Effects of a Tablet-Splitting Program in Patients Taking HMG-CoA Reductase Inhibitors: Analysis of Clinical Effects, Patient Satisfaction, Compliance, and Cost Avoidance

Validation of a Single-Patient Drug Trial Methodology for Personalized Management of Gastroesophageal Reflux Disease

Clinical and Economic Impact of Glatiramer Acetate Versus Beta Interferon Therapy Among Patients With Multiple Sclerosis in a Managed Care Population

Impact of Multi-tiered Pharmacy Benefits on Attitudes of Plan Members With Chronic Disease States

Economic Evaluation of Citalopram Use and Expenditures Among Recipients in the Texas Medicaid Program

Analysis of the Movement of Prescription Drugs to Over-the-Counter Status

Promotion of Prescription Drugs to Consumers: Case Study Results
CONTENTS

ORIGINAL RESEARCH

453 Effects of a Tablet-Splitting Program in Patients Taking HMG-CoA Reductase Inhibitors: Analysis of Clinical Effects, Patient Satisfaction, Compliance, and Cost Avoidance

Michael Gee, PharmD; Noelle K. Hasson, PharmD; Terri Hahn, BSPharm; and Russell Ryono, PharmD

459 Validation of a Single-Patient Drug Trial Methodology for Personalized Management of Gastroesophageal Reflux Disease

Barbara Wolfe, PharmD; Eve del Rio, PhD; Sidney L. Weiss, MS; Avishai Mendelson, MD; Tamer A. Elbaga, BS, RPh; Frederic J. Huser, MBA; and Donald P. Reitberg, PharmD

469 Clinical and Economic Impact of Glatiramer Acetate Versus Beta Interferon Therapy Among Patients With Multiple Sclerosis in a Managed Care Population

Daniel A. Ollendorf, MPH; Evgenia Jiilinskaia, PhD; and MerrylKay Oleen-Burkey, PhD

477 Impact of Multi-tiered Pharmacy Benefits on Attitudes of Plan Members With Chronic Disease States

Kavita V. Nair, PhD; Julie M. Ganther, PhD; Robert J. Valuck, PhD; Marianne M. McCollum, PhD; and Sonya J. Lewis, RPh

492 Economic Evaluation of Citalopram Use and Expenditures Among Recipients in the Texas Medicaid Program

Michael T. Johnsrud, PhD, RPh, and M. Lynn Crismon, PharmD

SUBJECT REVIEW

499 Analysis of the Movement of Prescription Drugs to Over-the-Counter Status

Patricia Harrington, BSc Pharm, MSc Clin Pharm, and Marvin D. Shepherd, PhD

509 Continuing Education

Post-Test, Record of Completion, and Program Evaluation

CONTEMPORARY SUBJECT

512 Promotion of Prescription Drugs to Consumers: Case Study Results

Christina Glasgow, PharmD; Jon C. Schommer, PhD; Kiran Gupta, MS; and Krista Pierson, PharmD

DEPARTMENTS

446 Cover Impressions

Lotus Glow (1999)

Jacqueline McAbery

Sheila Macho

519 Editorial

Effective Cholesterol Management With Fewer Dollars

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

525 Letters

527 Article Index by Subject Category

543 Thanks to JMCP Peer Reviewers
EDITORIAL MISSION

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

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

EDITORIAL STAFF

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

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

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

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

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

Contributing Editors
Perry Cohen, PharmD, The Pharmacy Group, LLC, Glastonbury, Connecticut
Katherine Knapp, PhD, Western University of Health Sciences, Pomona, California
J. Warren Salmon, RPh, MBA, University of Illinois at Chicago, Chicago, Illinois
Sheila Macho, St. Paul, Minnesota

EDITORIAL ADVISORY BOARD

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

Robert J. Anderson, PharmD, Mercer University, Jasper, Georgia
John P. Barbuto, MD, HealthSouth Rehabilitation Hospital, Sandy, Utah
Diana L. Britner, RPh, PhD, Department of Pharmacy Practice, University of Utah, Salt Lake City, Utah
Joan Deady, MS, PharmD, Sutter Health, Sacramento, California
Colonel George J. Dydek, PharmD, BCPS, U.S. Army, Gunpowder, Maryland
Leslie Fish, PharmD, Fallon Healthcare System, Worcester, Massachusetts
Alan Heaton, PharmD, Prime Therapeutics, Inc., Eagan, Minnesota
Tracy S. Hunter, PhD, College of Pharmacy, Nova Southeastern University, Ft. Lauderdale, Florida
Brent C. James, MD, MStat, Institute for Healthcare Delivery Research, Intermountain Health Care, Salt Lake City, Utah
Richard A. Kipp, MAAA, Millman USA, Radnor, Pennsylvania
Eric G. Klein, PharmD, Eli Lilly & Co., Indianapolis, Indiana

Neil J. MacKinnon, PhD, RPh, Dalhousie University, College of Pharmacy, Halifax, Nova Scotia, Canada
Daniel C. Malone, PhD, RPh, College of Pharmacy, University of Arizona, Tucson, Arizona
Brenda R. Motheral, PhD, Express Scripts, Inc., Maryland Heights, Missouri
Gene Reeder, PhD, College of Pharmacy, University of South Carolina, Columbia, South Carolina
Cathlene Richmond, PharmD, Kaiser Permanente, California, Oakland, California
Michael J. Sax, PharmD, The Pharmacy Group, LLC, East Glastonbury, Connecticut
Andy Stergachis, PhD, University of Washington, and Formulary Resources, Bellevue, Washington
William J. Waugh, PharmD, WellPoint Pharmacy Management, West Hills, California

Founding Editor
Louise J. Sargent, MS, RPh

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

Journal of Managed Care Pharmacy (ISSN 1083-4087) is peer reviewed and published bimonthly by the Academy of Managed Care Pharmacy, 100 North Pitt St., Suite 400, Alexandria, VA 22314; (703) 683-8416; 800/TAP-AMCP; (703) 683-8417 (fax). Postmaster: Send address changes to 100 North Pitt St., Suite 400, Alexandria, VA 22314. www.amcp.org
Managed Care Pharmacy Practice

Learning Goal — To enhance a student’s awareness of career options in managed care pharmacy practice by involvement in a structured preceptorship program associated with the daily activities of managed care practice sites, a managed care society, and the pharmaceutical industry.

To accomplish the above goal the student will:
- Work for eight weeks at a leading managed care organization under the supervision of a pharmacist preceptor.
- Work with a preceptor to conceptualize, develop, and complete a project related to “Improving the Quality of Pharmaceutical Care in Managed Care Pharmacy Practice.”
- Complete a structured rotation through a number of managed care pharmacy practice sites to gain a perspective of how they operate.
- Work for one week at the Academy of Managed Care Pharmacy (AMCP) under the supervision of a pharmacist.
- Complete a one-week structured rotation through the managed health care division of Pfizer to gain a perspective on the pertinent issues in managed care pharmacy and how they impact the pharmaceutical industry.
- Present a poster at the AMCP 2003 Educational Conference in Montreal, Quebec, Canada.

Eligibility Criteria
- Completion of a standard application postmarked by February 28, 2003.
- Full-time enrollment in an accredited school of pharmacy during the 2002–2003 school year with anticipated graduation in 2004 or 2005 with a PharmD degree. This internship may qualify as a specialty rotation, check with your school’s clerkship coordinator.
- Three letters of recommendation: Dean, faculty member, and non-relative pharmacist.
- Ability to complete the internship during a ten-week period between the months of May through August 2003.

Veterans Affairs Medical Center & Pharmacy Practice

Learning Goal — To enhance a student’s awareness of career options in a Veterans Affairs Medical Center (VAMC) and managed care pharmacy practice by involvement in a structured preceptorship program in conjunction with the VAMC, a pharmacy benefits management company, a managed care society, and the pharmaceutical industry.

To accomplish the above goal the student will:
- Work for seven weeks at a leading VAMC under the supervision of a pharmacist preceptor.
- Work with a preceptor to conceptualize, develop, and complete a project related to “Improving the Quality of Pharmaceutical Care in VAMC Pharmacy Practice.”
- Complete a structured rotation through a number of VAMC pharmacy practice sites to gain a perspective of how they operate.
- Work for one week at the Academy of Managed Care Pharmacy (AMCP) under the supervision of a pharmacist.
- Spend one week at a pharmacy benefits management company under the supervision of a pharmacist.
- Complete a one-week rotation with a government accounts manager from the pharmaceutical industry.
- Present a poster at the AMCP 2003 Educational Conference in Montreal, Quebec, Canada.

To be eligible, all application materials must be postmarked by February 28, 2003.

To receive an application package, contact:
Managed Care Pharmacy Internship Coordinator
Academy of Managed Care Pharmacy • 100 North Pitt Street • Suite 400 • Alexandria, VA 22314
Tel: (703) 683-8416 • Toll-Free: (800) 827-2627 • Fax: (703) 683-8417 • www.amcp.org

This annual internship for pharmacy students reflects the commitment of the Academy of Managed Care Pharmacy and Pfizer to pharmacy education and to improving the quality of pharmaceutical care.
An enigma of fragility and strength, Jacqueline McAbery's Lotus Glow is a fascinating work of art. The lotus flower image, with its ethereal petals, is energized by the solar-yellow core of a misty blue and green background. McAbery has achieved this transparent, luminous effect by applying ink and paint to muslin stretched over canvas.

Regarding her painting technique, she said, "I often start off with acrylic inks on my canvases—I choose the colors and place them in certain areas. Then as they dry, they spread, creating patterns of their own.” She added, “Originally, I had planned to paint the lotus in fully. However, after having drawn it in, I was delighted with it this way…it has a spiritual quality.”

According to Buddhist tradition, the lotus symbolizes the causality of the spiritual life. It rises from the mud of the swamp (the physical world, the body), grows up through its murky waters (the world of sensory desire and emotions), penetrates the air (the mental world of thoughts and ideas), aspires towards the light of the sun (spiritual illumination), and blossoms into a pure white flower.

In her Artist’s Statement, McAbery says, “Aspects of nature are the inspiration for my paintings. The heart of nature’s beauty instills in me a sense of awe, wonder, and fear as I am drawn into its world of mystery, power, depth, light, and dark. My paintings are archives of emotional and intuitive responses to nature/life/death. They are a way to interpret and catch the fleeting beauty that surrounds us and a way to embrace the unknown.”

One of McAbery’s first encounters with the art world, and certainly her most memorable, was a visit to the Galleria degli Uffizi museum in Florence while on a vacation to Europe with her parents when she was in high school.

Botticelli’s famous painting, The Birth of Venus, is on permanent display there, but, surprisingly, it wasn’t this magnificent work of art that most impressed the young artist-to-be. Rather, it was the Italian tour guide at the Uffizi who led the group through the museum. She remembers him as a person with such a tremendous passion for art that she was inspired to look at the art around her with newfound appreciation. McAbery surely possessed a similar passion for art—it merely took the spark of this experience to ignite the flame.

McAbery ultimately pursued art as a vocation, first earning a dual BA in psychology and art and a dual MA in clinical psychology and creative art therapy from Antioch University West in San Francisco, followed by a BFA in painting from the San Francisco Art Institute. She began her artistic career as a fine arts photographer and eventually progressed to expressing herself through painting. McAbery now works with several media, including oil, acrylic, ink, watercolor, collage and encaustic (a painting technique in which wax is mixed with pigment and applied using heat). About working with encaustic, she said, “When I discovered encaustic, I felt I had found an exciting process that allows me to include many of my artistic interests—painting, photography and mixed media—into one art piece. I am especially delighted to have found a way to incorporate my photographs into my paintings.”

Jacqueline McAbery’s Lotus Glow and many more of her stunning paintings and encaustic works can be seen on her Web site, www.createart.com. She produces her art in a studio at Hunter’s Point Shipyard, an abandoned military facility jutting into the San Francisco Bay, the largest artists’ colony in the country. Currently, she exhibits within the United States. Her work has won awards and is in private collections throughout the United States and Canada.

Sheila Macho
JMCP Contributing Editor
MARK YOUR CALENDAR!

REGISTRATION AND HOUSING WILL OPEN JANUARY 14, 2003 AT 1:00 PM EST.

innovations
IN PHARMACY PRACTICE

AMCP’s 15th Annual Meeting & Showcase is your opportunity to:

Attend the premier networking and educational event for managed care pharmacy professionals

Hear three General Sessions featuring prominent keynote speakers

Attend outstanding education sessions — as many as 40 to choose from

Walk through the Annual Showcase — almost 100 participating organizations

AND MUCH MORE!

Check the AMCP website for updated meeting information — www.amcp.org!

15th Annual Meeting & Showcase
April 9–12, 2003  Minneapolis Convention Center  Minneapolis, MN
OBJECTIVE: The primary objective was to determine the effect of a hydroxymethylglutaryl-CoA reductase inhibitor (HMG) tablet-splitting program on laboratory outcomes (lipid panel and liver enzyme tests). Other objectives were to assess patient compliance and satisfaction with splitting tablets and to measure the reduction in drug acquisition costs.

METHODS: Patients at a Veterans Affairs Health Care System facility were included in this study if they participated in the HMG tablet-splitting program between April and September 2000. Patients taking the same drug and dosage before and after implementation of the program were asked to complete a mailed questionnaire designed to measure satisfaction and compliance with the program. Data collected through electronic charts included patient demographics, prescribed medication, and the values for lipid panel and liver function tests.

RESULTS: A total of 2,019 patients were included in the study. The total cost avoidance achieved over one year for atorvastatin, lovastatin, and simvastatin was $138,108 (N=2,019). The majority of patients who responded to the questionnaire were satisfied and compliant with tablet splitting. In the laboratory analysis (N=512), there was no difference between prevalences and postvalues for total cholesterol and triglycerides. There was a statistically, but not clinically, significant decrease in LDL (102 versus 97, P=0.006) after the initiation of tablet splitting. There was no significant difference in blood pressure between patients taking whole versus split tablets. However, this study had a small sample size, and the duration for each treatment arm was short. The second study was a retrospective chart review analysis, which evaluated the effects of tablet splitting on the lipid panels of 125 patients taking simvastatin and atorvastatin. Patients were required to remain on the same dose at least 6 weeks before and after tablet-splitting initiation, and lipid panels were drawn at least 6 weeks after initiation of whole-tablet and half-tablet dosing. There was a statistically, but not clinically, significant reduction in LDL and total cholesterol levels, and no significant change in HDL and triglyceride levels. This study did not review ultimate clinical outcomes and, similar to the first study, had a small sample size.

Two studies measured the effects of tablet splitting on clinical outcomes. The first study was a randomized, crossover trial consisting of 29 patients taking lisinopril. In this study, both groups took whole tablets for 2 weeks and split tablets for 2 weeks. There was no significant difference in blood pressure between patients taking whole versus split tablets. However, this study had a small sample size, and the duration for each treatment arm was short. The second study was a retrospective chart review analysis, which evaluated the effects of tablet splitting on the lipid panels of 125 patients taking simvastatin and atorvastatin. Patients were required to remain on the same dose at least 6 weeks before and after tablet-splitting initiation, and lipid panels were drawn at least 6 weeks after initiation of whole-tablet and half-tablet dosing. There was a statistically, but not clinically, significant reduction in LDL and total cholesterol levels, and no significant change in HDL and triglyceride levels. This study did not review ultimate clinical outcomes and, similar to the first study, had a small sample size.

In an effort to maximize valuable patient resources, a tablet-splitting program was implemented at the Veterans Affairs Palo Alto Health Care System in April 2000. The medications included in our program were simvastatin, lovastatin, atorvastatin, sertraline, citalopram, and lisinopril. Tablet splitting was considered a reasonable strategy for these agents because the tablets...
Effects of a Tablet-Splitting Program in Patients Taking HMG-CoA Reductase Inhibitors: Analysis of Clinical Effects, Patient Satisfaction, Compliance, and Cost Avoidance

### FIGURE 1  Patient Satisfaction Questionnaire on Tablet Splitting

**Directions:** Please circle the most correct response (one response per question).

Which cholesterol medication do you take?
- atorvastatin(Lipitor)
- lovastatin(Mevacor)
- simvastatin(Zocor)

Please describe how you take this medication:__________________________________

<table>
<thead>
<tr>
<th>Question</th>
<th>Strongly agree</th>
<th>Agree</th>
<th>Neutral</th>
<th>Disagree</th>
<th>Strongly disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. It is easy to use the tablet splitter.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. The tablet splitter cuts the tablets into close-to-equal halves most of the time.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. How many times during the last month did the tablet splitter damage the tablet so that you were not comfortable taking the dose (one or both halves)?</td>
<td>Seldom</td>
<td>1-2 times</td>
<td>3-4 times</td>
<td>5-6 times</td>
<td>&gt;6 times</td>
</tr>
<tr>
<td>4. Tablets cut in half are _____________ to take compared to whole tablets.</td>
<td>Much easier</td>
<td>Slightly easier</td>
<td>About the same</td>
<td>Slightly harder</td>
<td>Much harder</td>
</tr>
<tr>
<td>5. Tablet splitting has had no effect on my willingness to take my medication.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Since I started splitting my tablets in half, I miss doses in a month.</td>
<td>Much more</td>
<td>Slightly more</td>
<td>About the same</td>
<td>Slightly less</td>
<td>Much less</td>
</tr>
<tr>
<td>7. How many times in the last month did you throw away a tablet (one or both halves) because you dropped it while trying to cut it or just after cutting it?</td>
<td>Seldom</td>
<td>1-2 times</td>
<td>3-4 times</td>
<td>5-6 times</td>
<td>&gt;6 times</td>
</tr>
<tr>
<td>8. It was much easier to take my medications when I did not have to split them in half.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Using the tablet splitter is too time-consuming and/or bothersome.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. The use of the tablet splitter was adequately explained to me.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Have you ever called the pharmacy because you had difficulty/confusion with the tablet splitter?</td>
<td>Yes</td>
<td></td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Have you ever come to the hospital because you had difficulty/confusion with the tablet splitter?</td>
<td>Yes</td>
<td></td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. If I had to pay the full expense of my medications, I would split tablets if it could save me some money.</td>
<td>Strongly agree</td>
<td>Agree</td>
<td>Neutral</td>
<td>Disagree</td>
<td>Strongly disagree</td>
</tr>
</tbody>
</table>

Please return questionnaire in the provided envelope.
(a) are amenable to splitting (scored or easy to split), (b) are not sustained-release or enteric-coated, (c) have a flat or similar price for each strength, (d) have a wide safety margin, and (e) account for high drug expenditures.

Before entering our program, patients were evaluated by the prescribing provider or an outpatient pharmacist for cognitive and physical barriers to assess whether or not they were able to effectively split the tablets in half. The provider could request that the prescription be filled with whole tablets if that provider determined the patient to be ineligible for the tablet-splitting program. If the provider did not indicate tablet splitting in the medication order, the pharmacist would then evaluate the patient for the tablet-splitting program. The pharmacist evaluation consisted of a brief review of the patient’s electronic medical record and a patient interview. If patients agreed to participate in the program, prescriptions were automatically converted by a pharmacist. A tablet splitter and instructions for use were also provided free of charge to patients. All patients were allowed to decline entry into the program upon request.

Because HMGs have objective clinical outcome measures that are consistent, easy to compare, and readily retrievable, we chose to focus our review on these agents. The primary objective of the study was to determine the effect of splitting atorvastatin, lovastatin, and simvastatin tablets on laboratory outcomes (lipid panel and liver enzyme tests). Other objectives of the study were to assess patient compliance and satisfaction with splitting tablets and to measure the reduction in drug acquisition costs.

## Methods

The study was conducted in the outpatient setting of the Veterans Affairs Palo Alto Health Care System. The study was conducted in 3 phases. In Phase I, a cost-avoidance analysis was conducted. In Phase II, patient compliance and satisfaction were measured using a patient questionnaire. In Phase III, laboratory outcomes were analyzed. The study protocol was approved by the Institutional Review Board, and all patients gave written, informed consent prior to enrollment.

### Phase I: Cost Avoidance

Patients were included in Phase I of the study if they were enrolled in our HMG tablet-splitting program between April 1, 2000, and September 30, 2000. The HMGs used at our institution were atorvastatin, lovastatin, and simvastatin (cerivastatin, fluvastatin, and pravastatin were not on the formulary). The patients were identified using the computerized pharmacy prescription database. To determine the cost avoidance in these patients, we obtained prescription records for HMGs in these patients over a one-year period (October 2000 to September 2001). Using the 2000-2001 VA actual drug acquisition cost for atorvastatin, lovastatin, and simvastatin, we calculated the cost of these prescriptions utilizing tablet splitting.

The calculation for cost avoidance per dose was:

\[
\text{Cost avoidance per dose} = \frac{\text{Cost of whole tablet} - \text{Cost of alternative half tablet}}{1/2}\text{cost of simvastatin 40 mg tablet}
\]

The cost avoidance per dose was multiplied by the total amount of doses filled by all the patients. The 2000-2001 VA acquisition cost of the tablet splitters was then subtracted to calculate the overall cost avoidance.

### Phase II: Patient Compliance and Satisfaction

Patients from Phase I who were on a stable dosage of an HMG for 12 weeks were enrolled in Phase II. A stable dosage was defined as no change in dosing of the HMG 6 weeks before and 6 weeks after tablet splitting was initiated. Patients were excluded prior to this phase if (a) therapy was initiated using split tablets, (b) there was a drug or dosage change at the time of conversion to tablet splitting or anytime within the 12 weeks, or (c) the patient was converted back to whole tablets within 6 weeks. Questionnaires were mailed to patients in January 2001, after the first exclusion phase, in order to measure both compliance and satisfaction with our tablet-splitting program (Figure 1). The questionnaire was adapted from the survey that was used in a prior study conducted by Carr-Lopez et al. To the questionnaire, 4 questions were designed to measure satisfaction and 2 questions were designed to measure compliance. The other questions served to identify which drug was split, how it was taken, and to determine the logistics of tablet splitting. Responses were collected through April 2001.

### Phase III: Laboratory Outcomes

The Phase III laboratory analysis was conducted on all patients in Phase II who had lipid panels drawn and recorded both before (prelab) and after (postlab) tablet splitting. The prelab was defined as a lipid panel taken between one year before and the day that tablet splitting was initiated. The postlab was defined as a lipid panel taken between 6 weeks and one year after tablet splitting was initiated. In patients with more than one preintervention and/or more than one postintervention lipid panel within the study period, the panel values closest to initiation of tablet splitting were used. Patients were excluded from Phase III analysis if the postintervention lab values were taken (a) within 6 weeks postconversion to tablet splitting, (b) after a drug or dosage change, or (c) if an interacting drug was initiated within 6 weeks of the lab test. Interacting drugs included cholestyramine, colestimol, cyclosporine, erythromycin, fenofibrate, gemfibrozil, nefazodone, niacin, phenytoin, antifungals (itraconazole, ketoconazole, fluconazole), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, abacavir).

To measure outcomes of tablet splitting, we evaluated lipid panels, liver enzyme tests, and creatine phosphokinase (CPK) laboratory values. Lipid panels included total cholesterol (TC),...
Effects of a Tablet-Splitting Program in Patients Taking HMG-CoA Reductase Inhibitors: Analysis of Clinical Effects, Patient Satisfaction, Compliance, and Cost Avoidance

low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG). Liver enzyme tests included aspartate aminotransferase (AST) and alanine aminotransferase (ALT). For both the lipid panels and liver enzyme tests, we compared the prelabs with the postlabs to determine if there was a change. CPK was used to identify if any patient experienced rhabdomyolysis after tablet splitting was initiated.

In a post hoc subgroup analysis, the laboratory results of dissatisfied and noncompliant patients identified from the questionnaires were compared. A dissatisfied patient was defined as anyone who had a negative response to all 4 questions that pertained to satisfaction. A noncompliant patient was defined as anyone who responded negatively to either of the questions pertaining to compliance.

Statistical Analysis

Interval data (TC, LDL, TG, HDL, AST, ALT) is presented as mean ± standard deviation, and comparisons were evaluated using the paired t test. For data that were not normally distributed (i.e., ALT), the data are presented as medians and compared using the Wilcoxon signed rank test. Statistical tests were performed using Sigma Stat (Version 2, Jandel, Sausalito, CA).

Results

We identified 2,019 patients enrolled in the HMG tablet-splitting program. The total cost avoidance over one year (October 2000 to September 2001) for atorvastatin, lovastatin, and simvastatin was $138,108 (Table 1), based upon actual acquisition costs for these 3 drugs.

After the cost-avoidance analysis, 1,111 patients were excluded prior to the Phase II analysis (Table 2). The remaining 908 patients were mailed questionnaires (Table 2). We received 454 responses (50%). Of the respondents, 83% were splitting simvastatin, 15% lovastatin, and 2% atorvastatin. These percentages are consistent with the overall use of these medications at our institution.

Patient satisfaction and compliance with tablet splitting were determined from the questionnaires. There were 4 questions that addressed patient satisfaction. The results of these questions showed that 84% believed that the tablet splitter was not difficult to use, 85% stated that split tablets were not harder to take compared to whole tablets, and 74% agreed that the tablet splitter was not too time-consuming or bothersome; 46% believed that it was easier to take medications when they did not have to split the tablets.

There were 2 questions that addressed patient compliance. Only 7% of the patients stated that tablet splitting had an effect on their willingness to take medications, and 7% stated that they missed more doses in a month while tablet splitting.

Five hundred-twelve patients were eligible for the laboratory analysis. The baseline demographics for these patients are listed in Table 3. The laboratory analysis showed that there was no difference between preintervention and postintervention laboratory values for total cholesterol and triglycerides (Table 4). However, there was a statistically significant decrease in LDL (102 versus 97, \( P<0.001 \)), a statistically significant increase in HDL (46 versus 48, \( P<0.001 \)), and statistically significant increases in both AST (26 versus 28, \( P<0.001 \)) and ALT (24 versus 26, \( P=0.006 \)) after the initiation of tablet splitting. No patients experienced rhabdomyolysis after tablet splitting was initiated, as determined by analysis of CPK laboratory values.
In the subgroup analysis, the laboratory results of the dissatisfied and noncompliant (self-reported) patients identified from the questionnaires were analyzed. There was no significant change in the laboratory values between preintervention and postintervention. (Table 5).

**Discussion**

This study suggests that tablet splitting for HMGs has no negative effects on lipid panels or liver enzyme tests. This study is larger than the previous studies that address tablet splitting and is the first one to measure laboratory outcomes that include changes in liver enzyme tests or adverse patient events associated with splitting HMG tablets.

In the laboratory analysis, there was no change in total cholesterol and triglycerides, but there was a statistically significant decrease in LDL and a statistically significant increase in HDL. Our findings are very similar to those reported by Duncan et al.4 The changes in LDL and HDL are most likely beneficial for the patients; however, the clinical significance and reasons for the changes are uncertain. There were also statistically significant increases in the liver enzyme tests, AST and ALT; however, these increases do not appear to be clinically significant since the levels of both the AST and ALT after the change are well within the normal range for these tests.

Among possible limitations of our study, the positive outcomes may be attributable in part to the screening process involved. Not all patients can split tablets in half effectively with a pill splitter, and, therefore, not all patients should be included in tablet-splitting programs. Patients who might be excluded from tablet-splitting programs include those with eyesight problems, arthritis in the hands, or cognitive impairment. To avoid some of these problems, outpatient pharmacists assessed the patients for both cognitive and physical barriers before initiating them in the program. If the pharmacist determined that the patient could not effectively split the tablets in half, a note was left in the patient’s medication profile stating not to enter the patient into the tablet-splitting program.

Another factor that may have contributed to the favorable laboratory outcomes is lifestyle modification. While we assessed laboratory outcomes up to 12 months postsplitting, we did not give consideration to changes in weight, smoking status, alcohol consumption, or dietary modifications during that time. Any of these factors may have influenced laboratory values. In addition, our study was not designed to objectively assess medication compliance using methods such as a pill count or refill analysis. This would have been particularly useful to ensure that patients were indeed taking split tablets (and not whole tablets), which could also have affected the laboratory outcomes.

The majority of patients included in the study were satisfied and compliant with the HMG tablet-splitting program, as shown from the questionnaire results. For the few patients identified as noncompliant or dissatisfied with the program, it was important to analyze whether splitting tablets was adversely affecting their outcomes. Neither the dissatisfied nor noncompliant patients had any significant changes in their lipid panels and liver enzyme tests when comparing their laboratory values before and after tablet splitting. These results suggest that tablet splitting is also effective in these patients; however, additional results from a larger study designed a priori to specifically address this question are necessary.

The HMG tablet-splitting program reduced actual outpatient drug acquisition costs by more than $138,000 for our institution during the time period between October 1, 2000, and September 30, 2001. The cost avoidance calculated in the study for this one-year period was for all patients included in Phase I (patients converted to split tablets between April 1 and September 30, 2000). Patients who were enrolled in the program after September 30, 2000, were not included in the cost analysis. Patients continue to be successfully enrolled in the tablet-splitting program; therefore, this cost-avoidance figure is
likely an underestimate of the total fiscal impact of the program over this one-year time frame. In addition, this analysis only takes into account the effect of splitting HMGs. The tablet-splitting strategy is used for a continually growing list of agents in our outpatient setting, resulting in cost avoidance of even greater magnitude. Finally, it is important to note that VA drug acquisition costs, which are considerably lower than average wholesale price, were used in our calculations. Therefore, other managed care organizations that face higher drug acquisition costs could expect a more substantial cost avoidance.

Unfortunately, due to the retrospective nature of this analysis, we were unable to precisely factor pharmacist time and effort into our analysis. These factors are, of course, very important to consider before implementing a program of this nature. If we were to assume that it took an extra 5 to 10 minutes for our pharmacists to counsel and educate the 2,019 patients, it would result in an opportunity cost of 168 to 336 pharmacist hours. Still, our cost avoidance was not offset by pharmacist salary because no additional staff were employed to implement this program.

With the recent availability of generic lovastatin, many institutions may benefit foremost from converting appropriate patients requiring HMGs to lovastatin. However, because generic lovastatin is considerably more expensive than Mevacor at our institution, and it is not flat or similar priced, we continue to use the brand-name product. Furthermore, at low doses of lovastatin (10 mg and 20 mg), the dose equivalent of simvastatin is less expensive, so we continue to offer both agents.

