Evaluation of Prescriber Responses to Pharmacist Recommendations Communicated by Fax in a Medication Therapy Management Program (MTMP)

Descriptive Analysis of Mail Interventions with Physicians and Patients to Improve Adherence with Antihypertensive and Antidiabetic Medications in a Mixed-Model Managed Care Organization of Commercial and Medicare Members

A Comparison of Daily Average Consumption (DACON) of Oxycodone and Oxymorphone Long-Acting Oral Tablets

Effects of Cohort Selection on the Results of Cost-Effectiveness Analysis of Disease-Modifying Drugs for Relapsing-Remitting Multiple Sclerosis

How Do Seniors Respond to 100% Cost-Sharing for Prescription Drugs? Quality of the Evidence Underlying Opinions About the Medicare Part D Coverage Gap
RESEARCH
345 Evaluation of Prescriber Responses to Pharmacist Recommendations Communicated by Fax in a Medication Therapy Management Program (MTMP)
Prasadini N. Perera, MS; Mignonne C. Guy, PhD; Ashley M. Sweeney, PharmD Candidate; and Kevin P. Boesen, PharmD

355 Descriptive Analysis of Mail Interventions with Physicians and Patients to Improve Adherence with Antihypertensive and Antidiabetic Medications in a Mixed-Model Managed Care Organization of Commercial and Medicare Members
Shu Jing, PharmD; Arthur Naliboff, BSPharm, MS; Michele B. Kaufman, PharmD, BPharm; and Mary Choy, PharmD

367 A Comparison of Daily Average Consumption (DACON) of Oxycodone and Oxymorphone Long-Acting Oral Tablets
Mark Rubino, BS Pharm, MHA; Kent H. Summers, PhD; R. Amy Punjpatom, PhD; Chunmay Fu, MS; Robert L. Ohsfeldt, PhD; and Rami H. Ben-Joseph, PhD

DEPARTMENTS
335 Cover Impressions
Superstitions (2010)
Sheila Macho, Cover Editor

377 Brief Communication
Effects of Cohort Selection on the Results of Cost-Effectiveness Analysis of Disease-Modifying Drugs for Relapsing-Remitting Multiple Sclerosis
Russell V. Becker III, MA, and Carole Dembek, MS

382 Editorial
How Do Seniors Respond to 100% Cost-Sharing for Prescription Drugs? Quality of the Evidence Underlying Opinions About the Medicare Part D Coverage Gap
Kathleen A. Fairman, MA, and Frederic R. Curtiss, RPh, PhD, CEBS
JMCP author guidelines

**JMCP Author Guidelines**

The Journal of Managed Care Pharmacy, including supplements, is indexed by MEDLINE/PubMed, the International Pharmaceutical Abstracts (IPA), Science Citation Index Expanded (SCIE), Current Contents/ Clinical Medicine (CC/CM), and Scopus.


Mesa, Arizona, artist Cynthia (CJ) Rider is also a photographer and accomplished poet. She was born in Sandusky, Ohio, and grew up in Redondo Beach, California, a small coastal town in Southern California. Since then, she has lived in many different states and visited even more. Rider’s appreciation of art began to flourish as she traveled across the United States, experiencing the local flavors of the small towns she passed through. Although she is fond of other parts of the country, her heart belongs to the Southwest. Its influence on her fine art and photography continues to this day. “My love of nature took seed during childhood where I spent many afternoons barefoot on the beach collecting shells and wiggly things,” Rider says. “That sand, the salty breeze, and California sun persist; nudging me to recreate the feeling they offered [me] as a child.”

A self-taught artist, Rider endeavors to capture the essence of each subject. This is especially true of her portraits—she has been told many times that “the expression is just right.” According to Rider’s biography on her website, Art by CJ Rider (ridercreations.com), “Her portraits are filled with emotion, her landscapes capture the rugged natural beauty of the land, and her book illustrations are poignant. Refusing to be restricted or stereotyped, she uses whatever medium best suits her subject. CJ’s goal is to lend a touch of meaning to the viewer that will evoke a strong emotional response.” Her preferred approach to painting is the plein-air method, but she does a significant amount of work in her home studio as well.

Rider worked for many years as a professional photographer, which helped her to learn the advanced technical aspects of photography. But it is her innate creativity that enables her to shoot a photograph that is also a work of art. Rider’s Superstitions photo is the perfect example. This peaceful view of Central Arizona’s Superstition Mountains at sunset, with its pastel-hued sky, rich earth tones, saguaro cactus, and prickly pear cactus clusters could be mistaken for a beautiful watercolor painting.

Located east of Mesa, the 160,000-acre Superstition Mountain range has a rich history. Its name hints at the intrigue this area has held for many years. Archeological evidence indicates that Native American Indians occupied the region as early as 9,000 years ago. Later inhabitants included Spanish explorers and Mexican gold miners. In the early 1800s, American trappers and adventurers also migrated to the area, and they were soon joined by cattle ranchers and farmers. During the 1870s, people began searching the Superstitions for what they believed was the richest gold mine in the world. This mine was made famous by Jacob Waltz, known as “The Dutchman,” who took the secret of his mine’s location to the grave in 1891. Even today, treasure hunters scour the mountains searching for the Lost Dutchman’s Mine.

Rider has been a judge for many art shows and events, such as the Gilbert Fine Art Show, the Lost Dutchman Days Art & Crafts Fair, and the art show at the Arizona State Fair. She has served as president of the Mesa Art League, and created the club’s dynamic newsletter. In addition, Rider is a member of Arizona’s Superior Art League, the Apache Junction Art League, and a juried member of the Arizona Art Alliance, which presented her with its “Art Angel” award in 2006 for her exceptional community outreach efforts. She founded the “Budding Artist” program in which art league and community members volunteer their time to mentor at-risk children in the arts.

Rider also teaches art through workshops, classes, and demonstrations. The “Workshops & Classes” page on her website provides information about encaustic (hot wax and colored pigments) painting, watercolor pencil instruction, and open media classes, where the students decide which medium to use for their creations. Regarding artists’ ethics, she says, “We all learn from example, but then [we] must break away and develop our own path.” Rider recently conducted art demonstrations in Phoenix at the Arizona Art Supply store and the National Art Materials Trade Association (NAMTA) trade show in the Pentel Arts booth.

The artist’s work has been shown at numerous Arizona galleries and museums, including Brio Fine Arts Center and Museum in Scottsdale, Karin Newby Gallery in Tubac, Superstition Mountain Museum Gallery in Apache Junction, and the gallery at Boyce Thompson Arboretum in Superior.

Rider’s art has also appeared in many different publications, including the Gold Canyon Ledger, the monthly journal of the Association for Development of a Better Environment (ADOBE), and several poetry books. Tapestries of the Heart: Emerging Poets of the 21st Century is one of those books—it is a compilation of the work of 17 poets from the United States and Europe. They were brought together through the Internet by virtue of their love for poetry. Rider contributed 15 of her poems to the volume.

Sheila Macho
Cover Editor

COVER CREDIT

SOURCES
JMCP publishes peer-reviewed original research manuscripts, subject reviews, and other content intended to advance the use of the scientific method, including the interpretation of research findings in managed care pharmacy. JMCP is dedicated to improving the quality of care delivered to patients served by managed care pharmacy by providing its readers with the results of scientific investigation and evaluation of clinical, health, service, and economic outcomes of pharmacy services and pharmaceutical interventions, including formulary management. JMCP strives to engage and serve professionals in pharmacy, medicine, nursing, and related fields to optimize the value of pharmaceutical products and pharmacy services delivered to patients. JMCP employs extensive bias-management procedures intended to ensure the integrity and reliability of published work.

EDITORIAL MISSION

EDITORIAL STAFF

Editor-in-Chief
Frederic R. Curtiss, PhD, RPh, CEBS
830.935.4319, fcurtiss@amcp.org

Associate Editor, Kathleen A. Fairman, MA
602.867.1343, kfairman@amcp.org

Cover Editor, Sheila Macho, 952.431.5993, jmcpcoverart@amcp.org

Copy Editor, Carol Blumentritt

Peer Review Administrator, Jennifer A. Booker
703.317.0725, jmcpreview@amcp.org

Graphic Designer, Margie Hunter, 703.297.9319, mhunter@amcp.org

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

EDITORIAL ADVISORY BOARD

The JMCP Editorial Advisory Board is chaired by Marvin D. Shepherd, PhD, Center for Pharmacoeconomic Studies, College of Pharmacy, University of Texas at Austin, Thomas Delate, PhD, Kaiser Permanente of Colorado, Aurora, serves as vice chair. They and the other advisers review manuscripts and assist in the determination of the value and accuracy of information provided to readers of JMCP.

J. Daniel Allen, PharmD, RegenceRx; Portland, OR
John P. Barbuto, MD, Modify Motion, LLC, Salt Lake City, UT
Mitchell J. Barnett, PharmD, MS, Touro University College of Pharmacy, Vallejo, CA
Christopher F. Bell, MS, Global Health Outcomes, GlaxoSmithKline Research & Development, Research Triangle Park, NC
Joshua Benner, PharmD, ScD, Brookings Institution, Washington, DC
Scott A. Bull, PharmD, ALZA Corporation, Mt. View, CA
Douglas S. Burgoyne, PharmD, RPh, VRx Pharmacy Services, Salt Lake City, UT
Norman V. Carroll, PhD, School of Pharmacy, Virginia Commonwealth University, Richmond, VA
Mark Conklin, PharmD, MS, Highmark Blue Cross Blue Shield, Pittsburgh, PA
Eric J. Culley, PharmD, MBA, Highmark Blue Cross Blue Shield, Pittsburgh, PA
Timothy Cutler, PharmD, School of Pharmacy, University of California, San Francisco, CA
Gregory W. Daniel, RPh, MPH, PhD, HealthCore, Inc., Wilmington, DE
Thomas Delate, MS, PhD, Kaiser Permanente of Colorado, Aurora, CO
Melissa S. Denno, PharmD candidate, Mercer University College of Pharmacy, Atlanta, GA
Patrick P. Gleason, PharmD, BCPS, Prime Therapeutics, LLC, Eagan, MN
Mark Jackson, BScPhm, BComm, RPh, Green Shield Canada, Windsor, Ontario
Richard A. Kipp, MAAA, Milliman USA, Wayne, PA
Stephen J. Kogut, PhD, MBA, College of Pharmacy, University of Rhode Island, Kingston, RI
Charneleda Gray Lewis, PharmD, BCPS, Kaiser Permanente, Atlanta, GA
Bradley C. Martin, PharmD, PhD, College of Pharmacy, University of Arkansas, Little Rock, AK
Brenda R. Mothaler, RPh, MBA, PhD, University of Kentucky College of Pharmacy, Lexington, KY

Robert P. Navarro, PharmD, University of Florida College of Pharmacy, Gainesville, FL
Robert L. Ohsfeldt, PhD, School of Rural Public Health, Texas A&M Health Science Center, College Station, TX
Mary Jo V. Pugh, RN, PhD, South Texas Veterans Healthcare System, San Antonio, TX
Brian J. Quilliam, PhD, RPh, College of Pharmacy, University of Rhode Island, Kingston, RI
Marsha Raebel, PharmD, Kaiser Permanente of Colorado, Denver, CO
Elan Rubinstein, PharmD, MPH, EB Rubinstein Associates, Oak Park, CA
Jeremy A. Schafer, PharmD, MBA, Prime Therapeutics, LLC, Eagan, MN
Jordana Schmier, MA, Exponent, Alexandria, VA
Marvin D. Shepherd, PharmD, College of Pharmacy, University of Texas, Austin, TX
Joshua J. Spooner, PharmD, MS, School of Pharmacy, Western New England College, Springfield, MA
Linda M. Spooner, PharmD, BCPS, Massachusetts College of Pharmacy, Worcester, MA
Marilyn Stebbins, PharmD, CHW Medical Foundation, University of California, Sacramento, CA
Karen Stockl, PharmD, Prescription Solutions, Irvine, CA
Burgunda V. Sweet, PharmD, FASHP, University of Michigan Health System, Ann Arbor, MI
Connie A. Valdez, PharmD, MEd, BCPS, School of Pharmacy, Aurora, CO
Peter Whittaker, PhD, School of Medicine, Wayne State University, Detroit, MI
Vincent Willey, PharmD, University of the Sciences in Philadelphia, Philadelphia, PA
Karen Worley, PhD, Competitive Health Analytics, Humana Inc., Louisville, KY
Andrew Yu, PhD, Analysis Group, Boston, MA

Journal of Managed Care Pharmacy (ISSN 1083–4087) is published 9 times per year and is the official publication of the Academy of Managed Care Pharmacy (AMCP), 100 North Pitt St., Suite 400, Alexandria, VA 22314, 703.683.8418; 800 TAP AMCP, 703.683.8417 (fax). The paper used by the Journal of Managed Care Pharmacy meets the requirements of ANSI/NISO Z39.48-1992 (Permanence of Paper) effective with Volume 7, Issue 5, 2001, prior to that issue, all paper was acid-free. Annual membership dues for AMCP include $60 allocated for the Journal of Managed Care Pharmacy.
Editorial Content and Peer Review

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

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

All manuscript submissions except Commentaries and Letters should include an abstract and 1-3 takeaway bullet points in each of 2 sections that immediately follow the abstract for “what is already known about this subject” and “what this study adds.”

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

Research

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

Subject Reviews

These are well-referenced, comprehensive reviews of subjects relevant to managed care pharmacy. The Methods section in the abstract and in the body of the manuscript should make clear to the reader the source of the material used in the review, including the specific criteria used for inclusion and exclusion of information and the number of articles included and excluded by each criterion. Narrative reviews, defined as noncomprehensive reviews that cover only a portion of the literature on a topic, are not considered for publication by JMCP. However, articles of this type may be considered as Commentary.

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 generally include description and interpretation of clinical evidence and comparative cost information.

Contemporary Subjects

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

Brief Communications

The results of a small study or a descriptive analysis that does not fit in other JMCP departments may be submitted as a Brief Communication. Brief Communications may warrant an Abstract with the typical JMCP categories (Background, Objective, Methods, Results, Conclusion).

Commentary

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

Letters

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

Advertising and Disclosure Policies

All aspects of the advertising sales and solicitation process are completely independent of the editorial process. Advertising is positioned either at the front or back of the Journal, and advertising is not accepted for placement opposite or near subject-related editorial content.

The Academy of Managed Care Pharmacy endorses the Uniform Requirements for Manuscript Submissions to Biomedical Journals, available at http://www.icmje.org/ including editorial freedom and management of conflicts of interest. Financial disclosure, conflict-of-interest statements, and author attestations are required when manuscripts are submitted, and these disclosures accompany the article in abstracted form if the article is published. See JMCP Author Guidelines in this issue or online including complete description of disclosure policies and requirements for author attestations at www.amcp.org.

See JMCP advertising opportunities at: www.amcp.org. Contact the Advertising Sales Office to receive a Media Kit.

Journal of Managed Care Pharmacy 340

JMCP Mission Statement and Editorial Policy

EDITORIAL MISSION AND POLICIES

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 Sales Office

RH Media LLC
1814 East Route 70, Suite 350
Cherry Hill, NJ 08003
Tel.: 856.673.4000
Fax: 856.673.4001
E-mail: bob.rhmedia@comcast.net
Evaluation of Prescriber Responses to Pharmacist Recommendations Communicated by Fax in a Medication Therapy Management Program (MTMP)

Prasadini N. Perera, MS; Mignonne C. Guy, PhD; Ashley M. Sweaney, PharmD Candidate; and Kevin P. Boesen, PharmD

ABSTRACT

BACKGROUND: As defined by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, medication therapy management programs (MTMPPs) must be designed to decrease adverse drug events and improve patient outcomes by promoting appropriate medication use. WellPoint Inc. contracted with the pharmacist-run University of Arizona College of Pharmacy Medication Management Center (UA MMC) to provide a pilot telephone-based MTMP to approximately 5,000 high-risk beneficiaries from among its nearly 2 million Medicare prescription drug plan (PDP) beneficiaries. Eligibility for the program was determined by a minimum of 2 of 6 chronic diseases (dyslipidemia, cardiovascular disease, depression, diabetes mellitus, congestive heart failure, and chronic obstructive pulmonary disease; at least 1 of the latter 2 diseases must be present), at least 3 Part-D covered medications, and greater than $4,000 per year in predicted drug spending. In addition to these criteria, WellPoint Inc. used the Johns Hopkins adjusted clinical groups (ACG) predictive model to identify the high-risk beneficiaries to be enrolled in the program. Medication therapy reviews were conducted for these patients. If any medication-related problems (MRPs) were identified, the patient’s prescribers were contacted via a fax communication with recommendation(s) to resolve these MRPs. The UA MMC fax interventions were categorized as cost saving, guideline adherence, or safety concerns.

OBJECTIVES: To (a) determine prescriber responses to pharmacist-initiated recommendations in an MTMP for the 3 intervention categories, (b) compare prescriber responses between intervention categories, and (c) compare prescriber response by prescriber type (primary care physician [PCP] vs. specialist) within each intervention category.

METHODS: A retrospective analysis of pharmacist-initiated interventions from August through December 2008 was performed using data collected from the UA MMC database. Data were collected on intervention category (cost saving, guideline adherence, or safety concerns), and responses of prescribers were recorded as either approval or decline (no response was considered decline). Prescriber specialty was identified from searching the records of state medical boards. Logistic regression analyses with the robust variance option to adjust for correlation within prescribers were considered decline). Prescriber specialty was identified from searching the records of state medical boards. Logistic regression analyses with the robust variance option to adjust for correlation within prescribers were conducted to compare prescriber approval rates between and within intervention categories. Significance was assessed at alpha 0.05.

RESULTS: Of 4,967 Medicare Part D beneficiaries determined to be MTMP-eligible, 4,277 beneficiaries (86.1%) were available for assessment (400 declined, 186 disenrolled, and 104 were deceased). Pharmacists initiated 1,548 valid medication recommendations (i.e., recommendations were excluded for deceased patients, incorrect prescribers, and where prescriber specialty was not identified). These recommendations for 1,174 beneficiaries (27.5% of those available) were faxed to prescribers requesting approval. Mean (SD) age for beneficiaries having recommendations was 72.9 (9.4) years, and the majority (57.6%) was female. By category of recommendation, 58.3% (n = 902) were guideline adherence, 33.3% (n = 515) were cost saving, and 8.5% (n = 131) were safety concerns. Prescriber approval rates were 47.2% overall (n = 731/1,548), 41.4% (n = 373/902) for guideline adherence, 58.3% (n = 300/515) for cost savings, and 44.3% (n = 58/131) for safety concerns; 817 recommendations were not approved by prescribers (n = 255 [16.5%] denials and 562 no response [36.3%]). Prescriber approval was significantly higher for cost-saving interventions compared with guideline adherence interventions (odds ratio [OR] = 1.98, 95% CI = 1.56-2.51, P < 0.001) and compared with safety interventions (OR = 1.76, 95% CI = 1.19, 2.59, P = 0.004); there was no significant difference in the prescriber approval rates for the interventions for safety versus guideline adherence. The overall approval rate was higher for PCPs (49.8%, n = 525/1,054) versus specialists (41.7%, n = 206/494; OR = 1.39, 95% CI = 1.08-1.78, P = 0.011) and for the category for guideline adherence interventions (44.0% for PCPs vs. 35.9% for specialists; OR = 1.40, 95% CI = 1.01-1.95, P = 0.044), but not for the other 2 intervention categories.

CONCLUSIONS: Prescriber approval rates for pharmacist recommendations for drug therapy changes for MTMP beneficiaries were approximately 47% overall and higher for recommendations that involved cost savings compared with recommendations for safety concerns or guideline adherence. Compared with specialists, PCPs had higher approval rates for pharmacist recommendations overall and for the intervention category guideline adherence.

J Manag Care Pharm. 2011;17(5):345-54

Copyright © 2011, Academy of Managed Care Pharmacy. All rights reserved.
Medication therapy management (MTM) encompasses a wide range of patient-centered services provided by pharmacists in a number of different care settings. MTM services, which involve a comprehensive evaluation of a patient’s medication regimen in its entirety, are separate from but can occur in conjunction with dispensing and product-centered delivery of pharmacy services. Examples of MTM services or components include medication reviews, therapeutic drug monitoring, disease management, wellness programs, immunizations, and other programs designed to optimize medication treatment. MTM was mandated by the Medicare Prescription Drug, Improvement, and Modernization Act (MMA 2003). The law requires all Medicare Part D prescription drug plan (PDP) sponsors to establish an MTM program (MTMP) for targeted beneficiaries. The program must be designed to “optimize therapeutic outcomes” through the improvement of medication utilization and reduction in the risk of adverse events. Additionally, the MMA 2003 mandates that MTMPs shall be developed in cooperation with licensed pharmacists and physicians but may be offered by other qualified providers.

Medication-related problems (MRPs) pose significant health risks to vulnerable populations within the United States and are a tremendous economic burden to individuals, the health care system, and society at-large. MRPs, as identified by Johnson and Bootman (1995), include untreated indications, improper drug selection, subtherapeutic dosage, drug use without indication, adverse drug reactions, drug interactions, and overdose. In 2000, morbidity and mortality costs attributed to MRPs were estimated to be more than $177 billion. Furthermore, the number of adverse drug events in the United States is estimated at 1.5 million annually. Given the extensive burden borne by individuals and systems, the promise of MTMPs to yield cost savings through the resolution and prevention of MRPs is substantial.

Successful implementation of MTM requires the collaboration of patients and their health care providers. Studies and several reviews conducted on the subject have shown that physicians in general respond favorably to pharmacist interventions and acknowledge clinical pharmacists as playing a valuable role as medication therapy specialists to improve the clinical status of patients. Furthermore, systematic reviews and studies conducted across a number of disease conditions and pharmaceutical care delivery settings have, in most instances, suggested improved patient outcomes following an active role by the pharmacist. However, perceptions of physician resistance as a barrier in providing services can differ among MTM providers and payers. In a nationwide survey by Schommer et al. (2008), barriers to MTM services were assessed for both pharmacists who provide MTM services and payers of the service. Pharmacists who provided MTM services did not indicate physician resistance as an important barrier; only 23% of pharmacists reported local physician resistance as a very important or somewhat important barrier to service provision (ranked 14th of 15 barriers assessed). However, the second most frequently reported barrier by payers of MTMPs was physician resistance or suboptimal cooperation. This resistance is important given that cooperation from physicians is essential for successful MTM.

Although not always described as MTM, pharmacists’ recommendations targeted at resolving potential MRPs have been the subject of numerous studies in various settings and countries. Reported physician acceptance rates among these studies varied between 32% and 98%. Higher acceptance rates were observed in the presence of face-to-face interaction or collaborative agreements between pharmacists and physicians. Rates of acceptance of recommendations consisting of less personal contact, such as letters and faxes, were lower. Pharmacist-initiated recommendations in these studies broadly consisted of achieving optimal treatment for patients (e.g., stoppage of unnecessary/ineffective medications, dosage adjustments, medication adherence, medication switches, and addition of new medications) and addressing safety concerns such as potential adverse events due to drug interactions or inappropriate drug use in the elderly.

