ ] M.P.H.  
- [ ] Ph.D.  
- [ ] J.D.  
- [ ] M.B.A.  
- [ ] R.Ph.  
- [ ] Other

III. Which of the following best describes your employer?  
- [ ] Association  
- [ ] Health Plan  
- [ ] Medical Group  
- [ ] Integrated System  
- [ ] Hospital  
- [ ] College or University  
- [ ] PBM/Mail Service  
- [ ] Home Care  
- [ ] Long-term Care  
- [ ] Retail Pharmacy  
- [ ] Consulting Firm  
- [ ] Pharmaceutical Manufacturer  
- [ ] Government (VA, PHS, Military, State)  
- [ ] Not Currently Employed  
- [ ] Other

IV. Which of the following best describes your job function(s)?  
- [ ] Director/President  
- [ ] Assistant Director/Vice President  
- [ ] Staff Pharmacist  
- [ ] Clinical Pharmacist  
- [ ] Clinical Coordinator  
- [ ] School/College Faculty  
- [ ] Student  
- [ ] Resident/Fellow/Graduate  
- [ ] Contract/Purchasing  
- [ ] Network Management  
- [ ] Professional Relations  
- [ ] Formulary Management  
- [ ] Distribution/Supply Chain  
- [ ] Customer Service  
- [ ] Consultant  
- [ ] Marketing/Sales  
- [ ] Other (specify)

V. How many years have you been in your current role?  

---

### Annual Membership Rates

- [ ] Active Member (pharmacists who support the mission and goals of AMCP): $225 per year
- [ ] Associate Member (non-pharmacists): $425 per year
- [ ] Student Member: $35 per year

- Required: Graduation date (mo/yr) ____________  
- [ ] School __________________________

- [ ] Resident/Fellow/Graduate Member: $75 per year

- Required: Resident/Fellow/Graduate completion date (mo/yr) ____________  
- [ ] Site ____________________________

---

### Method of Payment

- [ ] Check made payable to AMCP for $ _____________ (in U.S. funds drawn on a U.S. bank)
- [ ] Charge $ _____________ to my credit card  
- [ ] Visa  
- [ ] MasterCard  
- [ ] American Express

**Card Number**  
**Exp. Date**

**Cardholder Printed Name**

**Cardholder Signature**
Is Your Rebate Bottom Line Blurry?

Try a new PBM prescription – Argus. At Argus, rebates related to your program are clearly visible for you to see ... and fully auditable. You see the amounts. You see the fees. You see where every dime is going.

It’s called a transparent business model based on fairness and with full disclosure of administrative fees.

But we do more than rebate management. From recordkeeping to formulary development, we specialize in the pharmacy benefits services you really need.

All absolutely transparent. All absolutely in your best interests.

Call Argus and bring the bottom line back into focus.

1-800-RXARGUS

ARGUS

The Clear Choice.™