Another possible limitation to our study was that we had to exclude a large number of patients in phase II because they did not receive a postintervention laboratory panel. However, there is nothing to suggest that the patients who did not receive a postlab would have responded to tablet splitting differently than those patients who did receive postintervention laboratory testing. This ancillary finding is nonetheless important and enables us to target provider and patient education regarding the importance of appropriate follow-up laboratory monitoring.

An additional limitation to our study was that the questionnaire was not sent to all patients. We chose not to send out the questionnaire to patients who had drug or dosage changes at the time of tablet splitting. Our goal from the questionnaire was to determine the effects of tablet splitting on patient satisfaction and compliance while taking the same drug and dosage before and after initiation of the program. We felt that satisfaction and compliance could be affected if patients were on a different medication or if they had to swallow a different size tablet. Therefore, it would not be ideal to find out how satisfied or compliant patients were with one medication or dose before splitting and compare it to another one after they started splitting. If we wanted a broader analysis to determine what patients thought of tablet splitting in general, then we could have included these patients in the questionnaire analysis as well.

The positive results from our study reinforce and expand upon the findings presented by Duncan, et al.4 This study should be useful for many institutions and opens the door to future directions. It would be beneficial to assess outcomes of tablet splitting for other medications, such as antihypertensives and antidepressants. It will also be useful to determine significant patient barriers to effective tablet splitting.

Conclusion

Splitting HMG tablets is an effective way to reduce outpatient drug costs, improving the efficiency in treatment of hypercholesterolemia. We found favorable humanistic-service outcomes (patient satisfaction and compliance) and no short-term negative effects on laboratory outcomes associated with tablet splitting of HMG drugs for outpatients at our institution.

ACKNOWLEDGMENT

This paper was presented at the Western States Conference for Pharmacy Residents, Fellows and Preceptors, Asilomar Conference Center, Pacific Grove, California, on May 7, 2001, and at the California Society of Health-System Pharmacists, Seminar 2001, Santa Clara Convention Center, Santa Clara, California, on October 27, 2001.

DISCLOSURES

No outside funding supported this study. Author Michael Gee served as principal author of the study and was primarily responsible for drafting of the manuscript. Study concept and design, analysis and interpretation of data, and critical revision of the manuscript was the work of Gee and authors Noelle K. Hasson, Terri Hahn, and Russell Ryono. All authors contributed statistical expertise. Administrative, technical, and/or material support was provided by Hasson, Hahn, and Ryono.

REFERENCES

Validation of a Single-Patient Drug Trial Methodology for Personalized Management of Gastroesophageal Reflux Disease

BARBARA WOLFE, PharmD; EVE DEL RIO, PhD; SIDNEY L. WEISS, MS; AVISHAI MENDELSON, MD; TAMER A. ELBAGA, BS, RPh; FREDERIC J. HUSER, MBA; and DONALD P. REITBERG, PharmD

ABSTRACT

BACKGROUND: Single-patient trials (SPTs) are randomized, often multiple-crossover trials where patients serve as their own control to determine their appropriate treatment. Historically, SPTs have been individually customized, requiring significant time and cost for execution. The patient's progress is tracked and evaluated in a blinded, multiple-crossover design comparing different therapies. Standardized, cost-efficient SPTs could help avoid (a) inappropriate extrapolation of the average-group outcomes from parallel, clinical trials to community-practice patients and (b) wasteful prescribing of high-cost drugs. Aggregate SPT results can also provide new data on appropriate drug prescribing in subpopulations.

OBJECTIVE: To validate a standardized, commercially useful SPT method for comparing drugs/doses in patients with gastroesophageal reflux disease (GERD) requiring maintenance therapy.

METHODS: A double-blind, single-dummy, randomized, 3 paired-period (28 days per period, 14 days per leg), multiple-crossover, SPT comparing omeprazole 20 mg daily and ranitidine hydrochloride (ranitidine) 150 mg twice daily was employed for 32 patients with GERD taking acid-suppressing medications chronically. Endpoints to determine effectiveness were selected from a recently approved new-drug application. Heartburn, regurgitation, difficulty swallowing, epigastric pain, and nausea were evaluated, and use of rescue medications was also measured. Quality of life was measured weekly by the patient's global evaluation. Observations for days 1 to 4 were excluded by using aggregate database sensitivity analyses to define appropriate surrogate washout periods. Frequently reported adverse events found in labeling for acid-suppressing drugs were directly solicited and compared between treatments. Unsolicited events were recorded. Patients completed a test-kit-acceptability questionnaire.

RESULTS: Fourier of 27 evaluable SPTs (52%) showed significant superiority for omeprazole over ranitidine and 7 of 27 (26%) for ranitidine over omeprazole. Four of 27 (15%) showed parity.

CONCLUSION: Omeprazole was the appropriate treatment in only 52% of these chronic users of acid-suppressing drugs. Eleven of 27 trials (41%) indicated that ranitidine was the preferred treatment. The SPT method proved acceptable to patients, feasible to administer, and reproducible. It can statistically discriminate effectiveness and adverse events and serve as a useful, prognostic tool in community practice by determining the least costly, evidence-based, appropriate treatment.

KEY WORDS: Clinical trials, Single-patient trials, N-of-1, GERD, Gastroesophageal reflux, Esophagitis, Omeprazole, Ranitidine, Antulcer agents, Gastrointestinal agents

Gastroesophageal reflux disease (GERD) is the retrograde movement of stomach contents into the esophagus. More than 60 million American adults experience GERD and heartburn at least once a month and about 25 million adults experience heartburn daily. Erosive esophagitis (EE) is a part of the spectrum of GERD, but not all patients with GERD experience EE. The only Food and Drug Administration (FDA)-approved, chronic indication for GERD sufferers is maintenance of healing of EE.

In practice, the presence and healing of EE may not be objectively confirmed. Endoscopy is currently the most appropriate test to document the mucosal damage associated with EE due to GERD. However, in a managed care environment, this procedure is generally not performed when patients initially present with symptoms. Instead, patients are often treated symptomatically. GERD is a chronic condition, and patients often experience symptomatic relapses. Many patients with GERD may require pharmacologic maintenance regimens to prevent symptoms. Patients with less severe disease may not require maintenance therapy at all or may be successfully treated with intermittent treatment to control symptomatic recurrences.

GERD is commonly treated with acid-suppressing agents such as proton pump inhibitors (PPIs) and histamine₂-receptor antagonists (H₂RAs). Omeprazole, a PPI, and ranitidine hydrochloride (ranitidine), an H₂RA, are both FDA-approved for short-term, symptomatic relief of GERD with or without EE. In order to obtain FDA approval to market these drugs in the United States for these indications, the sponsoring companies were required to demonstrate the products' efficacy and safety through adequate and well-controlled clinical trials. However, prescribing physicians cannot use these data to reliably predict how their individual patients will respond to these specific drugs.

For example, in the clinical trials submitted to the FDA in support of omeprazole for the treatment of GERD, 48% of patients experienced complete relief after treatment with omeprazole 20 mg daily compared to 14% of those treated with a placebo. While this difference is statistically significant and was the basis for FDA approval of this drug for GERD, 52% of patients still experienced GERD symptoms that were not relieved by omeprazole treatment. Assuming that a placebo response occurs with equal frequency in active and placebo groups due to randomization, subtracting the placebo response rate (14%) from the omeprazole rate (48%) provides an estimated true drug response rate of only 34%. In fact, 22% of

Authors

BARBARA WOLFE, PharmD, is a Graduate Student, University of Florida College of Pharmacy, Gainesville, Florida; AVISHAI MENDELSON, MD, is Clinical Investigator, Radiant Research, Inc., West Palm Beach, Florida; EVE DEL RIO, PhD, is Vice President of Clinical Research; SIDNEY L. WEISS, MS, is Vice President of Biostatistics; TAMER A. ELBAGA, BS, RPh, is Pharmacy Operations Manager; FREDERIC J. HUSER, MBA, is Chief Executive Officer; and DONALD P. REITBERG, PharmD, is President of Scientific Affairs, at Opt-e-scrip, Inc., Morristown, New Jersey.

AUTHOR CORRESPONDENCE: Donald P. Reitberg, PharmD, President of Scientific Affairs, Opt-e-scrip, Inc., 25 Linsdale Drive, Suite 203, Morristown, NJ 07960. Tel: (973) 693-3849; E-mail: donreitberg@opt-e-scrip.com

Copyright © 2002, Academy of Managed Care Pharmacy. All rights reserved.
Validation of a Single-Patient Drug Trial Methodology for Personalized Management of Gastroesophageal Reflux Disease

JMCP November/December 2002 Vol. 8, No. 6 www.amcp.org

omeprazole-treated patients still reported heartburn on 5 to 7 days out of the last study week.

Single-patient drug trials (SPTs) have been accepted by both patients and physicians as a useful tool for guiding treatment decisions by evaluating drug effectiveness and tolerability in individual patients who serve as their own controls. These trials are only useful for management of chronic diseases in which therapy leads to temporary alleviation of manifestations rather than lasting modification of a disease process. Within the context of the hierarchy for evidence-based study designs, SPTs deliver the highest strength-of-evidence for making individual patient treatment decisions. According to the Evidence-Based Medicine Working Group (American Medical Association), SPTs are superior to group-randomized trials, observational studies, and physiologic studies for targeting individual-patient treatment. The weakest data in the hierarchy are unsystematic, clinical observations; unfortunately, these uncontrolled observations are routinely relied upon as the basis for treatment decisions.

In addition to providing treatment guidance for individual patients, SPT results can be aggregated to provide inferences regarding drug effects in populations/subpopulations. The aggregate database can also be applied to each individual patient to enhance statistical power to detect differences, permitting greater certainty of each individual’s prognosis.

Historically, SPTs have been individually customized, thus requiring a considerable effort for design, conduct, and analysis. Not surprisingly, the time and cost of such individually customized trials have severely limited their use. This paper reports the results of a standardized methodology that can be used routinely in clinical practice to optimize treatment decisions on an individual-patient basis for GERD.

The present effort is directed at the development of uniform, commercially available SPT kits, thereby creating economies-of-scale to support evidence-based treatment decisions for patients requiring GERD maintenance therapy. To scale-up this technology for widespread community use in medical practice, it was necessary to define an approach for validation of test kits based upon standards established for other forms of clinical research, such as group randomized, controlled trials. It was necessary to demonstrate that (a) the components are user-friendly, i.e., able to capture the required data with minimal supervision of patients, and (b) the methods have sufficient sensitivity and specificity with respect to the detection of clinically relevant differences between the compared drug treatments.

For this study, validation was facilitated by the fact that recent U.S. FDA approvals of drugs for GERD and for maintenance of healing of EE were based on pivotal trials in which many of the primary efficacy endpoints were obtained from diaries completed by patients. Therefore, it was possible to base the test kits on a “gold standard”; the diary questions used in a modern U.S. FDA approval. To complete the SPT validation, it had to be shown that those test instruments previously validated in new-drug applications are feasible to administer with minimal support by the physician’s office, reproducible when used in an SPT design, and able to statistically discriminate relevant clinical information when used in SPTs.

The divergence in cost of the 2 comparator drugs in this category at the time of this writing is an example of the potential financial advantage SPTs can offer. The generic availability of all H2RAs, including ranitidine, cimetidine, nizatidine, and famotidine, has made these drugs relatively inexpensive in comparison to the (currently) brand-only PPIs. Therefore, SPTs could decrease the cost of health care on those occasions when therapeutic substitution with the less expensive agent is suggested from test results. When targeted for use by appropriate patients, SPT methodology would make the therapeutic substitution obvious to the prescriber by providing reliable statistical data in place of unblinded and uncontrolled anecdotal patient reports. If head-to-head comparisons between PPIs and H2RAs can create a substantial opportunity for evidence-based substitution, the substitution rates may be even greater for comparisons between 2 PPIs, given the greater pharmacologic similarity between the compared drug treatments. Higher switch rates could occur, for example, when a generic omeprazole oral dosage form is marketed and compared to a brand-name PPI.

The purpose of this study was 2-fold: (1) to validate an SPT methodology for acid-suppressing medications, such as PPIs and H2RAs, in the treatment of patients with a clinical or empirical diagnosis of GERD not proven through 24-hour pH monitoring or barium swallows, and (2) to validate a method for substituting a less expensive agent, such as an H2RA, with an equivalent or better effectiveness/safety profile.

Unlike trial-and-error, financially driven, step-down approaches, the GERD SPT was designed to provide health care professionals with objective data based on each patient’s individual response to treatment, thus allowing the most appropriate, safe, and effective therapy to be individually tailored to meet each patient’s treatment goals (i.e., relief of symptoms). The test kit was designed for effective execution by minimally deviating from ordinary medical practice. The physicians need only write a simple prescription for a specific protocol, as they would for a laboratory test. They would then receive a report with the essential results boldly highlighted for rapid interpretation. By adding controlled evidence to decision making rather than relying on unsystematic clinical observation, the physician can have an opportunity to reduce risk to the patient of GERD sequelae, such as Barrett’s esophagus and esophageal cancer. The pharmacy-based, drug-therapy-management company that produced the SPT is structured to provide patient counseling and customer service and serves as an impartial, independent, unbiased provider of SPT testing services.

Materials and Methods

For the purpose of validation prior to commercial use of test kits for GERD, 32 patients were enrolled in SPTs. Each was a double-blind, randomized, 3-paired-period, multiple-crossover
Validation of a Single-Patient Drug Trial Methodology for Personalized Management of Gastroesophageal Reflux Disease

trial of 84 days duration comparing omeprazole to ranitidine. Patients served as their own control to determine the relative effectiveness and adverse event profile for the 2 drugs in each individual. In all trials, omeprazole 20 mg taken in the morning and placebo in the evening were compared to ranitidine 150 mg taken in the morning and evening, each taken for a 14-day course. Therefore, all patients experienced a twice-daily dosing regimen. Patients were instructed to take the morning dose before a meal, and the evening dose approximately 12 hours later. The doses selected were based on the usual recommended adult dose according to product labeling.

Selection for evaluation of a 14-day period for each leg was based on the pharmacologic profile of omeprazole, a long-acting PPI. The inhibition of gastric acid secretion by omeprazole persists for up to 72 hours and increases, with continued use reaching a plateau after about 4 days of therapy. Following discontinuation of omeprazole, gastric acid secretion returns to baseline over a 3- to 5-day period. This would theoretically provide for a substantial time period that is minimally affected by carryover effects.

Published data from SPTs suggest that 3 pairs of periods (6 treatment periods) can provide sufficient power to distinguish between active drug and placebo for a drug known to be safe and effective in group trials. Since there were no earlier published SPTs for GERD in the literature, we elected to conduct 30 trials to obtain sufficiently precise estimates of variance so that the power of various potential kit configurations to detect differences in the key variables could be evaluated. The purpose of each individual test was to generate data on the comparative effectiveness and adverse event profile of the 2 acid-suppressing agents to guide future prescribing for each individual patient.

For the ordinal variable, Patient Global Score, significance was assessed for each SPT by applying aggregate single-patient data from all patients to enhance statistical power. This was analyzed with a modified paired 2-tailed t test at $\alpha=0.10$, utilizing a pooled variance estimate based on a hierarchical linear model incorporating the data from all patients. Individual GERD symptoms were analyzed on the basis of percentage of symptom-free days using a 2-tailed $\chi^2$ test at $\alpha=0.10$ (see Discussion for further explanation). There was an a priori assumption that data collected late (on days 8 to 14) during the study leg can be weighted more heavily, or early data (on days 1 to 7) can be excluded to enhance discrimination, as warranted by sensitivity analysis of aggregate data. This could correct for carryover effects from the prior study leg, as appropriate, and serve as a surrogate washout period between the compared drug treatments. The observations for days 1 through 4 of each 14-day treatment period were thereby excluded from the analysis in order to minimize the potential for carryover effects from the previous treatment. There was approximately 75% power to detect a 20% difference in each effectiveness measure.

All adverse events were captured in a manner consistent with the FDA MEDWATCH program, and were measured and compared based on the percentage of study days in which the patient reported specific adverse events. Incidences of adverse events were compared via 2-tailed Fisher’s Exact tests at $\alpha=0.10$. All available data points were included in the analysis. The power to detect a 30% difference in adverse event incidence was greater than 80%.

Patients were recruited and follow-up was performed by Radiant Research, West Palm Beach, Florida. Recruitment began on January 22, 2001, and the trials were completed on August 17, 2001. The database was closed for final analysis on November 21, 2001. Because subject participation would directly benefit a commercial sponsor, the protocol was approved by an investigational review board, and subjects were required to provide written, informed consent.

A computer-generated randomization schedule was provided by the sponsor. Individual test kits were consecutively numbered in advance of patient enrollment, and the randomization key was not provided to physicians, the investigational site, or participants. Patients were enrolled by the study coordinator and assigned to a test kit in the order of presentation to the site. The randomization was revealed to the physician, investigational site, and participant only after all of the individual’s data had been collected and analyzed. All drug doses were blinded using Gallipot dark green #2 capsules, with lactose as filler. Drug doses were provided in consumer-friendly packaging, including an outer box bearing a brief description of the test kit and 12 envelopes each containing a 7-day, compliance-labeled blister card identifying AM and PM doses, a diary, and instructions. Patients were instructed to take their morning dose after a meal, and their evening dose approximately 12 hours later. Omeprazole was taken in the morning and a placebo in the evening. Ranitidine was taken both in the morning and evening.

Male or female patients 18 years or older in otherwise good general health and with chronic GERD were recruited to participate in the study. All patients were chronic users of acid-suppressing medications. The investigating physician relied on symptom history along with chronic use of acid-suppressing medications to identify patients who would potentially benefit from an SPT. At the first study visit (Screening Visit/Day 0), each patient was asked to confirm the presence of GERD symptoms. Patients with self-reported symptoms were evaluated by the investigator for confirmation of the diagnosis and a review of the inclusion and exclusion criteria. Investigators also confirmed that they would choose to prescribe the SPT to the patient and that, in their medical opinion, the patient would benefit directly from the trial.

Patients were to be excluded if (a) the investigator considered the patient to have medical conditions that would cause the patient to be placed at risk by trial participation, such as pregnancy (due to multiple-drug exposures) or renal failure; (b) the patient had known hypersensitivity to omeprazole or ranitidine or any components of the formulations; (c) the
Validation of a Single-Patient Drug Trial Methodology for Personalized Management of Gastroesophageal Reflux Disease

Each patient was unable or unwilling to comply with the protocol or was unable to comprehend and satisfactorily use the measurement scales as determined by the investigator or designee at screening; (d) the patient was on other medications that have known drug interactions with PPIs or H2RAs; (e) the patient was not willing to abstain from routine stomach remedies (i.e., PPIs, H2RAs, antacids, alginic acid preparations, bismuth preparations, prokinetics, sucralfate) other than the study drug, during the study; (f) the patient was initiating or changing a regimen including immunotherapy, anticholinergics, or prokinetics during the course of the study or was on maintenance therapy for less than one month; (g) the patient was treated with immunosuppressives, radiation therapy, PPIs, H2RAs, antacids, alginic acid preparations, bismuth preparations, anticholinergics, prokinetics, or sucralfate over the past 3 months and/or required such therapy during the course of the study; (h) the patient had a history of abuse of alcohol or any other recreational or prescription drug within the year prior to the study; or (i) the patient was using antidepressant pharmacotherapy (due to anticholinergic effects). A patient would be excluded if they had been on methotrexate, for example, and had the potential for drug-induced esophagitis. The use of rescue medications was allowed during the study. All patients were chronic users of acid-suppressing medications by history.

Three recruitment methods were employed concurrently: advertising with telephone screening, physician referrals, and outbound calls to potential GERD sufferers who participated in previously conducted clinical trials. Sixty-six potential subjects responded to advertising and were screened during in-bound telephone calls at a call center prior to the first visit. Of these, only one presented for an initial visit and was entered. The remaining 65 of these call center subjects were excluded during the telephone interview because they were not able or willing to comply with the protocol requirements. There were no other reported reasons for exclusion, and all subjects were entered at their initial visit. Thirteen subjects were referred by their physician. Eighteen subjects were recruited via an outbound telephone call because they had participated in another clinical trial and were known to have had GERD.

Patients responded to 9 distinct effectiveness questions on a daily basis and to 2 distinct effectiveness questions on a weekly basis. This represents a superset of the questions ordinarily asked of patients in clinical trials for regulatory drug approval and was intended to provide insight into possible optimization by targeting primary endpoints for a future commercial version of this SPT kit.

Effectiveness analyses were based on patient daily evaluations of the following symptoms: heartburn, regurgitation, difficulty swallowing, epigastric (stomach) pain, and nausea. The severity of each of these symptoms was rated using a 4-point scale: 0 (none), 1 (mild), 2 (moderate), or 3 (severe). The patients were also asked to respond either yes or no to the following questions every day: (1) Have you experienced a rising, spreading uncomfortable feeling behind your breastbone within the last 24 hours? (2) Was this feeling combined with a burning sensation in your chest? (3) Did you have these symptoms during the last 24 hours? and (4) Did you use anything else (besides study medication) for these symptoms? Question 4 was asked to determine if “rescue” medications were used. In addition, frequency of symptoms was recorded weekly using the following scale: none, 1 day, 2 to 4 days, 5 to 6 days, or 7 days.

Each patient recorded all adverse events experienced during the trial. Patients were asked daily about typical adverse events expected to occur frequently, based on product labeling for GERD medications. These included headache, dizziness, rash, diarrhea, lower abdominal pain, nausea, vomiting, constipation, weakness, back pain, upper respiratory infection, cough, bloating, and excess gas. Because patients served as their own control and the compared drug treatments were administered on a random schedule, no bias was introduced by soliciting for adverse events and statistically comparing the frequency of adverse events from one drug to the other.

At the end of the study, the patients were also asked to perform a quality evaluation of the test kit itself that involved providing a “liking/disliking” score for the test kit and all of its components, including ease of use and suggestions for improvement. Patients were offered a new prescription for treatment based on the guidance provided using the patient’s results from the SPT.

Results

A total of 32 subjects entered the study. Of these 32 subjects, 27 (84%) were evaluated for the effectiveness analysis. Five subjects discontinued the study prior to providing sufficient data for a meaningful analysis. Three patients (102, 111, and 130) were discontinued due to reported lack of effectiveness (all were taking ranitidine). The data available from these ranitidine patients were insufficient for any conclusions to be made regarding relative drug effectiveness and safety and/or subsequent disease management. One patient (117) was lost to follow-up while taking omeprazole, and one (129) was lost to follow-up with no treatment information. The returned compliance-packaged study medications were generally consistent with data recorded in patient diaries.

Of the 27 evaluable subjects, 19 (70%) were female and 8 (30%) were male. Twenty-five (92%) of the subjects were white, 1 (4%) was black, and 1 (4%) was Hispanic. The mean age was 62 years (SD±13.62), ranging from 35 to 84 years. The mean weight was 177 pounds (SD±35.41), ranging from 100 to 242
Validation of a Single-Patient Drug Trial Methodology for Personalized Management of Gastroesophageal Reflux Disease

The medical history of the subjects included the following concomitant conditions: dyslipidemia–12 subjects, hypertension–12 subjects, arthritis (i.e., osteoarthritis, gout)–5 subjects, asthma–2 subjects, diabetes mellitus–2 subjects, glaucoma–2 subjects, migraines–2 subjects, chronic obstructive pulmonary disease–1 subject, and hypothyroidism–1 subject. Five subjects (107, 108, 109, 119, 120) had irritable bowel syndrome. Four subjects (106, 108, 109, 132) had erosive esophagitis. No trends were discernible for differences in adverse-event profiles or effectiveness for these population subgroups.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Ethnicity*</th>
<th>Age (Years)</th>
<th>Height (Inches)</th>
<th>Weight (Pounds)</th>
<th>Ideal Weight (Pounds)</th>
<th>Total Symptoms (Score)</th>
<th>Heartburn (Score)</th>
<th>Regurgitation (Score)</th>
<th>Difficulty Swallowing (Score)</th>
<th>Stomach Pain (Score)</th>
<th>Nausea (Score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>101</td>
<td>m</td>
<td>w</td>
<td>67</td>
<td>68</td>
<td>170</td>
<td>150</td>
<td>0</td>
<td>0†</td>
<td>0</td>
<td>0†</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>103</td>
<td>f</td>
<td>w</td>
<td>69</td>
<td>65</td>
<td>219</td>
<td>126</td>
<td>3</td>
<td>2†</td>
<td>1</td>
<td>0†</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>104</td>
<td>f</td>
<td>w</td>
<td>80</td>
<td>61</td>
<td>148</td>
<td>106</td>
<td>6</td>
<td>2†</td>
<td>2</td>
<td>0†</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>105</td>
<td>f</td>
<td>b</td>
<td>49</td>
<td>62</td>
<td>176</td>
<td>111</td>
<td>4</td>
<td>2†</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>106</td>
<td>f</td>
<td>w</td>
<td>62</td>
<td>65</td>
<td>167</td>
<td>126</td>
<td>5</td>
<td>3†</td>
<td>0</td>
<td>0†</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>107</td>
<td>f</td>
<td>w</td>
<td>69</td>
<td>65</td>
<td>200</td>
<td>126</td>
<td>7</td>
<td>2</td>
<td>3†</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>108</td>
<td>f</td>
<td>w</td>
<td>82</td>
<td>62</td>
<td>182</td>
<td>111</td>
<td>7</td>
<td>2</td>
<td>3</td>
<td>2†</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>109</td>
<td>f</td>
<td>w</td>
<td>64</td>
<td>65</td>
<td>139</td>
<td>126</td>
<td>10</td>
<td>3</td>
<td>3†</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>110</td>
<td>f</td>
<td>w</td>
<td>60</td>
<td>64</td>
<td>175</td>
<td>121</td>
<td>4</td>
<td>2†</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>112</td>
<td>m</td>
<td>w</td>
<td>46</td>
<td>67</td>
<td>205</td>
<td>146</td>
<td>10</td>
<td>3†</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>113</td>
<td>f</td>
<td>w</td>
<td>58</td>
<td>67</td>
<td>220</td>
<td>136</td>
<td>7</td>
<td>3†</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>114</td>
<td>f</td>
<td>w</td>
<td>35</td>
<td>67</td>
<td>124</td>
<td>136</td>
<td>10</td>
<td>2†</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>115</td>
<td>f</td>
<td>w</td>
<td>66</td>
<td>66</td>
<td>165</td>
<td>131</td>
<td>5</td>
<td>3†</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>116</td>
<td>m</td>
<td>w</td>
<td>60</td>
<td>71</td>
<td>215</td>
<td>166</td>
<td>9</td>
<td>3</td>
<td>3†</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>118</td>
<td>f</td>
<td>w</td>
<td>76</td>
<td>65</td>
<td>175</td>
<td>126</td>
<td>5</td>
<td>2</td>
<td>3†</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>119</td>
<td>f</td>
<td>w</td>
<td>63</td>
<td>64</td>
<td>127</td>
<td>121</td>
<td>8</td>
<td>2†</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>120</td>
<td>m</td>
<td>w</td>
<td>75</td>
<td>71</td>
<td>210</td>
<td>166</td>
<td>2</td>
<td>2†</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>121</td>
<td>m</td>
<td>h</td>
<td>38</td>
<td>67</td>
<td>242</td>
<td>136</td>
<td>7</td>
<td>3†</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>122</td>
<td>f</td>
<td>w</td>
<td>54</td>
<td>67</td>
<td>185</td>
<td>136</td>
<td>4</td>
<td>2†</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>123</td>
<td>m</td>
<td>w</td>
<td>71</td>
<td>68</td>
<td>146</td>
<td>141</td>
<td>1</td>
<td>1†</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>124</td>
<td>f</td>
<td>w</td>
<td>84</td>
<td>61</td>
<td>100</td>
<td>106</td>
<td>15</td>
<td>3</td>
<td>3†</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>125</td>
<td>m</td>
<td>w</td>
<td>69</td>
<td>69</td>
<td>203</td>
<td>146</td>
<td>6</td>
<td>2</td>
<td>1†</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>126</td>
<td>f</td>
<td>w</td>
<td>44</td>
<td>62</td>
<td>160</td>
<td>111</td>
<td>13</td>
<td>3</td>
<td>3†</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>127</td>
<td>f</td>
<td>w</td>
<td>54</td>
<td>68</td>
<td>200</td>
<td>141</td>
<td>6</td>
<td>1</td>
<td>2†</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>128</td>
<td>m</td>
<td>w</td>
<td>72</td>
<td>71</td>
<td>176</td>
<td>166</td>
<td>1</td>
<td>1†</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>131</td>
<td>f</td>
<td>w</td>
<td>39</td>
<td>65</td>
<td>220</td>
<td>126</td>
<td>13</td>
<td>3†</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>132</td>
<td>f</td>
<td>w</td>
<td>74</td>
<td>64</td>
<td>125</td>
<td>121</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>1†</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* w = white, b=black, h = Hispanic.
† = Most bothersome symptom reported at baseline.

pounds. Nineteen subjects (70%) were classified as obese (more than 20% over ideal body weight). The mean height was 66 inches (SD±2.88), ranging from 61 to 71 inches. The most bothersome symptom for each patient as reported by the 27 patients was as follows: 17 (63%) heartburn, 7 (26%) regurgitation, and 3 (11%) difficulty swallowing. A summary of the demographic data and baseline symptom scores for the subjects is included in Table 1. The age and weight distributions are consistent with the reported association of higher age and weight with GERD. 20, 21

www.amcp.org  Vol. 8, No. 6  November/December 2002  JMCP  Journal of Managed Care Pharmacy  463
Validation of a Single-Patient Drug Trial Methodology for Personalized Management of Gastroesophageal Reflux Disease