The University of Arizona (UA) College of Pharmacy, through its Medication Management Center (MCC) provides MTM services to Medicare Part D beneficiaries from several...
TABLE 1  Frequently Occurring Pharmacist-Initiated Prescription Fax Interventions by Intervention Category

<table>
<thead>
<tr>
<th>Intervention Category</th>
<th>Reason for Intervention</th>
<th>Common Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost Saving Interventions</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Drug substitution      | Patient is on higher-tier (higher-cost) formulary medication when a lower-tier (lower-cost) medication alternative is appropriate for substitution. | • Generic substitution of brand (innovator) statin (e.g., replace rosuvastatin with simvastatin)  
• Generic substitution of brand (innovator) PPI (e.g., replace esomeprazole with generic omeprazole) |

| **Guideline Adherence Interventions** |                        |                 |
| Untreated indication    | Patient is not on medication recommended by clinical practice guidelines based on evidence of benefit for interventions were targeted for patients with diabetes, heart failure, post-myocardial infarction, chronic kidney disease, COPD, asthma, and angina. | • ACE inhibitor or an ARB is recommended to reduce the risk of adverse renal and/or cardiovascular outcomes in patients with diabetes and specific comorbidities (hypertension, known cardiovascular disease, or any degree of proteinuria).  
• Statin is recommended to reduce risk of adverse cardiovascular outcomes in patients with diabetes and specific comorbidities (known cardiovascular disease or age greater than 40 years and certain risk factors).  
• ACE inhibitor or ARB and a beta-blocker are recommended with the goal of improving survival in patients with heart failure.  
• ACE inhibitor and statin are recommended for secondary prevention in patients following an MI.  
• Short-acting beta2-agonists are recommended as first-line therapy for acute symptoms and exacerbations in patients with asthma and COPD.  
• Inhaled corticosteroids are recommended to manage asthma in patients experiencing symptoms more than twice weekly. |

| **Safety Interventions** |                        |                 |
| Drug-disease interactions | Patient is on medication that may worsen co-existing conditions. | • Recommend switch of nonselective beta-blockers to a cardio-selective beta-blocker in patients with asthma and COPD  
• Discontinue anticholinergic medications in elderly patients  
• Discontinue or adjust dosages of nephrotoxic drugs in patients with renal dysfunction  
• Assess alternative therapy to calcium channel blockers in patients with heart failure |
| Avoidance of ADEs | Adjustment of patient’s medication dosage or regimen is needed to prevent future or current side effects or complications. | • Adjust dosage when medication dose is too high (e.g., reduce dose of acetaminophen when daily dose exceeds 4,000 mg due to risk of liver damage)  
• Discontinue duplicate therapy while maximizing the dose of the other agent  
• Assess addition of PPI in patients using chronic NSAIDs with risk factors, including age older than 65 years or concomitant use of corticosteroids, anticoagulants, or aspirin |

ACE = angiotensin-converting enzyme; ADE = adverse drug event; ARB = angiotensin II receptor blocker; COPD = chronic obstructive pulmonary disease; mg = milligrams; MI = myocardial infarction; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor; statin = HMG-CoA reductase inhibitor.

This study focuses on prescription fax recommendations that requested prescriber response. Recommendations made at the UA MMC are grouped into 3 broad intervention categories pre-determined by the pharmacist: (a) cost savings, (b) safety concerns, and (c) adherence to pharmacotherapeutic recommendations in national clinical practice guidelines (CPGs). Table 1 presents the most commonly occurring interventions in these 3 categories.

Prior to the present study, prescriber response to the 3 intervention categories within the MTMP at the UA MMC was unknown. Thus, the primary aim of this study was to assess prescriber responses to an MTM service model that utilized faxes as the primary method of communicating medication recommendations to prescribers. The specific objectives of the study were to (a) determine prescriber approval rates for pharmacist-initiated recommendations overall and by intervention

national and regional PDPs. A comprehensive description of the MTMP has been reported previously. In brief, UA MMC pharmacists regularly conduct comprehensive reviews of patients’ medication profiles and make recommendations on identified MRPs via evidence-based faxes to the patient’s prescriber. Faxes are of 2 types—prescription (recommendation) faxes and informational (FYI) faxes. MRPs are communicated through prescription faxes when there is adequate information in prescription-related recommendations (i.e., a change in the patient’s prescription). For prescription fax interventions, the UA MMC requests a fax response from the prescriber approving or declining the recommendation. FYI faxes are sent to the prescriber in the absence of complete information to make a prescription recommendation, but a potential MRP is identified in the patient’s medication profile. FYI faxes do not require a signed response from the prescriber.
category (cost saving, guideline adherence, safety concerns), (b) compare prescriber responses between intervention categories, and (c) compare prescriber approval rates by prescriber type (primary care physician [PCP] versus specialist) overall and within each intervention category.

Methods
This study was a retrospective review of faxed prescriber responses to pharmacist-initiated prescription fax recommendations. This review included 1,548 prescription recommendations for 1,174 patients, 27.4% of the 4,277 patients who were enrolled to receive MTM services in a pilot MTMP developed in collaboration with, and for WellPoint Inc., from August to December 2008. The present study was conducted after receipt of approval from the UA Institutional Review Board.

Pilot Program and Study Setting
The pilot program was conducted for 4,967 Medicare Part D beneficiaries identified by WellPoint Inc. as eligible to receive MTMP services. Target enrollment in the pilot program was limited to approximately 5,000 beneficiaries as this was deemed appropriate by WellPoint Inc. to sufficiently develop and implement an MTMP pilot program in collaboration with the UA MMC. From nearly 2 million Medicare beneficiaries in WellPoint Inc.’s affiliated PDPs, beneficiaries were selected for this MTMP pilot if they had been diagnosed with at least 2 of 6 chronic conditions (dyslipidemia, cardiovascular disease, depression, diabetes mellitus, congestive heart failure, and chronic obstructive pulmonary disease; at least 1 of the latter 2 diseases must be present), received 3 or more Part D-covered medications, and had greater than $4,000 per year in predicted drug spending. In addition to these criteria, WellPoint Inc. used the Johns Hopkins adjusted clinical groups (ACG) predictive model to select the 4,967 high-risk beneficiaries for the MTMP pilot.

Enrollment for the pilot program was via an “opt-out” mechanism whereby all targeted beneficiaries were enrolled with the exception of disenrollment at beneficiary request that occurred when patients were contacted by telephone to perform medication reviews. Opportunities for interventions were evaluated by conducting reviews of medication profiles for 4,277 beneficiaries based on the 3 categories of cost savings, adherence to guidelines, and safety concerns, while 690 opted out of or were unavailable for the program (400 declined, 186 disenrolled, and 104 were deceased; Figure 1). Medication reviews were conducted via a telephone consultation with the patient, and if patients could not be contacted, a data (medication) review was conducted. Following these medication reviews, prescribers of 1,194 beneficiaries received 1,583 prescription fax recommendations from the UA MMC pharmacist. Prescription faxes included a short paragraph describing the rationale behind the intervention (e.g., reference to evidence-based national clinical practice guideline recommendations) followed by a recommended prescription. A fax response with an approval or decline of the recommendation was requested to be sent by the prescriber to the UA MMC. The remaining 3,083 beneficiaries without a prescription fax recommendation included patients whose prescribers received an FYI fax only (1,165 FYI faxes were generated during this study period), patients who did not consent to sending faxes to their prescriber, and patients without a MRP during the study period.

Data Collection
All pharmacist-initiated prescription recommendations requesting a fax response from the prescriber were included in this study. Faxes from prescribers stating “not my patient” (13 interventions in 7 patients) or “patient deceased” (7 interventions in 2 patients) were excluded from the analysis. This procedure identified a total of 1,563 interventions for 1,185 beneficiaries that were obtained from records maintained by the UA MMC. Records included a unique patient identification number, intervention category (cost savings, guideline adherence, or safety concern), target medications, and
Evaluation of Prescriber Responses to Pharmacist Recommendations
Communicated by Fax in a Medication Therapy Management Program (MTMP)

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>MTM Patient Characteristicsa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Characteristics</td>
<td>Overall n = 1,174</td>
</tr>
<tr>
<td>Female sex</td>
<td>676 (57.6)</td>
</tr>
<tr>
<td>Comorbiditiesd</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>1,148 (97.9)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>770 (65.6)</td>
</tr>
<tr>
<td>Respiratory (COPD or asthma)</td>
<td>624 (53.1)</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>599 (51.0)</td>
</tr>
<tr>
<td>Chronic pain</td>
<td>572 (48.7)</td>
</tr>
<tr>
<td>Depression/dementia</td>
<td>466 (39.7)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>110 (9.4)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>89 (7.6)</td>
</tr>
</tbody>
</table>

aThe MTM interventions with prescribers were made from August through December 2008.
bPatients with prescriptions from both PCP and specialist.
*cP values for comparison of PCP only versus specialist only; P values calculated with independent t-tests and Pearson chi-square.
*dComorbidities were inferred from medications.
COPD = chronic obstructive pulmonary disease; PCP = primary care physician; SD = standard deviation.

Prescriber response. Patient identification numbers were used to access the patient’s medication profile in the UA MMC database to verify the prescriber response for each recommendation. Additional demographic data such as age and sex were extracted from the patient medication profile. Comorbid conditions were inferred from drug therapy.

Three possible prescriber responses were identified in the UA MMC database: (a) signed and returned fax accepting the recommendation (i.e., approval), (b) signed and returned fax declining the recommendation, and (c) no returned fax (i.e., no response). For the purpose of this study, prescriber response was dichotomized as an approval or decline with the latter including both returned fax declines and no responses to the pharmacist recommendations.

For the analysis by prescriber type, prescribers were classified as either PCPs or specialists. The classification scheme was determined by first identifying the prescribers and their states of practice from the MMC database. Next, state medical board websites were accessed to determine the medical specialty for each individual physician. Physicians were from 30 different states, and the websites used to determine prescriber medical specialty included ABMS (American Board of Medical Specialties) and state medical boards (e.g., www.medbd.ca.gov for the Medical Board of California and www.med.ohio.gov for the State Medical Board of Ohio). Family medicine and/or internal medicine physicians without any documented specialty certifications were defined and grouped as PCPs. Family medicine and/or internal medicine physicians who also had a specialty certification were defined and categorized as specialists. All other practitioners were also categorized as specialists, which included but were not limited to cardiology, endocrinology, geriatrics, gastroenterology, nephrology, pulmonology, nursing (i.e., advance practice nurse prescriber, nurse anesthetist, nurse practitioner), and other categories. A de-identified database was constructed containing the aforementioned data elements. Due to incomplete information in the MMC database, prescriber type was not ascertained for 15 interventions; thus, these were excluded from the prescriber type analysis.

Analytic Strategy
Descriptive statistics were generated for all variables. Means (SD) were reported for continuous variables (patient age), while frequencies and percentages were reported for categorical variables (i.e., patient sex, comorbidities, intervention category, prescriber approval). Patient characteristics were presented for the overall sample as well as by prescriber type (i.e., patients with faxes sent to PCPs only, specialists only, and for both PCPs and specialists). Independent t-tests and Pearson chi-square were conducted to determine if patient characteristics differed between patients with faxes sent to PCPs only and patients with faxes sent to specialists only. Logistic regression analyses with the robust variance option to adjust for correlation within prescribers were conducted to compare prescriber approval of pharmacist recommendations between intervention categories for the overall sample and by prescriber type (PCP and specialist) and to compare prescriber approval by prescriber type (PCP versus specialist) for each intervention category. Results are presented as odds ratios (OR), 95% confidence intervals (CI) along with their P values. Significance was assessed at 0.05. Data were analyzed using Stata statistical software version 10.1 (StataCorp, College Station, TX).
### Table 3

**MTM Recommendation Approval Rates by Prescriber Type and Intervention Category**

<table>
<thead>
<tr>
<th>Intervention category – % approved (number approved/number of recommendations)</th>
<th>Overall</th>
<th>PCPs</th>
<th>Specialists</th>
<th>Comparison by Prescriber Type Odds Ratio (95% Confidence Interval)(^a)</th>
<th>Comparison by Prescriber Type P Value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost savings</td>
<td>58.2 (300/515)</td>
<td>60.8 (225/370)</td>
<td>51.7 (75/145)</td>
<td>1.45 (0.95-2.20)</td>
<td>0.082</td>
</tr>
<tr>
<td>Safety</td>
<td>44.3 (58/131)</td>
<td>42.5 (34/80)</td>
<td>47.1 (24/51)</td>
<td>0.83 (0.41-1.68)</td>
<td>0.608</td>
</tr>
<tr>
<td>Guideline adherence</td>
<td>41.4 (373/920)</td>
<td>44.0 (266/604)</td>
<td>35.9 (107/298)</td>
<td>1.40 (1.01-1.95)</td>
<td>0.044</td>
</tr>
<tr>
<td>Total for all types</td>
<td>47.2 (731/1,548)</td>
<td>49.8 (525/1,054)</td>
<td>41.7 (206/494)</td>
<td>1.39 (1.08-1.78)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

**Odds ratios (95% confidence intervals) for comparisons between intervention categories\(^d\)**

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>Odds ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Savings versus safety</td>
<td>1.76</td>
<td>(1.19-2.59)</td>
<td>0.003</td>
</tr>
<tr>
<td>Savings versus guideline adherence</td>
<td>1.98</td>
<td>(1.56-2.51)</td>
<td>0.001</td>
</tr>
<tr>
<td>Safety versus guideline adherence</td>
<td>1.13</td>
<td>(0.78-1.63)</td>
<td>0.571</td>
</tr>
</tbody>
</table>

**P values for comparisons by intervention category\(^e\)**

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Savings versus safety</td>
<td>NA</td>
</tr>
<tr>
<td>Savings versus guideline adherence</td>
<td>NA</td>
</tr>
<tr>
<td>Safety versus guideline adherence</td>
<td>NA</td>
</tr>
</tbody>
</table>

\(a\) Odds ratios and 95% confidence intervals from logistic regression analyses comparing approval rates for PCPs versus specialty prescriber. The analyses took into account the correlation that may be present among physicians that received more than 1 fax recommendation.

\(b\) P values from logistic regression analyses testing approval rates for PCPs versus specialist prescribers.

\(c\) There were 255 prescriber denials (16.5%) and 562 (36.3%) no responses of the 817 recommendations not approved by prescribers.

\(d\) Odds ratios and 95% confidence intervals from logistic regression analyses testing prescriber approval rates between intervention categories. The analyses took into account the correlation that may be present among physicians that received more than 1 fax recommendation.

\(e\) P values from logistic regression analyses testing prescriber approval rates between intervention categories.

**MTM** = medication therapy management; **PCP** = primary care provider.

### Results

During the 5 months of the 2008 pilot MTMP, UA MMC pharmacists initiated a total of 1,563 interventions that included a prescription recommendation for approval for 1,185 beneficiaries (27.7% of the 4,277 enrollees). Excluding the 15 interventions where prescriber information could not be found for prescriber categorization (PCP or specialist), a total of 1,548 interventions were sent to 1,164 unique prescribers for 1,174 beneficiaries. This was considered the final sample, and all analyses were conducted and reported for this sample. Of the 1,163 prescribers, 776 (66.7%) were PCPs, and 387 (33.3%) were specialists. Patient characteristics and comorbidities are presented in Table 2. Beneficiaries who were the subjects of the interventions were aged a mean (SD) 72.9 (9.4) years, and more than one-half (57.6%) were female. The most frequently occurring comorbidities were cardiovascular diseases (97.9%), diabetes mellitus (65.7%), and respiratory diseases (53.1%). It is expected that cardiovascular disease and respiratory disease occur frequently in this patient population because patients were required to have either congestive heart failure or chronic obstructive pulmonary disease to be included in the pilot program. With the exception of chronic kidney disease, there were no significant differences for patient age, gender, or other chronic conditions between patients with faxes sent to PCPs only versus specialists only.

**Prescriber Approval of Intervention Categories**

Table 3 presents the number of pharmacist-initiated prescription fax recommendations and prescriber approval of these recommendations by intervention category. Of the total of 1,548 recommendations, the largest intervention category was guideline adherence at 58.3% (n = 902), while the lowest was safety concerns with less than 8.5% (n = 131). Cost savings accounted for one-third of the total (n = 515). Across all intervention categories, overall prescriber approval of pharmacist recommendations was 47.2% (n = 731). Prescriber denials were 16.5% (n = 255), and no responses were 36.3% (n = 562). Approval was highest for cost saving interventions at 58.3% (n = 300) and lowest for guideline adherence at 41.4% (n = 373). Even among PCPs and specialists, approval was highest among cost saving interventions (60.8% and 51.7%, respectively). Approval was lowest for safety interventions among PCPs (42.5%) and for guideline adherence interventions among specialists (39.5%)

**Comparison of Prescriber Approval Rates Between Intervention Category**

Table 3 presents the results of the comparisons of prescriber approval between intervention categories. Prescriber approval of cost saving interventions was significantly greater than both guideline adherence (OR = 1.98, 95% CI = 1.56-2.519, P < 0.001) and safety interventions (OR = 1.76, 95% CI = 1.19-2.59, P = 0.004). There was no significant difference between
prescriber approval of guideline adherence and safety interventions (OR = 1.13, 95% CI = 0.78-1.63; P = 0.470). These relationships remained following the subgroup analyses by PCPs and specialists with 1 exception—among specialists there was no significant differences in approval between cost savings and safety interventions (OR = 1.21, 95% CI = 0.63-2.30, P = 0.571).

### Approval of Interventions by Prescriber Type

Table 3 presents the results of approval by PCPs and specialists for the overall sample and for each intervention category. Overall approval of all pharmacist recommendations by PCPs was significantly greater compared with approval by specialists (OR = 1.39, 95% CI = 1.08-1.78, P = 0.011). When approval by each intervention category was considered, significant differences in approval by prescriber type was only observed for guideline adherence interventions. Approval among PCPs were greater compared with approvals among specialists (OR = 1.40, 95% CI = 1.01-1.95, P = 0.044). It may be possible that these results are driven by the different patient populations that are treated by PCPs versus specialists, with specialists likely to be treating a sicker group of patients. From the available patient characteristics only, chronic kidney disease showed significant differences between prescriber type. Specialists only had a greater number of patients with chronic kidney disease compared with PCPs only (14.6% vs. 4.2%, P < 0.001). A sensitivity analysis was conducted for the overall sample among subgroups of patients with and without chronic kidney disease to explore if this is accounting for the significant differences in approval that were observed between prescriber type. No significant differences between PCPs versus specialists were found in this subgroup analysis. [data not shown]

### Discussion

This study presented the results of an analysis of prescriber approvals within an opt-out pilot MTMP providing services to Medicare Part D PDP beneficiaries. Recommendations were delivered via fax to prescribers, and approval rates ranged from 41.4% for guideline adherence recommendations to 58.2% for cost saving recommendations, with an overall approval rate of 47.2% across intervention categories. These values were within the range of physician acceptance of pharmacist-initiated recommendations (32% to 98%) reported in numerous other studies, albeit in differing settings, suggesting that prescribers are receptive to UA MMC’s MTM model in which recommendations are initiated and communicated via faxed prescription requests. In several studies that communicated recommendations via fax, physician acceptance ranged between 32% and 49.2%. Overall approval in the current study falls within the upper end of this range. Physician acceptance rates of greater than 90% of pharmacist recommendations reported in several studies are substantially higher than those in the present study and are likely attributable to collaborative agreements and/or face-to-face interaction between the pharmacist and the physician in family medicine or primary care clinic settings.15,16,26,32

A prescriber approval rate comparable to the rates in the present study was reported in an MTM service provision model similar to that of the UA MMC.26 In the study of an MTMP implemented by Iowa Medicaid reported by Doucette et al. (2005), physicians and community pharmacists were compensated for collaborating in the provision of MTM services to high-risk patients.26 Similar to the UA MMC’s MTMP, the community pharmacist performed an initial review of the patient’s medications and medical history and faxed all recommendations to the patient’s physician, who then faxed back an approval or decline. Of the total 659 pharmacist-initiated interventions, 313 were accepted by the physician, resulting in an approval of 47.5% of all recommendations.26

In the present study, interventions for guideline adherence constituted the largest number of pharmacist-initiated prescription recommendations (902 of 1,548 recommendations, 58.3%), followed by cost saving (n = 515, 33.2%) and safety interventions (n = 131, 8.5%). In support of this finding, a number of studies that evaluated MRPs reported “untreated indication” or the need to add a new medication to manage medical condition (in line with CPG recommendations) to be among the most frequently occurring MRPs.11,20,28,29,36

Comparison of prescriber approval by intervention category across studies is challenging due to the number of ways in which existing research has reported the categorization of pharmacist interventions. For guideline interventions, the study by Doucette et al. reported a physician acceptance rate of 41.7% for addition of new medication, which had the lowest approval rate among a number of recommendations. This finding is similar to that in the current study of a 41.41% prescriber approval rate for guideline adherence recommendations.26 In terms of cost-saving interventions, 1 study reported physician approval of formulary recommendations (i.e., generic substitution, conversion of nonformulary drug to formulary drug).25 This study by DeName et al. (2008) assessed MTM services provided via a free-standing ambulatory clinic and recommendations communicated to physicians through postal or intercampus mail.25 The approval rate for formulary recommendations was 67.5%, compared with 58.2% approval rate for cost-saving interventions in the current study.25 The higher approval rate in the study by DeName et al. may be due to the collaborative care agreements between physicians and pharmacists that were in place within the ambulatory clinic.25 Comparisons of prescriber approval of safety interventions between the present study and existing literature are more difficult for the 3 intervention categories because of reported rates of physician approval for individual safety recommendations or the incorporation of safety recommendations within a broader category of medication-related interventions.
Although several studies have reported physician approval of recommendations for different categories of interventions,\textsuperscript{25,26} the current study additionally evaluated if prescriber approval rates varied between intervention categories. In the current study, approval of cost-saving interventions (58.2\%) was significantly higher than approval for both guideline adherence (41.0\%) and safety concern recommendations (44.3\%), but prescriber approval rates for guideline adherence and safety concern recommendations did not significantly differ. One possible reason for higher approval of cost-saving interventions may be the ease of prescriber decision making for these recommendations, which often involved a switch from brand name drug to the generic equivalent and may be perceived by prescribers as “low risk.” Unlike brand to generic medication changes, guideline adherence and safety concern interventions frequently involved a notable change in medication therapy (e.g., addition of an angiotensin-converting enzyme inhibitor to the regimen of a diabetic patient). In a review of studies assessing prescriber response to drug safety alerts in computerized physician order entry, safety alerts were overridden by physicians in 49\% to 96\% of cases,\textsuperscript{37} suggesting that it is not uncommon to have low prescriber approval rates for safety recommendations.

The reasons for lower prescriber approval rates for guideline adherence can be numerous and should be considered for future research. As previously discussed, untreated indications are one of the most common MRPs, and a number of studies have shown that a considerable proportion of patients with certain indications do not receive appropriate pharmacotherapy established in CPGs.\textsuperscript{38-41} Addition of a new drug to a patient’s medication profile can be viewed as different from a cost-saving or safety concern intervention because it may require additional patient information or consume more of the prescriber’s time, perhaps causing the prescriber to set aside the fax recommendation. Excluding prescriber nonresponse in our study, the combined rate for returned faxes with either an approval or denial was lowest for guideline adherence (59.0\%) versus 68.7\% for cost saving and 76.3\% for safety concerns (data not reported in tables). Prescriber responses to clinical recommendations can involve the complex phenomenon of psychological reactance including implied threat, particularly for unsolicited recommendations.\textsuperscript{42}

The present study also found that overall approval of all recommendations and approval rates for guideline adherence recommendations were lower for specialty prescribers than for PCPs. However, differences were not observed for the other intervention categories. This finding may be attributed to a myriad of factors including specialist training, focus on a single morbidity of the patient, the lack of awareness of medications prescribed by other prescribers (e.g., a pain specialist may be prescribing a pain medication while paying less attention to a patient’s other diseases). On the other hand, PCPs in general may have more information regarding the patient’s total drug regimen along with greater responsibility to manage all of a patient’s conditions and, as such, may have a greater willingness to approve pharmacist recommendations. From the available information, assessment of baseline characteristics and sensitivity analysis did not indicate that the difference in rate of prescriber approval of pharmacist recommendations for specialists versus PCPs was attributable to treating clinically different patient populations. The findings in the present study suggest the potential need to approach the specialist differently than the PCP when initiating a medication-related recommendation.