### TABLE 2 Significant Findings in GERD Single-Patient Trials

<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>OME Superior for:†</th>
<th>RAN Superior for: ‡</th>
<th>OME AEs§</th>
<th>RAN AEs‖</th>
<th>Result¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>101</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Parity performance: use RAN</td>
</tr>
<tr>
<td>102</td>
<td>heartburn, regurgitation, burning chest, rescue meds</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>RAN superior: use RAN</td>
</tr>
<tr>
<td>103</td>
<td>heartburn, regurgitation, diff. swallow, stomach pain, nausea, breastbone, burning chest, last 24 hours, rescue meds</td>
<td>—</td>
<td>—</td>
<td>lower abdominal pain, excess gas</td>
<td>OME superior: use OME</td>
</tr>
<tr>
<td>104</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>lower abdominal pain, nausea, excess gas</td>
<td>OME superior: use OME</td>
</tr>
<tr>
<td>105</td>
<td>—</td>
<td>constipation, bloating, excess gas</td>
<td>—</td>
<td>—</td>
<td>RAN superior: use RAN</td>
</tr>
<tr>
<td>106</td>
<td>heartburn, regurgitation, breastbone, burning chest, last 24 hours, rescue meds, pt. global</td>
<td>—</td>
<td>—</td>
<td>lower abdominal pain, bloating</td>
<td>OME superior: use OME</td>
</tr>
<tr>
<td>107</td>
<td>—</td>
<td>rash, constipation</td>
<td>—</td>
<td>—</td>
<td>RAN superior: use RAN</td>
</tr>
<tr>
<td>108</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Parity performance: use RAN</td>
<td></td>
</tr>
<tr>
<td>109</td>
<td>—</td>
<td>regurgitation, stomach pain, nausea, breastbone, last 24 hours</td>
<td>—</td>
<td>—</td>
<td>RAN superior: use RAN</td>
</tr>
<tr>
<td>110</td>
<td>heartburn, breastbone, last 24 hours</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>OME superior: use OME</td>
</tr>
<tr>
<td>111</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Parity performance: use RAN</td>
<td></td>
</tr>
<tr>
<td>112</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Parity performance: use RAN</td>
<td></td>
</tr>
<tr>
<td>113</td>
<td>—</td>
<td>stomach pain, nausea</td>
<td>headache, lower abdominal pain</td>
<td>—</td>
<td>RAN superior: use RAN</td>
</tr>
<tr>
<td>114</td>
<td>—</td>
<td>heartburn, diff swallow, stomach pain</td>
<td>—</td>
<td>—</td>
<td>RAN superior: use RAN</td>
</tr>
<tr>
<td>115</td>
<td>—</td>
<td>—</td>
<td>lower abdominal pain</td>
<td>OME superior: use OME</td>
<td></td>
</tr>
<tr>
<td>116</td>
<td>heartburn, nausea, breastbone, burning chest, last 24 hours</td>
<td>—</td>
<td>—</td>
<td>diarrhea, lower abdominal pain, nausea, weakness, cough, bloating</td>
<td>OME superior: use OME</td>
</tr>
<tr>
<td>117</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Parity performance: use RAN</td>
<td></td>
</tr>
<tr>
<td>118</td>
<td>heartburn, breastbone, burning chest, last 24 hours, rescue meds, pt. global</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>OME superior: use OME</td>
</tr>
<tr>
<td>119</td>
<td>heartburn, pt. global</td>
<td>—</td>
<td>—</td>
<td>upper respiratory infection</td>
<td>OME superior: use OME</td>
</tr>
<tr>
<td>120</td>
<td>heartburn, breastbone, burning chest, last 24 hours, rescue meds</td>
<td>—</td>
<td>—</td>
<td>bloating, excess gas</td>
<td>OME superior: use OME</td>
</tr>
<tr>
<td>121</td>
<td>heartburn, stomach pain, burning chest</td>
<td>—</td>
<td>—</td>
<td>dizziness</td>
<td>lower abdominal pain</td>
</tr>
<tr>
<td>122</td>
<td>—</td>
<td>regurgitation, diff swallow, stomach pain, burning chest</td>
<td>—</td>
<td>—</td>
<td>RAN superior: use RAN</td>
</tr>
<tr>
<td>123</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>OME superior: use OME</td>
<td></td>
</tr>
<tr>
<td>124</td>
<td>regurgitation, burning chest, last 24 hours pt. global</td>
<td>—</td>
<td>constipation, bloating</td>
<td>nausea, excess gas</td>
<td>Neither agent can be recommended, both caused adverse events; may retest using different agents</td>
</tr>
<tr>
<td>125</td>
<td>pt. global heartburn, stomach pain</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>RAN superior: use RAN**</td>
</tr>
<tr>
<td>126</td>
<td>heartburn, regurgitation, nausea, breastbone, last 24 hours, rescue meds, pt. global</td>
<td>—</td>
<td>—</td>
<td>nausea, vomiting</td>
<td>OME superior: use OME</td>
</tr>
<tr>
<td>127</td>
<td>—</td>
<td>heartburn, breastbone, burning chest, rescue meds</td>
<td>diarrhea</td>
<td>headache, dizziness, nausea, constipation, upper respiratory infection, cough, bloating, excess gas</td>
<td>Neither agent can be recommended, may retest using different agents‡‡</td>
</tr>
<tr>
<td>128</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Parity performance: use RAN</td>
<td></td>
</tr>
<tr>
<td>131</td>
<td>heartburn, regurgitation, diff. swallow, stomach pain, nausea, breastbone, burning chest, last 24 hours, rescue meds</td>
<td>—</td>
<td>upper respiratory infection</td>
<td>nausea, vomiting</td>
<td>OME superior: use OME</td>
</tr>
<tr>
<td>132</td>
<td>heartburn, breastbone, burning chest, last 24 hours, rescue meds, pt. global</td>
<td>—</td>
<td>diarrhea</td>
<td>—</td>
<td>OME superior: use OME¶¶</td>
</tr>
</tbody>
</table>

* Effectiveness endpoints measured include heartburn, regurgitation, difficulty swallowing (diff. swallow), stomach pain, nausea, uncomfortable feeling behind the breastbone (breastbone), burning sensation in the chest (burning chest), reported symptoms during the last 24 hours of each treatment period (last 24 hours), less frequent use of rescue medications (rescue meds), and patient global rating (pt. global).
† Omeprazole (OME) shows superiority over ranitidine hydrochloride (RAN) for these effectiveness endpoints.
‡ Ranitidine hydrochloride (RAN) shows superiority over omeprazole (OME) for these effectiveness endpoints.
§ Omeprazole (OME) has a higher incidence than ranitidine hydrochloride (RAN) for these adverse events (AEs).
‖ Ranitidine hydrochloride (RAN) has a higher incidence than omeprazole (OME) for these adverse events (AEs).
¶ Guidance based on relative effectiveness and adverse event profiles. Less expensive agent chosen for parity performance.
# Pt. 127 discontinued on day 26 of the study due to a rash that had started on omeprazole and continued after the crossover to ranitidine. Recommend monitoring for recurrence of rash.
** Daily endpoints given greater weight than weekly endpoints.
‡‡ Pt. 127 had superior effectiveness but higher incidence of adverse events with ranitidine.
¶¶ Recommend monitoring for recurrence and severity of diarrhea.
Table 2 shows the statistically significant findings for all evaluable SPTs. All of the patients had been using an acid-suppressing medication prior to starting the study. Of 27 evaluable tests, only 14 (52%) showed significant superiority for omeprazole over ranitidine. Eleven patients (41%) had superior or parity response to ranitidine versus omeprazole, indicating that the less expensive agent (ranitidine) was the appropriate treatment. When no statistically significant differences were found between drugs for effectiveness measures and adverse events, or findings were equivocal, this was classified as parity performance, and guidance for future pharmacotherapy was determined by which drug treatment was less costly. In 2 of 27 trials (7%), neither agent could be recommended due to adverse events for both, and, therefore, the prescriber could appropriately conclude that the patient should cease drug treatment and/or seek other treatment modalities/SPTs. Given the significant cost difference between these 2 products, 48% of patients could be either placed on the less expensive agent or were shown to be poor candidates for either the expensive or inexpensive drug (90% confidence interval: 32% to 64%). That is to say, in only 14 of 27 trials (52%) was omeprazole found to be the agent of choice for an individual patient presenting as a chronic user of acid-suppressing drugs. Seven of 27 patients (101, 107, 108, 122, 123, 125, 132) were taking an H₂RA just prior to the study. Of these, 3 showed superiority for ranitidine, 2 showed parity performance, and 2 showed superiority for omeprazole. 

This sample size (7) is too small to subject to statistical analysis with regard to potential step-up therapeutic substitution rates from ranitidine to omeprazole. When these 7 patients were deleted from the analysis, the step-down substitution rate from the PPI to the H₂RA, combined with the drug therapy discontinuation rate, was 40% (90% confidence interval: 22% to 68%). For the 20 prior PPI users, omeprazole was superior in 12 (approximately 60%), ranitidine in 4 (20%), 2 (10%) showed parity performance, and for 2 (10%), neither drug was recommended.

Overall, 21 of 27 trials (78%) identified one drug or the other as superior, 4 of 27 (15%) showed no difference between drugs (parity performance), and 2 of 27 (7%) showed that neither drug was appropriate. Of the 11 of 27 trials (41%) indicating that ranitidine was the preferred treatment, 7 (26%) showed superiority for ranitidine over omeprazole. In 2 of these trials, ranitidine was shown to be superior despite the fact that there was no significant difference in effectiveness between omeprazole and ranitidine; these patients experienced a significantly higher incidence of adverse events in association with the use of omeprazole (rash and constipation in one patient, headache and lower abdominal pain in another patient). The remaining 4 of the 11 (ranitidine-preferred) trials showed parity performance as a basis for ranitidine substitution because it is the less expensive agent. Two of 27 trials (7%, patients 124 and 127) presented instances where neither drug could be recommended because both agents caused significant adverse events. For patient 127, this occurred despite having a superior response in effectiveness to ranitidine. Where neither drug can be recommended, the prescribing physician may choose to stop all treatment, use a nondrug, alternative treatment, or retest to compare 2 other drug treatments in an SPT.

As shown in Table 2, 9 subjects experienced a significantly higher incidence of specific adverse events in association with the use of omeprazole as compared with ranitidine, and 12 subjects experienced a significantly higher incidence of specific adverse events in association with the use of ranitidine as compared with omeprazole. The use of a multiple-crossover design served as an a priori decision to rechallenge and thereby established the relationship between the drug and the adverse event, thus permitting clear discrimination of which drug caused a given adverse event.

The patients were also asked to complete a kit-acceptability questionnaire. Ninety-six percent of the patients reported that they understood the diary questions, and all understood the dosing instructions as well as the purpose of the test kit. All wanted to see their test results. Sixty-one percent of the patients felt that the diary questionnaire was of appropriate length. Of the 10 patients who had previously taken an in-home test, 8 preferred this kit. Sixty-seven percent of the patients said that they would prefer to first use the kit before going on a chronic medication for GERD. The responses also confirmed that the clinical supplies were successfully blinded. An analysis of baseline symptom scores for heartburn and regurgitation did not suggest an association between disease severity and the patient’s preference for use of the kit (P=1.00 and P=0.66, respectively). Also, taking the patient global score, averaged over all treatment periods, as a measure of a patient’s well-being during the trial, there was no discernible relationship to global scores when comparing those patients who expressed preference for taking the test and those who did not (P=0.89). Therefore, patient ratings regarding the kit appeared to be independent of their disease state.

**Discussion**

The GERD SPT kit has completed validation. It was feasible to administer, and it could statistically discriminate valuable prognostic information using “gold standard” test instruments previously validated in large-scale parallel trials as well as discriminate for adverse events. On this basis, it can be recommended for routine use in community practice. The need for validated and reliable SPT methods in gastrointestinal pharmacology has been a topic of recent evaluation.22 PPIs and H₂RAs both have excellent safety records and are considered to be extremely well-tolerated.1 However, in this study, 9 subjects experienced a significantly higher incidence of specific adverse events in association with the use of omeprazole as compared with ranitidine, and 12 subjects experienced a significantly higher incidence of specific adverse events in
association with the use of ranitidine as compared with omeprazole. While the overall perception of these classes of drugs is that they are generally safe, the impaired quality of life of the patient who experiences an adverse event, even a mild to moderate one, may not be appropriately matched to the drug’s benefit. A clear advantage of this SPT methodology is the unique ability to definitively detect differences not only in effectiveness but also in adverse events for individual patients by virtue of a priori rechallenge.

These results indicate that for patients currently on PPIs, it is possible to therapeutically substitute with H2RAs (or discontinue therapy) in approximately 4 of 10 patients in clinical practice using this evidence-based approach. These SPT outcomes cannot be inferred from group, parallel trial data in part because group study designs rarely compare therapeutic alternatives head-to-head; they are usually conducted for the purpose of drug approval, requiring superiority to placebo only. When parallel, head-to-head comparisons of 2 active agents are available, discrimination of parity or superior performance is never possible for individual patients because they are exposed to a single drug/dose during the trial. Stated differently, in a group trial, there is no crossover comparison between drugs in the same individual to permit assessment of relative performance in that individual.

The results of this study show that the test kits can be used successfully to assist in determining the more appropriate drug for each patient. Only those patients who actually respond better to omeprazole need be treated with this considerably more expensive drug (at the time of this writing). The cost for a 30-day supply of Prilosec (omeprazole, 20 mg QD) is $62.37, using the Federal Supply Schedule. In contrast, the Federal Supply Schedule cost for a 30-day supply of generic ranitidine (150 mg BID) is $2.50. This is equivalent to an annual cost savings of $718.44 for each patient treated with ranitidine rather than with omeprazole.

It can be projected that payers in the United States will spend more than $10 billion this year on prescriptions for PPIs. The use of SPTs to optimize outcomes in a step-down therapy approach for GERD may have a secondary, but nevertheless profound, impact on health care costs. It is plausible that the substitution rate reported in the current work (via a series of individual tests for validation purposes) can be maintained or improved upon through formulary controls in actual health care practice.

The rate for step-down from a brand-name PPI to a generic PPI can be expected to be much higher than from a PPI to an H2RA because drugs in the same class can be expected to have a much higher incidence of parity performance. Speculatively, a step-down rate of 75% or greater can be realized where clinical and molecular differentiation between drugs are modest.

Therapeutic substitution performed by a prescriber may occur in 2 scenarios. The first scenario is a potentially biased anecdotal patient report of minimal or suboptimal treatment with the current therapy. Here, the prescriber may change medications only to find out that the replacement medication is less effective or has worse side effects than the initial one. The second scenario, which seems to be of greater consequence in recent times, is a change to satisfy a restriction or to reduce a copay based on a managed care formulary. In this case, the prescriber is forced to make substitutions based on financial savings, which may benefit the patient, payer, or both, but not necessarily based on outcomes.

SPTs can remedy the deficiencies of these approaches to treatment by providing unbiased, within-patient, statistical data to help the prescriber optimize therapy, in this case, at a rate of 78%, where one drug or the other is shown to be superior. Moreover, assuming that therapeutic substitution with a less expensive agent and/or drug discontinuation will occur at a rate of approximately 40%, managed care organizations (MCOs) can advantageously modify their current formularies to include evidence-based SPT methods in order to insure that patients get what they objectively need. Such a change, if mandated through “National Drug Code (NDC) lockouts” of brand-name drugs (unless initially dispensed in an SPT), can be expected to result in greatly improved effectiveness/safety outcomes, greater patient satisfaction with the physician and plan, less bureaucracy for the physician by eliminating prior-authorization paperwork, and reduced drug expense for the payer.

The execution of a GERD SPT program in an MCO can be particularly appropriate once there is widespread availability of generic omeprazole. Rebates paid by manufacturers of brand-name PPIs to obtain formulary access and preferred formulary positions at pharmacy benefit managers (PBMs) may account for a significant portion of a PBM’s total net profits and may discourage PBMs from aggressive promotion of generic therapeutic alternatives to brand PPIs. A GERD SPT program could be used to determine the most cost-effective drug therapies for individual patients suffering from GERD or EE.

To replace products losing patent protection, pharmaceutical companies periodically introduce new chemical entities, an isomer (or other new form of an older drug), more convenient dosing regimens, and drug combinations. These are heavily marketed to doctors and patients as the latest advancement in care, limiting the growth of generic drug market share. For example, the manufacturer of Prilosec launched Nexium (esomeprazole magnesium) and engaged in an advertising and marketing strategy to convert Prilosec users to Nexium before patent expiry and generic availability of omeprazole.

In this environment, SPT kits can provide significant value to patients and payers alike. When there are no effectiveness or side-effect differences between the 2 drugs as determined by a fully validated SPT, it is appropriate to prescribe the more established, predictable drug. As a step-down therapy approach, an SPT consisting of 2 PPIs can be used to switch patients back to the less expensive therapy. Thus, patients use a drug that has a more established safety profile, and payers can design a formula to objectively and independently get patients on the drug they need. Although rebates may influence the selection of particular drugs as step-down candidates, this does not limit the ability of
SPTs to appropriately reduce utilization and costs of step-down candidates once they are targeted, in consideration of existing contracts and financial projections.

Our discussions with physicians and MCOs indicate that the prior-authorization systems to restrict expensive brand-name drug use do not work satisfactorily for either party. Doctors resent dealing with restrictions and manage to overcome this hurdle. MCOs, therefore, experience growing usage of new, expensive drugs.

A health plan formulary can eliminate prior-authorization restrictions by instead requiring SPTs for short-term trial of 2 substitutable, chronic care drugs as a condition for refill. Patients could experience improved outcomes and fewer adverse events. Physicians could prescribe any brand-name drug they deem appropriate. Payers could avoid paying for inappropriate refills, or, alternatively, collect higher copayments on brand-name drugs that perform statistically no better or worse than the more established generic substitute. The requirement can be enforced through NDC lockouts, which only permit initial brand-name drug usage in an SPT kit. Once patients' data demonstrate that the brand-name drug is superior for them, the NDC lockout is lifted for that patient. Insurers and employers are currently considering such a formulary design. Indemnity health plans may be particularly well suited to this approach.

Each SPT result may represent a snapshot in time because disease and drug activities can wax and wane dynamically and interactively over time. Periodic retesting of comparative effectiveness and safety between 2 active drugs can be used to further optimize chronic disease treatment. Also, it may be appropriate to periodically conduct controlled “drug holidays” by comparing an active drug to a placebo. Comparisons of different doses of the same drug could also serve to optimize outcomes.

It is appropriate that different statistical criteria be applied to group trials conducted for drug approval and SPTs conducted to assess appropriate individual treatment. For group trials, the greater risk is to find a difference between active and placebo that is not real or relevant, resulting in marketing of a drug that performs inadequately and thereby adversely affects public health. Therefore, for group trials, the statistical barrier to declare a difference is appropriately high (P<0.05). For SPTs, a larger type I error (e.g., P<0.10) may be appropriate because the greater risk is to deprive the individual patient from enjoying a measurable but modest improvement, particularly when the tested drug has already been shown to be safe and effective (on average) in the general population via group trials.17

Limitations

Our work indicates that many GERD patients on PPIs may be converted to lower-cost treatments using SPTs, and with comparable or better outcomes. This is closely aligned with the purpose of managed care. However, the results of this trial cannot be definitively extrapolated to a managed care environment and require further validation in a setting where there are many GERD patients under management.

The observed SPT evaluable-study rate of 84% may well reflect the high level of interest patients have in understanding how to appropriately ease their pain and other undesirable symptoms. However, a limitation of the current work is that the study was conducted via investigative sites requiring several patient visits. Ideally, a commercial product would be self-explanatory, requiring few or no patient visits and would exert no extra burden on physicians and their routine practices. We are encouraged that the surveys conducted showed that, with modest instruction, patients understood how to use the kit.

Future Directions

The appropriate next step for product evaluation would be a formal “test market,” where test kits are dispensed by prescription directly to patients. Compliance would be monitored and reporting managed by a sophisticated and dedicated, pharmacy-based, medication therapy management operation rather than an investigational site. Patients would be followed to determine how many patients remained on a treatment based on study results, and their outcomes would be documented.

Pharmacogenomic technologies may also provide “personalized medicine” solutions in the future, although many years may be required to adequately validate the methods. These opportunities have been widely anticipated by the medical, financial, and lay press in recent years.24 It may, at some point, be reasonable to incorporate pharmacogenomic markers into SPTs as primary effectiveness and/or safety endpoints. The combined “personalization” technologies may serve to generate superior prognostic assessments compared to each used independently.

If routinely used, the validated SPT kit for GERD is anticipated to have an important impact on patient outcomes, satisfaction with health care, and public health. Moreover, the power of the current method to discriminate individual patient effectiveness and safety differences (and to permit full predictive use of concomitant prognostic information) can be expected to increase substantially as the database from similar patients enlarges and segmentation into population subgroups becomes feasible. This can permit more substantial adjustments between the population estimates and the individual patient's observed results. The enlarging database could permit an even more discriminating, user-friendly, continuously improving test kit design requiring fewer questions, fewer crossover periods, and shorter study durations, resulting in greater patient compliance.9, 30 The authors are developing additional SPTs for other chronic diseases, including allergic rhinitis17 and osteoarthritis.

Conclusion

Using SPTs, high rates of evidence-based, step-down/discontinuation from unnecessary drugs can be achieved. The SPT kit was judged useful and feasible to administer by patients. It can statistically discriminate effectiveness and adverse events and may serve as a useful tool in community practice, improving outcomes by determining the least costly, evidence-appropriate
treatment. When omeprazole becomes available as an inexpensive generic drug, the step-down rate for therapeutic substitution from a new-generation proton pump inhibitor to another biologically similar PPI can be substantially greater than that observed for ranitidine, a histamine-2 receptor antagonist.

ACKNOWLEDGMENTS

The authors thank study coordinator April Lambermont, MLT, BS, CCRC, and site director Juan Martinez, BS, CCRC, both at Radiant Research, Inc., for their insightful comments and overall support of the study; Barbara Wolfe’s contribution was in partial fulfillment of requirements for the Doctor of Pharmacy degree.

DISCLOSURES

Funding for this research was provided by Opt-e-scr, Inc., and was obtained by authors Frederic J. Huser and Donald P. Reitberg. Huser, Reitberg, and authors Eve del Rio, Sidney L. Weiss, and Tamer A. Elbaga are employed by Opt-e-scr, Inc. Author Barbara Wolfe served as principal author of the study. Study concept and design were contributed by Wolfe, del Rio, Weiss, and Reitberg. Analysis and interpretation of data were contributed by Wolfe, del Rio, Weiss, Elbaga, and Reitberg. Drafting of the manuscript was primarily the work of Wolfe, del Rio, Weiss, Elbaga, Huser, Reitberg, and author Avishai Mendelson. Statistical expertise was contributed by Weiss. Administrative, technical, and/or material support was provided by Wolfe, Elbaga, and Radiant Research, Inc.

REFERENCES

6. FDA summary basis of approval for Prilosec: NDA 19-810; Study I-1601a.
Clinical and Economic Impact of Glatiramer Acetate Versus Beta Interferon Therapy Among Patients With Multiple Sclerosis in a Managed Care Population

Daniel A. Ollendorf, MPH; Evguenia Jilinskaia, PhD; and Merrikay Oleen-Burkey, PhD

ABSTRACT

OBJECTIVE: To examine the outcomes of use of glatiramer acetate (GA) versus beta interferons-1a (intramuscular) (1A) and -1b (1B) in patients with multiple sclerosis (MS) in a managed care setting.

METHODS: Data were obtained from a national retrospective claims database from January 1996 to June 2001. Patients were followed from the first prescription for immunomodulatory therapy until plan disenrollment or end of study time frame. The incidence of all relapses (defined as hospitalization for MS or ambulatory visit followed by use of systemic corticosteroids) as well as utilization and costs of MS-related care were examined for each group. Data were adjusted for variable follow-up using survival techniques.

RESULTS: A total of 8,457 patients receiving immunomodulatory therapy were included in the study cohort; follow-up averaged 17.3 months. Three quarters of patients were female; the mean age was 42.2 years. The risk of relapse (defined as number of new cases) at one year was significantly increased for the beta interferons relative to GA (hazard ratio: 1.15 and 1.51 for 1A and 1B, respectively, P<0.01). Mean (±SD) costs of care also were reduced among GA patients ($9,522 ±$9,706) versus $9,957 ±$9,526 for 1A and 1B, respectively). These findings persisted in multivariate analyses, controlling for differences in demographic characteristics.

CONCLUSIONS: Glatiramer acetate is associated with reductions in the incidence of relapse and costs of care relative to the beta interferons among this large group of managed care patients with MS.

KEYWORDS: Multiple sclerosis, Immunomodulatory therapy, Costs and costs analysis, Relapse rates

J Managed Care Pharm. 2002(8)6:469-76

M ultiple sclerosis (MS) is a costly and debilitating disease. Approximately 350,000 persons in the United States are currently diagnosed with MS; it is the most common cause of chronic neurologic disability in young adults.1 While the clinical course of MS varies substantially by patient, the disease typically progresses to some level of disability in approximately two thirds of MS patients.2 Regardless of the level of disability, patients with MS often report negative psychological and social impacts from the disease. The direct medical costs of MS also are substantial. Total annual expenditures for medical services per MS patient have been reported to range from $7,000 to $13,000 in this country, reflecting levels 2 to 3 times higher than those for all private and public insurance enrollees.3

Historically, pharmacologic treatment of MS has revolved around amelioration of symptoms (e.g., use of benzodiazepines and muscle relaxants to control spasticity and use of corticosteroids to reduce the severity of MS relapses). Recently, however, the introduction of several new medications has changed MS management. These medications, which include glatiramer acetate (GA) (Copaxone, Teva Pharmaceutical Industries, Ltd.), a synthetic, noninterferon polypeptide of 4 amino acids, as well as the type 1 beta interferons (i.e., beta interferon-1a (1A) [Avonex, Biogen Inc.] and beta interferon-1b (1B) [Betaseron, Berlex Laboratories, Inc.]) have been demonstrated to be effective in reducing the rate of relapse as well as slowing disease progression in the “relapsing-remitting” form of MS.4,14 At the time this project was completed, the newest beta interferon 1a (Rebif, Serono S.A.) was not commercially available in the United States.

The precise action of beta interferons in MS is unknown. However, these drugs are known to decrease lymphocyte proliferation and interferon gamma expression, induce anti-inflammatory Th2 cytokines, and most importantly to the anti-inflammatory effect, diminish the migration of activated T cells across the blood-brain barrier.15-18 In contrast, the observed effects of glatiramer acetate are quite distinct from those of the beta interferon and include (a) competition with myelin-basic protein (MBP) for binding to the major histocompatibility complex (MHC) molecules; (b) competition of bound glatiramer acetate and MHC with MBP/MHC for binding to the T-cell receptor; (c) induction of compound-specific Th2 cells, leading to a profound Th2 shift; and (d) migration of compound-specific cells into the central nervous system.19-23 A fifth mechanism, that of a neuroprotective role, has also been observed in relation to optic nerve damage.24

Authors

Daniel A. Ollendorf, MPH, is Director, Analytic and Consulting Services, and Evguenia Jilinskaia, PhD, is Senior Biostatistician at PharMetrics, Inc., Watertown, Massachusetts; Merrikay Oleen-Burkey, PhD, is Director, Health Outcomes Research at Teva Neuroscience, Inc., Kansas City, Missouri.

Corresponding Author: Daniel A. Ollendorf, Director, Analytic and Consulting Services PharMetrics, Inc., 150 Coolidge Avenue, Watertown, MA 02472 Tel: (617) 972-8590; Fax: (617) 972-8587; E-mail: dollendorf@pharmetrics.com

Copyright © 2002, Academy of Managed Care Pharmacy. All rights reserved.
In addition to these mechanistic differences, data from clinical trials and postmarketing surveillance studies suggest that glatiramer acetate may have several distinct advantages relative to the interferons, including a relatively mild side-effect profile allowing for less use of concomitant medications such as acetaminophen and NSAIDs, lack of neutralizing antibodies, and reduced need for laboratory monitoring. These advantages may be associated with greater durability of treatment, better outcomes, and reduced utilization and costs relative to interferon therapy. Patterns of pharmacotherapy as well as the costs and effects of these 3 medications have never been compared under conditions of typical clinical practice, however. To address these needs, an examination of the impact of GA on the utilization and costs of MS-related care relative to that of beta interferon therapy was undertaken, using data from a proprietary database.

**Methods**

**Overview**

Data for this study were obtained on all patients with one or more institutional or provider claims with a listed diagnosis of MS (ICD-9-CM 340) who were in the database between January 1, 1996, and June 30, 2001. Patients were then classified into 3 treatment groups based on data on the first paid pharmacy claim observed during the study period (i.e., GA, 1A, or 1B). Each patient was assigned an “index date” based on the date of the first prescription for immunomodulatory therapy.

A variety of measures were then compared during the “follow-up period” (i.e., beginning with the index date) between patients in the 3 treatment groups, including the cumulative incidence of relapses, time to first relapse, and the mean number of relapses, as well as the utilization and costs of selected MS-related medications and health care services. Because the duration of eligibility for health and drug benefits during the follow-up period differed by patient, annualization as well as techniques of survival analysis (i.e., examination of data according to time observed without any specific threshold) were employed to estimate the above-described measures.

**Data Source**

Data were obtained from the proprietary database, which is comprised of fully adjudicated medical and pharmaceutical claims for nearly 27 million unique patients from 43 health plans across the United States. The database includes both inpatient and outpatient diagnoses (in ICD-9-CM format) and procedures (in CPT-4 and HCPCS formats) as well as both community pharmacy and mail-order prescription records; available data on prescription records include the National Drug Code (NDC) as well as days supplied and quantity dispensed (for a subgroup of datasets). Both paid and charge amounts are available for all services rendered as well as dates of service for all claims. Additional data elements include demographic variables (age, gender, geographic region), plan type (e.g., HMO, PPO), payer type (e.g., commercial, self-pay), provider specialty, and start and stop dates for plan enrollment.

Records in the database are representative of the national managed care population on a variety of demographic measures, including geographic region, age, gender, and plan type. The data are also longitudinal, with an average member enrollment time of 2 years. Only health plans submitting data for all members are included in the database, ensuring complete data capture and unbiased samples. Data contributions are also subjected to a series of quality checks to ensure a standardized format and minimal error rates.

**Measures**

Measures of interest in these analyses included the incidence of all relapses as well as utilization and costs of MS-related medications and health care services during the period of follow-up. MS relapses are typically defined using one of several disability or symptom scales. Analyses of claims data are limited, however, to measures that would be associated with care-seeking behavior. An operational definition of relapses was therefore employed and was defined on the basis of either (a) an inpatient claim (hospitalization) with a listed principal diagnosis of MS or (b) a claim for an outpatient visit with a listed diagnosis of MS in combination with a pharmacy or medical claim (within 7 days after the visit) for one of the following: intravenous methylprednisolone or corticotrophin or oral methylprednisolone, prednisone, prednisolone, or dexamethasone. If multiple claims were present within a 30-day window, this was treated as a single relapse event; the first available service date within such a grouping was deemed to be the relapse date.