Limitations
Although the results of this study are informative and represent a real-world intervention, there are several limitations. First, failure to receive a fax from the prescriber (i.e., no response) was conservatively defined as a prescriber decline in the present study. It is possible that the prescriber may have addressed the recommendation without informing the MMC. This information was unavailable, and if this occurred, prescriber approval could be higher than that reported. Lack of a response could be attributed to several reasons including but not limited to nonacceptance of MTM services by the prescriber, disagreement with recommendation, forgetting to respond, the decision to postpone action on the recommendation until the next consultation with the patient, following through on the recommendation without informing the MMC, recommendations not clinically appropriate, or incorrect fax number. Second, we were primarily interested in prescriber approval rates by category of intervention and therefore did not examine the reasons for prescriber denials and no response. The reasons for prescriber nonresponse and denials have potential implications for process quality improvement and should be explored in future studies.

Third, because prescriber categories were based on board certifications available on websites, these may not reflect complete accuracy of prescriber practice and thus could affect the reported findings by prescriber type. Furthermore, we incorporated the nurse category under specialty prescribers (39 interventions from 29 nurse prescribers); some nurses may work in primary care practices and would therefore be misclassified. Fourth assessment of baseline characteristics and sensitivity analysis from available information did not indicate that the difference in approval rates observed between PCPs and specialists were likely due to prescribers treating clinically different patient populations. However, it is possible that the available information may not be adequate to establish definitively that the patient populations were similar.

Fifth, it is possible that prescribers who are younger and who have fewer years in practice are more responsive to pharmacist recommendations than prescribers who are older and have
practiced for a longer period of time. Since such information on prescriber characteristics was not available, they were not controlled for in the analysis. Sixth, these study results pertain only to interventions for approximately 25% of the high-risk beneficiaries enrolled in the pilot MTMP. Finally, because of the method of referral of the 4,967 patients to this pilot MTMP from a population of approximately 2 million Medicare Part D beneficiaries, this sample may not be representative of MTM-eligible beneficiaries in Medicare PDPs.

Conclusions
Although lower than the prescriber approval rates of pharmacist recommendations reported previously for face-to-face interactions, prescribers overall responded favorably to an MTMP that communicated recommendations via prescription faxes. The differences in the rates of prescriber approval by category of pharmacist-initiated recommendations, as well as differences in approval by prescriber type, suggest an opportunity for future research, particularly in examination of the reasons for prescriber denial and nonresponse. Future research focusing on optimal communication and educational methods targeting observed differences may be useful to better understand how to increase prescriber response and approval of pharmacist-initiated recommendations.

REFERENCES

Authors
PRASADINI N. PERERA, MS, is Graduate Research Assistant, College of Pharmacy; MIGNONNE C. GUY, PhD, is Assistant Research Scientist, Center for Health Outcomes and PharmacoEconomic Research; ASHLEY M. SWEANEY, PharmD candidate, is a Pharmacy Intern, Medication Management Center; and KEVIN P. BOESEN, PharmD, is Director, Medication Management Center, University of Arizona, Tucson, Arizona.

AUTHOR CORRESPONDENCE: Mignonne C. Guy, PhD, Center for Health Outcomes and PharmacoEconomic Research, University of Arizona, 1295 N. Martin Ave., Tucson, AZ 85721-0202. Tel: 520.626.6478; E-mail: guy@pharmacy.arizona.edu.

DISCLOSURES
This work was supported in part by Wellpoint Inc. through a service contract with the Arizona Board of Regents at the University of Arizona’s College of Pharmacy Medication Management Center. The authors report no financial or other conflicts of interest.

Guy conceived and designed this study, Sweaney collected the data, and Perera interpreted the data. Perera wrote the manuscript with the assistance of Guy and Sweaney, and Guy revised the manuscript with the assistance of Boesen and Perera.
Evaluation of Prescriber Responses to Pharmacist Recommendations
Communicated by Fax in a Medication Therapy Management Program (MTMP)


ABSTRACT

BACKGROUND: Medication nonadherence is a major concern for many health care stakeholders. Improving medication adherence in health plan members who have both hypertension and diabetes is essential for the successful management of these chronic diseases, with anticipated outcomes in decreased health care utilization, all-cause mortality and cost.

OBJECTIVE: To (a) identify patients who are potentially nonadherent to antidiabetic or antihypertensive agents within 1 managed care organization and (b) determine the relationship of rates of medication nonadherence with 2 mail intervention programs that involved quarterly medication-specific profiles of patients with potential nonadherence sent to primary care physicians (PCPs) and general medication adherence letters sent to patients with potential nonadherence.

METHODS: The study sample consisted of commercial members, Medicare Advantage-Prescription Drug Plan (MA-PD) members and Medicare Prescription Drug Plan (PDP) members who filled prescriptions for antihypertensive and antidiabetic medications and utilized their managed care pharmacy benefit during each measurement quarter (3 months) in the 2-year study period. Nonadherence was defined as a medication possession ratio (MPR) less than 77.0% for 1 or more antihypertensives and/or antidiabetic medications for each standalone calendar quarter. The first intervention, letters to PCPs with patient-specific medication profiles for 2008 Q2, began 6-8 weeks after 2008 Q2 and continued for each standalone calendar quarter through the end of the study period in 2010 Q1 (January 1, 2010, through March 31, 2010). We assumed that patient care was managed by PCPs for hypertension and diabetes treatment. The medication profile also included antihyperlipidemic medication claims information, but there was no adherence analysis performed for antihyperlipidemic medications. The second intervention, letters sent to potentially nonadherent patients, began 6-8 weeks after 2009 Q1 for patients with MPR less than 77% for 1 or more antidiabetic or antihypertensive medications in 2009 Q1 and continued for each standalone calendar quarter through the end of the study period in 2010 Q1.

RESULTS: Because there were 2 different interventions, 2 baseline adherence rates were calculated, for 2008 Q2 for the PCP mailing and for 2009 Q1 for the patient mailing. Compared with the baseline nonadherence rate in 2008 Q2 (35.6%), a small increase in nonadherence was observed in 2008 Q3 (36.4%), following by 6 calendar quarters of lower rates of nonadherence with a 27.7% nonadherence rate in the last measurement period in 2010 Q1. Compared with the nonadherence rate of 30.8% in baseline 2 (2009 Q1), the patient mailings were associated with small increases in nonadherence to 31.4% in 2009 Q2 and 31.1% in 2009 Q3, respectively, followed by lower nonadherence rates in 2009 Q4 (29.2%) and 2010 Q1 (27.7%).

CONCLUSIONS: A 2-part intervention that involved mailings to PCPs for patients with both diabetic and antihypertensive medications who were potentially nonadherent to at least 1 medication, followed 9 months later by a general mailing sent to these potentially nonadherent patients regarding medication adherence, was associated with apparent improvement. However, the effect of the 2-part intervention on medication nonadherence could not be isolated because of coincident disease management interventions in diabetes and hypertension during the 2-year study period.

What is already known about this subject

- There are many barriers to medication adherence especially in members with chronic disease(s) such as diabetes, hypertension, and hyperlipidemia. Many different interventions have been used to improve medication adherence including educational strategies. Effects of educational strategies alone have produced inconsistent results, and multifaceted or multidisciplinary interventions are generally more effective.
- A real-time fax intervention with prescribers of antidepressant medications for patients with delayed refills (more than 10 days) did not improve adherence; average antidepressant nonadherence rates among patients with delayed refills were approximately 75% (Baumbauer et al., 2006). The combination of monthly mailed personalized letters to patients nonadherent to antidepressants and lists of nonadherent patients sent to prescribers was associated with a small difference in adherence rates (MPR of 67% or more) at 90 days (66.9% intervention vs. 65.5% control, P < 0.001) and at 180 days (52.3% intervention vs. 50.2% control, P < 0.001; Hoffman et al., 2003).
- Roumie et al. (2006) in a multifaceted intervention that included letters sent to patients combined with provider education (e-mail with Web-based link with hypertension treatment guidelines) and computerized alerts to providers found significantly better mean blood pressure after 6 months of follow-up compared with provider education alone or provider alerts plus provider education, and more patients in the combination intervention with patient letters attained systolic blood pressure control ([140 mm Hg]), 60% versus 42% for provider education only and 41% for provider education plus alert (P = 0.012).
Successful management of diabetes and hypertension is directly associated with patient adherence to prescribed drugs. A wide array of medications is used to manage these conditions, yet their clinical impact is limited by poor adherence rates. By receiving preventive care and by controlling blood glucose, hypertension, and hyperlipidemia through diet, exercise, and medication adherence, patients with diabetes can potentially avoid complications including (but not limited to) heart disease, stroke, blindness, and renal failure. Studies have shown that rates of refilling prescriptions are an accurate measure of overall adherence in a closed pharmacy system, provided that refills are measured at several points in time. Medication nonadherence is a recognized public health concern, and nonadherence rates vary considerably among studies. For example, nonadherence for diabetic patients receiving oral antidiabetic agents ranged from 36% to 93% in 1 systematic review by Cramer (2004). Most studies of nonadherence use medication possession ratios (MPRs), but other measures of adherence include proportion of days covered or the proportion of doses taken as prescribed. Investigators have found that improving medication adherence is associated with decreases in adverse drug events, hospitalizations, health care costs and utilization, and all-cause mortality. Due to the adverse consequences of uncontrolled diabetes and hypertension, medication adherence is important to improve treatment benefits and prognosis.

Numerous articles in the medical literature have described barriers to medication adherence. Interventions that have been associated with improved medication adherence include combined behavioral and educational approaches, such as (a) patient medication plan followed by patient visits and medication plan revisions, or telephone assessment of follow-up medication use; (b) pharmacist-tailored counseling session on medication adherence and knowledge; (c) pharmacist identification of potential drug-related problems (DRPs) or actual DRPs with specifically developed interventions; (d) patient-centered, educational-behavioral interventions, such as pharmacist tailored education programs and counseling sessions or patient education on self-monitoring of blood pressure/blood glucose; and (e) tablet counts and customized telephonic counseling and custom packaging of medications.

For patients receiving medications for chronic diseases, improvements in health outcomes and adherence are most often realized when multiple interventions have been utilized, such as information/education, counseling, reminders, psychological therapy, mailed communications, reinforcement, family therapy, manual telephone follow-up, involving patients in their own care through self-monitoring, and others. The Cochrane systematic review by Haynes et al. (2008) found that 4 of 10 interventions for short-term treatments reported in 9 randomized controlled trials (RCTs) had significant effects on both medication adherence and clinical outcome, and 1 intervention in 1 RCT improved patient adherence but not clinical outcome. Of 81 interventions for long-term treatments reported in 69 RCTs, 36 (44%) improved medication adherence, but only 25 (31%) improved at least 1 clinical outcome; almost all of the effective long-term interventions were complex (e.g., combinations of reminders, psychological therapy, telephone calls). Additionally, even effective interventions produced only modest results.

Kripalani et al. (2007) also found that most educational interventions to help patients understand their conditions and become empowered to adhere to treatment do not improve health outcomes or adherence rates. However, one of the studies reported by Haynes et al., by Márquez Contreras et al. (2005), did show significant improvement in antihypertensive medication adherence and blood pressure control when educational messages provided either by nurse telephone calls (separate calls at 15 days, 7 weeks, and 15 weeks to encourage compliance) or a patient letter (information about the importance of compliance mailed at 15 days, 2 months, and 4 months) were added to usual care. Rates of compliance and blood pressure control, respectively, were 96% and 63% for telephone calls, 91% and 61% for mail, and 69% and 47% for
usual care. Therefore, a multidisciplinary team approach and/or a multifaceted approach may increase medication adherence and improve patient outcomes.

Hoffman et al. (2003) conducted an RCT in which patients newly prescribed antidepressant medication were assigned either to a control group or to an educational intervention consisting of personalized letters to patients describing the importance of medication adherence and letters to physicians that included lists of nonadherent patients, with both sent 20–25 days after the end of each month. Outcomes were followed for 6 months using a pharmacy claims database and included (a) MPR indicating less than 10 gap days per 30-day period (i.e., 67% or more) and (b) the 2 principal Healthcare Effectiveness Data and Information Set (HEDIS) scores in depression pharmacotherapy, the percentages of patients who take the medication with no more than 30 gap days for the initial 12-week (84 days) acute phase and continue taking the medication with no more than 51 gap days for at least 6 months (180 days). In intention-to-treat analysis, the intervention group (n = 4,899 patients and 3,474 prescribers) displayed slightly greater adherence compared with the control group (n = 4,665 patients and 3,547 prescribers) at both 90 days (66.9% vs. 65.5%, respectively) and 180 days (52.3% vs. 50.2%, respectively, P < 0.01). After adjusting for covariates, the intervention showed a significant impact on adherence (P < 0.01).

Bambauer et al. (2006) used an interrupted time series analysis to evaluate the effects of real-time faxed alerts to physicians for potentially nonadherent adult, antidepressant therapy-naïve patients (n = 13,128) in a large nonprofit managed care organization (MCO). Potential nonadherence was defined as a gap of more than 10 days from the prior medication fill (or refill) during the initial 6 months of medication therapy. Nonadherence rates among patients with delayed refills remained constant at approximately 75% (P = 0.22) over the 2-year study period (2002–2004). Adherence rates decreased over time, with patients not having antidepressants available for approximately 40% of the days of treatment. The authors suggested that a multifaceted approach including multiple mailings, patient phone calls, or patient visits, or a multidisciplinary approach using pharmacists, nurses, or specific case managers might be more likely to improve adherence.

Roumie et al. (2006) evaluated the effects of provider and patient interventions on blood pressure control in a 6-month, cluster RCT in a hospital- and community-based Veterans Affairs (VA) population in Tennessee, using a sample of 1,341 veterans (n = 182 providers) who filled prescriptions at the VA, had 2 uncontrolled systolic blood pressure (SBP) values (greater than 140 millimeters mercury [mm Hg]) in the prior 6 months, and were taking 1 antihypertensive agent. Providers were randomly assigned to (a) provider education only, including an e-mail with a Web-link to the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) Guidelines; (b) provider education plus a computerized patient-specific electronic notification/alert; or (c) provider education, alert, and patient education, which consisted of a personalized patient letter containing educational information on hypertension, medication adherence, lifestyle modification, conversations with providers, and where to go to get more information. The primary outcome, the proportion of patients with an SBP less than 140 mm Hg at 6–month follow-up, was significantly better for the combination of provider education, alert, and patient education (60%) than for either provider education plus alert (41%) or provider education only (42%; P = 0.012). In a separate analysis under the conservative assumption that no patient lost to follow-up (27% of study patients) achieved SBP control, control rates for the 3 groups were 45%, 27%, and 33%, respectively (P = 0.013). Mean follow-up blood pressures were 138/77 mm Hg in the 3-intervention combination group, compared with 146/76 mm Hg for provider education plus alert and 145/78 mm Hg for provider education only.

Although many medication adherence improvement interventions are multifaceted and complex, we sought to develop an intervention based on an automated process for reporting to physicians and patients that is feasible for MCOs to use on a routine basis. Thus, we performed a descriptive, business-case analysis to assess the association of potential medication nonadherence with an intervention that involved quarterly letters mailed to primary care physicians (PCPs) with potentially nonadherent patient-specific medication profiles. We later added a patient educational mailing component to the intervention. The primary objective of this study was to determine whether these interventions would be associated with reduction in nonadherence rates for antihypertensive or antidiabetic medications in a target population of patients receiving at least 1 drug in both medication classes in standalone calendar quarters.

Methods

Study Sample and Design

EmblemHealth provides health insurance through its companies Group Health Incorporated (GHI) and HIP Health Plan of New York (HIP). Groups and individuals can choose a preferred provider organization, an exclusive provider organization, or a health maintenance organization (HMO). The Clinical Pharmacy Department serves as its own pharmacy benefit management (PBM) company and is integrally involved in the health plan’s Pharmacy & Therapeutics (P&T) Committee, which reviews the drug formulary to ensure that it is up-to-date and reflects evidence-based practice. The P&T Committee approved the present study.

The study involved a retrospective analysis of pharmacy claims data for approximately 380,000 Medicare and commercial members who obtained their pharmacy benefits through HIP, the largest HMO in New York City based on membership.
Only paid pharmacy claims (net of removal of matched paid and reversed claims) were used in an effort to minimize mailing of false-positive letters. The analysis was conducted for all pharmacy claims including both community and mail order pharmacy; members can receive up to a 90-day supply at either a community pharmacy or from mail order.

Data assessments were made for each calendar quarter, beginning at the end of the second quarter of 2008 (2008 Q2) using the pharmacy claims data from April 1, 2008, to June 30, 2008. Eight calendar quarters were included in this analysis—2008 Q2 (April 1, 2008, through June 30, 2008) through 2010 Q1 (January 1, 2010, through March 31, 2010). Each quarterly mailing was sent out approximately 6-8 weeks after the quarter ended. All Medicare Advantage-Prescription Drug Plan (MA-PD), Medicare Prescription Drug Plan (PDP), and commercial members regardless of age who had an assigned PCP and active pharmacy coverage as of the last day of each calendar quarter in the study period were eligible for this study. For example, in order to be included in the analysis for the first measurement quarter (April 1, 2008, through June 30, 2008), the patient must have had active status in the plan’s system on June 30, 2008. We did not exclude patients who joined the health plan during the analysis quarter (i.e., patients were included who may have had pharmacy benefits that commenced after the first day of the calendar quarter).

To identify the study sample at the end of each quarter, all members who had active pharmacy benefit coverage as of the last day of the previous quarter were separated into 2 groups using First DataBank GC3 codes (Table 1). Group 1 included members who had at least 1 pharmacy claim for an antidiabetic medication, and group 2 included members who had at least 1 claim for an antihypertensive medication. These 2 groups of patients were then cross-referenced to obtain our final total study sample for that particular quarter (Figure 1). Because some members move in and out of plan coverage for personal reasons (e.g., employment change, retirement), the study sample varied throughout the study period. During the study, we tried to keep the GC3 tables updated as new GC3 codes became available, were deleted, or were changed (e.g., the GC3 code for Exubera [inhaled insulin] was deleted after it was taken off the U.S. market; the GC3 code for Exforge hydrochlorothiazide [HCT] was added after it became available on the U.S. market).

### Table 1: First DataBank GC3 Codes and Code Descriptions

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A4A</td>
<td>Antihypertensives, vasodilators</td>
</tr>
<tr>
<td>A4B</td>
<td>Antihypertensives, sympatholytic</td>
</tr>
<tr>
<td>A4D</td>
<td>Antihypertensives, ACE inhibitors</td>
</tr>
<tr>
<td>A4F</td>
<td>Antihypertensives, angiotensin receptor antagonists</td>
</tr>
<tr>
<td>A4K</td>
<td>ACE inhibitor/calcium channel blocker combination</td>
</tr>
<tr>
<td>A4Y</td>
<td>Antihypertensives, miscellaneous</td>
</tr>
<tr>
<td>A9A</td>
<td>Calcium channel blocking agents</td>
</tr>
<tr>
<td>JFA</td>
<td>Alpha/beta-adrenergic blocking agents</td>
</tr>
<tr>
<td>JFB</td>
<td>Alpha-adrenergic blocking agents</td>
</tr>
<tr>
<td>JFC</td>
<td>Beta-adrenergic blocking agents</td>
</tr>
<tr>
<td>R1H</td>
<td>Potassium sparing diuretics</td>
</tr>
<tr>
<td>R1L</td>
<td>Potassium sparing diuretics in combination</td>
</tr>
<tr>
<td>R1M</td>
<td>Loop diuretics</td>
</tr>
<tr>
<td>R1F</td>
<td>Thiazide and related diuretics</td>
</tr>
<tr>
<td>A4C</td>
<td>Antihypertensives, ganglionic blockers</td>
</tr>
</tbody>
</table>

### Antidiabetics

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4F</td>
<td>Antihyperglycemic, (DPP-4) inhibitor and biguanide combinations</td>
</tr>
<tr>
<td>C4G</td>
<td>Insulins</td>
</tr>
<tr>
<td>C4H</td>
<td>Antihyperglycemic, amylase analog-type</td>
</tr>
<tr>
<td>C4I</td>
<td>Antihyperglycemic, incretin mimetic (GLP-1 receptor agonist)</td>
</tr>
<tr>
<td>C4J</td>
<td>Antihyperglycemic, DPP-4 inhibitors</td>
</tr>
<tr>
<td>C4K</td>
<td>Antihyperglycemic, insulin-release stimulant type</td>
</tr>
<tr>
<td>C4L</td>
<td>Antihyperglycemic, biguanide type (non-sulfonylurea)</td>
</tr>
<tr>
<td>C4M</td>
<td>Antihyperglycemic, alpha-glucosidase inhibitor (N-S)</td>
</tr>
<tr>
<td>C4N</td>
<td>Antihyperglycemic, insulin-response enhancer (N-S)</td>
</tr>
<tr>
<td>C4O</td>
<td>Antihyperglycemic, absorption modifier, unspecified</td>
</tr>
<tr>
<td>C4P</td>
<td>Antihyperglycemic, unspecified mechanism</td>
</tr>
<tr>
<td>C4Q</td>
<td>Antihyperglycemic combinations</td>
</tr>
<tr>
<td>C4R</td>
<td>Antihyperglycemic, insulin-response and release combinations</td>
</tr>
<tr>
<td>C4S</td>
<td>Antihyperglycemic, insulin-release stimulant and biguanide combinations</td>
</tr>
<tr>
<td>C4T</td>
<td>Antihyperglycemic, insulin-response enhancer and biguanide combinations</td>
</tr>
<tr>
<td>C4U</td>
<td>Antihyperglycemic, biguanide and dietary supplement combinations</td>
</tr>
</tbody>
</table>

### Antihyperlipidemics

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M4C</td>
<td>Lipotropics (continued 2)</td>
</tr>
<tr>
<td>M4D</td>
<td>Antihyperlipidemics—HMG-CoA reductase inhibitors</td>
</tr>
<tr>
<td>M4E</td>
<td>Lipotropics</td>
</tr>
<tr>
<td>M4F</td>
<td>Lipotropics (continued 1)</td>
</tr>
<tr>
<td>M4L</td>
<td>Antihyperlipidemics—HMG-CoA reductase inhibitor and niacin</td>
</tr>
<tr>
<td>M4M</td>
<td>Antihyperlipidemics—HMG-CoA reductase inhibitor and cholesterol absorption inhibitor</td>
</tr>
<tr>
<td>M4J</td>
<td>Antihyperlipidemics—HMG-CoA and platelet inhibitor combination</td>
</tr>
<tr>
<td>D7L</td>
<td>Bile salt sequestrants</td>
</tr>
</tbody>
</table>

### Descriptive Analysis of Mail Interventions with Physicians and Patients to Improve Adherence with Antihypertensive and Antidiabetic Medications in a Mixed-Model Managed Care Organization of Commercial and Medicare Members

Adherence Calculation

The MPR was the study adherence measure. Nonadherence was defined as an MPR less than 0.77 (77%), meaning that a patient missed an average of at least 7 days supply of medication within a 30-day period. Medication adherence rates were calculated at the end of each quarter as follows:

First, for each member in the sample, we calculated the MPR for each antihypertensive and antidiabetic medication using the sum of days supply during the measurement quarter divided by the total number of days in the measurement quarter (90 days for all measurement quarters). Prescriptions with the same generic composition but with different strengths were considered to be the same medication. If the calculated MPR was equal to or greater than 1.0 (100%) for any individual medication, the patient was considered to have perfect adherence.
adherence to that particular medication, and all subsequent claims for that particular medication were excluded from further analysis in that calendar quarter. However, if the patient had paid claims for other hypertension or diabetes medications in that quarter, those claims were analyzed. For example, if a patient took both lisinopril and metformin, and only the prescriptions for lisinopril had a total of 90 days supply in the measurement quarter, all claims for lisinopril were excluded after this step and the claims for metformin were analyzed. Because we analyzed claims by calendar quarter, without longitudinal analysis across quarters, false positive indications of nonadherence (i.e., MPR less than 0.77) could have occurred (see Limitations section).