Medications of interest included immunomodulatory therapy (i.e., 1A [NDC code 59627-0001-03, “J” code 1825], 1B [50419-0521-03, 50419-0521-15, J1830], and GA [00088-1150-03, Q2010]), as well as prescription medications indicated for control of MS symptoms and side effects of immunomodulatory therapy (e.g., antispasmodics, anticholinergics, corticosteroids).

Health care services included selected laboratory tests for monitoring of immunomodulatory therapy (i.e., complete blood counts [CPT-4 code 85031, 85022-85025], platelet counts [85007, 85027, 85585, 85590, 85595], and liver function tests [80076, 82040, 82247, 82248, 84075, 84155, 84460, 84450]), outpatient services (i.e., emergency room, physician office, home health, imaging [i.e., MRI], and other hospital outpatient visits), and hospitalizations for MS. Inpatient and outpatient services were deemed to be MS-related based on a relevant listed diagnosis (principal or secondary); lab tests were tallied regardless of diagnosis. Costs of all relevant medications and services were also assessed. A health plan perspective was adopted in these analyses; cost estimates were therefore based on the amount paid (less patient copayments and deductibles) for relevant claims.

**Analyses**

Primary analyses were conducted on an intent-to-treat basis; all patients with an MS diagnosis and receipt of immunomodulatory therapy were included in the database. Additional analyses included exploratory comparisons for overlapping medication use. Patients who met the criteria for inclusion in the database were classified into 3 treatment groups based on data on the first paid pharmacy claim observed during the period of follow-up (i.e., GA, 1A, or 1B).
tory therapy were therefore included in these analyses. Additional analyses focused attention on important subgroups, including patients newly starting immunomodulatory therapy as well as those remaining on only a single immunomodulatory medication (i.e., exclusive of switch or add-on therapy). New starts were determined based on the absence of any pharmacy claims for immunomodulatory therapy during a 9-month “pretreatment” period (i.e., prior to the first claim for the medication of interest).

Patients in the 3 treatment groups were first compared with respect to a variety of demographic and clinical characteristics, including age, gender, duration of follow-up, number of relapses and total costs during the pretreatment period (new starts only), type of health plan (e.g., PPO, HMO, fee-for-service), physician specialty, and geographic region.

Estimated propensity scores for use of immunomodulatory therapy also were calculated as a measure of patient severity of illness and disease progression. These scores represent a given patient’s probability, or “propensity,” of receiving a given treatment option and are calculated by summing coefficient values for a list of potential confounding variables. Use of these scores confers the advantage of having a single estimate available to adjust for confounding (i.e., effects on the findings of interest other than treatment effect) in any multivariate analysis, and have been widely used in clinical and economic research examining causal effects and in comparisons of nonrandomized groups.28,29 In this case, the outcome of interest was the probability of use of any of the 3 immunomodulatory medications of interest. Covariates (i.e., potentially confounding variables) were introduced to the model using stepwise logistic regression techniques; those achieving significance at a level of \( P < .10 \) were retained. In the final model, age, geographic region, a flag for the presence of at least one relapse during the pretreatment and follow-up periods, physi-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Glatiramer Acetate (n=1,674)</th>
<th>Interferon Beta-1a (n=5,031)</th>
<th>Interferon Beta-1b (n=1,752)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, SD)</td>
<td>42.3 (9.1)</td>
<td>41.8 (9.2)</td>
<td>43.4 (9.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>77.4</td>
<td>77.0</td>
<td>72.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Duration of follow-up, days (mean, SD)</td>
<td>432.9 (289.6)</td>
<td>527.8 (347.0)</td>
<td>580.8 (372.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Propensity score (mean, SD)</td>
<td>0.2631 (0.1349)</td>
<td>0.2575 (0.1326)</td>
<td>0.2437 (0.1277)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Plan type (n %):</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HMO</td>
<td>677 (40.4)</td>
<td>1,869 (37.2)</td>
<td>584 (33.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Indemnity</td>
<td>42 (2.5)</td>
<td>222 (4.4)</td>
<td>87 (5.0)</td>
<td></td>
</tr>
<tr>
<td>PPO</td>
<td>471 (28.1)</td>
<td>1,384 (27.5)</td>
<td>500 (28.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>POS</td>
<td>344 (20.6)</td>
<td>1,111 (22.1)</td>
<td>383 (21.9)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>140 (8.4)</td>
<td>445 (8.9)</td>
<td>198 (11.3)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physician specialty (n %):</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurology</td>
<td>1,062 (63.4)</td>
<td>3,165 (62.9)</td>
<td>1,051 (60.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>FP/GP</td>
<td>192 (11.5)</td>
<td>647 (12.9)</td>
<td>253 (14.4)</td>
<td></td>
</tr>
<tr>
<td>Internal medicine</td>
<td>124 (7.4)</td>
<td>351 (7.0)</td>
<td>131 (7.5)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>296 (17.6)</td>
<td>868 (17.3)</td>
<td>317 (18.1)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Geographic region (n %):</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Northeast</td>
<td>509 (30.4)</td>
<td>1,330 (26.4)</td>
<td>420 (24.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Midwest</td>
<td>596 (35.6)</td>
<td>1,627 (32.3)</td>
<td>674 (38.5)</td>
<td></td>
</tr>
<tr>
<td>South</td>
<td>258 (15.4)</td>
<td>1,296 (25.8)</td>
<td>460 (26.3)</td>
<td></td>
</tr>
<tr>
<td>West</td>
<td>311 (18.6)</td>
<td>778 (15.5)</td>
<td>198 (11.3)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pretreatment measures (mean, SD):</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of relapses</td>
<td>0.22 (0.64)</td>
<td>0.30 (0.88)</td>
<td>0.30 (0.82)</td>
<td>.064</td>
</tr>
<tr>
<td>Total costs of care</td>
<td>$13,018 ($14,067)</td>
<td>$14,853 ($19,455)</td>
<td>$16,697 ($18,052)</td>
<td>.003</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Therapy changes (%)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Add/switch to glatiramer acetate</td>
<td>–</td>
<td>7.1</td>
<td>5.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Add/switch to interferon beta 1a</td>
<td>0.0</td>
<td>–</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Add/switch to interferon beta 1b</td>
<td>0.0</td>
<td>2.8</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

### Table 1: Demographic and Clinical Characteristics of the Study Sample by Treatment Group
Relapse rates and risk of relapse by treatment group

<table>
<thead>
<tr>
<th>Measure</th>
<th>Glatiramer Acetate (n=1,674)</th>
<th>Interferon Beta-1a (n=5,031)</th>
<th>Interferon Beta-1b (n=1,752)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative incidence (rate/1,000 person-years)</td>
<td>291.2</td>
<td>314.4</td>
<td>241.1</td>
<td></td>
</tr>
<tr>
<td>Time to first relapse, days (mean, SD)</td>
<td>193.7 (160.1)</td>
<td>189.9 (163.1)</td>
<td>187.8 (157.1)</td>
<td></td>
</tr>
<tr>
<td>Risk of relapse at one year (relative to glatiramer acetate)*</td>
<td>–</td>
<td>1.147</td>
<td>1.512</td>
<td>.003</td>
</tr>
</tbody>
</table>

Note: *Hazard rates were calculated using Cox proportional hazards models, controlling for propensity scores and duration of follow-up.

Results

### Patient Characteristics

Demographic and clinical characteristics of the study sample are presented in Table 1. A total of 8,457 patients were selected for inclusion in these analyses (n=1,674, 5,031, and 1,752 for GA, 1A, and 1B, respectively). The mean age for the sample was 42 years; approximately 75% were female. Both age and gender differed significantly (P<.001) by treatment group. The mean duration of follow-up (approximately 520 days or 17.3 months for the overall sample) also differed significantly (P<.001) by group and was substantially lower among patients receiving GA versus those receiving the other drugs; this phenomenon is likely due to GA’s later introduction to the MS marketplace. As a result, unadjusted information on relapse, utilization, and costs is presented on an annualized basis.

Mean propensity scores for use of immunomodulatory therapy were highest for GA patients (0.2631 versus 0.2575 and 0.2431 for 1A and 1B, respectively). Significant (P<.001) differences also were noted for plan type, physician specialty, and geographic region. Patients receiving GA were more likely to be members of more managed plans (e.g., HMO, PPO), while those receiving 1A and 1B were somewhat more likely to be in less managed environments (e.g., indemnity, POS). Nearly two thirds of patients receiving immunomodulatory therapy were managed by a neurologist.

Among patients receiving GA, there were no switches to or polytherapy with either of the beta interferons. However, a total of 498 (9.9%) and 96 (5.5%) 1A and 1B patients, respectively, switched or added therapy during follow-up. The majority of these therapy changes involved GA (i.e., either as switch or add-on therapy).

Of all identified patients receiving immunomodulatory therapy, a total of 3,161 (37.4%) were identified as new starts (i.e., based on a 9-month pretreatment period with no use of such medication). Among these patients, the mean ±SD number of relapses during pretreatment did not significantly differ by treatment group (0.22 ±0.64 for GA versus 0.30 ±0.88 and 0.30 ±0.82 for 1A and 1B, respectively; P=.064). Mean costs during this period were significantly different, however, and were lowest for GA ($13,018 versus $14,853 and $16,697 for 1A and 1B, respectively; P=.003).
Relapse Rates

Information on relapse rates is presented in Table 2. The cumulative incidence of all relapses during follow-up was 291.2, 314.4, and 241.1 per 1,000 person-years for GA, 1A, and 1B respectively. Time to first relapse was somewhat longer among patients receiving GA (193.7 [±160.1] days versus 189.9 [±163.1] and 187.8 [±157.1] for 1A and 1B, respectively); correspondingly, the adjusted one-year risk of relapse was significantly (P<.005) higher for the beta interferons relative to GA (HR = 1.147 and 1.512 for 1A and 1B, respectively).

MS-related Resource Utilization

Utilization of MS-related medications and health care services is presented in Table 3. Other than study therapy, most other medications were used infrequently. The most commonly used medications were antidepressants (mean number of prescriptions per year: 2.5 to 2.3), skeletal muscle relaxants (1.6 to 1.7), and adrenals and combinations (1.3 to 1.7). Surprisingly, while periodic laboratory monitoring is recommended for the beta interferons but not for GA, the use of selected tests was infrequent among all groups and did not materially differ between

<table>
<thead>
<tr>
<th>Measure (per patient per year)</th>
<th>Glatiramer Acetate (n=1,674)</th>
<th>Interferon Beta-1a (n=5,031)</th>
<th>Interferon Beta-1b (n=1,752)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications (Prescriptions)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiolytics/sedatives/hypnotics</td>
<td>0.9 (3.1)</td>
<td>0.7 (2.6)</td>
<td>0.6 (2.4)</td>
</tr>
<tr>
<td>Antihistamines and combinations</td>
<td>0.0 (0.1)</td>
<td>0.0 (0.2)</td>
<td>0.0 (0.1)</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>0.0 (0.9)</td>
<td>0.0 (0.3)</td>
<td>0.0 (0.9)</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>0.0 (0.2)</td>
<td>0.0 (0.2)</td>
<td>0.0 (0.4)</td>
</tr>
<tr>
<td>Adrenals and combinations</td>
<td>1.7 (4.9)</td>
<td>1.4 (4.0)</td>
<td>1.3 (4.0)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>2.5 (5.1)</td>
<td>2.3 (4.9)</td>
<td>2.3 (4.7)</td>
</tr>
<tr>
<td>Antivirals</td>
<td>0.8 (2.8)</td>
<td>0.7 (2.5)</td>
<td>0.9 (3.0)</td>
</tr>
<tr>
<td>Antineoplastic agents</td>
<td>0.1 (0.9)</td>
<td>0.1 (0.9)</td>
<td>0.1 (0.6)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>0.1 (1.0)</td>
<td>0.1 (0.8)</td>
<td>0.1 (0.7)</td>
</tr>
<tr>
<td>Cerebral stimulants</td>
<td>0.6 (2.3)</td>
<td>0.5 (2.3)</td>
<td>0.4 (2.0)</td>
</tr>
<tr>
<td>Genitourinary smooth muscle relaxants</td>
<td>0.4 (2.2)</td>
<td>0.5 (2.2)</td>
<td>0.6 (2.3)</td>
</tr>
<tr>
<td>Hypotensive agents</td>
<td>0.0 (0.4)</td>
<td>0.0 (0.3)</td>
<td>0.0 (0.2)</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>0.1 (1.2)</td>
<td>0.1 (1.1)</td>
<td>0.1 (1.0)</td>
</tr>
<tr>
<td>Serums</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td>Skeletal muscle relaxants</td>
<td>1.6 (4.2)</td>
<td>1.6 (4.8)</td>
<td>1.9 (4.8)</td>
</tr>
<tr>
<td>Urinary anti-infectives</td>
<td>0.2 (1.2)</td>
<td>0.1 (0.9)</td>
<td>0.2 (1.1)</td>
</tr>
<tr>
<td>Other MS-related services</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete blood counts</td>
<td>0.7 (1.7)</td>
<td>0.9 (1.7)</td>
<td>1.0 (1.7)</td>
</tr>
<tr>
<td>Platelet counts</td>
<td>0.1 (0.4)</td>
<td>0.2 (0.6)</td>
<td>0.2 (0.6)</td>
</tr>
<tr>
<td>Liver function tests</td>
<td>0.6 (2.5)</td>
<td>1.0 (2.5)</td>
<td>1.0 (2.5)</td>
</tr>
<tr>
<td>Emergency-room visits</td>
<td>0.1 (0.5)</td>
<td>0.1 (0.6)</td>
<td>0.1 (0.4)</td>
</tr>
<tr>
<td>Physician office visits</td>
<td>3.1 (3.6)</td>
<td>3.2 (4.5)</td>
<td>2.7 (4.3)</td>
</tr>
<tr>
<td>Home health visits</td>
<td>0.1 (1.3)</td>
<td>0.0 (0.3)</td>
<td>0.0 (0.1)</td>
</tr>
<tr>
<td>Imaging visits</td>
<td>0.3 (0.8)</td>
<td>0.3 (0.8)</td>
<td>0.3 (0.7)</td>
</tr>
<tr>
<td>Other hospital outpatient visits</td>
<td>7.8 (21.1)</td>
<td>9.6 (26.5)</td>
<td>7.0 (14.1)</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>1.3 (8.7)</td>
<td>1.0 (4.9)</td>
<td>1.1 (4.8)</td>
</tr>
</tbody>
</table>

Note: All utilization measures are annualized.
them. Utilization of other services also is presented in Table 3. Use of physician office and other hospital outpatient services was highest among 1A patients, while use of inpatient services (i.e., for treatment of relapse and other MS-related services) was slightly higher among GA patients.

MS-related Costs

Annualized costs of medications and health care services are presented in Table 4. Mean (±SD) costs of all MS-related medications were lowest for GA ($7,256 [±$5,727]), followed by 1A ($7,992 [±$6,219]) and 1B ($8,083 [±$6,260]); these differences were statistically significant (P < .001). GA’s lower costs relative to the beta interferons were manifested almost entirely in lower acquisition costs for study therapy. Costs of outpatient services were similar for GA and 1A and slightly lower for 1B. Costs for inpatient care were lowest for 1A relative to the other 3 groups; neither outpatient nor inpatient costs differed statistically. Total costs of care averaged $9,522 (±$9,706), $9,957 (±$9,083), and $10,185 (±$9,526) for GA, 1A, and 1B, respectively (P=.004), which again primarily reflects differences in immunomodulatory drug costs. Findings persisted in multivariate analyses of cost; differences were mitigated somewhat between GA and 1A, while differences between GA and 1B were more marked ($10,879, $10,968, and $11,619 for GA, 1A, and 1B, respectively).

Additional Analyses

Among patients newly starting immunomodulatory therapy, the incidence of all relapses during follow-up was 17% to 22% higher with the beta interferons relative to GA (data not shown); while the one-year risk of relapse did not differ between 1A and GA, the risk among 1B patients was nearly double that of GA (HR=1.856, P=.020). Findings were similar among patients who did not switch or add on therapy (HR=1.389 for 1B relative to GA, P=.029).

Not surprisingly, in the cohort of patients newly starting immunomodulatory therapy, utilization of health care services was somewhat lower than for the entire cohort, particularly with respect to inpatient care; utilization of MS-related medications was similar, however (data not shown). On an annualized basis, total costs for GA patients remained lower than for 1A and 1B patients ($9,646 [±$10,209] versus $9,979 [±$10,815] and $10,553 [±$12,140], respectively); on an adjusted basis, costs for GA and 1A were similar ($11,310 and $11,192, respectively), and reduced relative to 1B ($12,347).

Discussion

To examine the impact of use of GA therapy on relapse rates as well as MS-related resource utilization and costs relative to that among patients receiving beta interferon 1A or 1B, we undertook a retrospective analysis of medical and pharmacy claims data among a cohort of MS patients receiving these medications. Data on the incidence of relapses was examined for these patients, as was information on the utilization and costs of MS-related medications, outpatient services, and inpatient care. The results of this study indicate that use of GA therapy in patients with MS results in a lower rate of relapse relative to those receiving either beta interferon therapies. In addition, therapy with GA appeared to be more “durable” than that of the beta interferons—patients receiving the former did not switch or add on immunomodulatory therapy, while nearly 10% of those receiving beta interferon therapy did experience a therapy change. Finally, total costs of MS-related care were reduced by $400 to $700 among GA patients relative to the beta interferons; findings persisted in multivariate analyses controlling for age, sex, and propensity scores for immunomodulatory therapy.

A number of previous studies have evaluated the cost-effectiveness of immunomodulatory therapy in multiple sclerosis.31-37 Without exception, all of the existing studies have compared the costs and effects of beta interferon or GA therapy to those among patients receiving therapy for symptomatic relief only. To the best of our knowledge, this is the first such study to com-
pare clinical and economic effects among these medications specifically. Most economic studies that have been performed to date have concluded that use of immunomodulatory therapy results in a substantial increase in costs and only modest clinical effects.32–36 These findings are at odds with current clinical opinion, however, which suggests that immunomodulatory agents should receive widespread use among patients with MS and should be used early in the course of the disease.38

**Limitations**

We note some limitations of our analysis. First, our comparison was limited to patients receiving immunomodulatory therapy, as noted above. In reality, many MS patients are still treated with only medications for the symptoms; in fact, nearly 75% of the patients with MS diagnoses in our database did not receive immunomodulatory medications. Examination of the economic and clinical impact of immunomodulatory medications as a group in an MS population requires comparison to a comparable population that did not receive these medications. Such an analysis is likely to be problematic in a retrospective database, however, as patients not receiving immunomodulatory therapy are historically likely to be at an earlier stage of disease progression and therefore less severely ill.

In addition, as with all quasi-experimental research based on retrospective data, we cannot rule out the possibility that our findings may have been influenced by differences in disease severity, duration of illness, and rate of disease progression between the 3 treatment groups that were the focus of our analysis. While it is true that these important factors are not detectable in any detailed way in claims data, the use of a propensity score in this circumstance does provide a method to control for differences in patient, physician, or health plan characteristics between patient groups. Indeed, our findings were nearly identical among the subgroup of patients newly starting immunomodulatory therapy (who would be expected to be more comparable in terms of disease progression and/or severity) as well as those remaining on a single agent during follow-up. Perhaps most importantly, the direction of these findings was unchanged in multivariate analyses controlling for propensity for immunomodulatory therapy and other covariates that were detectable in this particular data source.

In addition, our measure of relapse was limited to utilization proxies only; this definition was likely insensitive or conservative since overall annualized relapse rates (0.24 to 0.31 per patient) are lower than those reported in clinical studies.5–13, 39 However, this effect was equally distributed across treatment groups and therefore likely affects only the magnitude (and not the direction) of our findings. While GA appeared to confer some benefit with regard to relapse as measured in our study, it should be noted that differences in risk and time to event were moderate (albeit statistically significant); perceptions as to the clinical significance of these differences will vary.

Finally, we could not measure the impact of these medica-

**Conclusion**

Our findings suggest that use of glatiramer acetate may reduce rates of relapse as well as levels of MS-related utilization and costs relative to the beta interferons; further study is required, however, to document these benefits in a definitive manner. Our results are likely to be of interest to health care payers and providers as well as patients with multiple sclerosis who may be candidates for immunomodulatory therapy.

**DISCLOSURES**

Funding for this research was provided by Teva Neuroscience, Inc., U.S., a subsidiary of Teva Pharmaceutical Industries, Ltd., manufacturer of glatiramer acetate. Author Merri Kay Oleen-Burkey is employed by Teva Neuroscience, Inc. Authors Daniel A. Olleンドorf and Evgenia Jilinskaia are employed by PharMetric, Inc., a health care data and research company that has consulting contracts with Teva Neuroscience. Funding was obtained by Olleンドorf. Olleンドorf served as principal author of the study. Study concept and design and drafting of the manuscript were contributed primarily by Olleンドorf and Oleen-Burkey. Critical revision of the manuscript was the work of Jilinskaia and Oleen-Burkey. Analysis and interpretation of data were contributed primarily by Olleンドorf and Jilinskaia. Statistical expertise was contributed by Jilinskaia. Administrative, technical, and/or material support was provided by PharMetric.

**REFERENCES**


OBJECTIVE: To evaluate the effects of 2- and 3-tiered pharmacy benefit plans on member attitudes regarding their pharmacy benefits.

METHODS: We performed a mail survey and cross-sectional comparison of the outcome variables in a large managed care population in the western United States. Participants were persons with chronic disease states who were in 2- or 3-tier copay drug plans. A random sample of 10,662 was selected from a total of 25,008 members who had received 2 or more prescriptions for a drug commonly used to treat one of 5 conditions: hypertension, diabetes, dyslipidemia, gastroesophageal reflux disease (GERD), or arthritis. Statistical analysis included bivariate comparisons and regression analysis of the factors affecting member attitudes, including satisfaction, loyalty, health plan choices, and willingness to pay a higher out-of-pocket cost for medications.

RESULTS: A response rate of 35.8% was obtained from continuously enrolled plan members. Respondents were older, sicker, and consumed more prescriptions than nonrespondents. There were significant differences in age and health plan characteristics between 2- and 3-tier plan members: respondents aged 65 or older represented 11.7% of 2-tier plan members and 54.7% of 3-tier plan members, and 10.0% of 2-tier plan members were in Medicare+Choice plans versus 61.4% in Medicare+Choice plans for 3-tier plan members (P<0.05). Controlling for demographic characteristics, number of comorbidities, and the cost of health care, 2-tier plan members were more satisfied with their plan, more likely to recommend their plan to others, and less likely to switch their current plans to obtain better prescription drug coverage than 3-tier plan members. While members were willing to purchase higher cost nonformulary and brand-name medications, in general, they were not willing to pay more than $10 (in addition to their copayment amount) for these medications. Older respondents and sicker individuals (those with higher scores on the Chronic Disease Indicator) appeared to have more positive attitudes toward their pharmacy benefit plans in general. Higher reported incomes by respondents were also associated with greater satisfaction with prescription drug coverage and increased loyalty toward the pharmacy benefit plan. Conversely, the more individuals spent for either their health care or prescription medications, the less satisfied they were with their prescription drug coverage and less loyalty they appeared to have for their health plans. An inverse relationship also appeared to exist between the out-of-pocket costs for prescription medications and members’ willingness to pay for nonformulary medications.

CONCLUSIONS: Three-tier members had lower reported satisfaction with their plans compared to members in 2-tier plans. The financial resources available to members (which may be a function of being older and having more education and higher incomes), the number of chronic disease states that members have, and other factors may influence their attitudes toward their prescription drug coverage.

KEYWORDS: Three-tier plans, Prescription drug coverage, Patient satisfaction

J Managed Care Pharm. 2002(8):477-91

Authors

KAVITA V. NAIR, PhD; JULIE M. GANTHER, PhD; ROBERT J. VALUCK, PhD; MARIANNE M. MCCOLLUM, PhD; and SONYA J. LEWIS, RPh

Impact of Multi-tiered Pharmacy Benefits on Attitudes of Plan Members With Chronic Disease States

As managed care organizations continue to report double-digit increases in pharmacy-related expenditures, shifting some of the cost of prescription medications to consumers has become a growing trend in the management of pharmaceutical benefits. Multi-tiered pharmacy benefit plans have become a very popular structure in pharmacy benefits primarily as 2- and 3-tier plans. In 2-tier plans, the lower copayment amount is generally for formulary-based generic medications, and the higher copayment amount is for brand-name medications. Typical copayment amounts are $5 to $15 for generic (first-tier) medications and $10 to $30 for formulary, brand-name (second-tier) medications. Nonformulary medications can be obtained at the brand copayment amount, sometimes requiring health plan approval through prior authorization.

The 3-tier drug plan design is being adopted rapidly by managed care plans and is replacing the 2-tier plan design. Generally, 3-tier, like 2-tier plans, have the lowest copayment amount for generic formulary medications. The second copay tier applies to formulary brand-name medications, while the highest copayment, or the “third tier,” is usually reserved for nonformulary medications and can range between $30 and $50. Three-tier plans allow members to have a choice in their drug therapy needs if they are willing to pay for that choice. The implementation of 3-tier plans may be followed by a variety of responses from patients, depending on their financial resources, health status, and perceived health benefits. Patients may choose to switch to a generic or alternative brand-name medication in a less-expensive copay tier, or they may choose to pay the higher copayment for a third-tier drug. This decision may be based on a variety of factors such as satisfaction with the current therapy, the disease being treated, perceptions about the similarity of lower-tier substitutes, and personal financial resources. Other possible patient responses to conserve personal financial resources include reduction in dose frequency to reduce refill frequency or premature discontinuation of the medication. A main concern regarding 3-tier pharmacy benefit plans is that the increased amount of cost sharing may restrict access to medications for vulnerable populations such as those with chronic disease states. However, employers are rapidly adopting 3-tier pharmacy benefit plans for their employees to offset their own increasing costs of health care, and recent trends suggest that the copayment amounts for 3-tier plans will continue to increase.

While there has been some research that examines the impact of 3-tier plans on pharmaceutical, medical care utilization, and expenditures, there is little evidence regarding member attitudes and satisfaction regarding their 3-tier pharmacy...
Impact of Multi-tiered Pharmacy Benefits on Attitudes of Plan Members With Chronic Disease States

more members are willing to pay for these medications may provide employers and managed care decision makers with important information about their subsequent prescription-purchasing behavior. One method of assessing the willingness to pay is to survey individual preferences when hypothetical situations are posed. While consumers have expressed a desire to pay for pharmacist-related services, mean amounts have been small, ranging from $1 to $5 per prescription and, on average, between $15 and $30 for a set of pharmacist-provided services. While this research has looked at pharmacist-related services, little is known about how price-sensitive members are when purchasing their prescribed medications.

To better understand the issues outlined above, the overall purpose of this study was to measure various member attitudes regarding multi-tiered pharmacy benefit plans. Specific objectives were to assess member satisfaction, loyalty, and the willingness to pay higher copays for medications and the relationship between sociodemographic characteristics, cost of health care, and pharmacy plan type to these attitudes.

Methods

Study Sample

The study used a cross-sectional mail survey design that targeted enrollees of a large managed care organization in the western United States. The goal of sample selection was to obtain a representative group of plan members in 2- and 3-tier pharmacy benefit plans who would be most affected by variations in cost sharing. Five chronic disease states were chosen for prescription medications deemed important to health; i.e., those medications whose withdrawal could have serious effects on health outcomes.

The 5 disease states chosen were hypertension, diabetes, dyslipidemia, gastroesophageal reflux disease (GERD), and arthritis. Pharmacy claims data were used for sample selection. The study sample was identified in 2 steps: first, a random sample of 25,008 individuals who had at least 2 prescriptions for one of the 5 disease states of interest in calendar year 2000 and who were enrolled in a 2- or 3-tier plan for retail prescriptions in 2000 were identified. A variety of 2- and 3-tier plans were represented in the sample. The selected individuals were enrolled in a health maintenance organization (HMO), preferred provider organization (PPO), or Medicare+Choice managed care plan. Medicare+Choice individuals in the 3-tier plans had an annual benefit maximum of $1,000 at the time of the study. All of these individuals were mailed a survey. The sample subsequently was narrowed to include just the 10,662 individuals who were continuously enrolled in the plan between

benefit plans. Member attitudes and, in particular, member satisfaction are becoming an important criterion by which the quality of a health plan is evaluated. For example, the Consumer Assessment of Health Plans survey compares member satisfaction among health plans serving Medicare beneficiaries and is used as a measure of quality among competing Medicare+Choice plans. There has been limited research on member attitudes regarding prescription drug coverage. Desselle conducted a general examination of member satisfaction with prescription drug plans and found that respondents were very satisfied with the quality of their prescription drug plan. Satisfaction was primarily determined by perceptions about coverage limitations and having a choice of health plans. Most recently, Holdford et al. found that having a choice of medications and copayment amounts that patients were responsible for were the 2 most important attributes cited by individuals in selecting their prescription drug coverage.

However, an evaluation regarding member attitudes about their prescription drug coverage needs to go beyond member satisfaction. Attitudes about health plan choice and the willingness to pay for these higher-priced medications are examples of member perceptions that may provide some insight into the utility of 3-tier plans in influencing member behavior.

Analysis of health-plan switching behavior has shown that the provision of information about the quality of a health plan has a small effect on consumer plan choices, and employees were more likely to switch from health plans with lower reports of quality to plans that received higher ratings of quality. As consumers have repeatedly stated, the cost of health care is always one of the most important pieces of information used to make health plan choices. The increasing out-of-pocket costs of prescription medications in a 3-tier plan may influence their health plan choices. Therefore, attitudes of members such as willingness to switch health plans for better prescription drug coverage, recommend their pharmacy benefit plan to others, or choose a health plan based on the composition of its formulary are important aspects of member attitudes that need to be evaluated.

In addition to member attitudes about their prescription drug plans, their perceptions regarding higher-cost medications such as formulary versus nonformulary medications and, within the former, the lower-cost generic versus the higher-cost brand-name medications, may influence their prescription choices. For example, member perceptions about the equivalence of brand and generic medications have been reported, with individuals requiring greater cost savings to purchase generic medications for some disease states, such as heart disease, over others.

Finally, in 3-tier copay plans, the cost of medications to the members increases for each successive copay tier. Brand-name medications have a higher copay cost than generic drugs, and nonformulary medications have a higher copay cost than formulary, brand-name medications. An assessment of how much

Study Sample

The study used a cross-sectional mail survey design that targeted enrollees of a large managed care organization in the western United States. The goal of sample selection was to obtain a representative group of plan members in 2- and 3-tier pharmacy benefit plans who would be most affected by variations in cost sharing. Five chronic disease states were chosen for prescription medications deemed important to health; i.e., those medications whose withdrawal could have serious effects on health outcomes.

The 5 disease states chosen were hypertension, diabetes, dyslipidemia, gastroesophageal reflux disease (GERD), and arthritis. Pharmacy claims data were used for sample selection. The study sample was identified in 2 steps: first, a random sample of 25,008 individuals who had at least 2 prescriptions for one of the 5 disease states of interest in calendar year 2000 and who were enrolled in a 2- or 3-tier plan for retail prescriptions in 2000 were identified. A variety of 2- and 3-tier plans were represented in the sample. The selected individuals were enrolled in a health maintenance organization (HMO), preferred provider organization (PPO), or Medicare+Choice managed care plan. Medicare+Choice individuals in the 3-tier plans had an annual benefit maximum of $1,000 at the time of the study. All of these individuals were mailed a survey. The sample subsequently was narrowed to include just the 10,662 individuals who were continuously enrolled in the plan between

Methods

Study Sample

The study used a cross-sectional mail survey design that targeted enrollees of a large managed care organization in the western United States. The goal of sample selection was to obtain a representative group of plan members in 2- and 3-tier pharmacy benefit plans who would be most affected by variations in cost sharing. Five chronic disease states were chosen for prescription medications deemed important to health; i.e., those medications whose withdrawal could have serious effects on health outcomes.

The 5 disease states chosen were hypertension, diabetes, dyslipidemia, gastroesophageal reflux disease (GERD), and arthritis. Pharmacy claims data were used for sample selection. The study sample was identified in 2 steps: first, a random sample of 25,008 individuals who had at least 2 prescriptions for one of the 5 disease states of interest in calendar year 2000 and who were enrolled in a 2- or 3-tier plan for retail prescriptions in 2000 were identified. A variety of 2- and 3-tier plans were represented in the sample. The selected individuals were enrolled in a health maintenance organization (HMO), preferred provider organization (PPO), or Medicare+Choice managed care plan. Medicare+Choice individuals in the 3-tier plans had an annual benefit maximum of $1,000 at the time of the study. All of these individuals were mailed a survey. The sample subsequently was narrowed to include just the 10,662 individuals who were continuously enrolled in the plan between

Methods

Study Sample

The study used a cross-sectional mail survey design that targeted enrollees of a large managed care organization in the western United States. The goal of sample selection was to obtain a representative group of plan members in 2- and 3-tier pharmacy benefit plans who would be most affected by variations in cost sharing. Five chronic disease states were chosen for prescription medications deemed important to health; i.e., those medications whose withdrawal could have serious effects on health outcomes.

The 5 disease states chosen were hypertension, diabetes, dyslipidemia, gastroesophageal reflux disease (GERD), and arthritis. Pharmacy claims data were used for sample selection. The study sample was identified in 2 steps: first, a random sample of 25,008 individuals who had at least 2 prescriptions for one of the 5 disease states of interest in calendar year 2000 and who were enrolled in a 2- or 3-tier plan for retail prescriptions in 2000 were identified. A variety of 2- and 3-tier plans were represented in the sample. The selected individuals were enrolled in a health maintenance organization (HMO), preferred provider organization (PPO), or Medicare+Choice managed care plan. Medicare+Choice individuals in the 3-tier plans had an annual benefit maximum of $1,000 at the time of the study. All of these individuals were mailed a survey. The sample subsequently was narrowed to include just the 10,662 individuals who were continuously enrolled in the plan between
January 1, 2000, and December 31, 2000. This was done to enable the collection of data on the number of comorbidities such as the Chronic Disease Indicator (CDI) score for individuals (described in the next section) and to enable comparisons of survey respondents and nonrespondents on medication utilization characteristics.

Comparisons of the continuously enrolled sample to those who disenrolled from their health plan at the end of 2000 were conducted on age, gender, pharmacy plan type, managed care plan (HMO, PPO, or Medicare+Choice) and income (using median household income from the 2000 U.S. Census data), using a likelihood ratio chi-square test of equal proportions. Although tests of difference were statistically significant for some of the characteristics (age, gender, and income where \( P < 0.05 \)), the mean values of age (53 years for both groups), and income ($50,376 for the continuously enrolled and $50,550 for the disenrolled) and distribution of gender (+9% males for the continuously enrolled and +47% for those who disenrolled) in the 2 groups were similar and may be attributed to the large sample sizes employed in the study (10,662 for the continuously enrolled and 14,346 for the disenrolled sample).

**Study Measures**

The relevant study items, which were part of a larger questionnaire, are provided in the Appendix and described, in part, below.

General attitudes about satisfaction with prescription drug coverage were assessed by asking respondents to indicate how satisfied they were with various statements related to cost sharing, access to prescription medications, information about pharmacy benefits, and location of pharmacies such as “amount you pay for prescription medications” or “ability to get any medication prescribed by your doctor.” A 7-point Likert-type scale, where 1 was “dissatisfied” and 7 was “satisfied,” was used to measure general attitudes about prescription drug coverage. A “not applicable” choice was also provided.

Information sources used by members in making decisions about prescription use were also assessed. Respondents were asked when a physician prescribes a new medication how likely they were to use the following information sources before purchasing the medication: second opinion from another physician; consulting with a pharmacist, friends, family, or coworkers with similar health insurance plans; looking up information on the Internet, magazines, or reference books; and looking up availability of their medications on the health plan's formulary. The survey items were (1) If your doctor prescribes a brand-name medication but there is a generic medication available that would cost you less, how much more would you be willing to pay to get the brand-name medication? and (2) If a medication that you have been taking regularly is nonformulary, how much more do you think you would be willing to pay per month to stay on the medication? The response scale for both items was $0, $1-$5, $6-$10, $11-$15, $16-$20, and $20. The response scales on items were reverse-scored, when needed, to ease the interpretation of results.

Chi-square analysis was used to examine differences in categorical variables and the independent samples t test was used to examine differences for continuous measures. Statistical analyses were conducted using SPSS version 10.0 and the significance level was specified as \( P < 0.05 \).

Ordinary least squares and ordinal regression multivariate models were used to yield parameter estimates by pharmacy plan type (2-tier versus 3-tier) and other factors for ratings of each of the satisfaction, loyalty, and willingness-to-pay measures detailed above. To truly understand the differences between the 2 groups with regard to overall satisfaction with prescription drug coverage and the other outcome measures detailed above, relevant characteristics of the patient population, which may include demographic factors and health status measures, need to be taken into account as well to get more accurate estimates. Therefore, characteristics of the members themselves that were controlled in the multivariate models included the following: age, gender, employment status, pharmacy plan type, education, race, income, and number of comorbidities measured by the CDI. The CDI approximates the number of chronic diseases for each patient from pharmacy claims data by using an expert panel to determine if specific medication classes are indicative of a particular disease state. Higher CDI scores indicate a greater number of chronic illnesses. Other measures included the total amounts paid per month for prescription medications and health plan premiums by the respondents, willingness to purchase a formulary medication when prescribed a nonformulary medication, likelihood of purchasing a brand-name medication when prescribed a generic medication, and the perceived equivalence between brand-name and generic medications.

The survey instrument was based on a comprehensive liter-
Impact of Multi-tiered Pharmacy Benefits on Attitudes of Plan Members With Chronic Disease States

Table 1: Description of the Survey Respondents: Percentage of Respondents by Plan Type (N=3,815)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>2-Tier Plan Members (n=2,316) %</th>
<th>3-Tier Plan Members (n=1,499) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. 18-45</td>
<td>463 (19.9%)</td>
<td>136 (9.1%)</td>
</tr>
<tr>
<td>2. 46-55</td>
<td>730 (31.5%)</td>
<td>239 (16.0%)</td>
</tr>
<tr>
<td>3. 56-65</td>
<td>764 (32.9%)</td>
<td>186 (12.5%)</td>
</tr>
<tr>
<td>4. Over 65</td>
<td>269 (11.7%)</td>
<td>820 (54.7%)</td>
</tr>
<tr>
<td>5. Missing</td>
<td>90 (4.0%)</td>
<td>118 (7.7%)</td>
</tr>
<tr>
<td>Gender*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Male</td>
<td>1,199 (51.8%)</td>
<td>729 (48.6%)</td>
</tr>
<tr>
<td>2. Female</td>
<td>952 (41.1%)</td>
<td>617 (41.2%)</td>
</tr>
<tr>
<td>3. Missing</td>
<td>165 (7.1%)</td>
<td>153 (10.2%)</td>
</tr>
<tr>
<td>Type of managed care plan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. HMO</td>
<td>866 (37.4%)</td>
<td>443 (29.6%)</td>
</tr>
<tr>
<td>2. PPO</td>
<td>1,204 (52.0%)</td>
<td>121 (8.0%)</td>
</tr>
<tr>
<td>3. Medicare+Choice</td>
<td>232 (10.0%)</td>
<td>920 (61.4%)</td>
</tr>
<tr>
<td>4. Missing</td>
<td>14 (0.6%)</td>
<td>15 (1.0%)</td>
</tr>
<tr>
<td>Education*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. High school + some post-high school</td>
<td>1,095 (47.3%)</td>
<td>802 (53.5%)</td>
</tr>
<tr>
<td>2. 4-year college</td>
<td>414 (17.9%)</td>
<td>238 (15.9%)</td>
</tr>
<tr>
<td>3. Graduate education (MS/PhD)</td>
<td>658 (28.4%)</td>
<td>288 (19.2%)</td>
</tr>
<tr>
<td>4. Missing</td>
<td>149 (6.4%)</td>
<td>171 (11.4%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. White</td>
<td>2,033 (87.8%)</td>
<td>1,303 (87.0%)</td>
</tr>
<tr>
<td>2. Other (African American, Asian, American Indian)</td>
<td>106 (4.6%)</td>
<td>56 (3.7%)</td>
</tr>
<tr>
<td>3. Missing</td>
<td>177 (7.6%)</td>
<td>140 (9.3%)</td>
</tr>
<tr>
<td>Income*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Less than $24,999</td>
<td>338 (14.6%)</td>
<td>426 (28.4%)</td>
</tr>
<tr>
<td>2. $25,000 to $34,999</td>
<td>262 (11.3%)</td>
<td>220 (14.7%)</td>
</tr>
<tr>
<td>3. $35,000 to $49,999</td>
<td>404 (17.4%)</td>
<td>217 (14.5%)</td>
</tr>
<tr>
<td>4. $50,000 to $64,999</td>
<td>327 (14.1%)</td>
<td>162 (10.8%)</td>
</tr>
<tr>
<td>5. over $65,000</td>
<td>746 (32.2%)</td>
<td>245 (16.3%)</td>
</tr>
<tr>
<td>6. Missing</td>
<td>239 (10.4%)</td>
<td>229 (15.3%)</td>
</tr>
<tr>
<td>Employment status*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Full time (&gt;35 hours a week)</td>
<td>1,256 (54.2%)</td>
<td>432 (28.8%)</td>
</tr>
<tr>
<td>2. Part time (&lt;35 hours a week)</td>
<td>312 (13.5%)</td>
<td>136 (9.1%)</td>
</tr>
<tr>
<td>3. Not employed or retired</td>
<td>663 (28.6%)</td>
<td>830 (55.4%)</td>
</tr>
<tr>
<td>4. Missing</td>
<td>85 (3.7%)</td>
<td>101 (6.7%)</td>
</tr>
<tr>
<td>Family size†‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of people in the household</td>
<td>2.39 (±1.1)</td>
<td>2.16 (±1.0)</td>
</tr>
</tbody>
</table>

* Chi-square value significant at P ≤ 0.000.
† Mean and standard deviation in parenthesis.
‡ Independent samples t test (P ≤ 0.000).

ature review supplemented with 2 focus group meetings using a representative subset of individuals from the study sample. Individuals who participated in the focus groups were asked about their comprehension of pharmacy benefit terminology, concerns about their pharmacy benefit plans, factors affecting their access to medications, and their price sensitivity for higher-cost medications. The responses obtained from the focus group participants were used to develop the survey. To help respondents understand the survey, terms such as formulary and copayment were defined in the survey. The instrument was...
### TABLE 2  Comparison of the Survey Respondents to the Nonrespondents on Demographics, Prescription Utilization, and Cost Measures* (N=10,662)

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>Survey Respondents (n=3,815)</th>
<th>Nonrespondents (n=6,847)</th>
<th>P value§</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>57.7 (13.2)</td>
<td>52.6 (14.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>Female</td>
<td>1,976 (51.8)</td>
<td>3,396 (49.6)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1,839 (48.2)</td>
<td>3,451 (50.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Pharmacy plan type</strong></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2 tier</td>
<td>2,316 (60.7)</td>
<td>4,779 (69.8)</td>
<td></td>
</tr>
<tr>
<td>3 tier</td>
<td>1,499 (39.3)</td>
<td>2,068 (30.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Median household income†</strong></td>
<td>$50,245.66</td>
<td>$50,417.12</td>
<td>0.17</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>(16,407.211)</td>
<td>(17,019 552)</td>
<td></td>
</tr>
<tr>
<td><strong>Type of managed care plan</strong></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1. HMO</td>
<td>1,309 (34.3)</td>
<td>2,670 (39.0)</td>
<td></td>
</tr>
<tr>
<td>2. PPO</td>
<td>1,325 (34.7)</td>
<td>3,000 (43.8)</td>
<td></td>
</tr>
<tr>
<td>3. Medicare MC</td>
<td>1,152 (30.2)</td>
<td>1,177 (17.2)</td>
<td></td>
</tr>
<tr>
<td>4. Missing</td>
<td>29 (.007)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Family status</strong></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1. Family</td>
<td>1,705 (44.7)</td>
<td>3,786 (55.3)</td>
<td></td>
</tr>
<tr>
<td>2. Single</td>
<td>2,110 (55.3)</td>
<td>3,060 (44.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Health status‡</strong></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean Chronic Disease Indicator score</td>
<td>Mean (SD)</td>
<td>3.6 (2.4)</td>
<td>3.3 (2.3)</td>
</tr>
<tr>
<td>**Number of individuals in each disease state</td>
<td></td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1,489 (69.2)</td>
<td>5,029 (59.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>760 (35.3)</td>
<td>2,446 (28.8)</td>
<td>0.47</td>
</tr>
<tr>
<td>Arthritis</td>
<td>663 (30.8)</td>
<td>2,689 (31.6)</td>
<td>0.97</td>
</tr>
<tr>
<td>Diabetes</td>
<td>353 (16.4)</td>
<td>1,398 (16.5)</td>
<td>0.15</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>604 (28.1)</td>
<td>2,256 (26.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Prescription utilization</strong></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Average number of prescriptions per member per month</td>
<td>Mean (SD)</td>
<td>1.5 (1.2)</td>
<td>1.3 (1.2)</td>
</tr>
<tr>
<td>Formulary compliance rate (%)</td>
<td>81%</td>
<td>82%</td>
<td>0.51</td>
</tr>
<tr>
<td>Generic use rate (for multisource products ) (%)</td>
<td>98%</td>
<td>99%</td>
<td></td>
</tr>
<tr>
<td><strong>Prescription expenditures</strong></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Average monthly cost per member</td>
<td>85.73 (82.82)</td>
<td>72.22 (88.43)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average monthly cost per member to the health plan</td>
<td>Mean (SD)</td>
<td>64.62 (71.23)</td>
<td>55.19 (78.21)</td>
</tr>
<tr>
<td>Average monthly copayment amount per member</td>
<td>Mean (SD)</td>
<td>17.03 (19.83)</td>
<td>17.02 (18.32)</td>
</tr>
</tbody>
</table>

* Medication utilization patterns and prescription expenditures of survey respondents and nonrespondents, compared from June 1, 2000, to December 31, 2000.  
† Obtained from 2000 U.S. Census data by ZIP code.  
‡ Determined using pharmacy claims from January 1, 2000, to December 31, 2000.  
§ P value is based on a chi-square test for independent proportions for categorical variables and a 2-sample median test for continuous variables.  
|| Individuals may have been in more than one of the 5 disease states, and, hence, the numbers will not add up to 100.
pretested on a sample of 300 individuals (from a similar subset of the study sample), and modifications such as wording changes to questions, simplifying skip patterns of questions, and improving the overall flow of the instrument were made based on the results of the pretest. The survey instrument, along with a cover letter describing the study, was mailed to the remainder of the study sample in November 2000.

Results

Demographic Characteristics of the Sample

A total of 3,816 usable surveys (35.8%) were received from the sample of 10,662 members continuously enrolled during 2000, of which 2,316 individuals were in 2-tier plans and 1,499 in 3-tier plans (Table 1). There were varying structures of 2- and 3-tier pharmacy benefit structures represented in the study sample. The predominant 2-tier pharmacy benefit structure was a $7/$15 2-tier plan and a $15/$25/$40 3-tier plan. For members in 2-tier pharmacy benefit structure, half of the sample (53%) was in the $7/$15 plan, a little over a fourth (27%) was in a $5/$15 plan, and the remaining fifth (20%) was in a $5/$10 plan. For individuals in the 3-tier plan, more than three fourths of the sample (85%) was in a $15/$25/$40 plan, while the remaining 15% was in a $20/$35/$50 plan. Mail-order copayments for this sample were twice the amounts of the community pharmacy copayments, by tier, for a supply up to 90 days.

A majority of the respondents (87%) were white, with similar gender distributions in both plan types. Two-tier plan members appeared to be more educated, with higher incomes, and were more likely to be working full time compared to 3-tier plan members. Three-tier plan members were older and were more likely to be retired or not employed. More than half (54.7%) of the individuals in 3-tier plans were Medicare+Choice members versus 11.7% of 2-tier drug plan members in Medicare+Choice plans.

Three-tier plan members also appeared to pay more for their prescription medications per month (not shown), with 51.2% paying more than $50 per month, while 52.8% of 2-tier members paid less than $50 per month. However 2-tier plan members appeared to pay a higher premium per month for their health plan, with 40.5% paying between $100 and $300 or more per month, while a majority of the 3-tier members (49.7%) paid between $25 and $100 per month (possibly because the premium for Medicare+Choice members, which represented a third of the sample, was $69 per month). Three-tier plan members purchased more prescriptions for themselves and their family per month (mean=5.60, SD=±2.8) than 2-tier plan members (mean=4.61, SD=±2.7) and also had more chronic disease states according to the CDI scores (mean=3.93, SD=±2.4) than 2-tier plan members (mean=3.27, SD=±2.3).

Comparison of Survey Respondents and Nonrespondents

To check for potential response bias, survey respondents and nonrespondents were compared on available demographic, medication utilization, and prescription expenditure characteristics (Table 2). Survey respondents were older and more likely to be single, though there were no gender or income-level differences between the 2 groups. A greater number of survey respondents were in 2-tier plans, a third of whom were also

---

**TABLE 3** Member Satisfaction with Various Aspects of Prescription Drug Coverage*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Plan</th>
<th>N</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount you pay for prescription medications</td>
<td>2-tier</td>
<td>2,198</td>
<td>4.37</td>
<td>1.77</td>
<td>.000*</td>
</tr>
<tr>
<td></td>
<td>3-tier</td>
<td>1,362</td>
<td>3.75</td>
<td>1.67</td>
<td></td>
</tr>
<tr>
<td>Amount of time and effort it takes to get a prescription medication through your health plan</td>
<td>2-tier</td>
<td>2,130</td>
<td>5.34</td>
<td>1.71</td>
<td>.000*</td>
</tr>
<tr>
<td></td>
<td>3-tier</td>
<td>1,334</td>
<td>5.11</td>
<td>1.80</td>
<td></td>
</tr>
<tr>
<td>Ability to get any medication prescribed by your doctor</td>
<td>2-tier</td>
<td>2,132</td>
<td>4.82</td>
<td>1.95</td>
<td>.453</td>
</tr>
<tr>
<td></td>
<td>3-tier</td>
<td>1,331</td>
<td>4.87</td>
<td>1.97</td>
<td></td>
</tr>
<tr>
<td>How easy is it to get information about your prescription benefits</td>
<td>2-tier</td>
<td>2,104</td>
<td>4.93</td>
<td>1.69</td>
<td>.823</td>
</tr>
<tr>
<td></td>
<td>3-tier</td>
<td>1,317</td>
<td>4.92</td>
<td>1.74</td>
<td></td>
</tr>
<tr>
<td>Health plan’s promptness in resolving any coverage disputes</td>
<td>2-tier</td>
<td>1,622</td>
<td>4.09</td>
<td>1.87</td>
<td>.245</td>
</tr>
<tr>
<td></td>
<td>3-tier</td>
<td>963</td>
<td>4.18</td>
<td>1.87</td>
<td></td>
</tr>
<tr>
<td>The availability of conveniently located pharmacies</td>
<td>2-tier</td>
<td>2,179</td>
<td>6.15</td>
<td>1.32</td>
<td>.000*</td>
</tr>
<tr>
<td></td>
<td>3-tier</td>
<td>1,337</td>
<td>6.05</td>
<td>1.52</td>
<td></td>
</tr>
</tbody>
</table>

* Independent samples t test at P<.05.

Scale = 1-7, with 1= very dissatisfied and 7 = very satisfied. Respondents were asked, “How satisfied were you with each of the following aspects of prescription drug coverage?”
Impact of Multi-tiered Pharmacy Benefits on Attitudes of Plan Members With Chronic Disease States

Medicare+Choice members. More than half the respondents were single and had, on average, more disease states (3.6 versus 3.3) than nonrespondents. There were also more individuals taking antihypertensives and lipid-lowering agents among the survey respondents.

Both respondents and nonrespondents had similar generic use and formulary compliance rates (although formulary compliance rates were statistically significant at \(P<0.05\), these differences may be attributed to the large sample size). Respondents also consumed more prescriptions per month than nonrespondents and had higher prescription costs, although their cost-sharing amounts appeared to be similar. Thus, it appears that the survey respondents may represent an older and sicker group of individuals who may have higher and more expensive prescription use than the non-respondents and, therefore, chose to respond to the survey.

General Attitudes About Prescription Drug Coverage

There were no differences between members in 2- and 3-tier plans regarding some dimensions of overall satisfaction with their pharmacy benefit plan, namely, access to any prescription medication, ease of obtaining information about benefits, or the health plan’s promptness in resolving disputes (Table 3). Members in both plan types appeared to be moderately to very satisfied with these aspects. Two-tier plan members were more satisfied with the amount they pay for prescription medications (mean=4.37, SD=±1.77 versus mean=3.75, SD=±1.67 for 3-tier members). Of lesser practical significance perhaps was the finding that 2-tier plan members were more satisfied with the effort it takes to get prescription medications through their health plan (mean=5.34, SD=±1.71 versus mean=5.11, SD=±1.80 for 3-tier members).

Information Sources Used by Members in Making Decisions About Prescription Use

Table 4 shows that while there were some statistical differences in member’s responses from both groups to the informational influences on their decision-making process, the practical significance of these differences may not be important. For example, members were more likely to seek information about their prescription medications from the Internet (mean=3.55, SD=±1.80), magazines or reference books (mean=3.50, SD=±2.30), and consulting with a pharmacist (mean=3.22, SD=±2.0). Although members, in general, were less likely to get a second opinion from another physician about their prescribed medication, 2-tier plan members appeared to be more likely to do so than 3-tier plan members. Similarly, they were more likely to consult with friends and family than 3-tier plan members. However, 3-tier plan members were more likely to look up the cost of their medication than 2-tier plan members.

Member Satisfaction and Loyalty Regarding Their Prescription Drug Coverage

Overall, members appear to be moderately satisfied with their prescription drug coverage (mean=5.52, SD=±2.14). Controlling for the differences in demographic factors, number of comorbidities, and member cost-sharing amounts for health

**TABLE 4** Informational Sources Used by Members in Making Decisions When Purchasing Prescriptions

<table>
<thead>
<tr>
<th>Variable</th>
<th>Plan</th>
<th>N</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Get a second opinion from another physician</td>
<td>2-tier</td>
<td>2,202</td>
<td>1.81</td>
<td>1.33</td>
<td>.000*</td>
</tr>
<tr>
<td></td>
<td>3-tier</td>
<td>1,341</td>
<td>1.64</td>
<td>1.31</td>
<td></td>
</tr>
<tr>
<td>Consult with a pharmacist</td>
<td>2-tier</td>
<td>2,185</td>
<td>3.25</td>
<td>2.00</td>
<td>.177</td>
</tr>
<tr>
<td></td>
<td>3-tier</td>
<td>1,348</td>
<td>3.16</td>
<td>2.10</td>
<td></td>
</tr>
<tr>
<td>Consult with friends and family</td>
<td>2-tier</td>
<td>2,176</td>
<td>2.30</td>
<td>1.72</td>
<td>.000*</td>
</tr>
<tr>
<td></td>
<td>3-tier</td>
<td>1,327</td>
<td>2.07</td>
<td>1.73</td>
<td></td>
</tr>
<tr>
<td>Consult with coworkers who have the same health insurance plan</td>
<td>2-tier</td>
<td>2,163</td>
<td>1.86</td>
<td>1.48</td>
<td>.110</td>
</tr>
<tr>
<td></td>
<td>3-tier</td>
<td>1,301</td>
<td>1.77</td>
<td>1.49</td>
<td></td>
</tr>
<tr>
<td>Look up information about the medication on the Internet</td>
<td>2-tier</td>
<td>1,979</td>
<td>3.48</td>
<td>2.30</td>
<td>.764</td>
</tr>
<tr>
<td></td>
<td>3-tier</td>
<td>1,081</td>
<td>3.69</td>
<td>3.30</td>
<td></td>
</tr>
<tr>
<td>Look up information about the medication in magazines or reference books</td>
<td>2-tier</td>
<td>2,060</td>
<td>3.58</td>
<td>2.28</td>
<td>.075</td>
</tr>
<tr>
<td></td>
<td>3-tier</td>
<td>1,235</td>
<td>3.53</td>
<td>3.20</td>
<td></td>
</tr>
<tr>
<td>Look up the cost you would have to pay for the medication</td>
<td>2-tier</td>
<td>2,197</td>
<td>3.04</td>
<td>2.14</td>
<td>.034*</td>
</tr>
<tr>
<td></td>
<td>3-tier</td>
<td>1,339</td>
<td>3.20</td>
<td>2.26</td>
<td></td>
</tr>
</tbody>
</table>

* Independent samples t test at \(P<0.05\).  
Scale = 1-7, with 1 = very unlikely and 7 = very likely.  Respondents were asked, “When a doctor prescribes a new medication, how likely were you to use the following information sources before purchasing the medication?”
# TABLE 5

Effect of Demographic Characteristics, Number of Comorbidities, Cost of Health Plan and Prescription Medications on Overall Satisfaction with Prescription Drug Coverage, Switching Health Plans, Recommending Prescription Drug Coverage, and Choosing a Health Plan Based on Its Formulary (OLS Regression Results)

<table>
<thead>
<tr>
<th>Demographic/Plan Characteristics</th>
<th>Overall Satisfaction (n=2,795)§</th>
<th>Switching Health Plan for Better Prescription Drug Coverage (n=3,243)†</th>
<th>Likelihood of Recommending Prescription Drug Coverage to Others (n=3,244)¶</th>
<th>Likelihood of Choosing a Health Plan Based on Its Formulary (n=3,209)#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (46-55 years)**</td>
<td>-0.02</td>
<td>-0.38</td>
<td>0.04</td>
<td>-0.05</td>
</tr>
<tr>
<td>Age (56-64 years)</td>
<td>0.02</td>
<td>-0.079*</td>
<td>0.056‡</td>
<td>-0.24</td>
</tr>
<tr>
<td>Age (over 65 years)</td>
<td>0.33*</td>
<td>-0.088*</td>
<td>0.107*</td>
<td>-0.05</td>
</tr>
<tr>
<td>Educ (4-year college)**</td>
<td>-0.010</td>
<td>0.037</td>
<td>-0.039‡</td>
<td>-0.037</td>
</tr>
<tr>
<td>Educ (some graduate school or MS/PhD)</td>
<td>0.15</td>
<td>-0.016</td>
<td>-0.042‡</td>
<td>-0.072*</td>
</tr>
<tr>
<td>Income ($25,000-$34,999)**</td>
<td>0.037</td>
<td>-0.019</td>
<td>0.022</td>
<td>-0.002</td>
</tr>
<tr>
<td>Income ($35,000-$49,999)</td>
<td>0.062*</td>
<td>-0.043‡</td>
<td>0.072*</td>
<td>0.008</td>
</tr>
<tr>
<td>Income ($50,000-$64,999)</td>
<td>0.056</td>
<td>-0.051</td>
<td>0.036</td>
<td>-0.023</td>
</tr>
<tr>
<td>Income (over $65,000)</td>
<td>0.052‡</td>
<td>-0.084*</td>
<td>0.083</td>
<td>-0.021</td>
</tr>
<tr>
<td>Employment (part-time)**</td>
<td>0.02</td>
<td>-0.020</td>
<td>0.005</td>
<td>-0.012</td>
</tr>
<tr>
<td>Employment (not working or retired)</td>
<td>0.001</td>
<td>0.004</td>
<td>0.005</td>
<td>-0.004</td>
</tr>
<tr>
<td>Female**</td>
<td>0.06</td>
<td>-0.003</td>
<td>-0.026</td>
<td>-0.046</td>
</tr>
<tr>
<td>3-tier pharmacy benefit plan**</td>
<td>-0.105*</td>
<td>0.105*</td>
<td>-0.096*</td>
<td>-0.029</td>
</tr>
<tr>
<td>Race (other)**</td>
<td>-0.007</td>
<td>0.028</td>
<td>0.016</td>
<td>0.014</td>
</tr>
<tr>
<td>Amount paid for health plan premium</td>
<td>-0.074*</td>
<td>0.102*</td>
<td>-0.118*</td>
<td>0.020</td>
</tr>
<tr>
<td>Amount paid for prescriptions per month (individual and/or family)</td>
<td>-0.239*</td>
<td>0.219*</td>
<td>-0.202*</td>
<td>0.080*</td>
</tr>
<tr>
<td>Chronic Disease Indicator Score</td>
<td>0.113*</td>
<td>-0.058*</td>
<td>0.092*</td>
<td>0.038‡</td>
</tr>
</tbody>
</table>

* P<.001. † P<.01. ‡ P<.05.
§ Scale = 1-10. Respondents were asked, “Please rate your experiences with your prescription drug coverage where 0 is the worst possible prescription drug coverage and 10 is the best possible prescription drug coverage.” R² =9%.
† Scale = 1-5, with 1= very unlikely and 5 = very likely. Respondents were asked, “At the next available opportunity, how likely are you to switch your current health plan to obtain better prescription drug coverage?” R² =8.7%.
¶ Scale = 1-5, with 1= very unlikely and 5 = very likely. Respondents were asked, “How likely are you to recommend your current prescription drug coverage to a friend or coworker?” R² =7.8%.
# Scale = 1-5, with 1= very unlikely and 5 = very likely. Respondents were asked, “How likely are you to choose your health plan based on whether your prescription medications are on your health plan’s formulary?” R² =7%.
** Omitted categories:
- Age (18-45 years)
- Education (high school and some post-high school)
- Income ($0-$24,999)
- Employment (full-time)
- Gender (male)
- Plan type (2-tier pharmacy benefit plans)
- Race (white)
Impact of Multi-tiered Pharmacy Benefits on Attitudes of Plan Members With Chronic Disease States

In general, although members were somewhat neutral about switching their current health plan (mean=3.1, SD=±1.44) to obtain better prescription drug coverage, 3-tier plan members were 10.5% more likely to do so than 2-tier plan members. Age was related to the likelihood of switching health plans; individuals between the ages of 56 and 64 years were 7.9% less likely and those over the age of 65 were 8.8% less likely to change health plans for better prescription drug coverage than younger individuals (those between 18 and 45 years). A trend between higher income levels and a lower likelihood of changing health plans to obtain better prescription drug coverage was also observed. Individuals with a higher score on the CDI were less likely to switch their health plans. The more individuals paid for their health plan premium and prescription medications per month, the more likely they were to switch health plans.