Following this step, medications with an MPR less than 1.0 (100%) were separated into 2 groups for further analysis. If the MPR was less than 77% using any of the following methods, the member was considered to be nonadherent:

**Medications with 1 Claim.** For medications with only 1 claim during the measurement quarter, the MPR was calculated as the total days supply on the claim divided by the number of days from the claim date to the end of the quarter. For example, for a member with only 1 pharmacy claim for a 30-day supply of atenolol on October 10, 2008, the MPR was calculated using 30 days supply divided by 82 (number of days between October 10, 2008, and December 31, 2008). This example has an MPR of 0.366, and the patient was considered nonadherent to atenolol in 2008 Q4.

**Medications with 2 or More Claims.** For medications with 2 or more claims during the quarter, 2 calculations were performed. First, the MPR was calculated using the total days supply for all the claims (excluding the last claim’s days supply) divided by the total days from the date of the first claim to the date of the last claim. For example, for a member with three 30-day supply pharmacy claims for atenolol on October 1, 2008, November 15, 2008, and December 25, 2008, the MPR was calculated using 60 (total of 90 days supply for all 3 prescriptions minus 30, which is the days supply on the last claim on December 25) divided by 84 (number of days between October 1, 2008, and December 25, 2008), which yielded an MPR of 0.714, and the patient was deemed nonadherent to atenolol in 2008 Q4. Second, the MPR was calculated by dividing the last claim’s days supply by the number of days supply for all the claims (excluding the last claim’s days supply) divided by the total days from the date of the first claim to the date of the last claim.
Descriptive Analysis of Mail Interventions with Physicians and Patients to Improve Adherence with Antihypertensive and Antidiabetic Medications in a Mixed-Model Managed Care Organization of Commercial and Medicare Members

from the date of the last claim to the end of the measurement quarter. For example, for a member with two 30-day supply pharmacy claims for atenolol on October 1, 2008, and November 1, 2008, the MPR was calculated using 30 (the days supply for the last claim on November 1, 2008) divided by 60 (the number of days between November 1, 2008, and December 31, 2008), which yielded an MPR of 0.50, and the patient was deemed nonadherent to atenolol in 2008 Q4.

Approximately 6 to 8 weeks after identifying potentially nonadherent patients at the end of each quarter, we mailed a cover letter and patient medication profiles to PCPs who had at least 1 nonadherent patient. Each PCP received a cover letter explaining the initiative (Appendix 1) and a patient-specific medication profile for each nonadherent patient (i.e., some PCPs received as little as 1 patient medication profile and other PCPs received multiple patient medication profiles). The medication profile included information about medication names, dosage, dispensing date(s), quantity dispensed, days supply, and name of the prescriber(s). If patients were also taking antihyperlipidemic medications based on the GC3 codes in Table 2, they were also included in the report; however MPRs were not calculated for these antihyperlipidemic medications.

In an effort to further improve medication adherence and potentially enhance clinical outcomes related to diabetes and hypertension treatment, we added a second quarterly intervention beginning after the analysis for 2009 Q1 (January 1, 2009, through March 31, 2009). This intervention, mailings to patients, provided general educational materials related to hypertension and diabetes medication adherence (e.g., specific medication use history derived from pharmacy claims was not part of the intervention), as well as information about the importance of taking medication as prescribed. The mailings also included a “tip sheet” with likely situations that members may encounter as obstacles to adherence to their medication regimens and a list of possible solutions to overcome these obstacles (Appendix 2). All members identified as potentially nonadherent each quarter (i.e., MPR of less than 77% for any antihypertensive or antidiabetic medication) received this general patient mailing approximately 6-8 weeks after the end of each calendar quarter beginning on approximately May 15, 2009, through May 31, 2009.

Measurement and Analysis
Because 2 types of interventions were implemented at different times, 2 baseline nonadherence rates were calculated. The first baseline (baseline 1) was the percentage of potentially nonadherent patients for claims with dates of service in 2008 Q2 (i.e., from April 1, 2008, through June 30, 2008). The second baseline (baseline 2) was the percentage of potentially nonadherent patients calculated for claims with dates of service in 2009 Q1 (i.e., from January 1, 2009, through March 31, 2009). In keeping with the descriptive, business-case nature of the analysis, rates of potentially nonadherent patients in each quarter were compared with one or both baseline rate(s) using a 2x2 Pearson chi-square test when applicable. For example, the rate of potentially nonadherent patients from October 1, 2008, through December 31, 2008 (2008 Q4) was compared with baseline 1 rate (2008 Q2) to assess the physician letter intervention; and the rate of potentially nonadherent patients from October 1, 2009, through December 31, 2009 (2009 Q4) was compared with both the baseline 1 rate (2008 Q2) and the baseline 2 rate (2009 Q1) to assess both the physician and patient interventions. Statistical analyses were performed using Minitab version 15 (Minitab Inc., State College, PA) and an a priori alpha level of 0.025.

Results
In the first baseline measurement period (2008 Q2), 30,132 total members were included in the sample, of whom 10,722 (35.6%) had an MPR less than 77% for 1 or more antihypertensive or antidiabetic drugs (Table 2). The number of members identified with pharmacy claims for antihypertensive and antidiabetic medications differed each quarter, ranging from 29,051 (2008 Q3) to 32,833 (2010 Q1). The number of potentially nonadherent members varied from 9,086 (2010 Q1) to 10,722 (2008 Q2).

The percentage of nonadherent members increased slightly in 2008 Q3 during the quarter in which the first mailings to PCPs occurred and then decreased to 34.0% in 2008 Q4 and 30.8% in 2009 Q1 (Table 2, Figure 2). Following the addition of the member intervention, the medication nonadherence rate decreased further to 27.7% in 2010 Q1, the last measurement quarter in this study.

Discussion
Numerous types of interventions have been utilized in various disease states and patient populations to improve medication adherence.9,23,24 A small number of other researchers have utilized combined mailed (or e-mailed) interventions to prescribers and patients. Examples of these interventions include patient education, reinforcement, and reminding; simplification of the drug regimen (e.g., once-daily versus multiple-daily dosing, insulin pens versus vials); and allied health care professional consulting. Because most MCOs are required to supply HEDIS reports for the effectiveness of antidepressant medication management, some published data are available on medication adherence and the pharmacologic management of depression using mailed interventions. Bambauer et al. performed a physician-only faxed letter intervention and found that adherence rates did not improve but remained unchanged at approximately 75% among patients who were late with refills.23 However, in the study by Hoffman et al., the combination of a personalized prescriber letter and patient letter slightly improved antidepressant adherence compared
with usual care.20 Although the present study did not have a control or comparison group, we found that adherence was enhanced, as it was in the study by Hoffman et al., when a second intervention (the member letter) was added to the initial intervention (the PCP letter). This finding suggests that the standalone physician intervention may not have been sufficient to enhance medication adherence. Two additional studies conducted in samples of patients with hypertension have shown that interventions aimed at health care providers and/or nonadherent patients can enhance medication adherence.21,22 These include the study by Roumie et al., which found better SBP control for a combination of provider education, alerting, and patient education compared with provider-only interventions, and by Márquez Contreras et al., which found better medication adherence and blood pressure control for either mailed or telephonic patient education compared with usual care.21,22 The interventions in the present study were similar to those of Roumie et al., in that the PCP received both a personalized letter with a list of nonadherent patients and guideline information, and patients received a letter describing issues related to medication adherence and education about hypertension and diabetes. Similar to the findings of the study by Roumie et al., when the mailed interventions were intensified in the present study, a better response was obtained.

The goal of the PCP mailing was to improve physician awareness of nonadherence with antihypertensive and antidiabetic agents. We hoped that PCPs would use the information to initiate personalized discussions with their patients about the importance of medication adherence. Copher et al. (2010) reported on a study of providers’ awareness of patient adherence to treatments for postmenopausal osteoporosis.23 Physicians who responded to a written questionnaire estimated that the patient adherence rate (defined as an MPR of at least 80%) would be approximately 69%. However, the actual adherence rate based on a retrospective analysis of pharmacy claims data was only 48.7%. Additionally, in a study by Lapane et al. (2007) using a convenience sample, 83% of patients reported they would never tell their physician that they were planning not to fill their prescriptions or that they did not want certain medications, and physicians did not seem to know that this lack of communication existed.24 These interesting data suggest that physicians may not be aware of medications that their patients are taking (or are not taking). By having a copy of each patient’s medication profile, PCPs have the “evidence” of potential patient nonadherence that they can use to discuss with patients during patient encounters.

We sent the patient medication adherence report to PCPs (“gatekeepers”) even if they were not the prescriber so they could discuss the report with the patient and assist in coordinating the patient’s care with other members of the multidisciplinary team (e.g., endocrinologist, cardiologist, ophthalmologist, nurse, case manager, nurse practitioner, diabetes educator, nutritionist, pharmacist) to “close the loop.” Additionally, the mailed patient interventions informed members about how to be more medication adherent. If these members realized that they were being closely monitored, which we were unable to

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Member Adherence Rates for Antihypertensive or Antidiabetic Drug Therapy and Counts of Interventions by Calendar Quarter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2008 Q2 Baseline 1</td>
</tr>
<tr>
<td>Total patients with antihypertensive and antidiabetic drug therapy – n</td>
<td>30,132</td>
</tr>
<tr>
<td>Commercially insured patients – n (%)</td>
<td>9,560 (31.7%)</td>
</tr>
<tr>
<td>Total potentially nonadherent patients – n (%)</td>
<td>10,722</td>
</tr>
<tr>
<td>Potentially nonadherent commercial patients – n (%)</td>
<td>3,569 (37.3%)</td>
</tr>
<tr>
<td>Number of patient letters</td>
<td>2,304</td>
</tr>
<tr>
<td>Number of PCPs</td>
<td>2,504</td>
</tr>
<tr>
<td>P value compared with Baseline 1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P value compared with Baseline 2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Baseline 1 is 2008 Q2; the pre-intervention period for quarterly mailing of member-specific nonadherence profiles that began 6–8 weeks after June 30, 2008 (i.e., the first mailing to PCPs was sent between August 15, 2008, and August 30, 2008).

*Baseline 2 is 2009 Q1; the pre-intervention period for the quarterly mailing to the potentially nonadherent members that began about 6–8 weeks after March 31, 2009 (i.e., the first mailings were sent to potentially nonadherent members between May 15, 2009, and May 31, 2009).

*Nonadherence was defined as MPR less than 77% in each (standalone) calendar quarter.

*The count of PCs is equal to the count of letters (i.e., each PCP received 1 or more profiles for all PCP-assigned members found potentially nonadherent to 1 or more antihypertensive or antidiabetic agent).

*P value calculated by Pearson chi-square; a priori critical alpha value was 0.025.

MPR = medication possession ratio; PCP = primary care physician; Q = calendar quarter.
Descriptive Analysis of Mail Interventions with Physicians and Patients to Improve Adherence with Antihypertensive and Antidiabetic Medications in a Mixed-Model Managed Care Organization of Commercial and Medicare Members

In the present study, antihyperlipidemic medication claims information was also provided to PCPs for their information; however, there was no adherence analysis performed for antihyperlipidemic agents. Including antihyperlipidemic agents in the patient medication profile to PCPs was meant to provide a more comprehensive list of the most common types of medications used to manage the metabolic syndrome.27

Another issue raised by the present study is the optimal adherence measure for an MCO. Adherence measurements are typically expressed as a percentage of the total number of doses taken, such as a pill count (if measured prospectively), or the number of days supply of the prescription received (if measured retrospectively) over a specified time period.28 Currently, there is no uniform agreement as to what percentage is the best measure of adherence. Pharmacy refill claims have been widely used to assess medication adherence, and this approach is considered a credible and objective way to evaluate medication adherence in large population-based studies.3,28-30

The type of mailing used to motivate potentially nonadherent patients is also of importance to MCOs. In the present study, a general educational mailing, rather than a mailing containing patient-specific data, was used because we felt that (a) a specific mailing targeting nonadherent patients might engender negative perceptions of the health plan; (b) patients could be falsely identified as nonadherent due to study limitations; and (c) a general educational mailing did not require as much time and resources as an individually targeted intervention would have. Informational interventions, such as the member mailing used in the present study, are cognitive strategies that have been used to improve adherence to chronic therapies and are designed to educate and motivate patients.31 This type of intervention assumes that patients who have an understanding of their medical conditions and how these conditions are best treated will be better informed, more engaged in their own care, and more likely to adhere to treatment. Our member mailing can also be thought of as a behavioral intervention because it acted as a “reminder” to the patients of their hypertension and diabetes and the importance of taking their medications.

Finally, the present study has potential implications for the use of multifaceted (combination) versus single-focus interventions in MCOs. According to Williams et al. (2008) and McDonald et al. (2002), studies that combined cognitive, behavioral, and educational components were more effective than single-focus interventions.10,16 The present study intervention included a combination of behavioral and

FIGURE 2  Percentage of Patients Potentially Nonadherent with At Least 1 Antihypertensive or Antidiabetic Drug—by Calendar Quarter

PCP = primary care physician; Q = calendar quarter.
educational components and was associated with positive results; however, if we were able to include more components, we might have been able to more significantly improve medication adherence.

This pharmacy quality initiative served as the baseline for establishing a model for future programs in the study health plan. A continuous evaluation of the literature will be done to make enhancements to this initiative. The program will be potentially modified in the near future to include an analysis of antihyperlipidemic medications and to increase the percentage of adherent patients. Additionally, a proactive approach of reminding patients to refill their prescriptions at the pharmacy may further improve adherence.

Limitations
First, the study sample was identified solely from pharmacy claims data. Therefore, some patients may have been mistakenly identified as nonadherent if the patient had another insurance carrier and used it for some of his or her prescriptions, participated in a community pharmacy generic drug discount program to obtain some medication, or the patient’s treatment was changed for any reason during the calendar quarter. Without access to medical records or comparison with medical claims data, we could not restrict the intervention to patients with diagnoses of diabetes and hypertension. Therefore, some members may have been incorrectly identified as nonadherent if they were taking antihypertensive and antidiabetic medications for other purposes (e.g., migraine prophylaxis, polycystic ovarian syndrome, or situational anxiety) that may not require daily use.

Second, we initially assumed that the decreased medication nonadherence rates observed in this targeted sample were a result of our interventions. However, when the results of this initiative were shared with the Care Management Department, we learned that other quality improvement initiatives, disease management programs targeting a similar patient population, were ongoing at EmblemHealth and may have contributed to the reduction in nonadherence rates observed in our study. The disease management programs each targeted one disease state, and each program included more than one intervention. All of these programs had been in place for many years; however, the specific interventions changed from year to year. For example, for members with diabetes, the outreach included but was not limited to a health plan member and provider newsletter article, health coaching, and a mailing to PCPs reporting nonadherence to schedules such as hemoglobin A1c and eye exams. For members with hypertension, the major initiative focused on both blood pressure control and stroke prevention using the health plan member and provider newsletters, educational hotline for members, electronic messaging via emails to members, annual birthday card reminder to members for preventive screening, and others.

Third, the analysis was performed quarterly, and there was no longitudinal analysis (i.e., across calendar quarters). Therefore, if a member had received more than 90 days supply of a medication in 1 quarter (e.g., 2 fills of 90 days supply in a given calendar quarter), the member could have been deemed nonadherent if there were no fills in the subsequent calendar quarter. This situation would cause a false-positive nonadherence record for this member for this medication for the succeeding quarter. A member could also be deemed nonadherent in the following example: a member who had claims for HCT 30-day supply on January 1, January 30, February 28, March 30, April 30, May 30, and July 2 would have an MPR of 1.0 (100%) in Q1 and 0.57 (67%) in Q2 and would therefore be deemed nonadherent in Q2.

Fourth, our study was based on the assumption that if a prescription was filled at the pharmacy, then the member received the medication and took it, which may not have been the case. Fifth, although MPR is considered to have high predictive validity for medication adherence, it does not provide adequate information on the consistency of medication refill patterns.

Sixth, several study-specific barriers included incorrect/ out-dated provider and member mail addresses in the study MCO’s system that may have affected the successful delivery of information to the targeted PCPs and/or members. Additionally, some members had incorrectly listed PCPs; and although the study MCO uses the PCP-gatekeeper model, some members may not visit their PCPs regularly but instead visit specialists for their antihypertensive or antidiabetic medications.

Seventh, the objective of this study was to decrease the rate of medication nonadherence in the targeted population, and we did not measure the clinical or economic outcomes associated with nonadherence. Eighth, we did not compare the adherence rates for different classes of medications, although other studies have shown that adherence rates vary among different drug classes both in the same or different therapeutic areas.

Finally, we did not calculate the administrative costs of conducting these interventions. However, after the initial setup, there was only 1 clinical pharmacist and 1 communication specialist working on this project, 4 times per year. We estimate that the average cost including both the labor costs (salary) and mailing costs was approximately $4,500 per quarter in the initial phase of the study for the PCP mailings and approximately $9,000 per quarter in the second phase of the interventions that involved both PCP and member mailings.

Conclusion
Over a nearly 2-year study period, a quality improvement initiative consisting of PCP letters with patient-specific information about nonadherence to antihypertensive and antidiabetic medications and general education letters sent to potentially nonadherent patients, was associated with decreased rates of medication nonadherence.

www.amcp.org  Vol. 17, No. 5  June 2011  JMCP  Journal of Managed Care Pharmacy  363


Descriptive Analysis of Mail Interventions with Physicians and Patients to Improve Adherence with Antihypertensive and Antidiabetic Medications in a Mixed-Model Managed Care Organization of Commercial and Medicare Members

APPENDIX 1

Letter to Primary Care Physicians for Potentially Nonadherent Members

Date

<PCP First Name>, MD
<Address 1>
<Address 2>
<Address 3>, <State>, <Zip Code>

Subject: 2nd Quarter 2009 Hypertensive, Diabetic and/or Antihyperlipidemic Medication Non-Adherence Report

Dear Dr. <PCP Last Name>:

The enclosed report identifies your HIP patients who had an interruption in either their antihypertensive or hyperglycemic medication during the second quarter of 2009. The interruption of treatment can be a result of a lapse in drugs or a change to an alternative product.

The data for this report is based on pharmacy claims data from the HIP Pharmacy Benefits Program as of June 30, 2009. Please note that not all HIP patients get their drugs (first fill and subsequent refills) through HIP. Therefore, the omission of their names from the enclosed report should not be used to validate their compliance with their medication treatment.

We ask that you discuss the importance of adhering to medication with your patients. The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) * describes the presence of multiple risk factors for coronary heart disease as “metabolic syndrome.” Factors of metabolic syndrome are abdominal obesity, hyperlipidemia, hypertension and insulin resistance. Individuals who have both hypertension and diabetes, with or without hyperlipidemia, are at higher risk for cardiovascular events than individuals with only one of the conditions.

Successful treatment of hypertension and diabetes is directly associated with patient adherence to prescribed drugs. The enclosed report will help you evaluate if there is an adherence issue to medications that not only treat hypertension and diabetes, but also hyperlipidemia. We hope that this report helps you optimize patient care.

We appreciate your continued support in providing quality care to HIP members. If you have any questions, please contact Shu Jing, Clinical Pharmacy Case Manager, at 1-646-447-7284.

Sincerely,

Chief Medical Director

Enclosure: Patient Non-Adherence Medication Report

APPENDIX 2  Member Letter Regarding Nonadherence

Date
<Member First Name> <Member Last Name>
<Address 1>
<Address 2>
<City>, <State>, <Zip Code>

Dear <Member First Name> <Member Last Name>:

HIP Health Plan of New York is dedicated to providing access to quality health care that will give you the best results. We see from our records that you recently have been seen by your doctor for high blood pressure and diabetes. We are writing to share with you how important it is to stay on top of your medications.

High blood pressure (or hypertension) has no warning signs and is often called the “silent killer.” If left untreated, it can hurt arteries and even organs, like the heart and kidneys. Eventually, a person could end up with heart attacks, kidney failure and strokes. Diabetes is an illness in which the level of blood sugar (blood glucose) is above normal. If left uncontrolled, diabetes can raise your chances for many problems that can affect nearly every part of the body including the heart, eyes, kidneys, gums, and teeth.

Many drugs can help. They work in many different ways to lower high blood pressure and blood sugar level. No matter how they work, the most important way to make sure your treatment is successful is to take the medicines as prescribed by your doctor. Skipping doses without telling your doctor can lead to complications or even the illness getting worse. You should never stop taking your medication on your own before talking to your doctor.

Most of the time there is a reason for having skipped a dose. To help you stay on top of your drug schedule we have enclosed a list of possible reasons and their solutions. Also, remember to ask questions and talk to your doctor about your concerns. This is key to staying on top of your health. Only you know how you feel and what kind of questions you have.

At HIP, we are here to help you take care of your condition and you will be hearing from us from time to time with important information to help you have a healthy life.