Three-tier plan members were 9.6% less likely to recommend their prescription drug coverage to coworkers and friends compared to 2-tier plan members (mean=3.2, SD=±1.30). Among older individuals, those between the ages of 56 and 64 years were 5.6% more likely and those over the age of 65 years were 10.7% more likely to recommend their prescription drug coverage to others than those between the ages of 18 and 45 years.

Individuals with higher incomes appeared to be more likely to recommend their prescription drug coverage to others. Individuals with a college or graduate education were also approximately 4% less likely to recommend their prescription drug coverage to others than those with a high school (and some post-high school) education. Individuals with a higher score on the CDI were more likely to recommend their prescription drug coverage to others. Finally, the more individuals paid for their health plan and prescription medications per month, the less likely they were to make recommendations about their prescription drug coverage.

No differences in pharmacy plan type were observed in the likelihood of members selecting a health plan based on the availability of medications on the health plan’s formulary. In gen-

---

**FIGURE 1** Amount Consumers Were Willing to Pay Extra Per Month to Stay on a Nonformulary Medication (N=3,454)

![Graph showing the percentage of respondents for different extra amounts consumers are willing to pay for a nonformulary medication.](image-url)
Impact of Multi-tiered Pharmacy Benefits on Attitudes of Plan Members With Chronic Disease States

**TABLE 6** Influence of Demographic Characteristics, Number of Comorbidities, Cost of Health Plan and Prescription Medications, and Attitudes Toward Formulary and Nonformulary Medications on the Willingness to Pay More Per Month for a Prescribed Nonformulary Medication (N=2,102)*

<table>
<thead>
<tr>
<th>Estimate†§</th>
<th>Standard Error</th>
<th>Wald Statistic</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Switch to a formulary medication (when taking a nonformulary medication regularly)</td>
<td>-209</td>
<td>.030</td>
<td>47.39</td>
</tr>
<tr>
<td>Chronic Disease Indicator Score</td>
<td>-.0007</td>
<td>.018</td>
<td>.162</td>
</tr>
<tr>
<td>Male†</td>
<td>.287</td>
<td>.081</td>
<td>12.698</td>
</tr>
<tr>
<td>Education (high School and some post-high school)†</td>
<td>-.472</td>
<td>.097</td>
<td>23.441</td>
</tr>
<tr>
<td>Education (4-year college)</td>
<td>-.178</td>
<td>.115</td>
<td>2.81</td>
</tr>
<tr>
<td>Income ($0-$24,999)†</td>
<td>-.453</td>
<td>.124</td>
<td>13.320</td>
</tr>
<tr>
<td>Income ($25,000-$34,999)</td>
<td>-.009</td>
<td>.130</td>
<td>.386</td>
</tr>
<tr>
<td>Income ($35,000-$49,999)</td>
<td>-.008</td>
<td>.116</td>
<td>.563</td>
</tr>
<tr>
<td>Income ($50,000-$64,999)</td>
<td>-.004</td>
<td>.121</td>
<td>.131</td>
</tr>
<tr>
<td>Amount spent on prescriptions per month (individual and/or family)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$0-$10</td>
<td>-.934</td>
<td>.210</td>
<td>19.842</td>
</tr>
<tr>
<td>$11-$30</td>
<td>-.457</td>
<td>.130</td>
<td>12.329</td>
</tr>
<tr>
<td>$31-$50</td>
<td>-.392</td>
<td>.126</td>
<td>9.641</td>
</tr>
<tr>
<td>$51-$100</td>
<td>-.388</td>
<td>.118</td>
<td>10.863</td>
</tr>
</tbody>
</table>

* P<.05
† Omitted categories:
  - Education (some graduate school or MS, PhD)
  - Gender (female)
  - Income (over $65,000)
  - Amount spent on prescriptions per month (more than $100)
‡ Estimates from the ordinal regression model. Nagelkerke Pseudo R²=.064. Wald statistic, which has a chi-square distribution, is used to test a hypotheses about an individual effect in a model. For example, in the table above, a statistically significant Wald statistic shows that gender is significantly associated with a willingness to pay for nonformulary medications.
§ Race, age, pharmacy plan type, health plan premium, employment, and general attitudes toward formulary and nonformulary medications were not significantly correlated with the willingness-to-pay variable and were not included in the model.

Members were likely to choose a health plan based on its formulary content (mean=4.2, SD±1.12). Those who had some graduate education were 7.2% less likely to choose their health plan based on this criterion than those with a high school (and some post-high school) education. The more individuals paid for their prescription medications per month and the greater the number of chronic disease states they had (as measured by the CDI) the more likely they were to choose a health plan based on whether their prescription medications were on the formulary.

**Willingness of Members to Pay Extra to Purchase Higher-Cost Medications**

Figure 1 shows that approximately a third of the respondents stated that they were not willing to pay anything extra to purchase their nonformulary medication, a third were willing to pay between $1 and $5, and only a fourth were willing to pay between $6 and $10. Thus, 83% of the respondents reported that they were not willing to pay more than $10 extra per month to purchase a nonformulary medication. No statistically significant differences between 2- and 3-tier plan members were observed.
When examining the factors that influence the willingness to pay extra for a nonformulary medication, Table 6 shows that individuals who stated that they were likely to switch to a formulary medication if taking a nonformulary medication were less willing to pay more per month for their nonformulary medication. Similarly, those with graduate education were also more likely to be in the higher categories than those with lesser education. One of the income categories ($0 to $24,999) was also a statistically significant predictor of the outcome variable, although the practical significance of this relationship is not clear.

Similar results were obtained in assessing the willingness to pay more for a brand-name medication when prescribed a generic medication (model results are not shown). Figure 2 shows that approximately one half of the respondents stated that they were not willing to pay anything extra for a prescribed brand-name medication when a generic alternative was available.

Members who stated that they were likely to purchase a generic medication when prescribed a brand-name medication and those who considered brand-name generic medications to be equivalent were less likely to be willing to pay more for the brand-name medication than those who had higher scores on these measures. As in the previous model, those with graduate education were also more likely to be willing to pay higher amounts for brand-name medications than those with less education.

**Discussion**

Findings regarding member satisfaction with their pharmacy benefit plan corroborate to some extent those of previous studies and support the proposed hypotheses. Mean satisfaction scores with prescription drug coverage were between 5 and 6 on a 10-point scale suggesting that, in general, overall satisfaction with pharmacy benefit plans is not very high. However, this sample represented individuals with chronic disease states enrolled in managed care plans; previous work found lower satisfaction with health care among persons with chronic disease enrolled in managed care plans compared to those in traditional fee-for-service plans. One possible explanation that might mediate the relationship between satisfaction and chronic illness in managed care plans may be that, due to the nature of their illnesses, members with chronic illness may be more aware of their health care and pharmacy benefits, in particular, the cost-control mechanisms such as multi-tier copay plan designs. Hence, they may be less satisfied with their prescription drug coverage.

The results of this study show that clearly there are differences in perceptions of members in 2- and 3-tier copay plans regarding their prescription drug coverage. Specifically 2-tier plan members are more satisfied with their plan, more likely to recommend their plan to others, and less likely to switch their current health plan to obtain better prescription drug coverage than those in 3-tier plans. The differences in perceptions between members in 2-tier and 3-tier plans may be due to differences in the cost-sharing amounts for health care and prescription medications. Members in 2-tier plans appear to be more concerned about the cost of their medication and are more likely to look it up than their 2-tier counterparts. Controlling for the differences in demographic factors, number of comorbidities, and member cost-sharing amounts for health care and prescription medications, members in 2-tier plans are more satisfied with their plan, more likely to recommend their plan to others, and less likely to switch their current health plan to obtain better prescription drug coverage than those in 3-tier plans.
plans. These findings corroborate, to some extent, those of previous studies, where individuals with higher out-of-pocket costs have reported lower satisfaction levels with their health plan as well.24-26 Also, it has been seen that, in general, individuals with chronic disease states have reported lower satisfaction with the cost of medical care than healthy enrollees of managed care organizations.23 These findings support, to some extent, the importance of copayments as a determinant of member satisfaction with their health plans. Holdford et al. found that higher copayment amounts were associated with a lower preference for prescription drug plans, and increasing the copayment from $8 to $15 had 3 times more impact on consumer preference than increasing it from $0 to $8.8

The findings may be, in part, attributed to the characteristics of the 2-tier plan members represented in this sample. This group appeared to be a younger, working group of individuals with higher incomes and in a better state of health than 3-tier plan members. Medicare+Choice members were overrepresented in the 3-tier drug plans. (Table 1) These individuals are older, retired, or not employed, with greater medication use, greater number of comorbidities, and they represent a population that would be more likely to be vulnerable to the increased cost-sharing effects of 3-tier plans. About 55% of the 3-tier plan members were older than 65 years, and only 12% of the 2-tier plan members were in the similar age category. Thus, it may be expected that prescription utilization may be higher for the 3-tier plan members, and they may have more experience with their medical and pharmacy benefits than those in 2-tier plans. These differences in age and, subsequently, prescription purchasing behaviors between the 2- and 3-tier groups may explain some of the responses related to satisfaction with cost-sharing amounts (Table 3) and the propensity to look up the cost of medications (Table 4).

However, older respondents and sicker individuals (those with higher scores on the CDI) appeared to have more positive attitudes toward their pharmacy benefit plans in general. In a similar finding, Desselle found that those aged 60 or older were more satisfied with their prescription drug coverage than younger individuals.27

Although a correlation between better health status and member satisfaction has been observed, the inverse relationship found in this study may, in part, be due to the nature of the older population represented in the extant study sample, a third of whom were Medicare members.27 Medicare+Choice members have reported higher satisfaction with the costs of care compared to nonmanaged care individuals.28 One explanation for this finding may be that the Medicare+Choice population, in general, has little access to prescription drug coverage, and any access provided through managed care plans, however limited, might contribute to member satisfaction.24

Higher incomes were also associated with greater satisfaction with prescription drug coverage and increased loyalty toward the pharmacy benefit plan. It is possible that individuals with higher incomes are less price-sensitive to cost-sharing amounts, both for prescription medications and medical care and, hence, have more positive feelings about their prescription drug coverage in general than those with lower incomes.

Conversely, the more individuals spent for either their health care or prescription medications, the less satisfied they were with their prescription drug coverage and the less loyalty they appeared to have for their health plans.9 An inverse relationship exists between the out-of-pocket costs for prescription medications and members’ willingness to pay for nonformulary medications. This is an intuitive finding since individuals confronted with higher out-of-pocket costs are likely to be more price-sensitive. While income has been shown to be associated with the willingness to pay for medical care in past research, in this study, the education levels of the respondents could be a proxy for income: those with lower education levels were less willing to pay for brand-name or nonformulary medications compared to those with a higher education.27,30

Both 2- and 3-tier pharmacy plan members expressed similar opinions about their willingness to purchase lower-cost medications, but a majority of the sample were reluctant to pay more than $10 more per month (in addition to their copayment) to stay on either a brand-name or a nonformulary medication that they had been using regularly when there was a less expensive alternative available. A low threshold for willingness to pay for pharmacy services, in general, has been demonstrated. In a field experiment comparing hypothetical and real purchase decisions for a pharmacist-oriented asthma management program, a majority of the sample that purchased the program did so at the lowest offered price of $15.18 Thus, it appears the same holds true for prescription medications where the willingness to pay threshold for a majority of this sample is under $10. As some evidence of this finding, there has been some research to show that when confronted with increases in cost sharing for prescription medications, members are willing to try lower-cost alternatives.3 Member satisfaction also appears to be related to the amount of cost sharing. In a recent study, members in prescription drug plans with a $1 to $5 copayment for brand-name medications were 10% more satisfied with their plans than those in a higher cost-sharing plan with a $11 copayment for brand-name medications.32

This presents an interesting dilemma for employers and managed care decision makers as copayment amounts for each tier in a 3-tier plan are continuing to increase between $5 and $15 more per year. Multi-tier copayment plans will generally most affect those persons who have the greater prescription drug needs, creating a paradox for policy makers and insurers.35 These findings then raise important questions for the purchasers and providers of health care. If multi-tiered plans create greater dissatisfaction among managed care members and increase the cost burden for them, how will these attitudes influence prescription purchasing behavior? Will vulnerable individuals such as those with multiple or chronic disease states...
be confronted with decisions about which medications they can afford and which medications they will purchase when their copayments are increased? Second, will the long-term effects of these increased cost-sharing mechanisms result in unintended effects such as medication noncompliance and the failure to purchase prescription medications? And, will these effects, in turn, lead to a greater utilization of other medical care resources such as increased office and emergency room visits? Third, what are the characteristics of individuals that could be used to predict their prescription purchasing behavior in 3-tier plans? The findings of this study have shown that age, income, number of comorbidities, education, and the cost of care to the individual are some of the characteristics that could influence their prescription purchasing behavior.

## Limitations

There were several limitations to this study. First, the respondents appear to represent a self-selected group of individuals who are older, sicker, with greater cost sharing and, hence, were more eager to respond to the survey. It is possible that statistical differences found between the respondents and nonrespondents may be, in part, due to the large sample sizes employed in the study. If these differences do exist, the study findings may reflect the experiences of such a population and may not be generalizable to a larger, commercially insured population. Yet, these respondents are arguably those health plan members most affected by higher copay costs of prescription drugs, and the perceptions of these individuals may be of greater interest to managed care decision makers and employers. Second, the 2 groups (those in 2- and 3-tier plans, respectively) examined in this study were different with respect to certain characteristics, noticeably age, income, education, employment status, prescription cost-sharing amounts, and the cost of health plan premiums. To the extent possible, these differences were controlled for in the analyses, but it is possible that the responses obtained from these individuals on the various study measures may have been influenced by unmeasured differences between the 2 groups. Therefore, member attitudes about their prescription drug coverage may not entirely represent a response to the copayment amounts and access to medications that each group experienced with their respective pharmacy benefit plan but also may be a function of certain demographic and cost-sharing characteristics of each individual. The findings in this study should be considered in light of the differences that exist between the 2 groups.

Third, the survey data were cross-sectional; therefore, only the current association between pharmacy plan type and member attitudes could be determined, and the long-term effects of increased cost sharing on member satisfaction and loyalty of individuals in 3-tier plans could not be assessed. Additional research using a longitudinal design should be conducted that examines whether these member attitudes about 3-tier plans persist over time.

Finally, there may be other covariates, not included in the models, that may explain the low predictive value of the multivariate models used in the analyses. These may include other medical care utilization behavior such as number of physician visits. The analyses used in this study focused on demographic, cost of medical care, and the number of comorbidities that have shown to affect member satisfaction and related attitudes.

## Conclusion

There are differences in patient perceptions regarding their prescription drug coverage. Specifically 2-tier plan members were more satisfied with their cost-sharing amounts than 3-tier members. Members in 2-tier plans were more satisfied with their prescription drug coverage, were more likely to recommend their plan to others, and were less likely to switch their current plans to obtain better prescription drug coverage compared to those in 3-tier plans. Older and sicker respondents and those with higher education and income appeared to have more positive attitudes toward their prescription drug coverage in general. The more cost sharing that members experienced for their prescription medications and health care premiums, the less favorable were their attitudes regarding their prescription drug coverage. Finally, while members expressed a willingness to buy lower-cost medications (e.g., a generic drug when prescribed a brand-name medication or a formulary alternative to a nonformulary medication), they were reluctant to pay more than $10 extra (in addition to their copayment) per month for medications in the higher tiers. These findings suggest that the cost of health care and prescription drug medications, in particular, have important effects on patient attitudes. The financial resources available to members (which may be a function of being older and having more education and higher incomes) and the number of chronic disease states may influence their attitudes toward their prescription drug coverage. Among the questions unanswered by this study is the effect of member attitudes on actual prescription-purchasing behavior of members.

## DISCLOSURES:

Funding for this research was provided by Merck and Company through the Academic Medicine and Managed Care Forum and was obtained by authors Kavita Nair, Robert J. Valuck, Marianne M. McCollum, and Julie M. Ganther. Nair served as principal author of the study. Study concept and design was the work of Nair, Valuck, McCollum, Ganther, and author Sonya J. Lewis. Drafting of the manuscript, analysis and interpretation of data, and statistical expertise were contributed primarily by Nair and Ganther. Critical revision of the manuscript was the work of Nair, Valuck, McCollum, and Ganther.

## REFERENCES:

4. Schneeweiss S. Maclure M, Walker AM, Grootendorst P, Soumerai S. On the evaluation of drug benefits policy changes with longitudinal claims data. the
Impact of Multi-tiered Pharmacy Benefits on Attitudes of Plan Members With Chronic Disease States


17. Suh DC. Consumers’ willingness to pay for pharmacy services that reduce the risk of medication related problems. *J Am Pharm Assoc.* 2000;40(6);818-27.


21. SPSS Inc. (version 11.0) 233 South Wacker Drive, Chicago, Illinois.


27. Desselle P. Patient satisfaction with knowledge of their prescription drug coverage. *J Managed Care Pharm.* 2001; 17(4);34-42.


34. Aharony L, Strasser S. Patient satisfaction: what we know what we still need to explore. *Med Care Rev.* 1993;50;1;49-79
### General Attitudes About Prescription Drug Coverage

1. The amount you pay for prescription medications
   - Dissatisfied
   - Satisfied
   - Not applicable
   - 1 2 3 4 5 6 7 8

2. The amount of time and effort it takes to get a prescription medication from your health plan
   - Dissatisfied
   - Satisfied
   - Not applicable
   - 1 2 3 4 5 6 7 8

3. Your ability to get any medication prescribed by your doctor
   - Dissatisfied
   - Satisfied
   - Not applicable
   - 1 2 3 4 5 6 7 8

4. How easy it is to get information about your prescription benefits
   - Dissatisfied
   - Satisfied
   - Not applicable
   - 1 2 3 4 5 6 7 8

5. Your health plan's promptness in resolving any coverage disputes
   - Dissatisfied
   - Satisfied
   - Not applicable
   - 1 2 3 4 5 6 7 8

6. The availability of conveniently located pharmacies
   - Dissatisfied
   - Satisfied
   - Not applicable
   - 1 2 3 4 5 6 7 8

Next, we would like some information about factors affecting your decisions about prescription drug use.

### Information Sources Used by Members in Making Decisions About Prescription Drug Use

When your doctor prescribes a new medication, how likely are you to use each of the following information sources before purchasing the medication:

1. Get a second opinion from another physician
   - Very unlikely
   - Very likely
   - 1 2 3 4 5 6 7

2. Consult with a pharmacist
   - Very unlikely
   - Very likely
   - 1 2 3 4 5 6 7

3. Consult with your friends and family
   - Very unlikely
   - Very likely
   - 1 2 3 4 5 6 7

4. Consult with coworkers who have the same health insurance plan
   - Very unlikely
   - Very likely
   - 1 2 3 4 5 6 7

5. Look up information about the medication on the Internet, in magazines, or in reference books
   - Very unlikely
   - Very likely
   - 1 2 3 4 5 6 7

6. Look up the cost you would have to pay for the medication
   - Very unlikely
   - Very likely
   - 1 2 3 4 5 6 7

### Outcome Measures Related to Member Satisfaction and Loyalty About Prescription Drug Coverage

1. Please rate your experiences with your prescription drug coverage. Check one number of the scale listed below, where 0 is the worst prescription drug coverage and 10 is the best prescription drug coverage possible.
   - Worst prescription drug coverage
   - Best possible prescription drug coverage
   - 0 1 2 3 4 5 6 7 8 9 10

2. How likely are you to recommend your current prescription drug coverage to a friend or coworker?
   - Very likely
   - 1 2 3 4 5 6 7

3. At the next available opportunity, how likely are you to switch your current health plan to obtain better prescription drug coverage?
   - Very likely
   - 1 2 3 4 5 6 7

4. How likely are you to choose your health plan based on whether your prescription medications are on the health plan’s formulary?
   - Very likely
   - 1 2 3 4 5 6 7

### Willingness to Pay Extra to Purchase Higher-Cost Medications

1. If your doctor prescribes a brand-name medication but there is a generic medication available that would cost you less, how much more would you be willing to pay to get the brand-name medication?
   - $0
   - $1 to $5
   - $6 to $10
   - $11 to $15
   - $16 to $20
   - More than $20

2. If a medication that you have been taking regularly is nonformulary, how much more do you think you would be willing to pay per month to stay on the medication?
   - $0
   - $1 to $5
   - $6 to $10
   - $11 to $15
   - $16 to $20
   - More than $20

### Equivalence Between Brand-Name and Generic Medications

1. Check your level of agreement with the following statement (think about your general preferences and not any specific situation).
   - Generic medications are equivalent to brand-name medications.
   - Strongly agree
   - Neither agree or disagree
   - Disagree
   - Agree
   - Strongly disagree

### Willingness to Purchase a Formulary Medication When Prescribed a Nonformulary Medication

1. If a medication that you have been taking regularly is nonformulary, how likely are you to switch to a similar medication that is on the formulary?
   - Very likely
   - 1 2 3 4 5 6 7
Over the past 15 years, significant advances have occurred in the pharmacotherapy of depression. Previous first-line antidepressants such as tricyclic antidepressants (TCAs) have been largely replaced by selective serotonin reuptake inhibitors (SSRIs) and other newer medications.1 In particular, the SSRIs have become popular because of more tolerable side effects, greater safety in overdose, and ease in dosing and administration.

People experiencing depression who do not receive adequate antidepressant treatment are more likely to have high rates of concurrent medical disorders, are less productive in the workplace, and utilize more health care resources than non-depressed people.2 Those who tolerate medications and comply with their antidepressant medication regimens for a full course of therapy are more likely to achieve positive clinical outcomes, leading to improved quality of life and cost avoidance for both additional outpatient and inpatient psychiatric care. The majority of antidepressant medications dispensed in the United States are SSRIs. Within the Texas Medicaid program, SSRIs accounted for 52% of all antidepressants dispensed to clients in 2000. Due to their higher unit costs, compared to older agents, these newer generation agents accounted for 71% of all antidepressant costs over the same year.

While SSRIs may cost more in direct drug cost compared to older antidepressants, multiple outcomes studies show that SSRIs are as efficacious as the traditional medications and are better tolerated by patients, indicating clinical and economic benefits for the medication costs expended.3-13 Only one administrative database study has been published comparing both pharmacy and health service utilization and costs associated with citalopram use. Results of the study, conducted by Sclar et al. in a health maintenance organization, showed that amitriptyline and sertraline were associated with higher health service utilization costs than citalopram, and there were no significant differences in costs among citalopram, fluoxetine, and paroxetine.5 However, since the study period shortly followed the market release of citalopram, a relatively small sample size within the citalopram group was used for the comparisons.

As the use of SSRIs continues to increase within the Texas Medicaid Program, total expenditures for this drug class will similarly continue to increase. Because the economic impact of this particular class of drugs is significant within the program, an analysis of the growing impact was undertaken. The objective of this paper is to evaluate trends in the use of selected SSRI agents and venlafaxine and their associated pharmaceutical expenditures within the Texas Medicaid Vendor Drug Program during 1999 and 2000.
Methods
All paid prescription drug claims were extracted from the Texas Medicaid Vendor Drug Program’s paid prescription claims database for the study period of January 1, 1999, to December 31, 2000. Clients aged 18 to 64 years were included in the study if they had at least one prescription dispensed for one of the selected study agents (citalopram, fluoxetine, sertraline, paroxetine, venlafaxine, and venlafaxine XR) at any time during the study period. Although venlafaxine is not strictly an SSRI at higher doses, it is included in this study because it is a newer antidepressant that is frequently used in primary care as well as psychiatric settings.

Utilization and Expenditure Measurements
Mean Reimbursed Cost per Day
Cost per day was calculated by dividing the pharmacy-reimbursed prescription payment (drug cost plus dispensing fee) by the number of days found in the “days supply” field within the prescription record. This “days supply” value is submitted by the pharmacy during the claims adjudication process and represents the number of treatment days for the dispensed quantity, based upon the therapy regimen prescribed by the physician. Reimbursed amounts represent the actual amount paid to the pharmacies and do not include rebates paid to the Texas Medicaid program on behalf of drug manufacturers, as mandated under OBRA ‘90 requirements. The pharmacy payment amount excludes copayments since there are no Medicaid recipient copayments in Texas. The cost per day reported in this study is equivalent to the allowed cost per day in private drug plans, before member copayment, which includes the effects of “lowest-of” pricing (i.e., the lower of usual and customary price or the contract price calculated as the drug cost plus dispensing fee).

Mean Dose per Day
For each study agent prescription dispensed, a daily dose was calculated by dividing the quantity dispensed by the days supply field within the prescription record. This created the “treatment window” for each prescription. If no subsequent prescription was dispensed within 15 days of the previous prescription, then the end date for the last prescription constituted the last day of treatment and, thus, the end of the treatment window.

Adherence Rates
Adherence (compliance) rates were compared by calculating days of medication possession for the first 120 days of therapy for newly started patients. New starters were defined, as described earlier, as clients having no previous prescription dispensed for any study agent for 120 days prior to the first appearance of a claim for the study agent. The date of the first claim served as an index date. Total days supplied were summed for all dispensed prescriptions during the first 120 days following the index date. Any occurrence of overlapping days supply was corrected by subtracting the total overlapped days from the total days supply calculated. Days of therapy that carried over past the 120th day of therapy were subtracted from the total days supply calculated. Newly started patients were selected, as opposed to ongoing patients, in order to measure medication possession across a well-defined period of time that included a definitive starting date.

Concomitant Psychotropic Medication Use
McFarland notes that the costs associated with concomitant drug use should be considered when comparing the economic impact of antidepressant agents. Therefore, the cost of these agents was considered in our comparisons. Patients included in the calculation of mean treatment days were also included in an analysis to measure the frequency and additional costs associated with concomitant psychotropic medication use. Concomitant agents were identified based on the utilization of any sedative, hypnotic, anxiolytic, or psychostimulant agent while concurrently taking one of the study agents. Concomitant medication use was defined as the dispensing of the concomitant medication between the start and end date of either study agent during the client’s treatment course of therapy. All available strengths of each concomitant agent were included in the analysis. Total costs of all concomitant agents were summed for each patient and divided by the study agent treatment days to calculate a concomitant agent cost per day.

Rates of Switching
Patients were defined to have “switched” therapy if, at any time during the study period, the patient received one prescription for a study agent, then received a subsequent prescription for the other study agent within 30 days of the end of the previous prescription end date (defined earlier as the dispensing date plus the days supply of the prescription). For example, if a
A trend of increasing mean cost per day (CPD) was calculated between 1999 and 2000 for all agents (Table 1). A comparison between all study agents showed that citalopram had a significantly lower prescription CPD than all other agents in 1999 and compared to all other agents, except venlafaxine, in 2000 (Table 1). Fluoxetine had the highest mean CPD for all agents in both 1999 ($3.49) and 2000 ($3.66). Compared to citalopram, the calculated mean CPD for fluoxetine was $1.31 higher in 1999 and $1.30 higher in 2000. Following fluoxetine, the highest calculated CPD in 1999 and 2000, respectively, was venlafaxine XR ($3.06, $3.22), sertraline ($2.61, $2.68), paroxetine ($2.49, $2.63), and venlafaxine ($2.29, $2.31).

**Mean Study Agent Dose**

In all study groups, except venlafaxine, the mean maximum dose per patient was significantly higher than the mean starting dose per patient (Wilcoxon signed rank test versus mean starting dose, P<0.001). There was no difference between citalopram and all other agents (except venlafaxine, chi-square versus citalopram, P=0.001) with respect to the percent of patients having an increase from their initial starting dose over the course of the treatment period. However, the incidence of dose increases was extremely low with all medications (citalopram 9.9%, fluoxetine 8.1%, paroxetine 9%, sertraline 10.2%, venlafaxine IR 5.3%, and venlafaxine XR 12.7%).

**Length of Treatment Days (Persistence)**

Table 2 shows that the mean treatment days for newly started citalopram patients was 83.2 days. There was no significant difference in mean treatment days between citalopram and all

---

* TABLE 1: Texas Medicaid SSRI Patients Summary and Cost-per-Day Comparison

<table>
<thead>
<tr>
<th>Study Agent</th>
<th>1999 Rxs</th>
<th>Days of Therapy</th>
<th>Patients</th>
<th>% Female</th>
<th>Mean Age (SD)</th>
<th>CPD (SD)</th>
<th>2000 Rxs</th>
<th>Days of Therapy</th>
<th>Patients</th>
<th>% Female</th>
<th>Mean Age (SD)</th>
<th>CPD (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>15,369</td>
<td>584,632</td>
<td>6,137</td>
<td>79.5</td>
<td>40.3 (12.3)</td>
<td>$3.49</td>
<td>28,582</td>
<td>1,100,388</td>
<td>9,630</td>
<td>78.0</td>
<td>40.4 (12.5)</td>
<td>$2.36</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>58,210</td>
<td>2,203,139</td>
<td>15,325</td>
<td>78.8</td>
<td>40.6 (12.7)</td>
<td>$2.61</td>
<td>60,362</td>
<td>2,219,104</td>
<td>15,363</td>
<td>78.4</td>
<td>40.6 (12.7)</td>
<td>$3.66</td>
</tr>
<tr>
<td>Sertraline</td>
<td>62,458</td>
<td>2,416,470</td>
<td>17,797</td>
<td>77.0</td>
<td>40.7 (13.0)</td>
<td>$2.64</td>
<td>69,566</td>
<td>2,718,010</td>
<td>19,308</td>
<td>76.9</td>
<td>40.7 (13.1)</td>
<td>$2.68</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>31,735</td>
<td>1,927,512</td>
<td>15,541</td>
<td>77.5</td>
<td>41.0 (12.7)</td>
<td>$2.49</td>
<td>61,968</td>
<td>2,367,116</td>
<td>18,220</td>
<td>77.5</td>
<td>40.7 (12.7)</td>
<td>$2.63</td>
</tr>
<tr>
<td>Venlafaxine IR</td>
<td>7,922</td>
<td>280,768</td>
<td>2,672</td>
<td>75.3</td>
<td>40.5 (11.9)</td>
<td>$3.06</td>
<td>7,094</td>
<td>254,522</td>
<td>2,333</td>
<td>75.8</td>
<td>40.3 (12.4)</td>
<td>$2.31</td>
</tr>
<tr>
<td>Venlafaxine XR</td>
<td>17,840</td>
<td>667,052</td>
<td>5,861</td>
<td>78.6</td>
<td>40.2 (11.8)</td>
<td>$3.18</td>
<td>26,365</td>
<td>1,021,802</td>
<td>7,605</td>
<td>78.8</td>
<td>40.9 (12.1)</td>
<td>$3.22</td>
</tr>
</tbody>
</table>

* Chi-square versus citalopram, P<0.001.
† ANOVA versus citalopram, P<0.001.
‡ ANOVA versus citalopram, P<0.001.

---

* Results

**Study Population Description**

Table 1 describes the patient populations included in the study based upon (1) number of prescriptions, (2) days of therapy, (3) number of patients, (4) percent females, and (5) mean age. Prescription use, days of therapy, and the number of patients treated with an SSRI increased between 1999 and 2000 for all study agents except venlafaxine. The study agent accounting for the highest SSRI utilization, based on the number of prescriptions, days of therapy, and patients, was sertraline. The largest growth in SSRI utilization was among citalopram patients, increasing by nearly 57% between 1999 and 2000. Chi-square analysis showed significant differences across all study agents with respect to gender distribution. Citalopram patients had a significantly higher proportion of females (79.5%) during 1999 than sertraline (77.0%) and venlafaxine (75.3%). Citalopram patients were significantly younger (mean=40.1 years) than sertraline (41.0), paroxetine (41.0), and venlafaxine (42.7) patients during 1999; however, the practical significance in age difference between the groups is debatable.

**SSRI Cost per Day (CPD) Comparison**

In all study groups, except venlafaxine, the mean maximum dose per patient was significantly higher than the mean starting dose per patient (Wilcoxon signed rank test versus mean starting dose, P<0.001). There was no difference between citalopram and all other agents (except venlafaxine, chi-square versus citalopram, P<0.001) with respect to the percent of patients having an increase from their initial starting dose over the course of the treatment period. However, the incidence of dose increases was extremely low with all medications (citalopram 9.9%, fluoxetine 8.1%, paroxetine 9%, sertraline 10.2%, venlafaxine IR 5.3%, and venlafaxine XR 12.7%).
other study agent patients, except venlafaxine patients, who had significantly lower mean treatment days (66.0 days). Additionally, a comparison of the percent of patients receiving at least 120 days of treatment with the study agent was conducted. A total of 44.1% of citalopram patients had at least 120 days of continuous treatment, significantly less than fluoxetine (48.3%) and significantly more than venlafaxine (29.1%).

**Adherence Rates**

Total days of medication during the first 120 days of therapy for all newly started study agent patients were summed to determine the rate of adherence across agent patient groups (Table 3). Newly started citalopram patients had significantly higher mean days of adherence (69.4 days) during the first 120 days of therapy, compared to all other study agents except fluoxetine (68.5 days). Patients newly started on venlafaxine had the lowest calculated adherence rates of all study agents (55.1 days). The calculated adherence rate for citalopram was 57.8%, followed by fluoxetine (57.1%, \(P=0.478\)), sertraline (55.4%, \(P<0.001\)), venlafaxine XR (55.3%, \(P=0.001\)), paroxetine (53.2%, \(P<0.001\)), and venlafaxine (45.9%, \(P=0.001\)). While these differences are statistically significant, the clinical significance of these differences should be considered here where the differences are mostly 2 to 3 total days between agent groups with large sample sizes.

**Rates of Agent Switching**

Table 4 shows the rates of switching for newly started SSRI patients within 180 days of starting the initial study agent. The majority of newly started patients did not switch agents during the first 180 days of SSRI therapy. A total of 13.4% of citalopram patients switched to another study agent, and similar rates were calculated for patients starting on sertraline (10.6%), fluoxetine (12.0%), and paroxetine (12.9%). Compared to all other study agents, venlafaxine (34.7%) and venlafaxine XR (20.9%) had larger rates of switching between agents; however, the majority of the switching was between the immediate and sustained-release tablets.

The mean number of days to the first switch for newly started study agents that were actually switched was calculated and is shown in Table 4. Patients started on citalopram who switched to another study agent did so, on average, after 83.5 days of starting the agent. There was no significant difference between citalopram and all other study agents, except venlafaxine (70.9 days).

**Concomitant Medication Use**

The prevalence and expenditures related to concomitant medication use for each study agent are shown in Table 5. Among newly started patients, citalopram had a slightly higher rate of concomitant medication use (46.1%) during treatment days on the study agent compared to patients started on fluoxetine (39.7%), sertraline (38.6%), paroxetine (42.8%), and venlafaxine (45.7%). Of the study agents, only venlafaxine XR had a higher rate of concomitant use (47.6%), compared to citalopram.

Mean CPD of concomitant agents used during treatment

---

**TABLE 2** Mean Treatment Days (Persistence) Comparison for Newly Started Patients

<table>
<thead>
<tr>
<th>Study Agent</th>
<th>N</th>
<th>Mean Treatment Days</th>
<th>P versus Citalopram</th>
<th>% of Patients With 120 Days or More</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>3,575</td>
<td>83.2 (99.6)</td>
<td>n/a</td>
<td>44.1</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>6,590</td>
<td>85.5 (103.5)</td>
<td>0.883</td>
<td>48.3*</td>
</tr>
<tr>
<td>Sertraline</td>
<td>8,905</td>
<td>83.8 (103.5)</td>
<td>0.999</td>
<td>46.4</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>7,961</td>
<td>79.0 (99.1)</td>
<td>0.312</td>
<td>44.8</td>
</tr>
<tr>
<td>Venlafaxine IR</td>
<td>979</td>
<td>66.0 (84.3)</td>
<td>&lt;0.001</td>
<td>29.1*</td>
</tr>
<tr>
<td>Venlafaxine XR</td>
<td>2,535</td>
<td>80.6 (96.4)</td>
<td>0.929</td>
<td>43.5</td>
</tr>
</tbody>
</table>

* Chi-square versus citalopram, \(P<0.001\).

**TABLE 3** Mean Adherence Rates for Newly Started Patients

<table>
<thead>
<tr>
<th>Study Agent</th>
<th>N</th>
<th>Mean Adherent Days (Out of 120)</th>
<th>Adherence Rate</th>
<th>P versus Citalopram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>4,432</td>
<td>69.4 (34.3)</td>
<td>57.8%</td>
<td>n/a</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>8,208</td>
<td>68.5 (33.8)</td>
<td>57.1%</td>
<td>0.478</td>
</tr>
<tr>
<td>Sertraline</td>
<td>10,084</td>
<td>66.5 (33.9)</td>
<td>55.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>8,943</td>
<td>63.8 (33.5)</td>
<td>53.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Venlafaxine IR</td>
<td>1,482</td>
<td>55.1 (32.3)</td>
<td>45.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Venlafaxine XR</td>
<td>3,707</td>
<td>66.3 (33.9)</td>
<td>55.3%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
days for newly started patients is shown in Table 5. Patients
started on citalopram had additional mean daily prescription
costs of $0.19 related to concomitant agent use. Patients started
on sertraline had a significantly lower mean CPD for concomi-
tant agents ($0.14), compared to citalopram ($P < 0.001). There
was no significant difference in mean CPD of concomitant
agents between citalopram and any other study agent.

Discussion

Retrospective prescription claims databases are useful in
describing prescription utilization and expenditure trends with-
in drug benefit programs. In the case of SSRI prescribing within
the Texas Medicaid Program, our analyses showed that the use
of these newer generation antidepressant agents continues to
increase, both in the number of prescriptions dispensed and
the number of patients treated. The use of citalopram within the
Texas Medicaid program has increased steadily over the last 2
years, outpacing the growth in prescriptions and patients treat-
ed with other SSRI agents.

In measuring the overall impact of citalopram on the Texas
Medicaid program, we focused on making comparisons to other
SSRI agents and venlafaxine with respect to selected measure-
ments of utilization and expenditure trends. We first measured
the difference in relative product costs for the treatment with
the respective agents. We chose to compare calculated costs per
day, since a comparison could be made between agents without
regard to differences in days supply associated with each pre-
scription. We found that citalopram was significantly less expen-
sive, on a cost-per-day basis, than all other agents in 1999 and in
2000, except for venlafaxine. As a comparison, citalopram was
55% less expensive than fluoxetine during 2000 (Table 1). Mean
daily costs were also significantly lower for citalopram compared
to venlafaxine XR (36% lower), sertraline (14%), and paroxetine
(11%). These results obviously do not reflect the advent of gener-
ic fluoxetine, which was not available at the time of this study.

Cost trends need to be monitored over time as the marketplace
changes secondary to generic competition.

We found that there was no significant difference between
citalopram and the comparison agents, except rapid-release ven-
lafaxine, with respect to the mean length of treatment for newly
started patients (Table 2). This indicator is important because
length of treatment can be affected by factors related to side
effects of the medication, disease response, denial of illness, and
patient adherence, in general.15 Sclar has used the achievement of
90 days of continuous treatment as a marker of clinical response
in treating an acute depressive episode.16 The absence of a statis-
tical difference between citalopram and the comparator antide-
pressants may be an indicator that similar treatment responses are
being experienced within the Texas Medicaid Program.

Contemporary treatment guidelines for major depressive dis-
order typically recommend an increase in antidepressant dosage
within 6 weeks if the patient is experiencing an inadequate
improvement in depressive symptoms.1 Additionally, naturalistic
studies indicate that only about 50% of depressed patients receive

### TABLE 4 Percent of Newly Starting Patients Switching From Starting Agent Within 180 Days From New Start

<table>
<thead>
<tr>
<th>Starting Agent</th>
<th>Total N</th>
<th>Patients Switching (%)</th>
<th>Mean Days to First Switch (SD)</th>
<th>to Citalopram</th>
<th>to Fluoxetine</th>
<th>to Sertraline</th>
<th>to Paroxetine</th>
<th>to Venlafaxine IR</th>
<th>to Venlafaxine XR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>7,196</td>
<td>964 (13.4)</td>
<td>83.5 (51.0)</td>
<td>n/a</td>
<td>3.1</td>
<td>3.0</td>
<td>3.7</td>
<td>0.8</td>
<td>2.7</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>12,364</td>
<td>1,480 (12.0)</td>
<td>84.8 (50.2)</td>
<td>n/a</td>
<td>3.4</td>
<td>3.4</td>
<td>0.7</td>
<td>0.6</td>
<td>1.8</td>
</tr>
<tr>
<td>Sertraline</td>
<td>18,408</td>
<td>1,960 (10.6)</td>
<td>82.4 (49.8)</td>
<td>2.1</td>
<td>2.4</td>
<td>n/a</td>
<td>3.7</td>
<td>0.6</td>
<td>2.3</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>16,717</td>
<td>2,150 (12.9)</td>
<td>82.9 (50.5)</td>
<td>2.8</td>
<td>2.9</td>
<td>4.1</td>
<td>n/a</td>
<td>0.7</td>
<td>2.3</td>
</tr>
<tr>
<td>Venlafaxine IR</td>
<td>1,927</td>
<td>669 (34.7)</td>
<td>70.9* (49.2)</td>
<td>2.6</td>
<td>3.0</td>
<td>2.9</td>
<td>3.9</td>
<td>n/a</td>
<td>22.4</td>
</tr>
<tr>
<td>Venlafaxine XR</td>
<td>4,828</td>
<td>1,011 (20.9)</td>
<td>76.9 (48.9)</td>
<td>2.8</td>
<td>3.0</td>
<td>3.2</td>
<td>4.4</td>
<td>7.5</td>
<td>n/a</td>
</tr>
</tbody>
</table>

*ANOVA versus citalopram, $P < 0.001.

### TABLE 5 Concomitant Agent Use and Expenditures for Newly Started SSRI Patients

<table>
<thead>
<tr>
<th>Concomitant Variable</th>
<th>Citalopram</th>
<th>Fluoxetine</th>
<th>Sertraline</th>
<th>Paroxetine</th>
<th>Venlafaxine</th>
<th>Venlafaxine XR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly started patients</td>
<td>3,575</td>
<td>6,590</td>
<td>8,905</td>
<td>7,961</td>
<td>979</td>
<td>2,535</td>
</tr>
<tr>
<td>Percent of patients on</td>
<td>46.1%</td>
<td>39.7%</td>
<td>38.6%</td>
<td>42.8%</td>
<td>45.7%</td>
<td>47.6%</td>
</tr>
<tr>
<td>concomitant therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean concomitant therapy</td>
<td>$0.19 (0.51)</td>
<td>$0.15 (0.44)</td>
<td>$0.14 (0.43)</td>
<td>$0.17 (0.53)</td>
<td>$0.21 (0.56)</td>
<td>$0.21 (0.56)</td>
</tr>
<tr>
<td>cost per day (SD)</td>
<td>n/a</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>0.112</td>
<td>0.964</td>
<td>0.783</td>
</tr>
<tr>
<td>$P$ versus citalopram (CPD)</td>
<td>n/a</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>0.112</td>
<td>0.964</td>
<td>0.783</td>
</tr>
</tbody>
</table>
a clinically significant improvement in symptoms in a real-world setting. This, combined with a dosage increase in only about 10% of patients in this study, would suggest that patients with depression are receiving inadequate treatment.

We evaluated the adherence rate that newly started patients achieve with each antidepressant agent. Poor patient adherence is a major factor affecting successful outcomes with antidepressant treatment. Studies have shown that 28% of patients drop out of treatment within the first month, 44% by the third month, and that only 20% to 34% have 4 or more prescriptions filled within 6 months of the initial prescription. Adherence, as with length of treatment (persistency), may be affected by lack of improvement in symptoms, improvement in symptoms and failure to follow through with continuing treatment, dosing schedule, side effects or adverse events associated with taking the medication, or dissatisfaction with the care being provided by a provider or organization. Patients who have higher levels of adherence will typically achieve more positive clinical outcomes than patients who are nonadherent. Thus, the low persistence and adherence rates indicated in Tables 2 and 3 are suggestive of overall inadequate treatment outcomes among this patient population. Our analysis showed that there was not a significant difference in adherence between citalopram and fluoxetine, but all other comparator agents had a significantly lower adherence rate than citalopram (Table 3). The mean adherence rate (57.8%) that we calculated for citalopram patients during the first 120 days of therapy is consistent with typical adherence rates for antidepressant therapies. Whether these stated statistical differences are clinically significant is suggestive of overall inadequate treatment outcomes among this patient population. Our analysis showed that there was not a significant difference in adherence between citalopram and fluoxetine, but all other comparator agents had a significantly lower adherence rate than citalopram (Table 3). The mean adherence rate (57.8%) that we calculated for citalopram patients during the first 120 days of therapy is consistent with typical adherence rates for antidepressant therapies. Whether these stated statistical differences are clinically significant is suggestive of overall inadequate treatment outcomes among this patient population.

We evaluated the degree to which newly started SSRI patients switch from the starting drug to another SSRI within the first 180 days of therapy. This time frame is critical as 6 months of pharmacotherapy represents the minimum duration of successful treatment for an acute depressive episode (i.e., successful acute treatment plus a minimum continuation phase to prevent relapse). Early discontinuation of antidepressant treatment and switching to alternate antidepressants have been associated with increased direct medical costs. This measurement may be indicative of many factors, including symptom improvement and tolerability of the medication. In addition, product switching may increase the number of office visits for patients who are not well controlled on their initial agent, which has been shown to be associated with increased health services expenditures. As a general trend, across the antidepressant comparator groups, most patients did not switch to another agent (Table 4). Of the patients who were started on citalopram, 13.4% switched to a comparator agent during the first 6 months of therapy. Similar trends were seen across the other SSRI agent groups. While venlafaxine and venlafaxine XR patients had higher rates of switching than the other study agents, the majority of the switching was between the shorter- and longer-acting venlafaxine agents and not necessarily between other chemical entities. The high rate of switching from venlafaxine to venlafaxine XR might be explained either by the better tolerability of the long-acting product or the promotion of the XR form to physicians. Although these data do not address causality for a higher switch rate from venlafaxine to the sustained release product, Entsuah and Chitra, in a head-to-head comparison, found that venlafaxine XR had a significantly superior benefit-to-risk ratio of 2:1 over venlafaxine IR for the side effects of nausea and dizziness. Extrapolating from Sclar's work looking at the relationship between antidepressant switching and service utilization costs, these data may indicate increased health care costs with venlafaxine and suggest that the sustained-release form should be the only form of venlafaxine on drug formularies. The preferential use of venlafaxine XR over the immediate-release product is also recommended in practice guidelines.

As discussed earlier, the use of concomitant agents is important to consider when making economic comparisons between treatment agents, as their increased use will further increase the overall costs of the drug therapy regimen. We found that 46.1% of newly started citalopram patients used at least one concomitant agent during their treatment period (Table 5). This rate was slightly higher than most other study agents except venlafaxine XR. However, when comparing the additional costs related to the use of concomitant agents, we found no significant differences in the cost per day of treatment with these agents between citalopram and all other agents, except fluoxetine. In the case of fluoxetine, the difference in mean concomitant agent cost per day was approximately $0.05 per day per patient. While this difference is statistically significant, it is substantially less than the $1.30 difference per day per patient between citalopram ($2.36) and fluoxetine ($3.36) in 2000.

Limitations

As is common with many naturalistic studies, there are study design limitations that should be considered when making generalizations from these results. Diagnostic information and service utilization data are not available for analysis within the prescription drug claim records. The database also provides no indication of disease severity or response in symptoms or function associated with treatment. Therefore, no attempt was made to classify or control for any differences in diagnosis types or disease severity. Prescription claims included in this analysis may also represent antidepressant use for disorders other than depression. Furthermore, accurate information regarding patient eligibility periods was not available for comparison across study agent groups. While the sample sizes included in these analyses are quite robust, utilization patterns exhibited by Medicaid patients may not be generalizeable to non-Medicaid populations.

Clinical trials of antidepressants in the outpatient environment have failed to find any meaningful overall differences in efficacy or
effectiveness among agents. While studies of pharmacy claims databases do not contain information that directly reflect patient clinical outcomes or service utilization, a number of markers for this information can be used. The fact that there were no clinically meaningful differences among agents in duration of treatment, dosage increases, patient adherence, or medication switching suggests that the compared agents, with the possible exception of venlafaxine IR, are similar with regard to clinical outcomes. The switch data from venlafaxine IR to XR is consistent with reports of less tolerability with the rapid-release product. Therefore, our comparisons that identify lower costs per day for citalopram patients suggest that cost minimization may be realized with the use of citalopram within this Medicaid population.

Finally, because our analyses included available prescription claims data for the time period of 1999 to 2000, we did not include the generic version of fluoxetine in our analyses, since patent protection on brand fluoxetine was maintained through August 2001. Future studies that compare utilization and costs within this class of drugs should include generic fluoxetine in product comparisons.

**Conclusion**

Based on our analyses, citalopram has had a positive economic impact within the Texas Medicaid Program in 1999 and 2000 due to (1) its similar treatment pattern measurements and (2) its significantly lower mean costs per day associated with its use in patients. The shorter length of treatment and higher switch rate with rapid-release venlafaxine suggest poorer clinical and economic outcomes with this particular product.

**DISCLOSURES**

This study was supported by grants from Forest Laboratories, Inc., and the Texas Department of Mental Health and Mental Retardation, Inc., and was obtained by author M. Lynn Crismon. Crismon and author Michael T. Johnsrud have received honoraria to present the results of this research at scientific meetings. Crismon served as principal author of the study. Drafting of the manuscript was primarily the work of Johnsrud. Study concept and design, analysis and interpretation of data, and critical revision of the manuscript was the work of Crismon and Johnsrud. Statistical expertise was contributed by Johnsrud. The Texas Department of Human Services provided the database for analysis.

**REFERENCES**

The planned introduction of over-the-counter (OTC) loratadine (Claritin, marketed by Schering-Plough) at year-end 2002 and the proposed OTC status for omeprazole (Prilosec, marketed by AstraZeneca) brought renewed attention to the subject of prescription drug to OTC “switches.” These 2 developments alone are significant.

Total retail community pharmacy sales of loratadine were $2.25 billion in 2001. It ranked number 11, representing approximately 1.2% of total community pharmacy prescription drug sales. The total prescription antihistamine market was approximately $4.69 billion for that year, with loratadine accounting for nearly 50%. Two other second-generation antihistamines, fexofenadine (Allegra) and cetirizine (Zyrtec), accounted for 24.8% and 20.8%, respectively, of this market. Omeprazole ranked number 2 in terms of community pharmacy expenditures on prescription drugs in the United States in 2001. It had retail sales of $3.99 billion, accounting for 2.6% of the total community pharmacy prescription drug market. The combined antiulcer therapeutic category accounted for nearly $10.81 billion in prescription drug sales in 2001, or about 7% of all such sales in the United States.

This paper will focus on the regulatory background governing the change in status of drugs from prescription to OTC availability. It will also examine the mechanism of the switch process; proposed, permitted, and rejected switches; and also a number of therapeutic categories in which the switch process has, or is likely to have, a significant effect. Finally, it will review the impact of prescription-to-OTC changes on health care costs and the perspectives of managed care and the pharmaceutical industry on the switch process.

The Pharmaceutical Market

Expenditures on prescription drugs in the United States continue to rise faster than any other medical service sector. Over the past several years, prescription drug spending has risen by more than 15% per annum. These rising costs have attracted considerable attention, politically, from consumer protection groups and the health care industry. The rise in costs has not been limited to that of the prescription market. In 2000, U.S. consumers were estimated to spend $19.1 billion on OTC drugs. The OTC market has expanded significantly in the last 10 years, from an estimated $10.81 billion in prescription drug sales in 2001, or about 7% of all such sales in the United States.

This paper will focus on the regulatory background governing the change in status of drugs from prescription to OTC availability. It will also examine the mechanism of the switch process; proposed, permitted, and rejected switches; and also a number of therapeutic categories in which the switch process has, or is likely to have, a significant effect. Finally, it will review the impact of prescription-to-OTC changes on health care costs and the perspectives of managed care and the pharmaceutical industry on the switch process.
The Growth of U.S. OTC Retail Drug Sales

Source: Consumer Healthcare Products Association (CHPA)

- 77% of consumers used an OTC medication in the past year
- Consumers used OTC medications to treat 38% of all their health conditions now than they were a year ago,
- 59% reported that they would be more likely to treat their own health conditions as self-care.

Findings included the following:
- a steady increase in the number of OTC products.

Consumer choice within the OTC market has also increased. Approximately 600 of the currently available OTC products use ingredients and dosages only available by prescription 20 years ago. U.S. consumers have embraced this concept of self-care. In January 2001, the Consumer Healthcare Products Association, the trade organization that represents manufacturers and distributors of OTC medicines and dietary supplements, commissioned a survey on OTC product usage by Roper Starch Worldwide. This survey on OTC product usage by Roper Starch Worldwide.1 The survey of 1,505 adults revealed a more empowered American public.

Findings included the following:
- 59% reported that they would be more likely to treat their own health conditions now than they were a year ago,
- Consumers used OTC medications to treat 38% of all their health care problems, and
- 77% of consumers used an OTC medication in the past year (compared to 43% who consulted a physician and 38% who took a prescription medication).4

Despite these trends, OTC drugs account for less than 2 cents of every dollar spent annually on health care in the United States.2

Depending on the perspective of the study, there are conflicting arguments as to the cost savings associated with the switch-process of prescription to OTC drugs. In a study by Kline and Company, it was estimated that American consumers saved almost $13 billion a year by using medications switched from prescription-only availability to OTC status.3 Furthermore, they reported that 63% of total U.S. OTC sales in 1996 (approximately $10.2 billion) were from prescription-to-OTC-switched products and products formulated with switched ingredients. Others argue that the trend merely transfers the burden of costs from third parties to consumers.

OTC products benefit consumers in a number of ways. The switch to OTC availability means that consumers can take an OTC medication without professional oversight, using the information available on the product label; and

- new drugs if they have been approved as a result of new-drug applications for use under professional supervision.a

The Durham-Humphrey Amendment eliminated the 1938 labeling requirements for prescription drugs. Labeling needed to be directed only to the physician and pharmacist and no longer needed to meet the criteria of being understood by the ordinary individual under customary conditions of purchase and use.4 An important component of this amendment is that the same drug, at the same dose, and for the same indication, cannot be simultaneously available on a prescription and nonprescription basis. However, drugs switched to OTC status may continue to have prescription-only status for certain doses and treatment indications.b

The 1962 Kefauver-Harris Amendment further expanded regulatory requirements for drug approval.10 The primary component of this amendment is that the FDA must test that the new drugs are proven to be safe and efficacious for their stated therapeutic claims before they can be marketed.6 It also mandated a review of existing prescription and OTC drugs. Specifically, it requires proof that an OTC product is effective when used without supervision by a health care practitioner. These amendments established the OTC Drug Review panels, which evaluated more than 700 ingredients contained in OTC products for safety and efficacy.9

The Drug Price Competition and Patent Restoration Act of 1984 (Waxman-Hatch) provides for a patent extension of 3 years for drugs switched from prescription to OTC status if the company has been required to provide additional clinical trials for the switch to be evaluated.11 The period of exclusivity begins at product approval and is limited to changes in the product license supported by the new clinical study.10

Source: Consumer Healthcare Products Association (CHPA)
Mechanism of Switch

Under current regulations, there are 2 modalities by which either a new drug or a drug already approved for prescription-only sale can be exempted from prescription-only status:

- Food and Drug Administration (FDA) approval of a new-drug application supporting the use of a drug on an OTC basis. This requires submission of additional information showing that a drug is appropriate for self-administration. This information is usually submitted by a manufacturer as an addendum to the original new-drug application. However, there are no regulations to specify who may petition the FDA, so long as the petitioner provides the FDA with sufficient information demonstrating the drug’s safety and effectiveness.12

- A product is exempt if the ingredients of a product are included in previously published regulations defining the requirements for OTC sale and if the labeling of the product complies with these regulations. Panels of nongovernment experts are involved in ongoing OTC drug reviews assessing the effectiveness of drugs approved prior to 1962 (before a proof of efficacy was a requirement). These panels also review current prescription ingredients to assess appropriateness for OTC marketing. This process has approved approximately 40 former prescription-only drugs.12

Typically, a manufacturer submits results of clinical trials with issues specifically related to OTC availability. These include studies of label comprehension to assess ability to read and understand important information on the proposed label and package insert, or actual-use studies, that is, trials conducted in a manner to simulate the use of a drug without professional supervision.

Demonstration of safety and efficacy for an OTC drug includes a number of requirements that are distinct from those for a prescription drug:

- Is the condition self-diagnosable?
- In reading a product label, can the patient extract the key information necessary to use the drug properly?
- Is the OTC drug effective when used as instructed? This places a substantial onus on the patient to understand the label and determine whether or not contraindications or drug interactions apply.12

### TABLE 1 Some Recent Popular Prescription-to-OTC (Switch) Products

<table>
<thead>
<tr>
<th>OTC. Product</th>
<th>Active Ingredient</th>
<th>Manufacturer</th>
<th>Switch Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actron</td>
<td>Ketoprofen</td>
<td>Bayer</td>
<td>1995</td>
</tr>
<tr>
<td>Aleve</td>
<td>Naproxen</td>
<td>Bayer</td>
<td>1994</td>
</tr>
<tr>
<td>Axid AR</td>
<td>Nizatidine</td>
<td>Whitehall Robins</td>
<td>1996</td>
</tr>
<tr>
<td>Children’s Advil</td>
<td>Ibuprofen</td>
<td>Whitehall Robins</td>
<td>1996</td>
</tr>
<tr>
<td>Children’s Motrin</td>
<td>Ibuprofen</td>
<td>McNeil Consumer</td>
<td>1995</td>
</tr>
<tr>
<td>Femstat 3</td>
<td>Butoconazole nitrate</td>
<td>Bayer Consumer</td>
<td>1995</td>
</tr>
<tr>
<td>Gyne-Lotrimin</td>
<td>Clotrimazole</td>
<td>Schering-Plough</td>
<td>1990</td>
</tr>
<tr>
<td>Lamisil AT</td>
<td>Terbinafine</td>
<td>Novartis</td>
<td>1999</td>
</tr>
<tr>
<td>Monistat 3 Combination Pack</td>
<td>Miconazole nitrate</td>
<td>Advanced Care Products</td>
<td>1996</td>
</tr>
<tr>
<td>Motrin-Migraine Pain</td>
<td>Ibuprofen</td>
<td>McNeil Consumer</td>
<td>2000</td>
</tr>
<tr>
<td>Mycelex-7</td>
<td>Clotrimazole</td>
<td>Bayer</td>
<td>1991</td>
</tr>
<tr>
<td>Nasalcrom</td>
<td>Cromolyn sodium</td>
<td>Pharmacia &amp; Upjohn</td>
<td>1997</td>
</tr>
<tr>
<td>Nicorette</td>
<td>Nicotine polacrilex</td>
<td>SmithKline Beecham</td>
<td>1996</td>
</tr>
<tr>
<td>Nicotrol</td>
<td>Nicotine transdermal</td>
<td>Pharmacia &amp; Upjohn</td>
<td>1996</td>
</tr>
<tr>
<td>Orudis KT</td>
<td>Ketoprofen</td>
<td>Whitehall Robins</td>
<td>1995</td>
</tr>
<tr>
<td>Pepcid AC</td>
<td>Famotidine</td>
<td>Merck</td>
<td>1995</td>
</tr>
<tr>
<td>Rogaine</td>
<td>Minoxidil</td>
<td>Pharmacia &amp; Upjohn</td>
<td>1996</td>
</tr>
<tr>
<td>Tagamet HB</td>
<td>Cimetidine</td>
<td>SmithKline Beecham</td>
<td>1995</td>
</tr>
<tr>
<td>Tavist-1</td>
<td>Clemastine fumarate</td>
<td>Novartis Consumer</td>
<td>1992</td>
</tr>
<tr>
<td>Vagistat-1</td>
<td>Tioconazole</td>
<td>Bristol-Myers Squibb</td>
<td>1997</td>
</tr>
<tr>
<td>Zantac-75</td>
<td>Ranitidine</td>
<td>Warner Lambert</td>
<td>1995</td>
</tr>
</tbody>
</table>

The extent to which a product line is switched varies. For example,

- there is a complete switch in which all of the doses and all of the indications, which are currently marketed as prescription products, are taken OTC, eliminating the need for a prescription product;
- There is a partial switch in which some of the doses and some of the indications are taken OTC and some remain unchanged in the prescription form; and
- a new lower dose of a prescription product or a product with a new indication is marketed that would not require a learned intermediary’s (e.g., a pharmacist’s) intervention.