Sincerely,

Chief Medical Director

Enclosure: How to Keep to Your Drug Schedule Flyer

Tips for Taking Your Medicine Regularly

<table>
<thead>
<tr>
<th>Problem</th>
<th>Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>I always forget to take my medicine or order refills.</td>
<td>• Set up a routine for taking your medicine. Try mixing it in with your daily activity, such as brushing your teeth.</td>
</tr>
<tr>
<td></td>
<td>• Use technologies to remind you, such as a cell phone alarm or a digital assistant alert.</td>
</tr>
<tr>
<td></td>
<td>• Let your pharmacy remind you. Many pharmacies have programs that send you refills by mail or remind you to take your medicine.</td>
</tr>
<tr>
<td>My pills are too big, hard to swallow or taste bad.</td>
<td>• Try cutting large pills in half. Some pills are available at smaller sizes, so you can make up the dose with extra smaller pills. Talk to your doctor before making any changes.</td>
</tr>
<tr>
<td></td>
<td>• If you are taking generic drugs, talk to your doctor about switching to a drug from another manufacturer. Other pills may have a different size or taste.</td>
</tr>
<tr>
<td>I have too many pills. It’s too hard to keep track of them</td>
<td>• See if your medicine comes in a long-acting form, or if there is a combination medicine you can take to lower the pill count. Talk to your doctor before making any changes.</td>
</tr>
<tr>
<td></td>
<td>• Use a daily or weekly pillbox to organize your medicine.</td>
</tr>
<tr>
<td>I don’t need to take my medicine because I feel fine. I feel sick when I take the pill.</td>
<td>• Tell your doctor right away if you feel any discomfort or pain because of your drugs. Your doctor can choose a different medicine for you. Don’t stop taking your medicine without talking to your doctor first.</td>
</tr>
<tr>
<td>I can’t read the medicine label. I don’t understand the label or the directions.</td>
<td>• Ask your pharmacist to explain how to take your medicine.</td>
</tr>
<tr>
<td></td>
<td>• Request larger print or another language on your medicine label.</td>
</tr>
<tr>
<td>I can’t pay for my medicine.</td>
<td>• Ask your doctor if your drugs come in a generic form and if it’s OK for you to switch.</td>
</tr>
<tr>
<td></td>
<td>• If your medicine does not have a generic form, ask your doctor to choose a medicine for you that does come in a generic form.</td>
</tr>
<tr>
<td></td>
<td>• Call the pharmaceutical company. You may be eligible for their drug assistant program.</td>
</tr>
<tr>
<td></td>
<td>• Try using a mail order pharmacy for some of your medicine. This may save you money.</td>
</tr>
<tr>
<td>I don’t understand why I need to take my medicine.</td>
<td>• See your doctor regularly. Form good relationships with your doctor and pharmacist.</td>
</tr>
<tr>
<td></td>
<td>• Don’t be afraid to ask questions. It’s your doctor’s job to help you understand why you need your medicine.</td>
</tr>
</tbody>
</table>
A Comparison of Daily Average Consumption (DACON) of Oxycodone and Oxymorphone Long-Acting Oral Tablets

Mark Rubino, BS Pharm, MHA; Kent H. Summers, PhD; R. Amy Puenpatom, PhD; Chunmay Fu, MS; Robert L. Ohsfeldt, PhD; and Rami H. Ben-Joseph, PhD

ABSTRACT
BACKGROUND: The utilization of high-potency opioids is an important component of chronic pain management, and appropriate utilization of these medicines is a common concern of payers. Two of the most commonly prescribed oral long-acting opioids, oxycodone controlled-release (CR) and oxymorphone extended-release (ER), are FDA-approved for twice-daily dosing, which equates to a theoretical average consumption (DACON) of 2 tablets per day. DACON values greater than 2 have budget and policy implications for managed care pharmacists.

OBJECTIVES: To assess from the perspective of the pharmacy benefit decisions for managed care pharmacists.

METHODS: The main outcome measure for the analysis was DACON. Pharmacy and medical claims data from a large commercially insured population (13 InVision Data Mart database) were analyzed to identify patients with at least 1 pharmacy claim for either oxycodone CR or oxymorphone ER from July 1, 2007, to September 30, 2009. After an initial 30-day titration period, all subjects included in the study had 1 or more claims totaling at least a 90-day supply of either study drug during the subsequent 90 days (DACON measurement period). Patients were excluded if there was evidence of a switch from one to the other study opioid during the 90-day measurement period. There were no limitations on the use of other opioids, either short- or long-acting, during either the DACON measurement period or the previous 6 months (baseline period). In addition, patients were excluded if the enrollee was younger than 18 years old, pregnant, did not have continuous insurance coverage for the 6 months before and after the start of the 90-day DACON measurement, or were enrolled in an HMO plan. Bivariate analyses were performed with between-group differences in DACON values assessed using t-tests and Wilcoxon rank sum tests. Patient characteristics including age, sex, geographic location, and baseline Charlson Comorbidity Index (CCI) for each drug group were evaluated descriptively using either the Pearson chi-square test or t-test. Multivariate analyses were conducted using generalized linear models (GLM) to adjust for the observed heterogeneity among patients in the observational database. For the GLMs, the gamma distribution and log link function were chosen to account for non-normal distributions of DACON. Independent variables included study drug, tablet strengths, age, sex, CCI, the maximum days gap between prescription refills during the DACON measurement period, and other opioid medication use. Several sensitivity analyses were conducted to verify all findings.

RESULTS: The final analyses were conducted on 6,567 oxycodone CR patients and 796 oxymorphone ER patients. The unadjusted DACON mean value for the highest strength of oxycodone CR 80 milligrams (mg) was 3.9, compared with 2.9 for oxymorphone ER 40 mg (P<0.001); mean DACON values were 3.0 versus 2.4, respectively, for lower strengths (P<0.001) and 3.1 versus 2.5 for all strengths (P<0.001). After adjusting for age, sex, CCI, maximum gap days, and other opioid medication use, a risk-adjusted mean difference in DACON remained, with oxycodone CR patients receiving on average 0.6 tablets more per day than those dispensed oxymorphone ER (P<0.001). The direction, magnitude, and statistical significance of these differences were essentially unchanged in sensitivity analyses.

CONCLUSIONS: On average during a 90-day time period, patients taking oxymorphone ER consumed 0.6 fewer tablets per day than did patients taking oxycodone CR. Further research is necessary to see if this difference amounts to cost savings for health plans that provide prescription reimbursement for patients with chronic pain syndromes.

J Manag Care Pharm. 2011;17(5):367-76

Copyright © 2011, Academy of Managed Care Pharmacy. All rights reserved.
Opioid analgesics are indicated for moderate to severe pain and are an important component of chronic pain management. In the United States in 2009, 62% of outpatient prescriptions for long-acting opioid (LAO) analgesics were used for musculoskeletal conditions and injuries, 14% for headaches and nerve pain, and 11% for pain associated with neoplastic disease. LAOs represented approximately 9% of all U.S. outpatient opioid prescriptions in 2009. The global market for all opioids was $9.6 billion in 2008 and is expected to grow to almost $12 billion by 2018.4-7 Commercial and government payers have identified this class of medicines as an opportunity for cost and quality management to curb inappropriate utilization with step-therapy, quantity limits, and prior authorization programs. These programs have focused on the management of chronic pain with LAOs.5-7

Two commonly used, oral, branded LAOs are OxyContin (oxycodone controlled-release [CR]) and Opana ER (oxymorphone extended-release). Unpublished data suggest that these 2 products had prescription shares of 86.4% and 11.4%, respectively, in the branded LAO market as of October 2010.8 In assessments of the utilization of these 2 products, it may be helpful to consider daily average consumption (DACON), the term often used to describe the average number of dosage units dispensed per day based on claims data. The term has been used in association with the treatment of chronic diseases, such as diabetes,9 hypertension,10 and arthritis.11 Both oxycodone CR and oxymorphone ER are U.S. Food and Drug Administration (FDA)-approved for twice-daily dosing,12,13 which equates to a theoretical DACON of 2 tablets per day. DACON values greater than 2 have budget and policy implications for managed care pharmacists.

A study by Malkin et al. (2002) compared pharmacy claims for oxycodone CR and fentanyl transdermal patches with dose administration guidelines in each manufacturer’s prescribing information.14 For all dosage strengths of oxycodone CR, the average number of tablets supplied per day was 3.4, ranging from 2.9 for the 10 milligram (mg) tablets to 5.2 for the 80 mg tablets. This analysis measured all pharmacy claims for these medications regardless of the number of claims for each patient. As such, the selection criteria did not include a requirement for chronic use.

A recent retrospective analysis of administrative claims data for commercially insured patients, conducted by Berner et al. (2011), compared the DACON of oxycodone CR and oxymorphone ER in patients with lower-back pain.15 DACON was 3.2 tablets per day for all strengths of oxycodone CR, compared with 2.7 tablets per day for all strengths of oxymorphone ER (P<0.01). DACON for the maximum strength tablet of oxycodone CR 80 mg was 3.9 tablets per day, which was significantly higher than the DACON of 2.9 for equipotent oxymorphone ER maximum strength tablet of 40 mg (P<0.01). Berner et al. estimated that if a health plan were to substitute oxymorphone ER 40 mg tablets for oxycodone CR 80 mg tablets in the 688 patients in their analysis, the monthly cost difference would be $217,985 based on the DACON difference, assuming per tablet wholesale acquisition costs (WAC) of $10.96 and $10.83, respectively.

Since these drugs are indicated for moderate to severe pain regardless of etiology14,15 and most managed care pharmacists do not have access to or include diagnostic codes in their drug utilization evaluations, a broader analysis using information readily available to managed care professionals might be more relevant to payers than a disease-specific analysis.

Methods

Study Scope

We conducted a retrospective analysis of a database from United Healthcare, a large U.S. managed health care plan. The study data were gathered from a commercially insured population using the 13 InVision Data Mart database (Ingenix, Eden Prairie, MN). The database consists of aggregated medical and pharmacy claims for more than 20 million members during the study period. This database was chosen because both oxycodone CR and oxymorphone ER were subject to the same formulary tier status and quantity limits, (i.e., tier 3 coverage without prior authorization and equal quantity limits of 124 tablets per month). The study period encompassed dates of service from January 1, 2007, to March 31, 2010, in order to collect data for a sufficient number of patients with claims for the 2 study LAOs and provide a 6-month roll-in and a 6-month roll-out period to demonstrate continuous health plan coverage. The database consists of de-identified integrated records from outpatient, inpatient, pharmacy claims, lab result records, and enrollment data sets. Because all records were de-identified, Institutional Review Board approval for the study was not sought.

Sample Selection and Characteristics

The objective of the study was to measure DACON for each study drug (oxycodone CR or oxymorphone ER) for the treatment of chronic pain in usual practice. In the prescription drug claims data, there is no specific identification as to whether a prescription for a study drug was filled for treatment of an acute episode of pain or chronic pain. Accordingly, the days supplied for each prescription were used to infer whether treatment was for acute pain (generally less than 15 days supplied) or chronic pain (30 or more days supplied).

Given that the focus of the study was on the use of opioids for chronic pain, the beginning of a treatment episode for chronic pain was defined as the first instance of a 30-day supply of the patient’s initial opioid therapy, identified using pharmacy claims with dates of service from July 1, 2007, to September 30, 2009 (Figure 1). The 30-day supply requirement could be satisfied by either an initial pharmacy claim with 30
days supplied, or by multiple pharmacy claims for the initial opioid therapy with less than 30 days supplied, each closely proximate in time, such that the sum of the days supplied was at least 25 over the first 30 days after the date of the initial study drug fill. Patients were included if gap(s) between pharmacy claims were 5 days or less during the 30-day adjustment period. From the database, 26,921 oxycodone CR users and 2,842 oxymorphone ER users satisfied the criteria for chronic opioid use.

An additional sample restriction was that individuals with an initial pharmacy claim for oxycodone CR could not have a subsequent claim for oxymorphone ER (or vice versa) during the 120 days following the date of the initial study drug claim. A total of 29,308 patients satisfied these requirements: 26,721 oxycodone CR users and 2,587 oxymorphone ER users (Figure 2). No sample exclusions relating to the use of opioids, other than the 2 study drugs, were applied. However, the use of short- or long-acting opioids during the 30 days prior to the DACON measurement period was measured and examined in all multivariate analysis.

As shown in Figure 1, DACON was measured during the 90-day period beginning 30 days after the initiation of the study opioid therapy. The rationale for skipping the first 30 days of therapy when measuring DACON was an assumption that potential dosage modifications would be most likely to occur during the initial phase of a new treatment episode for chronic pain therapy. In terms of the measurement of DACON, the most relevant potential modification is a change in the number of units prescribed per day. Because the intent of the study was to measure DACON for “stable” chronic therapy, the first 30 days were excluded from the measurement of DACON. Focusing DACON measurement over a 90-day period is consistent with the current standard of care for chronic pain management according to treatment guidelines. All study patients were required to have a cumulative total of at least 90 days supply for the initial study drug on 1 or more claims during the DACON measurement period.

Patients younger than 18 years of age were also excluded, as were patients who might have been pregnant, identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 633, 640-646, 761, V23.2, V22, V61.5-V61.7, V72.40, or V72.42 in any diagnosis field on the claim. Individuals without continuous insurance coverage for the 6 months before and after the start of the 90-day measurement period were excluded, as were patients enrolled in a health maintenance organization (HMO) because some claims were missing due to capitated arrangements with certain physicians. After all sample inclusion and exclusion criteria were applied, the final study cohort consisted of 6,567 oxycodone CR patients and 796 oxymorphone ER patients (Figure 2). As a sensitivity analysis, we also evaluated a subsample (n = 6,501 oxycodone CR, n = 788 oxymorphone ER) after excluding patients representing the highest 1% of the DACON sample distribution.

Calculation of DACON

The DACON for each patient was calculated by dividing the total number of tablets dispensed during the 90-day DACON measurement period by 90 days. Measurement of total number of tablets dispensed was based on the sum of units supplied on all insurance claims submitted by all pharmacies during the 90-day DACON measurement period. For patients with a pharmacy claim for a study drug during the 90-day DACON measurement period with days supplied extending beyond the end of the DACON measurement period, the total number of tablets for the last pharmacy claim was converted to an average number of tablets per day, with that daily average applied to the number of days between the final pharmacy claim and the end of the 90-day DACON measurement period. For days representing gaps between days supplied within the 90-day DACON period, a daily value of zero (0) units supplied was applied. For example, if a patient filled a 30-day prescription on day 1 of the DACON measurement period, and then filled another 30-day prescription on day 35 of the DACON period, there was a gap of 4 days (days 31 through 34), during which no units were supplied. No sample restriction relating to the
maximum number of gap days allowed was applied, as long as the cumulative days supplied for all pharmacy claims during the DACON period was at least 90 days. However, as part of the sensitivity analysis, DACON results for patients with different frequencies of maximum gap days are reported.

Patients were assigned to dosage strength groups based on the dosage strength on the first day of the DACON measurement period. An equivalent potency assumption for the 2 products was employed to provide potentially more relevant comparisons of DACON within similar dosage strengths. The equivalent potency assumption used a 2:1 (oxycodone CR: oxymorphone ER) dosage conversion ratio, which was derived from a study examining the efficacy and safety of oxymorphone ER compared with placebo, with oxycodone CR as the active control, among patients with low back pain. Both drugs demonstrated similar analgesia that was superior to placebo,

| Continuous enrollment was measured 6 months prior to and after the start of the DACON measurement period. |
| Possible pregnancy was identified using International Classification of Diseases, Ninth Revision, Clinical Modification codes 633, 640-646, 761, V23.2, V22, V61.5-V61.7, V72.40, or V72.42 in any diagnosis field on the claim 6 months prior to and after the start of the DACON measurement period. |
| Indicates that patient had 1 or more claims with a cumulative days supply totaling at least 90 days during the 90-day DACON measurement period following the 30-day adjustment period. |

CR = controlled-release; DACON = daily average consumption; ER = extended-release; HMO = health maintenance organization.
where the relative dose of oxymorphone ER (79.4 mg per day) was approximately one-half that of oxycodone CR (155 mg per day). Thus, we calculated DACON separately for the highest dosage strengths of the 2 drugs (oxycodone CR 80 mg and oxymorphone ER 40 mg) and for all lower dosage strengths (oxycodone CR 60, 40, 30, 20, 15, and 10 mg; oxymorphone ER 30, 20, 15, 10, 7.5, and 5 mg).

**Statistical Analysis**

Bivariate analyses were performed to illustrate the type of analysis that most managed care pharmacists could replicate using pharmacy claims data alone. Differences in mean (standard deviation [SD]) values of DACON between oxycodone CR and oxymorphone ER were analyzed using t-tests for continuous variables. Since median values are less sensitive than means to outliers, we also calculated medians and Wilcoxon Rank Sum nonparametric tests.\(^{19}\) Patient variables for age, sex, geographic location, Charlson Comorbidity Index (CCI, a proxy measure for comorbidity that assigns weights for 19 chronic conditions calculated from all diagnosis code fields in patient medical claims in the 6-month baseline period prior to the start of the DACON measurement period\(^{20,21}\)) other opioid use, and maximum gap days were evaluated descriptively using Pearson chi-square tests for categorical variables and t-tests for continuous variables.

In addition, multivariate analyses were conducted using generalized linear models (GLM) to adjust for the observed heterogeneity among patients in the observational database. The normality assumption was tested by using the Kolmogorov-Smirnov Test. For the GLM model, the gamma distribution and log link function were chosen to account for the non-normal distribution of the dependent variable (DACON). Independent variables included study drug (oxycodone CR vs. oxymorphone ER), the highest strength versus the lower strengths of each drug, age, sex, the number of maximum gap days during the DACON measurement period, and the CCI. Since other opioid analgesic use prior to the DACON measurement period may affect DACON, both short-acting opioid (SAO) and LAO use during the 30 days before the DACON measurement period were also included in the GLM model as independent variables. The variables were (a) the use of 1 or more SAOs; (b) the use of 1 or more LAOs in addition to the study LAO; and (c) the use of both SAOs and LAOs.

The mean values from the GLM models were the estimated marginal means (sometimes called least square means) of the dependent variable (DACON), calculated as predicted values of DACON for each of the 2 study drug groups holding all independent variables at mean values. The estimated marginal SD values were also calculated from the predicted dependent variable using the same method as the marginal means calculation.

The following sensitivity analyses were conducted. First, a subsample excluding the top 1% DACON outliers from each study drug group was analyzed because the means of DACON from the claims databases can be sensitive to extreme outliers.\(^{22}\) Second, we analyzed a subsample excluding patients with a diagnosis of cancer, measured during the 6-month periods before and after the start of the 90-day DACON measurement period and defined as ICD-9-CM codes 140-208 but including those with nonmelanoma skin cancer (ICD-9-CM code 173) because this type of neoplasm would not be considered as cancer in our definition.\(^{23,24}\) This analysis was done to reflect utilization by patients managing chronic noncancer pain, a common subset used in pain studies. Third, we calculated DACON results for patients with different frequencies of maximum gap days to determine if differences in the continuity of chronic pain therapy affected DACON measurement. Fourth, we evaluated these populations without cancer in both scenarios: including DACON outliers and excluding outliers. Fifth, we analyzed the cohorts including cancer patients in both scenarios but omitting opioid medication variables including (a) the use of 1 or more SAOs; (b) the use of 1 or more LAOs in addition to the study LAOs; and (c) the use of both SAOs and LAOs. All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina) and an a priori alpha level of 0.05.

## Results

### Demographics

Oxycodone CR users were older than those using oxymorphone ER (mean ages of 49 vs. 47 years, respectively, \(P<0.001\); Table 1). There was no significant difference in sex distribution between the 2 groups; females were 48.3% and 51.8% of the oxycodone CR and oxymorphone ER groups, respectively (\(P=0.065\)). There were differences in the regions in which the prescriptions were dispensed. The proportion of patients who had a CCI of 3 or more was higher for oxycodone CR (32.2%) than oxymorphone ER (25.6%, \(P<0.001\)). In terms of other opioid use 30 days prior to the DACON measurement period, there were no statistically significant between-group differences in the proportion using SAOs (70.6% vs. 73.0% for oxycodone CR and oxymorphone ER, respectively, \(P=0.163\)) or LAOs (13.6% vs. 12.2%, \(P=0.275\)). There was no statistically significant between-group difference in the proportion of patients with both at least 1 SAO claim and at least 1 LAO in addition to the study drug (9.5% vs. 7.4%, respectively, \(P=0.058\)). In addition, there was no statistically significant between-group difference in the average maximum gap days during the DACON measurement period for oxycodone CR users and oxymorphone ER users (3.1 days vs. 2.9 days, respectively, \(P=0.343\)).

### Bivariate Analyses of DACON

In the entire sample, (including the top 1% DACON outliers),
the unadjusted DACON mean value for the highest strength of oxycodone CR was 3.9 tablets compared with 2.9 tablets for oxymorphone ER (P<0.001), 3.0 versus 2.4 for lower strengths (P<0.001), and 3.1 versus 2.5 for all strengths (P<0.001; Table 2a). For all dosage strengths, the difference in median DACONs was 0.7 tablet (P<0.001), which was consistent with the difference in means of 0.6 tablet (P<0.001). When excluding the top 1% DACON outliers (DACON range of 9.7 to 33.0 for oxycodone CR and 6.5 to 10.4 for oxymorphone ER), there was again a statistically significant difference in DACON means overall and at the higher and lower strengths (0.6, 0.9, and 0.5 tablet, respectively, all P<0.001; Table 2b). Over all dosage strengths after excluding outliers, the differences in median and mean DACONs were again 0.7 and 0.6 tablet, respectively (P<0.001).

In analyses stratified by continuity of therapy during the DACON measurement period, among the 48.3% (n=3,181) of oxycodone CR patients and 47.9% (n=381) of oxymorphone ER patients with no gap in days supplied during the DACON measurement period, median DACON was 3.4 tablets for oxycodone CR and 2.7 tablets for oxymorphone ER, for a difference of 0.7 tablets per day (P<0.001; Table 2c). The median DACON was 3.1 tablets for oxycodone CR and 2.2 tablets for oxymorphone ER, for a difference of 0.9 tablets per day (P<0.001). Among the 33.9% (n=2,226) of oxycodone CR patients and 37.2% (n=296) of oxymorphone ER patients with 1-5 day maximum gaps in days supplied during the DACON period, the differences in mean and median DACONs were 0.6 and 0.7 units, respectively. Finally, among the remaining 17.7% (n=1,160) of oxycodone CR patients and 14.9% (n=119) of oxymorphone ER patients with a maximum gap of more than 5 days supplied during the DACON period, the differences in mean and median DACONs were 0.6 and 0.3 units, respectively. Thus, DACON differences were larger among patients with no gap in daily supply compared with patients with gaps. DACON differences for every maximum gap day category were statistically significant (P<0.001).

Multivariate Analyses
After adjusting in GLMs for age, sex, comorbidities, highest strength versus lower strengths, maximum gap days, and concurrent SAO and LAO use during the 30 days prior to the measurement period, a statistically significant risk-adjusted mean difference in DACON remained, with oxycodone CR patients receiving on average 0.6 tablets more per day than those dispensed oxymorphone ER (P<0.001; Table 3). The same results were obtained when DACON outliers were excluded from the analysis and when variables relating to the extent of maximum

### Table 1: Demographic Characteristics of the Study Sample, All Patients Including Top 1% DACON Outliers

<table>
<thead>
<tr>
<th>Demographic Variable</th>
<th>Oxycodone CR (n = 6,567)</th>
<th>Oxymorphone ER (n = 796)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) mean [SD]</td>
<td>49.3 [11.9]</td>
<td>47.1 [10.9]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximum gap days mean [SD]</td>
<td>3.1 [5.7]</td>
<td>2.9 [5.6]</td>
<td>0.343</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.065</td>
</tr>
<tr>
<td>Female</td>
<td>3,172 [48.3%]</td>
<td>412 [51.8%]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>3,395 [51.7%]</td>
<td>384 [48.2%]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Regionb</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Northeast</td>
<td>625 [9.5%]</td>
<td>56 [7.0%]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Midwest</td>
<td>1,423 [21.7%]</td>
<td>185 [23.2%]</td>
<td>0.343</td>
</tr>
<tr>
<td>South</td>
<td>3,091 [47.1%]</td>
<td>426 [53.5%]</td>
<td>0.343</td>
</tr>
<tr>
<td>West</td>
<td>1,427 [21.7%]</td>
<td>129 [16.2%]</td>
<td>0.343</td>
</tr>
<tr>
<td>Charlson Comorbidity Index, 6-month baseline period</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0</td>
<td>2,040 [31.1%]</td>
<td>254 [31.9%]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1</td>
<td>561 [8.5%]</td>
<td>83 [10.4%]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>1,852 [28.2%]</td>
<td>255 [32.0%]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3 or more</td>
<td>2,114 [32.2%]</td>
<td>204 [25.6%]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>At least 1 SAO in the 30 days prior to the DACON measurement period</td>
<td>4,637 [70.6%]</td>
<td>581 [73.0%]</td>
<td>0.163</td>
</tr>
<tr>
<td>At least 1 LAO in addition to study drug in the 30 days prior to the DACON measurement period</td>
<td>892 [13.6%]</td>
<td>97 [12.2%]</td>
<td>0.275</td>
</tr>
<tr>
<td>Both at least 1 SAO and at least 1 LAO in addition to study drug in the 30 days prior to the DACON measurement period</td>
<td>622 [9.5%]</td>
<td>59 [7.4%]</td>
<td>0.058</td>
</tr>
</tbody>
</table>

*Pearson chi-square tests for categorical variables (sex, region, CCI category, and use of LAOs and SAOs) and t tests for continuous variables (age, maximum gap days).

CCI = Charlson Comorbidity Index; CR = controlled-release; DACON = daily average consumption; ER = extended-release; LAO = long-acting opioid; SAO = short-acting opioid; SD = standard deviation.
The direction, magnitude, and statistical significance of these differences were essentially unchanged in the sensitivity analyses conducted.

**Sensitivity Analyses**

After excluding patients with a diagnosis of cancer, GLM results showed that patients taking oxycodone CR were more likely to utilize more tablets compared with the oxymorphone ER.
patients (P < 0.001). The results also confirmed that higher tablet strengths were associated with higher DACON. Additional sensitivity analyses were conducted, including the removal of 1% DACON outliers. All of these GLM analyses yielded results similar in magnitude to the differences observed in the bivariate analyses, with all statistical differences remaining (P < 0.001).

## Discussion

The use of LAOs for moderate to severe chronic pain associated with cancer and nonmalignant conditions continues to increase and represents a significant cost for payers. It is expected to be a $12 billion global market by 2018 even with the anticipated introduction of several generic versions by that time. If the average number of tablets paid per day is significantly different among various products as DACON would indicate, payers could develop strategies to prefer the lower-cost agent.

Across all of the statistical analyses performed in the present study, a consistent and robust finding is that DACON is higher for patients using oxycodone CR compared with those using oxymorphone ER. Specifically, over all dosage strengths, mean DACON is approximately 0.6 units higher and median DACON is approximately 0.7 units higher for oxycodone CR than for oxymorphone ER (P < 0.001). The differences in mean and median DACON were greater among patients using the highest dosage strength for each drug (1.0 and 0.9 units, respectively, P < 0.001). The estimated difference in mean DACON over all dosage strengths remained the same after adjusting for differences between oxycodone CR and oxymorphone ER users in terms of age, sex, comorbidities, maximum gap days, and other opioid use.

These results are consistent with those of the study by Malkin et al., which found that the DACON for all strengths of oxycodone CR was 3.4 and that higher strengths were associated with higher DACON values, ranging from 2.9 for the 10 mg tablets to 5.2 for the 80 mg tablets. In the work by Berner et al., similar DACON differences were observed, including a DACON of 3.9 for the oxycodone CR 80 mg tablet and 2.9 for the oxymorphone ER 40 mg tablet. In addition, Berner et al. calculated the cost implications of DACON differences for these equipotent doses of oxycodone CR and oxymorphone ER using WACs, estimating an average additional cost of $10.56 per day per patient for oxycodone CR 80 mg.

The present study expanded the measurement of daily average use of oxycodone CR and oxymorphone ER to include all patients on chronic therapy with these medications, not just those patients with a medical claim for a specific diagnosis, such as low back pain. We did not include a cost analysis because that had already been estimated using WAC in the study by Berner et al. In addition, manufacturer rebate information, which might significantly affect net cost to the payer, is not available in the 13 database.

## Limitations

First, a key limitation of the DACON analysis presented in this study is that it relies exclusively on claims data. Accordingly, it is not possible to determine if higher DACON among oxycodone CR users is clinically appropriate. For example, some unmeasured patient characteristics more prevalent among oxycodone CR users could be associated with a therapeutic need for more frequent dosing. Second, it also is not possible to ascertain whether all tablets supplied were actually used by patients. For example, if a physician changed the prescribed dose for either study drug, the patient could have discarded any remaining supply for the previously prescribed dose. However, from the perspective of managed care pharmacy, an important consideration in drug benefit management is that each tablet supplied resulted in a cost to the plan. Third, this study did not include an analysis of patient diagnosis. Since different pain syndromes might require different doses of opioid analgesics, DACON values might vary between the 2 cohorts. Fourth, managed care organizations commonly impose quantity limits in an attempt to manage overuse and abuse of LAOs. Although most health plans represented in this database imposed a maximum quantity limit of 124 tablets per pharmacy claim for LOAs, the top 1% of DACON values had a range of 9.7 to 33.0 for oxycodone CR and 6.5 to 10.4 for oxymorphone ER.

## Conclusions

This study can serve as a benchmark for prescription benefit managers to compare DACON values for LAOs in their prescription claims. DACON analyses are simple yet effective tools to gain an understanding of overall utilization.
A Comparison of Daily Average Consumption (DACON) of Oxycodone and Oxymorphone Long-Acting Oral Tablets

DISCLOSURES
This research was sponsored by Endo Pharmaceuticals, and 4 study authors are employees of Endo Pharmaceuticals. Fu is a contract employee with Endo Pharmaceuticals.

Concept and design were performed primarily by Summers, Ohsfeldt, and Rubino. Data were collected by Fu with the assistance of Puenpatom and interpreted primarily by Summers, Puenpatom, and Rubino. The manuscript was written by Ben-Joseph with the assistance of Puenpatom, Rubino, Ohsfeldt, and Summers. Revisions were made primarily by Rubino with the assistance of Ohsfeldt and Puenpatom.

ACKNOWLEDGEMENTS
The authors wish to acknowledge Niveda Rajan, PhD, Senior Analyst (contract), Endo Pharmaceuticals, and Alex Li, PhD, Senior Fellow, Leonard Davis Institute of Health Economics, University of Pennsylvania, for quality control support of the research.

REFERENCES
A Comparison of Daily Average Consumption (DACON) of Oxycodone and Oxymorphone Long-Acting Oral Tablets

### Generalized Linear Model Regressions

<table>
<thead>
<tr>
<th>Variables</th>
<th>GLM 1 (All Patients)</th>
<th>GLM 2 (Excluding Top 1% DACON Outliers)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient</td>
<td>Standard Error</td>
</tr>
<tr>
<td>Constant</td>
<td>1.209</td>
<td>0.024</td>
</tr>
<tr>
<td>Oxycodone CR</td>
<td>0.209</td>
<td>0.016</td>
</tr>
<tr>
<td>All lower strengths</td>
<td>−0.227</td>
<td>0.013</td>
</tr>
<tr>
<td>Years deviation from mean age</td>
<td>−0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Female</td>
<td>−0.011</td>
<td>0.010</td>
</tr>
<tr>
<td>CCI = 1</td>
<td>0.017</td>
<td>0.020</td>
</tr>
<tr>
<td>CCI = 2</td>
<td>0.002</td>
<td>0.014</td>
</tr>
<tr>
<td>CCI = 3 or more</td>
<td>0.006</td>
<td>0.015</td>
</tr>
<tr>
<td>Having at least 1 SAO in the 30 days prior to the DACON measurement period</td>
<td>−0.123</td>
<td>0.012</td>
</tr>
<tr>
<td>Having at least 1 LAO in addition to study drug in the 30 days prior to the DACON measurement period</td>
<td>0.188</td>
<td>0.027</td>
</tr>
<tr>
<td>Having both at least 1 SAO and at least LAO in addition to the study drug in the 30 days prior to the DACON measurement period</td>
<td>0.107</td>
<td>0.032</td>
</tr>
<tr>
<td>Maximum gap days</td>
<td>−0.014</td>
<td>0.001</td>
</tr>
<tr>
<td>Log likelihood</td>
<td>−11,918.6</td>
<td>1,294.4</td>
</tr>
<tr>
<td>Number of patients</td>
<td>7,363</td>
<td>7,289</td>
</tr>
</tbody>
</table>

*Reference cases: oxymorphone ER, male, highest strength, CCI = 0, no other opioid use.*

CCI = Charlson Comorbidity Index; CR = controlled-release; DACON = daily average consumption; ER = extended-release; GLM = generalized linear model; LAO = long-acting opioid; SAO = short-acting opioid.
Effects of Cohort Selection on the Results of Cost-Effectiveness Analysis of Disease-Modifying Drugs for Relapsing-Remitting Multiple Sclerosis

Russell V. Becker III, MA, and Carole Dembek, MS

ABSTRACT

BACKGROUND: Decision-analytic cost-effectiveness models are used to determine the most cost-effective treatment option on the basis of the best available data. Guidelines for pharmacoeconomic model development indicate that models should be updated as new evidence becomes available.

OBJECTIVE: To evaluate the appropriateness of the clinical data that were selected for Goldberg et al.’s 2009 model of cost-effectiveness in multiple sclerosis and calculate results based on a revised cohort selection method for intramuscular (IM) interferon (IFN) beta-1a.

METHODS: The original model compared cost per relapse avoided for IM IFN beta-1a, subcutaneous (SC) IFN beta-1a, IFN beta-1b, and glatiramer acetate (GA) based on intent-to-treat (ITT) results from clinical trials. However, due to lower-than-expected subject dropout rates, the IM IFN beta-1a trial had sufficient statistical power to be terminated early and was subsequently found to have met its primary endpoint, time to sustained 1.0-point Expanded Disability Status Scale progression. Within the “all-patient” (ITT) cohort (n = 301), approximately 43% of patients were followed for less than 2 years; 172 patients were followed for 2 years or more. In contrast, the proportions of patients followed for at least 2 years in the clinical trials of IFN beta-1b, SC IFN beta-1a, and GA were 92%, 90%, and 86%, respectively. To test the impact of data selection on the cost-effectiveness model results, we recreated the original model using both the all-patient and 2-year cohorts from the IM IFN beta-1a pivotal trial. We then compared our results with those of the original model.

RESULTS: In the original model, costs per relapse avoided were $141,721 for IM IFN beta-1a, $80,589 for SC IFN beta-1a, $87,061 for SC IFN beta-1b, and $88,310 for GA. In the reanalysis using the 2-year completer data for IM IFN beta-1a, costs per relapse avoided were $77,980 for IM IFN beta-1a, $80,121 for SC IFN beta-1a, $86,572 for IFN beta-1b, and $87,767 for GA. The cost per relapse avoided for IM IFN beta-1a was approximately 45% lower than in the original analysis, whereas the recreated results for the other 3 therapies differed from the original results by less than 1%. Sensitivity analyses showed that the recreated model was robust and that the rank order of cost-effectiveness results was unaffected by changes to any univariate parameter.

CONCLUSIONS: The current study highlights the importance of data selection in cost-effectiveness analyses. After limiting the pivotal trial data for IM IFN beta-1a to patients followed for at least 2 years, we found that IM IFN beta-1a was more cost-effective than in the original analysis, while results for the other first-line disease-modifying drugs remained stable.

What is already known about this subject

• Disease-modifying drugs (DMDs) comprise a significant portion of total health care costs in patients newly diagnosed with multiple sclerosis (MS). In an analysis of all-cause health care costs in 1,411 U.S. patients with newly diagnosed MS, Asche et al. (2010) found that 24% of total all-cause health care costs was attributable to injectable MS drugs.
• The costs of these MS drugs are partially offset by the savings incurred by preventing relapses, which, depending on severity, were calculated by O’Brien et al. (2003) to cost (at 2002 price levels) an average of between $243 for the mildest cases and $12,870 for severe relapses that required hospitalization.
• Decision-analytic models have been developed to assess the cost-effectiveness of DMDs used to treat MS and to provide an additional tool for decision makers evaluating health care interventions. A U.S. cost-effectiveness analysis of 4 first-line DMDs in patients with relapsing-remitting MS, conducted by Goldberg et al. (2009), estimated costs per relapse avoided of $80,589, $89,061, $88,310, and $141,721 for interferon (IFN) β-1a subcutaneous (SC), IFNβ-1b SC, glatiramer acetate, and IFNβ-1a intramuscular (IM), respectively.

What this study adds

• The analysis by Goldberg et al. included a patient cohort for IFNβ-1a IM in which approximately 43% of patients had received treatment for less than 2 years compared with 8%-14% of patients in the other treatment cohorts. The current study replicated the model by Goldberg et al. but applied it to patient cohorts that are more consistent with each other by using data from patients who had received IFNβ-1a IM for at least 2 years.
• The revised economic model estimated costs per relapse avoided of $77,980 for IFNβ-1a IM, $80,121 for IFNβ-1a SC, $86,572 for IFNβ-1b SC, and $87,767 for glatiramer acetate. The results for IFNβ-1a SC, IFNβ-1b SC, and glatiramer acetate were consistent (within 0.6%) with the original analysis, whereas the results for IFNβ-1a IM were approximately 45% lower.
• The change in the result for IFNβ-1a IM highlights the importance of careful consideration of data selection for input into models and heightens awareness that seemingly small inconsistencies may have a large impact on analysis results and conclusions.
Decision-analytic models are often used to determine the most cost-effective treatment option on the basis of the best available data, providing a useful tool for decision makers evaluating health care interventions. Accordingly, several best practice guidelines for the development of cost-effectiveness models have been published. These guidelines are intended to assist researchers in identifying and selecting the best available evidence to incorporate into models.

Numerous cost-effectiveness analyses have been published on multiple sclerosis (MS). A study by Goldberg et al. that was published in JMCP in 2009 compared the cost-effectiveness of 4 injectable disease-modifying drugs (DMDs) used for the first-line treatment of relapsing-remitting multiple sclerosis (RRMS). Such comparisons are relevant since it has been reported that in the United States up to one-quarter of the total all-cause health care costs in patients with MS can be attributable to injectable MS therapies. The model compared the cost per relapse avoided for intramuscular (IM) interferon beta-1a (IFNβ-1a), subcutaneous (SC) IFNβ-1a, IFNβ-1b, and glatiramer acetate (GA). This outcome measure is particularly relevant in U.S. managed care settings due to the significant short-term impact that relapses can have on MS-related expenses. O’Brien et al. (2003) reported that the most severe relapses, defined as those requiring hospitalization, cost an average of $12,870 (at 2002 price levels). Even the mildest relapses requiring only physician care and medications to treat symptoms had an average cost of $243.

As pointed out by Hakim in a 2003 JMCP editorial, models should “never be regarded as complete, but should be repeatedly updated and/or replaced as new evidence becomes available regarding their structure or inputs.” He also commented, “When model predictions are evaluated, it is more important to focus on the modeled relationship between inputs and outputs than on the outputs only.” Hakim’s observations are consistent with practice guidelines for decision-analytic model development.

Taking these points into consideration, we reinvestigated the model used by Goldberg et al., making 1 important substitution to the model input: the patient cohort selected for analysis in the IM IFNβ-1a group. Whereas the patient cohorts for SC IFNβ-1a, IFNβ-1b, and GA consisted primarily (86%-92%) of patients who had completed at least 2 years of therapy, the IM IFNβ-1a patient cohort included a much smaller proportion of patients (57%) who had received therapy for at least 2 years when the study was terminated.

In the original report of the Multiple Sclerosis Collaborative Research Group (MSCRG) trial, Jacobs et al. (1996) offered an explanation for the differing lengths of time on IM IFNβ-1a. MSCRG, the pivotal phase 3 trial for IM IFNβ-1a, was a multicenter, double-blind, placebo-controlled study initiated in 1990 with funding from the National Institutes of Health (NIH). In 1993, it was determined that the patient dropout rate was considerably lower than expected, and the accrued patient population provided sufficient statistical power to terminate the study early at the recommendation of the drug and safety review committee. The study was subsequently found to meet the primary endpoint, time to progression of at least 1.0 point on the Expanded Disability Status Scale (EDSS) sustained for 6 months. As a result of the early termination, of the 301 patients in the intent-to-treat (ITT, “all-patient”) cohort, only 172 (57.1%) were followed for 2 or more years (the “2-year” cohort). The remaining 129 (42.9%) patients were followed for less than 2 years, including 7 patients (4.4%) who were followed for less than 1 year, 1 of whom was followed for less than 6 months.

In economic models, the inclusion of patients with less than 1 year of follow-up becomes problematic when annualizing relapse rates. In the MSCRG trial, annualized relapse rate (ARR) was calculated as the number of relapses divided by the number of months on study drug, multiplied by 12. For example, a patient on study drug for 9 months with 1 relapse would have an ARR of 1.3 (i.e., [1/9] × 12). If the same patient were on study drug for 2 years (24 months) with no further relapses, the ARR would fall to 0.5 (i.e., [1/24] × 12). Conversely, for a patient not receiving active therapy (i.e., in the placebo group), an opposite effect may be apparent. Using a similar example, a patient on placebo for 9 months with 1 relapse would have an ARR of 1.3. If the patient continued to receive placebo for 2 years and experienced an additional relapse (assuming that additional relapses over time are more likely in a nontreated patient), the ARR would decrease to a value of 1 (i.e., [2/24] × 12). Thus in this example, a 9-month analysis of placebo-treated and drug-treated patients would show no difference in ARRs, but a 2-year analysis would indicate that the active treatment reduced the observed ARR by 50%.

This effect may, in part, explain why in the MSCRG trial the ARR was reduced from 0.67 in the all-patient cohort to 0.61 in the 2-year cohort for the IM IFNβ-1a group and yet increased from 0.82 to 0.90 in the placebo group. As these results suggest, the IM IFNβ-1a patient cohort selected for analysis in the model could be expected to have an impact on the analytical outcome. Therefore, it seemed logical to include the cohort that allows the best like-with-like comparison with the other first-line injectable DMDs; 90%-92% of patients in the IFN studies and 86% of patients in the GA study were followed for at least 24 months. We suggest that the 2-year patient cohort from the IM IFNβ-1a study provides a more appropriate comparator group for cost-effectiveness analyses.

In order to assess the similarity of the all-patient and 2-year cohorts in the timing of beneficial effects, Jacobs et al. determined the percentage of patients with sustained progression onset occurring during year 1 and year 2. This assessment showed that over the first 52 weeks of the MSCRG study,
there were only minor differences in sustained progression onset between the all-patient and 2-year cohorts in both the placebo group (22.0% vs. 21.8%, respectively, a relative difference of 0.9%) and the IM IFNβ-1a treatment group (12.5% vs. 12.9%, a relative difference of −3.2%). However, over the second 52-week period, the differences in the percentages of patients with sustained progression onset were considerably larger for both placebo (16.5% vs. 14.7%, a relative difference of 10.9%) and IM IFNβ-1a (10.8% vs. 9.5%, a relative difference of 12.0%). Although it is not possible to directly relate disease progression with relapse occurrence, these data are indicative of differences between the 2 patient cohorts that may contribute to differences in model outcomes.

The objective of the present study was to test the impact of selecting the 2-year cohort rather than the all-patient cohort for IM IFNβ-1a on the results of the original model.

### Methods

A full description of the original model has previously been published. In summary, the model was developed from the perspective of health care payers in the United States. Direct costs and health outcomes were modeled over a 2-year time horizon. The model used ITT data for relapse rates and disease progression from the pivotal clinical studies of the 4 DMDs. Resource use and costs were obtained from several sources, including the published literature, the Red Book, and expert opinion. The primary outcome measure was cost per relapse avoided.

We recreated the original model using the same data sources for cost and effectiveness but replaced the MSCRG all-patient cohort ARRs with the 2-year cohort ARRs for both IM IFNβ-1a (0.67 vs. 0.61, respectively) and placebo (0.82 vs. 0.90, respectively). Using these data, the relative risk reduction for IM IFNβ-1a as compared with placebo increased from 18.3% in the all-patient cohort (as used by Goldberg et al. in their original analysis) to 32.2% in the reanalysis. The models were estimated using Microsoft Excel (Microsoft Corporation, Redmond, WA).

### Results

A comparison of the results of the original analysis and the reanalysis is shown in Table 1. Ranked from most to least cost-effective, costs per relapse avoided in the recreated model using the revised inputs for IM IFNβ-1a were $77,980 for IM IFNβ-1a, $80,121 for SC IFNβ-1a, $86,572 for IFNβ-1b, and $87,767 for GA. For SC IFNβ-1a, SC IFNβ-1b, and GA, the costs per relapse avoided in the reanalysis were within approximately 0.6% of the results reported in the original model. The stability in these results for these DMDs confirms the accuracy of our replication of the original model. However, the cost per relapse avoided using the 2-year patient cohort for IM IFNβ-1a was 45% less than that originally reported. Univariate sensitivity analyses were conducted on key clinical (Table 2) and cost (Table 3) parameters. These sensitivity analyses showed that the recreated model had stable results, similar to the analytic results of the original model. No univariate parameter changes...
in any of the sensitivity analyses altered the rank order of the cost-effectiveness of the therapies.

- **Discussion**
  
  The objective of this research was to highlight the impact that varying input parameters can have on the output of a cost-effectiveness model. It was not intended to “correct” the previously published model but to explore how our interpretation of published best practice guidelines provide an alternative conclusion to those that have been previously reported. Nor was it our purpose to expand on the original cost-effectiveness model; rather, our intention was to replicate as closely as possible the analysis of Goldberg et al. For example, although results from other studies, such as the Independent Comparison of Interferon (INCOMIN) and Evidence for Interferon Dose-response: European-North American Comparative Efficacy (EVIDENCE) trials, may provide data on the relative efficacy of interferons in the treatment of MS, we did not set out to provide “definitive” answers as to the relative clinical efficacy of the compounds under study. Indeed, as was outlined in the editorial by Hakim, “models and their results should not be considered as claims about the facts or as predictions about the future.”

  Results of the reanalysis suggested that the original model by Goldberg et al. was particularly sensitive to the ARR or, more precisely, the reduction in the relative risk of relapse. Therefore, particular attention must be paid to the values for this parameter that are entered into the model. Given that 86%-92% of patients in the other treatment groups had received therapy for at least 2 years, the most appropriate IM IFNβ-1a cohort to use is, similarly, patients who had completed at least 2 years of therapy. Using this alternative patient cohort, we found that the cost-effectiveness of IM IFNβ-1a was improved compared with what the original model showed, whereas that of the other first-line DMDs remained stable.

- **Limitations**
  
  As this reanalysis utilized the same model as the original analysis, the limitations discussed in the original manuscript apply equally to this study. Because the fundamental difference between the 2 analyses is the relative risk reduction for IM IFNβ-1a, a major limitation is the determination of an accurate estimate for this parameter. Although we considered data from the 2-year patient cohort most appropriate for inclusion in the model, it should be noted that studies that served as sources of input data for the original model employed strict ITT analysis. In the reanalyzed model estimated in the present study, the data for IM IFNβ-1a were taken from a subsample that had completed 2 years of therapy, whereas the data for IFNβ-1b, SC IFNβ-1a, and GA included subjects who had withdrawn from the studies. Specifically, 20 (8.1%) of 247 patients in the study of SC IFNβ-1a, 36 (9.7%) of 371 patients in the study of SC IFNβ-1a, and 36 (14.3%) of 251 patients in the study of GA did not complete 2 years of therapy but still contributed data to the model. We believe that these relatively low rates of withdrawal, particularly from the IFN studies, had a minimal impact on the analyses.

- **Conclusions**
  
  The results of this analysis underscore the importance of data selection in cost-effectiveness models. This study suggests that in economic analyses of first-line injectable DMDs for the treatment of RRMS, using a different patient population can substantially change the results and conclusions of the model. Our reanalysis, using patient populations that are more mutually consistent, provides an alternative interpretation of previously published cost-effectiveness data reflecting the results for patients from the source pivotal trials who received at least 2 years of therapy with IFNβ-1a IM, IFNβ-1a SC, IFNβ-1b, or GA.

### Authors

RUSSELL V. BECKER III, MA, is HEOR Consultant, Russell Becker Consulting, Chicago, Illinois. CAROLE DEMBEK, MS, is Associate Director, Global Market Access, Biogen Idec Inc., Weston, Massachusetts.

AUTHOR CORRESPONDENCE: Russell V. Becker III, MA, Russell Becker Consulting, 856 W. Sheridan Rd., Unit 1, Chicago, IL 60613. Tel: 773.549.8415; E-mail: rbecker@russellbeckerconsulting.com.
DISCLOSURES

Funding for this study was provided by Biogen Idec Inc., for which Russell Becker was a paid consultant. Carole Dembek is employed by Biogen Idec Inc. Medical writing support was provided by Mark Hughes, PhD, from Infusion Communications and was funded by Biogen Idec Inc.

Concept and design, data collection, and data interpretation were the work of Becker with the assistance of Dembek. Becker wrote the manuscript assisted by Dembek and Hughes. The manuscript was revised by Becker with the assistance of Dembek and Hughes.

REFERENCES


How Do Seniors Respond to 100% Cost-Sharing for Prescription Drugs?
Quality of the Evidence Underlying Opinions About the Medicare Part D Coverage Gap

Kathleen A. Fairman, MA, and Frederic R. Curtiss, RPh, PhD, CEBS

A September 2008 New York Times editorial described as “very troubling” the results of a Kaiser Family Foundation/National Opinion Research Center (KFF/NORC) study of the coverage gap in Medicare Part D.1,2 Described in the editorial as “notorious,” the gap was triggered when a beneficiary’s total drug costs exceeded $2,400, requiring the beneficiary to pay 100% of drug costs until reaching a catastrophic coverage threshold of $5,451 in total drug costs (2007 thresholds).2 In a standard prescription drug plan (PDP) for an average annual premium of $328, the beneficiary’s share of total drug cost up to the $2,400 threshold was 25% after a $265 deductible (i.e., approximately $800 of a total $2,400 drug cost). After the catastrophic coverage level was reached, the beneficiary paid about 5% of total drug cost.2

As described in the Times editorial, the findings of the KFF/NORC study certainly seemed to merit concern about how the gap affected the health of Medicare beneficiaries: “15% of the beneficiaries taking drugs in [8] categories said they stopped taking their medications when they reached the gap. Another 1% reduced their use by skipping doses, and 5% switched to another drug that was cheaper but might or might not be as effective.” The health consequences of these behaviors, the editorial opined, could be “immediate and serious” for patients with diabetes and longer-term “but still… serious” for those treated for high cholesterol or osteoporosis.1

The editorial was marred by an important inaccuracy: the beneficiaries in the KFF/NORC study certainly seemed to merit concern about how the gap affected the health of Medicare beneficiaries: “15% of the beneficiaries taking drugs in [8] categories said they stopped taking their medications when they reached the gap. Another 1% reduced their use by skipping doses, and 5% switched to another drug that was cheaper but might or might not be as effective.” The health consequences of these behaviors, the editorial opined, could be “immediate and serious” for patients with diabetes and longer-term “but still… serious” for those treated for high cholesterol or osteoporosis.1

The editorial was marred by an important inaccuracy: the beneficiaries in the KFF/NORC study didn’t actually “say” anything to the researchers about their use of prescription drugs after reaching the coverage gap. Instead, the study was based on pharmacy claims data and, as in many retrospective analyses of administrative claims, the truth about study findings lies in important details that are often missed in popular press coverage. More comprehensive analyses of the medication adherence behaviors of seniors reveal a much different and more complicated picture, as well as numerous critically important but unanswered questions.
advise seniors to use a variety of strategies to obtain medication. These include switching to a generic or over-the-counter (OTC) alternative, ordering large (“bulk”) supplies of medications, comparison shopping to identify lowest-price sources, using mail order pharmacies, and applying for assistance through a variety of programs.9-12

A Closer Look at the KFF/NORC Study. The omission of mail order pharmacy data from the KFF/NORC database may have had a major effect on study results. For beneficiaries who changed from a community pharmacy to a mail order pharmacy to save on their drug bills after reaching the coverage gap, even perfect adherence would have been erroneously measured as discontinuation. The amount of missing data for these chronic medications is difficult to estimate but potentially substantial. The proportions of seniors who have reported turning to mail order to save money during a year in which they reached the coverage gap vary widely—for example, 11% in one national small-sample survey by the Office of Inspector General (OIG)13 and 60% in a survey conducted in a large managed care organization (MCO).14 An estimated 17% of prescriptions nationwide were filled in U.S. mail order pharmacies in 2009,15 and mail order pharmacies operating outside the United States routinely market to seniors with the message that they can “beat the ‘donut’ and extend your Medicare coverage” by turning to mail order to save money during a year in which they reached the coverage gap.16 Notably, this latter trend has raised considerable concern for a number of good reasons, not the least of which is that foreign drug importation is illegal;17 nonetheless, it highlights the inadequacy of measuring the clinical risks and benefits of the coverage gap using community pharmacy transactions data alone.

Additionally, the KFF/NORC report did not indicate the extent to which community pharmacies offering discounted generic programs were included in the database, a potentially important omission because generic drugs are routinely available through these programs for $4 per month or $10-$12 for a 3-month supply.8 The 15% discontinuation rate estimated in the KFF/NORC study was not evenly distributed across drug classes, and the pattern of distribution is generally what one would expect if a portion of beneficiaries obtained generic or OTC alternatives through sources other than pharmacies represented in the study database (Table 1). That is, except for osteoporosis therapies, for which utilization generally declined during 2007 because of public concerns about the adverse effects of bisphosphonates,18-21 the percentages of patients who “stopped taking medication” in the KFF/NORC report were generally higher in therapy classes in which lower-cost generic drugs were available and widely used. The highest reported discontinuation rate (20%) was for proton pump inhibitors (PPIs), a class with many inexpensive generic and OTC therapeutic alternatives.18 And, the lowest rate of discontinuation (8%) was found for anti-Alzheimer’s agents, costly drugs (annual cost approximately $1,800)22 for which there were no generic alternatives at the time of the study.

Two features of the work by KFF/NORC are especially noteworthy. First, the problem of false-positive discontinuation was probably exacerbated by a flawed methodological decision to consider only changes within the “therapy class,” which was actually a therapy subclass, in categorizing patient behaviors (Table 1). For example, a patient who switched from an ARB to an ACE inhibitor or from an oral antidiabetic to insulin) were erroneously counted as discontinuations, not as switches. Second, in showing higher discontinuation rates for lower-cost therapy classes,

---

**TABLE 1**

<table>
<thead>
<tr>
<th>Therapy Class</th>
<th>Discontinuation Rate Reported by KFF/NORC</th>
<th>Switch Rate Reported by KFF/NORC</th>
<th>Generic Dispensing Ratio or OTC Availability in 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton pump inhibitors</td>
<td>20%</td>
<td>6%</td>
<td>Available OTC, switch to H2 blocker, or generic omeprazole also available</td>
</tr>
<tr>
<td>Osteoporosis treatments</td>
<td>18%</td>
<td>3%</td>
<td>No generic available</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>16%</td>
<td>4%</td>
<td>59% GDR for antihypertensive class overall</td>
</tr>
<tr>
<td>ARBs</td>
<td>14%</td>
<td>3%</td>
<td>No generic ARBs available</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>15%</td>
<td>6%</td>
<td>67% GDR</td>
</tr>
<tr>
<td>Statins</td>
<td>13%</td>
<td>5%</td>
<td>38% GDR</td>
</tr>
<tr>
<td>Oral antidiabetics</td>
<td>10%</td>
<td>8%</td>
<td>55% GDR for class overall</td>
</tr>
<tr>
<td>Alzheimer’s treatments</td>
<td>8%</td>
<td>4%</td>
<td>No generic available</td>
</tr>
</tbody>
</table>

---

*Notes:
* proportion classified as “stopped taking a medication in that drug class.” Patients who switched from one therapy class to another to treat the same condition (e.g., from an ARB to an ACE inhibitor or from an oral antidiabetic to insulin) were erroneously counted as discontinuations, not as switches.
* Reflects only switches within the drug class shown (e.g., from one ARB to another ARB).
* Source: Express Scripts Drug Trend Report, 2007, 18
* The Express Scripts Drug Trend Report notes that utilization in this class was “down due to potential side effects publicized in 2007.”
* Appropriately, the Express Scripts Drug Trend Report counts ACE inhibitors and ARBs in the same drug class because of therapeutic equivalence. Because no generic ARBs were available in 2007, the 59% figure in this class reflects 0% GDR for ARBs plus a much higher rate for ACE inhibitors.
* Reflects antihyperlipidemic class, which includes mostly statins as well as other products (e.g., fenofibrate).
* Reflects antidiabetic class, including insulin and other injectables (e.g., exenatide).
* The GDR for oral antidiabetics is likely to be considerably lower.

---

ACE = angiotensin-converting enzyme; ARB = angiotensin-II receptor blocker; GDR = generic dispensing ratio; H2 = histamine-2; KFF/NORC = Kaiser Family Foundation/National Opinion Research Center; OTC = over-the-counter.
the study results displayed the opposite of the pattern that one would expect from cost-related nonadherence.

**Earlier Evidence that Database Details Matter (A Lot) to Study Findings**

The KFF/NORC study was perhaps not the first time that alarm bells were sounded about drug utilization declines that in reality may have been caused in part by missing data, not actual medication nonadherence. A meticulous analysis by Martin et al. (1996) took a second look at the highly publicized findings of a 1991 study by Soumerai et al. of the effects of a “cap” (limit) of 3 prescriptions per month for Medicaid beneficiaries in New Hampshire.24,25 The original study, an interrupted time series analysis of Medicaid claims that compared New Hampshire with a state that had no cap (New Jersey), found that the cap was associated with a 30% drop in medication use for a small subgroup of elderly patients using multiple medications for chronic health conditions, suggesting the possibility of negative health consequences.25

In the follow-up analysis, Martin et al. assessed a similar policy change in Georgia, which in 1991 had reduced its monthly reimbursable medication cap from 6 to 5, by studying a sample of beneficiaries who had filled at least 6 prescriptions per month during the 6 months prior to the cap change. However, instead of using a dataset limited to Medicaid claims, Martin et al. matched the claims to computerized prescription dispensing data gathered directly from pharmacies, producing a more complete database. Study findings illustrated the hazards of using claims data alone to measure adherence; many drugs that would have been identified as “discontinued” because of cessation of pharmacy claims activity actually had been obtained by the beneficiaries in out-of-pocket cash transactions. As a result, a claims-based analysis would have overestimated the effects of the cap by approximately 2-fold, with a coefficient estimate suggesting a decline of 0.71 prescriptions per beneficiary per month, versus a decline of 0.34 using the more complete dataset. Additionally, for some therapy classes (e.g., central nervous system agents, antidiabetic drugs), statistically significant effects of the cap that were observed in the Medicaid claims database became nonsignificant when the complete database of dispensed medications was used. Martin et al. concluded that for accurate assessment of caps and other policy changes that limit coverage for medications, it is necessary to monitor “total prescription utilization … not simply the number and amount of reimbursement from some third party.”24

**More Comprehensive Evidence About How Seniors Respond to 100% Cost Sharing**

Several studies have used survey data, sometimes in combination with pharmacy claims data, to assess the responses of Medicare beneficiaries to 100% cost sharing for prescription drugs, including caps and the coverage gap. As one would expect in a series of studies of relatively new policy changes, they reflect an iterative approach, with study methodologies becoming increasingly robust and detailed over time.

**Response to Caps in Medicare + Choice.** In a study conducted from March through July 2002, prior to the availability of generic drug discount programs in community pharmacies, Tseng et al. (2004) surveyed Medicare + Choice beneficiaries, comparing those who had exceeded their cap of $750 or $1,200 and experienced a coverage gap of 75-180 days in 2001 (n = 665) with a comparison group of enrollees who had a higher cap of $2,000, which they had not exceeded (n = 643).26 The 2 groups were matched by average monthly total drug expenditures. A response rate of 65% was achieved using a combination of 20-minute telephone survey with mailed follow-up surveys to initial nonrespondents. Respondents were presented with a list of behaviors and asked in which of these behaviors they had engaged to save money; respondents were asked to report only behaviors attributable to medication cost.

The results of the study by Tseng et al. suggested both desirable responses to the cap and opportunities for improvement. After multivariate adjustment for a number of factors including demographics, self-reported household income, and health status, respondents with a coverage gap were more likely to report engaging in behaviors that are typically viewed as an intended goal of cost-sharing. That is, they were more likely to switch medications (adjusted predicted percentages 15% vs. 9%, respectively, \(P = 0.002\)); obtain free samples (34% vs. 27%, \(P = 0.006\)); call pharmacies to identify the best price for their medications (46% vs. 29%, \(P < 0.001\)); and obtain a senior discount (12% vs. 7%, \(P = 0.003\). They were not more likely to use mail order (63% vs. 62%, \(P = 0.64\)) or to obtain medications outside of the United States (3% in both groups, \(P = 0.92\)).26

With respect to the association of the cap with use of health care services, results were mixed. Respondents who experienced a coverage gap were more likely than those without a coverage gap to report using less than the prescribed amount of a medication (18% vs. 10%, respectively, \(P < 0.001\)) but were not more likely to report discontinuing a drug (8% in both groups, \(P = 0.86\)) or failing to fill a new prescription (6% vs. 5%, respectively, \(P = 0.39\)). Although respondents who reached the cap were much more likely than those who had not reached the cap to report that paying for medication was somewhat or very difficult (62% vs. 37%, respectively, \(P < 0.001\)) and slightly more likely to say that they had difficulty paying for rent or other bills because of medication costs (24% vs. 18%, \(P = 0.02\), they were not more likely to decide against getting other medical care because of drug costs (15% vs. 13%, \(P = 0.20\)).26

Educational opportunity was suggested by the finding that of the top 20 drug classes for which respondents reported decreasing medication use (i.e., using less than the prescribed amount, stopping a drug, or not starting a drug) because of
cost, 15 had generic or OTC alternatives available at the time of the study. And, although Tseng et al. reported no generic or OTCs available in 2002 for the cyclooxygenase (COX)-2 inhibitors, the third most common drugs with reported decrease in use (n = 20, 6.2% of 323 respondents), there were in fact many inexpensive nonselective nonsteroidal anti-inflammatory therapeutic alternatives, and all but 1 of the COX-2 inhibitors were later withdrawn from the market because of cardiovascular safety concerns.

**Large-Sample Survey Comparing Knowledgeable with Less Knowledgeable Beneficiaries.** Hsu et al. (2008) conducted a telephone survey of community-dwelling Medicare Advantage beneficiaries in 2007 (response rate 74.9%) and reported results for a stratified sample of beneficiaries who had incurred total drug expenses high enough to trigger the coverage gap in 2006 ($2,250, n = 514) and beneficiaries with lower drug expenses (n = 526); the sample was further stratified by level of total drug expenditure in 2006. Outcomes included (a) “cost-coping behaviors” (splitting or skipping pills with doctor’s advice, switching to a less expensive drug, receiving samples, receiving help from an assistance program, borrowing a prescription medication, or using an OTC drug); (b) nonadherence (splitting or skipping pills without doctor’s advice, not filling a new prescription, not refilling an existing prescription); and (c) financial burden (borrowing money or going without a necessity to pay for medication). All outcomes were assessed separately for beneficiaries with versus without knowledge of the gap—defined as awareness that the gap existed; accurate identification of gap starting and ending dollar amounts (within margins of error); and knowledge of specific drug cost sharing requirements before, during, and after the gap. Results for the sample strata were appropriately weighted by the mathematical inverses of the selection probabilities so that outcomes for the sample represented the membership overall.

Hsu et al. found that knowledge about the gap was generally poor. For example, after weighting, only 40.1% of the beneficiaries were aware that the coverage gap existed; and, of those who were aware of the gap’s existence, only about one-half were able to identify the coverage gap starting threshold within a $250 margin of error. Gap knowledge was greater among those with higher drug expenses but was imperfect even among those whose expenses were so high that they had reached the gap in the year prior to the survey. For example, the rate of gap awareness was 32.9% for those with total drug expenditures of $0-$750, compared with 75.2% for those with total drug expenditures of $2,251-$3,500 and 88.7% for those with total drug expenditures of $3,501 or more.

Although gap-aware respondents were more likely than unaware respondents to report engaging in any behavior to reduce drug costs (42.8% vs. 31.4%, respectively, logistic regression-adjusted for demographics, health status, and income), relationships between awareness of the coverage gap and nearly all specific behavioral strategies were weak. Despite a relatively large sample size of approximately 950 respondents included in the logistic regression analyses, only 1 of 12 behavioral strategies examined by Hsu et al. was significantly related to knowledge of the coverage gap; switching to a less expensive medication was more likely for gap-aware respondents (18.6%) than unaware respondents (11.2%, 95% confidence interval [CI] for percentage point difference = 0.2-14.6). Nonadherence trended higher for gap-aware versus unaware respondents, but was not significantly associated with awareness in any comparison, either overall (aware vs. unaware: 19.0% vs. 10.9%, respectively, 95% CI for difference = –0.1-16.3) or for any individual nonadherence behavior (did not refill=11.4% vs. 5.5%; took less than prescribed= 7.4% vs. 5.9%; did not fill a new prescription= 5.2% vs. 4.8%). However, gap-aware respondents were slightly less likely than unaware respondents to report financial burden (4.5% vs. 10.1%, respectively, 95% CI for difference = –10.0 to –1.1). Although Hsu et al. concluded that their results suggested “the need to closely monitor clinical outcomes under Part D, especially with respect to the coverage gap” because “cost-related responses appear to be more common among patients with better knowledge of their benefits,” their specific findings actually suggested only weak and mostly nonsignificant associations between gap awareness and nonadherence.

**Small-Sample National Survey of Behaviors Associated with the Coverage Gap.** A 2009 report by the OIG used a combination of pharmacy claims data and national survey with an 81% response rate to assess the experiences of Medicare Part D beneficiaries “without financial assistance” (e.g., LIS or state assistance) who reached the coverage gap in 2006. Like the work of Tseng et al., the OIG analysis suggested a considerably more complex picture of beneficiary response to the coverage gap than would have been revealed using pharmacy claims data alone.

Based on its analysis of pharmacy claims data, the OIG reported that of the 7% of Medicare Part D beneficiaries who entered the coverage gap and did not receive financial assistance with prescription drug costs in 2006, 69% decreased, whereas 29% increased, the average monthly number of drugs purchased while in the gap. Among those purchasing 1 to 8.9 unique drugs per month prior to entry into the coverage gap, the average monthly number of unique drugs purchased while in the coverage gap declined by 9%-10% (from 3.5 to 3.2 for those using 1 to 4.9 drugs and from 6.2 to 5.6 for those using 5 to 8.9 drugs). The utilization decline was steeper, from 10.1 to 8.3 (18%) for those using 9 or more drugs.

Results of the OIG survey, like those in the survey by Tseng et al., suggested a mix of desirable and undesirable behaviors. In response to the question “how did you change your
prescription drug use after you entered the coverage gap?” with a structured list of response choices, about one-fifth (21.1%) of respondents reported using a drug less often than prescribed, 15.8% said that they discontinued a medication, 14.0% said that they did not start a new medication, and a total of 33.3% reported engaging in at least 1 of these strategies. However, 25.4% reported obtaining free drug samples, 22.8% reported comparison price shopping, and 14.9% reported receiving “at least 1 type of help in purchasing their prescription drugs” (e.g., state pharmacy assistance program, private pharmaceutical company, charitable organization). Again highlighting the risks associated with measuring the effects of coverage gaps using community pharmacy claims data, the OIG found that 11.4% of respondents reported switching to a mail order pharmacy, and 7.9% reported that they “purchased drugs outside my health plan.” Suggesting an additional educational opportunity for seniors who reach the coverage gap, 20% of respondents were potentially eligible for LIS according to their self-reported incomes (below 150% of the federal poverty limit); yet, none had LIS status (by sample design), suggesting that they had perhaps not applied to receive assistance for which they may have qualified.15

In interpreting the OIG results, it is important to note that community pharmacy discount generic programs were available for at least part of 2006 (the Walmart $4 generic program was launched in September), and 55% of those who entered the gap did so prior to the fourth quarter of the year. Additionally, the OIG survey sample was small (n = 114), making some CIs around the estimates wide; for example, the 95% CI for the percentage of respondents who reported that they stopped taking a medication during the gap was 9.0%-22.6%. Finally, an important limitation of the OIG study was that it lacked a comparison group of seniors with comparable total drug expenditure levels but no coverage gap.13

MCO Survey Comparing Beneficiaries With Versus Without a Gap. A report by Cronk et al. (2008), which assessed medication cost-saving strategies used by Medicare Part D beneficiaries who reached the coverage gap in 2006, was strengthened by several positive methodological features that enhanced both internal validity (accuracy of inference) and external validity (applicability to the groups in which results will be applied).14,26 First, it compared self-enrolled “direct pay” beneficiaries who reached the gap threshold (total drug expenditures of $2,250) in a standard Medicare Part D benefit (n = 332) with enrollees in a group retiree drug subsidy (RDS) plan who reached the same drug expenditure threshold but experienced no gap because they had a more generous benefit design (n = 290). Enrollees who had no gap because of LIS or end-stage renal disease (ESRD) status were excluded from both study groups. This cohort assignment process was more exogenous (i.e., less affected by respondent characteristics) and therefore methodologically less likely to produce confounded findings compared with other commonly used research designs (e.g., comparing beneficiaries with expenditures high enough to reach the gap vs. those with lower expenditures, or respondents with more vs. less knowledge of the gap). Second, Cronk et al. used both pharmacy claims data and survey data, a method similar to that used in the OIG report, but with a larger sample size. Third, the survey by Cronk et al. was a modified version of the questionnaire used by Tseng et al., which had previously been used in a demographically similar group. Fourth, Cronk et al. analyzed pharmacy claims for Part D beneficiaries to provide information specific to the Part D threshold, instead of the $750-$1,200 expenditure caps that had been studied by Tseng et al. 4 years earlier.14,26

Like previous surveys on medication cost-related behaviors of seniors, the survey by Cronk et al. suggested a mix of desirable and undesirable behaviors; however, results indicated more cost-related nonadherence than had been suggested previously. Among direct pay (standard benefit) enrollees, the proportions reporting using less medication than prescribed, stopping a medication, or not filling a new prescription were 29.1%, 20.1%, and 21.8%, respectively, compared with rates of 11.0%, 4.6%, and 6.1% for RDS enrollees. Use of a mail order pharmacy to save money was reported by 59.7% of direct pay and 18.0% of RDS enrollees, and switching to a different medication was reported by 32.1% of direct pay and 10.9% of RDS enrollees. In contrast to the finding by Tseng et al. of no significant relationship between the drug expenditure cap and seeking other (nondrug) medical care, Cronk et al. found that direct pay enrollees were more likely than RDS enrollees to report not seeking medical care because of medication costs (34.0% vs. 16.6%, respectively, P < 0.001).14

Cronk et al. also reported the results of a logistic regression analysis of predictors of nonadherence attributable to cost (defined as using less medication than prescribed, stopping a medication, or not filling a prescription for a new medication). These included younger age (odds ratio [OR] for each year = 0.97, 95% CI = 0.94-0.99, P = 0.009); not using a second-generation antipsychotic (OR = 0.30, 95% CI = 0.11-0.82, P = 0.019, for using an antipsychotic); poor health status (OR = 0.55, 95% CI = 0.34-0.89, P = 0.015, for excellent, very good, or good health status); higher educational levels (OR = 1.70, 95% CI = 1.06-2.71, P = 0.027, for high school or postsecondary education); and annual household income below $30,000 (OR = 0.57, 95% CI = 0.33-0.98, P = 0.040, for income of $30,000 or more). Controlling for these factors and for other nonsignificant comorbidity measures, the OR for the direct pay plan was 5.21 (95% CI = 2.17-12.53, P < 0.001).14 Although the associations of low income and poor health status with nonadherence were as expected, the associations of antipsychotic use with better adherence and of higher educational levels with nonadherence were counterintuitive, providing an important reminder that patient adherence behaviors are complex and not always easily understood.
Several differences between the work of Tseng et al. and Cronk et al. are noteworthy. First, samples dispensed by physician offices, a major source of medication for seniors in the survey by Tseng et al. (34% and 27% for the cap and no-cap groups, respectively)26 were seldom used by the MCO enrollees in the survey by Cronk et al., who reported that the MCO had a policy that prohibited the dispensing of samples by its participating physicians.14 Second, Cronk et al. did not ask respondents about calling different pharmacies to find the best price, an important cost-saving strategy in the survey by Tseng et al. (65%)26 or the OIG survey (81%),13 as well as inclusion of only self-enrolled beneficiaries in the Medicare standard plan (direct pay) group; self-enrolled beneficiaries may have been more likely than RDS (group-insured) plan beneficiaries to engage in cost-saving strategies, regardless of the coverage gap.

MCO Study of Association of the Coverage Gap with Medical and Pharmacy Utilization. A study by Raebel et al. (2008), conducted in the same MCO and using a similar cohort construction method as in the Cronk et al. study, assessed changes in both pharmacy and medical care utilization from before to after reaching a coverage gap threshold of $2,250 in 2006.29 Raebel et al. compared self-enrolled direct-pay beneficiaries who experienced a coverage gap of at least 60 days with RDS beneficiaries who had similar drug expenditures but no coverage gap. Cohorts were matched by age, chronic disease score, and a comorbidity index, and enrollees with LIS or ESRD status were excluded from both groups.

Results suggested no clear relationship between reaching the coverage gap and medical utilization. Among the 1,237 beneficiaries who experienced any coverage gap, representing 6% of enrollees in the direct pay plan, 783 (63% of those reaching threshold, about 4% of direct pay enrollees overall) experienced a gap of at least 60 days. In both the direct pay (coverage gap) group (n = 759 after matching) and in the matched RDS cohort (n = 2,818), total office visit utilization rates were slightly lower in the post-threshold period in 2006 than in the same months in 2005 (incidence risk ratio [IRR] vs. 2005 = 0.90 in both groups), and no significant between-group differences were noted for change in emergency room use (IRR = 0.91, 95% CI = 0.71-1.16 in direct pay plan; IRR = 1.14, 95% CI = 0.96-1.35 in RDS) or hospitalization (IRR = 1.08, 95% CI = 0.88-1.33 in direct pay plan; IRR = 1.06, 95% CI = 0.93-1.21 in RDS). Medication refill adherence (defined as total days supply divided by total number of calendar days times 100) also declined slightly for both groups, but the between-group differences in the adherence reduction amounts were significant only for antihyperlipidemic agents (91.0% before vs. 87.3% after gap in the direct pay plan, between-group difference \( P = 0.031 \)) and antihypertensives (89.8% before vs. 84.5% after gap in the direct pay plan, between-group difference \( P = 0.006 \)) and not significant for beta-blockers, diuretics, or antidiabetic medications.29

Raebel et al. observed that their results were different from those of a study of Medicare + Choice conducted by Hsu et al. (2006), which had compared medical and pharmacy utilization in 2003 for self-enrolled beneficiaries who had a $1,000 medication cap (n = 157,275) with employer-enrolled retirees who had “unlimited” drug benefits (n = 41,904) using a cross-sectional design with statistical controls for demographics, comorbidities, and cost-sharing levels.30 As Raebel et al. pointed out, the difference between their results and those of Hsu et al. could have been partly attributable to statistical power because of the enormous differences in sample size. The differences in rates of medication nonadherence (defined as percentage of days covered less than 80% in the study year for those with use of the same drug in the prior year) that were observed by Hsu et al. were small and similar to those of Raebel et al. (for no-cap vs. cap, respectively: 14.6% vs. 18.1% for antihypertensives; 26.5% vs. 31.4% for lipid-lowering drugs; 21.2% vs. 26.2% for antidiabetics). More importantly, the medical utilization differences reported by Hsu et al. were small despite statistical significance (e.g., all-cause emergency room visits 45.2 vs. 49.2 per 100 person-years; all-cause hospitalizations 38.4 vs. 39.7 per 100 person-years).30 An additional possible explanation is the use of a cross-sectional design in the utilization analysis by Hsu et al. in contrast to the Raebel et al. quasi-experimental analysis, which consisted of by-group comparisons of changes from comparable time periods in the previous year (e.g., for a member whose cap was reached in September 2006, Raebel et al. measured utilization change for September 2006-December 2006 vs. September 2005-December 2005).29

The Multifaceted Nature of Nonadherence: Difficulties in Isolating (Let Alone Controlling) a Single Causal Agent “What can be done about a problem that has been studied in thousands of articles and yet barely improved in decades?”31 This question was posed by Gellad et al. in the introduction to a 2009 Rand technical report on barriers to medication adherence, which noted that studies of the topic were “heterogeneous and of variable quality,” hampering the “ability to form policy recommendations rooted in the literature.” In their systematic review of studies of nonfinancial causes of nonadherence, Gellad et al. identified beliefs about medications, including “perceived risks of having a side effect and perceived impact and need for the medication,” as “key barriers to and facilitators of medication adherence.” Of 21 articles assessing the association between medication beliefs and adherence, 16 found “strongly positive” relationships.31

Qualitative interview studies, especially those conducted...
in publicly funded health care systems with little or no out-of-pocket cost, help provide in-depth understanding of the relationships between patient beliefs and nonadherence. For example, Barber et al. (2004) interviewed English patients aged 75 years or older by telephone at 2 points in time: first at 10 days (n = 239), then at 4 weeks (n = 197), following initiation of new medication for stroke, coronary heart disease, asthma, diabetes, or rheumatoid arthritis. At 10 days, 13 patients (5.4%) had discontinued the medication on the advice of their physician. Of the remaining 226, 67 (29.6%) reported nonadherence to the new medication, defined as missing any doses in the previous 7 days, and 18 (8.0%) had discontinued the medication without medical advice. Notably, of 208 patients still taking medication at 10 days, 138 (66.3%) reported a problem or issue with the medication, including side effects (50% of problems reported); “concerns about the medication” including “don’t believe in taking pills” and “worried about taking new medicine” (43%); and “difficulties with the practical aspects of taking the medication” (7%). After the first 10 days of therapy, only 37 patients (16.4% of the 226 whose physicians had not discontinued their medication) reported that they were “adherent, problem free, and had received sufficient information” about their medication.

Similarly, Sale et al. (2011) reported the results of qualitative in-depth (1- to 2-hour) interviews with 21 patients aged 65 to 88 years in Ontario, Canada, who had been prescribed drugs to treat osteoporosis after sustaining a fracture within the previous 5 years. For 12 patients, the decision to take the medication “involved minimal contemplation … because they liked/trusted their health care provider.” However, 9 patients described the decision to take the prescribed medication as “difficult” because they “were unconvinced by their health care provider, engaged in risk-benefit analyses using other information sources, and were concerned about side effects.” Eleven of the 21 patients indicated that their decision about medication “was not permanent and that they might be persuaded to start or stop taking medication depending on a number of circumstances.”

In a U.S. study, Fried et al. (2011) used in-person interviews with 356 community residents recruited from senior centers and an assisted living facility (mean [standard deviation] age 76 [7] years) to estimate associations of the beliefs about the benefits and risks of medication with willingness to take medication for primary prevention of cardiovascular disease. Fried et al. found that willingness to take medication was “relatively insensitive” to beliefs about benefits. When seniors were presented with a baseline scenario that 20 in 100 untreated patients and 14 in 100 treated patients would have a myocardial infarction (MI) during a 5-year period (i.e., 6 MIs prevented), 87.9% responded “yes” when asked if they would take a medication with “no adverse effects.” Still assuming no adverse effects, of those unwilling to take the medication (n = 33) or not sure (n = 9), only 16.7% (n = 7) expressed willingness to take the drug if the drug reduced the MI risk from 20 to 10 (i.e., 10 MIs prevented). Of those willing to take the medication (n = 313), only 13.7% (n = 43) said that they would change their minds about taking the drug if the MI risk were reduced from 10 to 7 (i.e., just 3 MIs prevented).

In contrast, medication-taking decisions were strongly associated with concerns about adverse effects. Of the 313 who expressed willingness to take medication in the initial scenario, the proportions who remained willing to take the medication when told that it would result in daily fatigue and dizziness, daily mild to moderate nausea, and daily fuzzy or slowed thinking were 52%, 35%, and 31%, respectively. Only 3% of respondents reported willingness to take a medication with adverse effects serious enough to affect activities of daily living. Fried et al. commented on the “notable” finding that in response to the initial scenario in which respondents were told that a drug would have no adverse effects, 13 (31%) of 42 respondents who expressed either uncertainty or unwillingness to take the drug told the investigators that they did not believe that the drug would actually have no adverse effects, and 7 (17%) said that they disliked medications.

Information about other nonfinancial factors affecting medication adherence is somewhat limited. For example, Ingersoll and Cohen (2008) conducted a systematic review of the literature on the relationship between drug regimen characteristics and adherence to treatment for multiple chronic diseases. They reported that of 110,218 PubMed articles identified using the search terms “adherence” or “compliance” from 1998 to 2007, only 61 examined regimen characteristics, and studies in most therapy classes “failed to use state-of-the-art methods of measuring adherence.” Despite these limitations, Ingersoll and Cohen “identified regimen complexity,” including number of daily doses, “as a likely determinant of adherence.” Still, Ingersoll and Cohen acknowledged that, with the exception of patients with human immunodeficiency virus, there are “few behavioral methods targeting improved adherence with known efficacy” in “most areas of chronic illness.” Supporting their viewpoint was a systematic review of randomized controlled trials (RCTs) of adherence-improvement interventions by Haynes et al. (2008), which found that only 39 of 81 interventions “to help patients follow prescriptions for medications for medical problems” (n = 69 trials for long-term treatments) were associated with adherence improvements, and only 25 “led to improvement in at least 1 [treatment] outcome.”

In interpreting findings about the sometimes complex patient perspectives on medication, it is worth noting that some fears of potential side effects with long-term use turn out to be well-founded; the risks of newer medications are often not fully understood at the time of market launch. Well-known examples include COX-2 inhibitors, biphosphonates, and several antidiabetic medications including rosiglitazone, sitagliptin, and exenatide.
100% Medication Cost Sharing for Seniors: What We Know and What We Need to Know

The Rand Health Insurance Experiment, to date the most rigorously designed study of the effects of cost sharing on health outcomes, found that requiring insured enrollees to pay a portion of the cost of their care results in savings without negative effects on health outcomes. However, that study was limited to enrollees aged 64 years or younger, and its results may not have external validity for seniors. The unfortunate result is that many public policy decisions about health care benefit designs for seniors have been made based solely on observational evidence, which is suboptimally rigorous.

Even more unfortunate is the tendency of authors of observational studies to extrapolate beyond study results—or even the outcomes that were actually measured—in describing the clinical and economic consequences of various benefit designs. For example, in an observational analysis of Medicare beneficiaries in 2006, Zhang et al. (2009) found a decrease of 0.7 pharmacy claims per month paid by the health plan (0.4 generic, 0.3 brand), approximately 14%, after entry into the coverage gap. For beneficiaries with generic drug coverage in the gap, the reduction in pharmacy claims was smaller, 0.14 claims per month, which represented “the net effect of a decrease of 0.5 brand-name prescriptions and an increase of 0.36 generic prescriptions.” Without analyzing the medical utilization data that were included in their study database, Zhang et al. concluded that “on the assumption that the generic drugs taken by beneficiaries…were appropriately prescribed, one can assume not only that the lack of coverage in the doughnut hole had adverse health consequences but also that it could have increased costs for hospital and physician services.”

Based on the limited evidence available to date, it seems likely that a small proportion of seniors is negatively affected by 100% cost sharing. That is, they enter the coverage gap without LIS (approximately 6%-7% in the analyses by OIG and Raebel et al.); they are more likely to be nonadherent than beneficiaries who have comparable drug expenditure levels but no coverage gap (percentage point difference about 15%-20%, or about 1% of beneficiaries overall); the nonadherence occurs because they need medication for which there is no low-cost generic substitute (proportion unknown); and they are either unable to obtain medication from or are unaware of alternative resources, such as patient assistance programs (proportion unknown). Yet, we know little about the characteristics and behaviors of this small group of beneficiaries—and therefore we know little about how to help them obtain medication affordably—because research in the topic area has generally used incomplete data sources and/or left unanswered critically important questions. The areas of greatest need include the following:

Examination of Cost-Related Behaviors by Therapy Class. Beneficiary surveys have certainly been a great improvement over claims data alone in providing information about whether

the absence of a pharmacy claim represents nonadherence versus the use of a medication source not reflected in a claims database. However, surveys to date have not examined the critically important question of whether therapy classes are affected by nonadherence. For example, the OIG survey and the survey by Cronk et al. both indicated that, of beneficiaries who entered the coverage gap without LIS, about 16%-20% (or about 1% of beneficiaries overall) reported stopping a prescription medication because of cost during 2006. However, the therapeutic implications—and therefore the policy implications—of these findings are uncertain without information about the discontinued prescription drug. For example, it is important to know if the discontinued drug was an antihypertensive for a patient with congestive heart failure (clearly clinically problematic), a PPI for which a patient with heartburn substituted an OTC alternative (cost-saving with probably no clinical effect), or an oral antidiabetic drug with a higher-risk cardiovascular profile for which a patient with type 2 diabetes substituted metformin available for $4 through a community pharmacy discount program (possibly clinically beneficial in addition to cost-saving). Additionally, because of the gradual transition of many specialty injectable medications (e.g., glatiramer acetate and interferon β-1a for multiple sclerosis) from in-office administration reimbursed by Medicare Part B to Medicare Part D, depending on the Medicare intermediary in a patient’s geographic region, more information is needed about the effect of the Medicare Part D design on patients with catastrophic illnesses. Surveys that “drill down” to drug therapy class and type of cost-related response should be used to determine the circumstances in which responses to 100% cost sharing are clinically harmful, neutral, or beneficial.

High-Quality Survey Data to Assess Incentives Associated with 100% Cost-Sharing. As observed by editorialists Shrank and Choudhry, the provision in the Affordable Care Act that in 2011 discounts brand-name drugs by 50% but generic medications by only 7% is unfortunate; “by disproportionately reducing the cost of brand-name medications, the legislation creates incentives for patients to use more expensive drugs and will leave the federal government on the hook for increased medication costs during the catastrophic-coverage period” because “exposure to out-of-pocket costs in the coverage gap may encourage seniors to consider the cost of their medications and to seek more cost-effective options.” Shrank and Choudhry’s observations make sense in principle, and it seems clear from the limited evidence available to date that the coverage gap does encourage seniors to “shop around” for the best price—a behavior that public policy presumably should encourage. However, the question of how often this comparison price shopping actually results in identification of the lowest price is critically important because price differences among medication sources can be large. For example, Internet prices for a 90-day supply of gabapentin 400 milligrams (mg) taken 3...
times daily (i.e., 270 tablets) are $69 at one pharmacy $48 and $210 at another; $48 and, for those with incomes less than 300% of federal poverty level (e.g., $32,670 for a single adult and $44,130 for a couple in most states), $35 at RxOutreach. $31 Additionally, more detailed information is needed about the sources from which beneficiaries obtain their drugs, especially for survey respondents who report that they used a “mail order pharmacy” while in the coverage gap. The policy implications of “mail order” use vary considerably depending on the specific source—for example, health plan mail order or a reputable U.S. discount Internet pharmacy versus a foreign Internet pharmacy.

Surveys of Medicare beneficiaries, coupled with verification (e.g., pharmacy records audits) whenever possible, should be used to determine whether and from what sources patients obtain their medications in the coverage gap, as well as whether patients accessed the best price or paid more than necessary.

More Knowledge About Knowledge Gaps. Limited survey evidence available to date suggests that educational interventions may be needed in several critical areas. First, the study by the OIG suggested that up to one-fifth of Medicare beneficiaries who entered the coverage gap without LIS assistance in 2006 may have been LIS-eligible but failed to apply. $13 Second, the survey by Hsu et al. suggested that only about 40% of Medicare Part D beneficiaries were even aware that a coverage gap existed, and only a minority was able to identify key features of the gap, at least shortly after implementation of Medicare Part D. $29 Additionally, more detailed information is needed about the sources from which beneficiaries obtain their drugs, especially for survey respondents who report that they used a “mail order pharmacy” while in the coverage gap. The policy implications of “mail order” use vary considerably depending on the specific source—for example, health plan mail order or a reputable U.S. discount Internet pharmacy versus a foreign Internet pharmacy.

Surveys of Medicare beneficiaries, coupled with verification (e.g., pharmacy records audits) whenever possible, should be used to determine whether and from what sources patients obtain their medications in the coverage gap, as well as whether patients accessed the best price or paid more than necessary.

More Knowledge About Knowledge Gaps. Limited survey evidence available to date suggests that educational interventions may be needed in several critical areas. First, the study by the OIG suggested that up to one-fifth of Medicare beneficiaries who entered the coverage gap without LIS assistance in 2006 may have been LIS-eligible but failed to apply. $13 Second, the survey by Hsu et al. suggested that only about 40% of Medicare Part D beneficiaries were even aware that a coverage gap existed, and only a minority was able to identify key features of the gap, at least shortly after implementation of Medicare Part D. $29 Similarly, Cronk et al. found that about 22% of their respondents in 2007 “were unaware or unsure if they had an initial threshold on medication purchases.” $14 Third, the survey by Tseng et al. suggested that seniors may not always correctly identify opportunities to substitute generic medications for brand drugs, although it is possible that knowledge has improved since that study period (2002). $26 It is also possible that the extent and type of knowledge gaps may depend in part on medical condition. Bayliss et al. found that Medicare beneficiaries in 1 HMO who reached the coverage gap in 2 consecutive years (4% of the sample) were somewhat more likely than those who reached the gap in only 1 year to have 2 or more medical conditions (e.g., chronic obstructive pulmonary disease, Parkinson’s disease) for which generic drug treatment options were limited (41% vs. 32%, respectively). $32

Thus, it seems that many seniors lack knowledge of the medication resources available to them and of the coverage gap design. In addition to suggesting a need for education and outreach, these findings perhaps suggest that a different design—such as a high upfront deductible or flat coinsurance percentage that would apply to all beneficiaries except those currently excluded from cost-sharing (e.g., LIS, ESRD)—could encourage efficient drug purchasing and produce the same cost savings without confusing patients who make drug-purchasing decisions. Surveys that provide detailed information about gaps in beneficiary knowledge are needed to inform educational efforts and potential benefit design changes.

More Comprehensive Examinations of Factors Contributing to Nonadherence Under 100% Cost Sharing. To date, surveys assessing behaviors after cap or during coverage gap periods have asked only about cost-related behaviors, not about nonadherence attributable to other factors. Although this approach is consistent with the generally accepted survey research practice of reducing respondent burden to enhance response rate, it may be misguided. Previous research suggests that the causes of nonadherence are multifaceted and include adverse drug effects, beliefs about medications, and regimen complexity. As Cronk et al. observed, social desirability factors may affect the results of surveys in which beneficiaries are asked about the effects of medication costs. $15 Especially in a survey sponsored by his or her health plan, a respondent may find it considerably more comfortable to report that cost was the cause of nonadherence than to report negative beliefs about medication or fears of adverse effects; and beneficiaries are highly unlikely to report beliefs or fears if they are not asked about them directly, using appropriate survey research techniques. Analysis of the probably complex relationships between financial and nonfinancial causes of nonadherence requires a more comprehensive approach to questionnaire construction than has been used to date. Conjoint analysis (also known as discrete choice analysis), an analytic technique that permits calculation of patient preferences on multiple dimensions (e.g., price, adverse effects, efficacy), would likely be a good approach to analyzing surveys of this type. $33 Surveys intended to address financial or benefit design issues should in addition ask respondents about nonfinancial factors to assess the relative importance of a variety of causes of nonadherence and enable more effective policy approaches.

More RCTs. A number of studies, especially claims-based studies, have documented a decrease in pharmacy claims utilization upon entry into the coverage gap. $2-6 Putting aside the problem of incomplete claims data, more focus in future research should be placed on RCTs of interventions to improve both awareness of pharmacy benefit design and medication adherence. For example, it is one thing to document that beneficiary knowledge may be associated with certain behaviors; it is quite another to test whether a particular educational intervention to improve beneficiary knowledge actually results in improvement in health-related behaviors or clinical outcomes. More rigorous testing of interventions, and less documentation of associations that may have little actionable value, are needed.
Obtaining Necessary Information About the Effects of 100% Cost Sharing on Seniors: Moving Forward

Although the current information deficit about the coverage gap is not entirely unexpected because the Medicare Part D program is relatively new, reliance on claims-based analyses to inform questions that claims data cannot possibly address accurately has tended to mislead and politicize rather than produce constructive policy guidance. Moreover, pronouncements of dire health consequences without examination of medical claims data are unhelpful—not just because they are potentially inaccurate, but also because they have drawn attention away from important health policy questions that remain unaddressed. These questions are becoming especially important as optimal approaches to providing health care to seniors are the subject of an increasingly vigorous debate.

With the burgeoning number of options for seniors to access affordable medications to treat chronic illness, most observational analyses of nonadherence based solely on pharmacy claims data have become obsolete and uninformative, depending in part on the therapy class studied. Absent an RCT of the effects of various benefit designs on seniors—the ideal information source—high-quality survey data are probably the best source of information at the present time. In other words, if we want to know how health care policies affect seniors, it makes sense to ask them.

DISCLOSURES

The authors report no conflicts of interest related to the subjects or products discussed in this article.

REFERENCES

22. Internal analysis of pharmacy claims database for a single employer in the fourth quarter of 2007, reflects allowed charge after discount rather than average wholesale price.


51. RxOutreach medications available. Pricing is based on any strength and quantity (e.g., a patient using 1 tablet per day pays the same price as a patient paying 3 tablets per day). Available at: http://www.rxoutreach.org/medications/. Accessed May 27, 2011.