**Previous Prescription-to-OTC Switches**

As noted earlier, more than 600 currently available OTC products include ingredients or doses only available by prescription 20 years ago. Table 1 illustrates a list of recent popular switched products. A review of a number of switched products is included here to illustrate some of the issues pertaining to this matter. In addition, the literature documenting cost savings for the products is presented.

**Vaginal Antifungal Agents**

In June 1990, following petitions by several sponsors, the FDA conducted an advisory committee meeting to examine the feasibility of switching a number of vaginal antifungal agents to OTC status. This committee approved the OTC use of 7-day treatment courses of clotrimazole and miconazole for candidal vaginitis. Subsequently, several other prescription antifungal medications were switched to OTC status. A number of studies have investigated the impact of these switches. Gurwitz et al. examined switch-related changes to the use of prescription drugs, professional services, and laboratory services for a one-year period after clotrimazole was switched from prescription to OTC status. They examined the database records of 50,000 Health Maintenance Organization (HMO) enrollees, and they noted a significant decrease in the number of prescriptions dispensed for vaginal antifungal agents (6.42 per 100 female members age 11 years or older). A decline in the number of physician visits (0.66 per 100 members) and laboratory charges were also noted for female enrollees. On the basis of these changes, it was estimated that, in one year, the HMO saved approximately $42,000 in medication costs. Depending on the assumptions made about foregone laboratory tests and physician visits, the HMO saved an additional $13,000 to $26,000. This study concluded that the prescription-to-OTC switch of vaginal antifungal treatments reduced health care costs to the insurer in the managed care setting. However, the authors also noted that these favorable effects on costs should be weighed against shifts in medication cost to consumers and potential adverse consequences to the patient relating to errors in self-diagnosis.

In 1999, Lipsky et al. corroborated the findings of Gurwitz’s study. Using National Ambulatory Medical Care Survey data, they documented a 15% decline in the number of visits to practitioners for vaginitis from 1991 to 1994. This, they theorized, could be potentially attributed to the availability of OTC antifungal preparations. Using a rough estimate of $61 per physician office visit, this decrease amounted to more than $45 million in direct cost savings per year. An additional saving of $18.75 million could be attributed to savings in indirect costs associated with time lost from work when visiting a physician.

In a study published in 2000, Ferris et al. concluded that women who self-diagnose and use an OTC product for the treatment of presumed vulvovaginal candidiasis frequently do not have that condition. Neither a history of a previous clinical-based diagnosis of vulvovaginal candidiasis nor reading the package label helped women to accurately self-diagnose vulvovaginal candidiasis. They concluded that ready access to these products is associated with wasted financial expenditures and a delay in a correct diagnosis for a substantial number of patients. The authors noted that the sale of antifungal preparations almost doubled since being approved for OTC status. This occurred despite little evidence of a concomitant increase in the incidence of candidal vaginitis. This they believed strengthened the position that these products may be overused, particularly in those patients for whom the initial diagnosis of a candidal infection was not established.

**Histamine-2 Receptor Antagonists (H2RAs)**

Famotidine (Pepcid AC) was the first of the H2RAs to be switched to an OTC status, in April 1995. Three other agents from this class—cimetidine, ranitidine, and nizatidine—were also switched within the ensuing year. In each case, the manufacturers pursued a dual marketing strategy for their products, that is, continued prescription availability of the product for the existing doses and indications and a new OTC status at a lower dose for the symptomatic relief of heartburn, acid indigestion, and “sour stomach.”

The switching of agents within this product class provoked significant debate. Of primary concern was the potential for increased patient morbidity and mortality due to widespread indiscriminate use of these agents. Specifically, there was the potential for these agents to mask symptoms of severe disease such as cancer, thereby delaying patient presentation to physicians. However, a link between the use of H2RAs and gastric or esophageal cancer has not been established.

The economic savings to managed care organizations (MCOs) and patients have been investigated in a number of studies. Kunz et al. estimated that the OTC availability of H2RAs would result in $6 million savings over a 5-year period for a 260,000-member managed care organization, that is, a 25% reduction in the overall cost of treatment of nonsevere heartburn and nonulcer dyspepsia. Estimated savings were based on the avoidance of unnecessary physician visits, laboratory tests, and prescriptions. Similar savings were noted in a study investigating the impact of OTC availability of H2RAs on medication and health care utiliza-
tion patterns among chronic users of H$_2$RAs in a health maintenance organization. Kalish et al. assessed the societal costs associated with the treatment of initial dyspepsia prior to and subsequent to the OTC availability of the H$_2$RAs. Costs to both the patient and the MCO were identical, regardless of the status of the product ($204/$203 and $149/$149, respectively). This finding was based on 2 assumptions: that the efficacy of the H$_2$RAs in the treatment of initial dyspepsia is similar to that of the antacids and that there would be an increase in physician-ordered diagnostic tests following symptom-relief failure on OTC H$_2$RAs.

### 2. Emergency Contraception

Considerable attention was given to the issue of emergency oral contraception (EC) in 2001. Currently, there are 2 FDA prescription-approved products (Preven and Plan B) for emergency contraception. Medical and legal commentators argued that under long-standing federal legislation, the FDA is authorized and should be required to switch EC to OTC status without delay. Experts predicted that widespread access to EC could prevent up to half of the 3 million unintended pregnancies in the United States each year. They argued that the designated EC products meet all the criteria for OTC use: low toxicity, no potential for overdose or addiction, no risk of causing birth defects, no need for medical screening, self-identification of need, uniform dosing, and no important drug interactions; that is, that there is no medical reason for the prescription status of EC. In February 2001, the Planned Parenthood Federation of America and 56 other organizations filed a citizen's petition to the FDA to request a switch from prescription to OTC status for Preven and Plan B and any new drug eligible for filing an abbreviated NDA because of equivalence to these products.

### 3. Second-Generation Antihistamines

The prescription antihistamine market is lucrative and growing. In 2001, sales of these agents totaled $4.69 billion, an increase of 22.4% ($3.74 billion) from 2000. Three of the nonsedating antihistamine class agents, loratadine (Claritin), fexofenadine (Allegra), and cetirizine (Zyrtec), accounted for more than 96% of this market and ranked at numbers 11, 22, and 31, respectively, in terms of year-2001 total retail community pharmacy sales. In a landmark case, WellPoint Healthcare, Inc., the parent company of Blue Cross of California, petitioned the FDA in July 1998, to exempt a number of second-generation antihistamines, notably cetirizine, fexofenadine, and loratadine, from prescription requirements. WellPoint proposed the following arguments in favor of its petition:

- The second-generation antihistamines have favorable adverse-event profiles over the traditional OTC antihistamines and decongestants in terms of sedation and anticholinergic profiles.
- Patients are being deprived of access to quality pharmaceutical care.
- Patients are currently being exposed to more dangerous and less tolerable OTC antihistamine products.

---

### 1. Proton Pump Inhibitors

In June 2002, the joint Nonprescription Drugs Advisory Committee (NDAC) and the Gastrointestinal Drugs Advisory Committee reversed an earlier October 2000 decision by voting 16 to 2 in favor of an OTC status for Prilosec. This OTC status was approved for a dose of 20 mg daily for 14 days for the prevention of symptoms of frequent heartburn and was conditional, based on certain OTC label revisions and the completion of a patient-label-comprehension study. Continued concern was voiced in relation to the suitability of the proton pump inhibitor agents for OTC use, and, in particular, the potential link between proton pump inhibitor therapy and the proliferation of preexisting esophageal adenocarcinoma. Prilosec 10 mg, 20 mg, and 40 mg capsules would continue to be marketed as prescription products for their existing indications. Prilosec, with 2001 sales of approximately $4 billion ranked number 2 in U.S. retail sales.

The Prilosec patent expired in October 2001, but its availability as a generic drug was held up by litigation.
• It places undue time and financial constraints on patients by requiring them to schedule an office visit to obtain a safe mediation.
• It trivializes the patient-physician relationship.
  They cited that, based on recent historic precedent, the cost of the OTC version of the drugs would be 50% of the prescription drug cost. WellPoint has also stated that it would save $45 million a year if the drugs were available OTC.31
  The petition by WellPoint was initially opposed by a number of parties, including Schering-Plough, the maker of Claritin. The company stated that it believed that there was not an adequate basis to support the OTC use of the drugs being considered. This is in spite of the fact that Claritin and Zyrtec were, at that time, approved in 80 countries as nonprescription allergy drugs. Schering-Plough made the following allegations:
  • The WellPoint petition lacked the data to support an OTC switch.
  • Self-care and self-treatment are often inappropriate.
  • Further labeling was required to ensure safe and effective OTC use, and this could not be developed without further study.
  • While safety was generally established, there was a need for further study to establish safety in the OTC setting without physician supervision and in at-risk groups of patients.
  • The switch would cause cost shifting to patients that would reduce access to care.
  • The physician role is critical to optimal patient care.
  • Allergies may be a complex disease.32
  The Pharmaceutical Research and Manufacturers of America (PhRMA) supported this position, asserting that
  • the FDA did not have the statutory authority to switch a drug over the objection of the NDA holder and without following the adjudicatory hearing processes set forth in section 505(e) of the Food Drug and Cosmetic Act,
  • a forced switch would violate the NDA holder’s proprietary rights to its safety and effectiveness data, and
  • forced switches would represent poor public health policy.13
  The switch of the second-generation antihistamines to OTC status was also strongly opposed by the American Academy of Allergy, Asthma and Immunology.34
  Its position regarding the proposed switch was based on the following arguments:
  • It would result in reduced availability of these medications to patients who currently receive them through insurance-covered formularies.
  • It would eliminate the role of the physician, with the potential for overuse of these agents in conditions for which there is no proven efficacy and underutilization in appropriate allergic disorders. This would be associated with increased health care costs.
  • Allergies are not necessarily self-diagnosable. Whereas public surveys indicate that up to 75% of U.S. consumers feel that they have allergies, the actual prevalence in the United States is 20% to 30%.
  • It trivializes allergies, possibly leading to a delay in the diagnosis of other conditions.34
  The Academy argued that it was clear that the real motive is the fiscal bottom-line of the insurance companies. Countering this, it was alleged that the reason for physician opposition to the switch was in part financial, with some physicians expected to experience significant losses due to loss of revenue from office visits.35
  On May 11, 2001, the NDAC and the Pulmonary and Allergy Drugs Association of the FDA voted to recommend that the agency switch Claritin, Allegra, and Zyrtec to OTC status.36 This prompted a swift response from the pharmaceutical industry. Robert J. Spiegel, chief medical officer of Schering-Plough, stated that they “strongly believed that Claritin should remain a prescription product,” and that “the prescription status of these medications is necessary to protect and optimize public health.” They also asserted that significant legal and public policy issues would be raised if the FDA were to require such a switch without drug sponsor’s support.37
  By March 2002, with the imminent patent expiration of Claritin in December, Schering-Plough had rethought its policy in relation to OTC Claritin. In a company newsletter, Richard W. Zahn, president of Schering Labs, the U.S. prescription pharmaceutical marketing arm of Schering-Plough, announced that “with the market introduction of Clarinex”…”moving Claritin” to OTC status would give Schering-Plough an opportunity to establish brand leadership in both the prescription and OTC categories.”38
  He stated that “rapid market acceptance of Clarinex and the proposed conversion of Claritin to OTC status represents a strategic business and medical decision designed to address potential changes in the regulatory, health, and legal environment,” that it allowed the “introduction of a safe second-generation antihistamine in the OTC marketplace,” and that it would “position these products as the premier brands in the prescription and OTC categories” and would serve to “maximize the combined value of the Claritin and Clarinex brands.” Consistent with previous arguments of the company, he noted that “it is the continued medical position of the company that allergies are a complex disease often requiring physician management and oversight,” a niche it is presumed that Clarinex will conveniently fill.
  WellPoint announced that it planned to steer allergy patients from prescription medications to OTC drugs, causing a major dilemma for Aventis and Pfizer, the manufacturers of Allegra and Zyrtec.39 It announced that it would raise copayments on Allegra and Zyrtec to $30 to $40 per month, up from $17. Besides increasing the copayment, WellPoint signaled its intent to not cover Allegra or Zyrtec unless Claritin does not work for a patient. Coverage of Clarinex was uncertain. Other insurers were expected to follow suit. Faced with higher copays, patients may choose to switch to the cheaper, OTC Claritin. There is an expectation that the companies may be required to launch OTC versions of their drugs long before their patents expire in 2013 and 2007, respectively.
At the time of preparation of this manuscript, Schering-Plough had not announced the price it intended to charge for OTC Claritin, but it was expected that uninsured consumers would benefit substantially because the price is expected to drop significantly from the current prescription price of $80 to $90 per month. It was predicted that the price of Allegra, Claritin, and Zyrtec would drop by as much as 80% when switched to OTC status. This would make them comparable in price to other existing OTC antihistamine products. As a final complication to the picture, 2 other drug companies, units of Johnson & Johnson, Inc., and American Home Products Corp., had filed applications with the FDA to market generic OTC versions of Claritin. Schering filed a lawsuit arguing that the generics violate a separate patent that does not expire until 2004.

The switch of the second-generation antihistamines is expected to have a significant impact on the U.S. market for OTC cough and cold remedies. This market had contracted, falling by 2.7% in 2000 following strong sales in 1999, to a value of $3.9 billion. Reasons cited for this decline included a mild winter and the growing popularity of prescription medications on which substantial sums had been spent on direct-to-consumer advertising. Led by the prescription-to-OTC switch of Claritin, the market is now expected to grow 14.5% to a value of $4.5 billion by 2005, with the expansion of the antihistamine component of the sector by 36.6%, for a projected market size of $734.4 million.

Unapproved OTC Switches

OTC status has been rejected for a number of products. For example, in 1994, OTC status for oral acyclovir for the treatment and suppression of genital herpes was rejected at a joint meeting of the FDA and the Antiviral NDAC. Although the committees appreciated that concerns existed in relation to self-diagnosis, misdiagnosis, misuse, and safety, the switch was rejected on the grounds that it would give precedence for the OTC use of other anti-herpetic agents, hastening the development of viral and accelerated microbial resistance.

In July 2000, the FDA’s NDAC, together with the Endocrinologic and Metabolic Drugs Advisory Committee, rejected requests by Merck for its agent lovastatin (Mevacor) and by Bristol-Myers Squibb for pravastatin (Pravachol) to be sold OTC. In issuing the rejection, the panel said that it had not been demonstrated that these products could be used safely and effectively in the consumer setting. Pravachol, with 2001 sales of $1.42 billion, ranked number 17 in terms of U.S. 2001 retail sales. Its patent is scheduled to expire in January 2003.

Effect of Prescription-to-OTC Switches on Health Care Costs

In addition to the studies mentioned on cost savings estimated from switching products from prescription to OTC status, the following study published in 2002 by Gianfrancesco et al. illustrates economic implications of the switch process. The authors examined out-of-pocket health care costs and medical service use for 4 products newly switched from prescription to OTC status: cromolyn sodium (Nasalcrom), tioconazole (Vagistat), ketoconazole (Nizoral), and terbinafine (Lamisil) and for 3 different insurance scenarios: indemnity/managed care plan, Kaiser Permanente HMO, and Maryland Medicaid. They noted that prescription charges for all 4 products were much higher than OTC retail prices. However, for persons who had prescription drug coverage, out-of-pocket payments for the prescription products were far less than the OTC prices. For all 4 products and all 3 insurance plans, consumer drug costs at point of purchase were higher when products were obtained OTC. Costs ranged from 2% to 113% below consumer OTC costs for the indemnity/managed care plan and 54% to 233% below for the HMO. The greatest difference obviously was for Medicaid, for which copayments were miniscule. The effect on medical service use varied by product. However, it appeared that OTC approval was associated with elevated rather than reduced medical service use. They suggested that users of cromolyn and tioconazole experienced more-costly visits after OTC approval. This, they postulated, would be consistent with complications resulting from self-care or due to more-costly visits resulting from non–self-treatment by patients because of increased out-of-pocket expenses.

The combined effect of increased out-of-pocket medical expenses and out-of-pocket drug costs contributed to higher out-of-pocket health care costs for all categories of consumers. From the perspective of the third-party payer, savings were noted for all insurance plans for these products despite the increase in medical services utilization.

The Perspective of Managed Care on Prescription-to-OTC Switches

Approximately 75% of Americans have prescription drug coverage. As noted earlier, Americans without prescription drug coverage generally benefit from the switch process since OTC prices of the switched products are generally lower than the previous prescription prices. The American Medical Association has stated that while it is in favor of drugs that are appropriately switched from prescription status, there is a concern that the effect of out-of-pocket expenditures may reduce the availability of these products to patients. For this reason, it actively advocates for the provision of drugs for medically indigent populations, including the payment by Medicaid for OTC drugs when they are the drugs of choice.

In recent years, MCOs have investigated the possibility of extending coverage to OTC products. It is thought that in doing so, they would encourage the use of these medications in preference to their higher-cost prescription counterparts. Results of MCO pharmacy director surveys for the year 2000 suggested that, among MCOs, Medicaid had the most liberal OTC policy, with 11.5% of plans covering all OTC products and nearly 81% covering selected products. Some OTC coverage was reported for 80.6% of commercial/group plans and for 87.9% of Medicare plans. According to a 1999 Novartis Pharmacy Benefit Report, only 32.4% of plans covered selected OTC products. Similarly, only 31.5% reported continued coverage of products switched for non–self-treatment by patients because of increased out-of-pocket expenses.
The Industry Perspective on Prescription-to-OTC Switches

From a pharmaceutical industry perspective, having a monopoly on the prescription market is preferred. However, the OTC sector, while less profitable than the prescription market, is evidently still viewed as being immensely profitable by the industry. In its first year of sales after an April 1995 switch to OTC status, Pepcid AC had sales of more than $200 million, making it the most profitable switch of its era. 49 In 1996, Warner-Lambert spent $125 million in a marketing blitz of Zantac 75, the OTC version of Zantac, the world’s largest selling prescription drug at the time. 49 Companies market the drugs accordingly, with budgets of $50 to $100 million allocated to many new OTC products. 50 Marketers are taking a dual strategy—marketing directly to consumers and persisting in detailing physicians in order to gain advantage from additional credibility of an OTC recommended by a physician. Warner Lambert was estimated to have spent $11 million in detailing physicians about OTC Zantac 75. 49

If a drug is switched to OTC status prior to patent expiration, it can be difficult to maintain the same market share and profit levels. Drug manufacturers typically do not submit their own product for consideration for OTC status until a patent is close to expiration. Recouping the expense of research and development of a product and the payment of FDA fees ($937,000 per dosage per drug for 5 years) are factors. 31 In a study published in 1999, Christopher Hollenbeck presented a model of the effect of generic competition on prescription-to-OTC switches. 32 He concluded that it was in the best interest of the pioneer company to keep its drug in the prescription market for as long as possible in order to maximize its monopoly profits and to reveal harmful side effects. He noted that the best time to switch a product is just before the patent expires so that the pioneer has a period of marketing exclusivity to build brand loyalty and name recognition in the OTC market. While elasticity of demand and per-unit prices may be higher in the prescription market, total quantity demanded may be much higher in OTC, where access is less limited and the costs of obtaining the drug may be lower. A pioneer drug manufacturer may switch its prescription product to OTC status as a response to generic entry if it believes the holder of the generic will apply for the switch if it does not. The belief here is that within the pharmaceutical market there is “first-mover advantage,” which is defined as product differentiation advantages that allow the first firm in the market to charge high prices and maintain significant market share despite subsequent market entry by competitors.

Managed care is another factor that influences pioneer drug manufacturers in deciding to move a drug from prescription to OTC status. In particular, MCOs commonly attempt to contain costs by allowing full or partial reimbursement only for generic versions of prescription drugs that have lost patent protection. As managed care generally does not cover OTC preparations, these preparations are more immune to the influences of managed care policies, potentially encouraging pioneer drug companies to switch their products to OTC status once a generic prescription drug competitor emerges.
Conclusion

The prescription-to-OTC switch movement is complex and multifactorial. Forces impacting on the movement of prescription drugs to OTC status include the market expansion motives of the pharmaceutical industry, a national trend toward deregulation, the growth of the self-help movement among consumers, and cost-containment efforts by the health care industry. Actions by MCOs such as WellPoint Healthcare, Inc., signify a new aggressive trend in the switch process. As noted by Bert Spilker, former senior vice president for science and regulatory affairs of the Pharmaceutical Research and Manufacturers of America, “it is likely that many products will be proposed for such changes of status on a very frequent basis by those who have a strong self-interest in the change.” Given the number of interested parties and the monetary value of both the prescription and OTC markets in the United States, it is likely that the volume of prescription-to-OTC switches will continue to grow in the years to come.

DISCLOSURES

No outside funding supported this study. Author Patricia Harrington served as principal author of the study. Drafting of the manuscript and critical revision of the manuscript was the work of Harrington and author Marvin D. Shepherd.

REFERENCES


47. Aventis Pharmaceuticals Managed Care Digest Series. HMO-PPO/Medicare-Medicaid Digest. 2000.

48. Flowers AS, Cassard SD. Coverage exclusion of OTCs and OTC equivalents can lead to higher drug benefit costs. Presented at: 13th Annual Meeting of the Academy of Managed Care Pharmacy, April 18-21, 2001; Tampa, FL.


Learning Objectives
Upon completion of this program, the participant will be able to:

1. List 4 reasons to explain the increase in over-the-counter drug sales in the last 10 years.
2. Describe the evolution of the regulatory changes that promoted the over-the-counter drug status in the United States.
3. Cite the 2 methods by which products are approved for OTC use in the United States.
4. List the 4 requirements for switching products from prescription drug status to OTC status in the United States.
5. Recognize at least 3 examples of successful prescription-to-OTC drug switches.
6. Recall and describe why some attempts to move prescription drugs to OTC status have failed.
7. Explain the role managed care has played in switching products from prescription status to OTC status in the United States, and explain the managed care economic and health care issues for offering OTC coverage to beneficiaries.

Self-Assessment Questions
Please indicate the correct answers on the Record of Completion.

1. Which one of the following is a false statement?
   a. OTC sales have quadrupled in the last 10 years and have surpassed the increase in prescription drug sales.
   b. Approximately 600 OTC products available today were not available 20 years ago.
   c. OTC drugs are the number one choice for consumers in treating minor ailments.
   d. More than 60% of OTC sales are from products that were recently switched from prescription-only status to OTC status.
   e. OTC sales only represent 2% of the total health care costs in the United States.

2. Which one of the following is a reason for the recent increase in OTC sales?
   a. Emphasis on self-care and patient autonomy.
   b. Recent trend to contain drug costs by health care organizations.
   c. Profit interest of pharmaceutical manufacturers.
   d. Steady increase in number of prescription-to-OTC product switches.
   e. All of the above.

3. Which one of the following statements is false?
   a. OTC sales only represent 2% of the total health care costs in the United States.
   b. The Food and Drug Cosmetic Act of 1938 established the OTC category of drug products.
   c. The 1962 Kefauver-Harris Amendment established that OTC products must be effective when used without supervision by a health care practitioner.
   d. Manufacturers can receive an additional 3 years of patent protection if clinical trials are conducted for switching a product from prescription to OTC status.
   e. The 1951 Humphrey Amendment states that the same drug at the same dosage and same indication cannot simultaneously be a prescription drug and an OTC drug.

4. Which one of the following is not considered to be a requirement when considering a product for the switch from prescription to OTC status?
   a. Is the drug effective as an OTC product?
   b. Is the condition for the OTC product self-diagnosable?
   c. Will the OTC product save the public money?
   d. Is the drug safe when used as directed?
   e. Is the product label readable and understandable by the lay public?

5. Which one of the following products received a rejection from the FDA for the application of switching the product status from prescription drug to OTC?
   a. Lovastatin
   b. Ranitidine
   c. Loratadine
   d. Omeprazole
   e. More than one of the above

6. Which one of the following organizations is permitted to submit an application to move one of its OTC drugs to OTC status?
   a. Only the manufacturer holding the patent can initiate the switch.
   b. FDA can initiate the switch.
   c. A health care organization (managed care plan, insurance company) can initiate a switch application.
   d. All of the above.

7. Which of the following statements is false?
   a. The pioneer drug companies use the strategy of switching their product to OTC status in response to generic drug competition.
   b. Because of product elasticity, OTC drug products are more profitable than the same product as a prescription drug.
   c. It is in the best interest of the pioneer drug company to keep its products as prescription drugs for as long as possible because it is more profitable.
   d. Pioneer drug companies usually wait to submit an application to move one of its products to OTC status until the patent is close to expiration.
   e. Medicaid program have the most liberal prescription-to-OTC switch because drug costs are shifted from the plan to the patient.

8. Regarding the 2 methods used by the FDA to approve drugs for OTC status, which one of the following statements is not true?
   a. The manufacturer can specify in the new drug application that the drug is for OTC use.
   b. Manufacturers must submit labeling information and conduct studies on readability and comprehension of the proposed OTC labeling.
   c. Manufacturers must conduct “actual use studies” as an OTC product.
   d. If the drug product has been used previously as an OTC product in a different country, it is an easier task for the approval process.
   e. No regulations exist specifying who may petition the FDA for switching a drug from prescription to OTC status.

9. Which one of the following switched products could be considered a ‘surprise move’ due to its characteristic of being an addictive product?
   a. Monistat 3
   b. Rogaine
   c. L amisil
   d. Nicorette
   e. V agisest-1

10. Which of the following statements is false?
    a. The vast majority of managed care firms cover most OTC drugs in their plans.
    b. Some in managed care view the switch from prescription to OTC status as an opportunity to shift cost to consumers; this is reflected in the finding that only 31% of the managed care plans continued coverage of products that were switched from prescription status to OTC status.
    c. Network-model HMOs covered more ‘switched products’ than IPA- model HMOs.
    d. Raising copayments for prescription drug products may be an incentive for beneficiaries to use the switched OTC product, especially if the copayment is greater than the cost of the OTC product.
    e. Medicaid program have the most liberal coverage of OTC products.
Continuing Education
Analysis of the Movement of Prescription Drugs to Over-the-Counter Status

Date: __________________________

In order to receive CE credit for this program, you must complete this form and the Program Evaluation form in addition to completing the post-test with a score of at least 70% (forms may be photocopied). Please mail all materials to the Academy of Managed Care Pharmacy, 100 N. Pitt Street, Suite 400, Alexandria, VA 22314. To receive credit, these forms must reach the Academy of Managed Care Pharmacy by December 1, 2005. CE certificates will be mailed to your address (below) as soon as possible after receipt of the Record of Completion and Program Evaluation forms and the post-test is graded and successful completion is determined.

All information will be kept confidential; it is used only for the processing and mailing of your CE certificate. You must complete and sign this form in order to receive CE credit for attending this program.

❑ I verify that I have completed the program and post-test for “Analysis of the Movement of Prescription Drugs to Over-the-Counter Status.”

Signature: ____________________________________________

Please print your name as you would like it to appear on the CE certificate:

Last name:___________________________ First name: __________________________

Company: __________________________ State & License No: __________________________

Address: ____________________________________________

City: __________________________ State: ____________ ZIP: ____________

Daytime phone: ____________ Social security #: ____________

Fax number: ____________ E-mail: ____________

Member Type:  ❑ Active  ❑ Supporting Associate  ❑ Student  ❑ Nonmember

Post-test Answers:

1. ☐ ☐ ☐ ☐ ☐  6. ☐ ☐ ☐ ☐
2. ☐ ☐ ☐ ☐ ☐  7. ☐ ☐ ☐ ☐
3. ☐ ☐ ☐ ☐ ☐  8. ☐ ☐ ☐ ☐
4. ☐ ☐ ☐ ☐ ☐  9. ☐ ☐ ☐ ☐
5. ☐ ☐ ☐ ☐ ☐  10. ☐ ☐ ☐ ☐

The Academy of Managed Care Pharmacy is approved by the American Council on Pharmaceutical Education (ACPE) as a provider of pharmaceutical education. A total of 1 CEUs (1 contact hour) will be awarded to pharmacists for successful completion of this continuing education program. Successful completion is defined as receiving a minimum score of 70% on the post-test questions and completion of the Program Evaluation form. Continuing education certificates will be mailed to pharmacists within 8 weeks of receipt of the post-test questions and Program Evaluation form. Universal Program No. 233-000-02-005-H04 (Expiration date: 12/1/05)
Using the scale above for Questions 1–8, please rate how well you will be able to accomplish the following objectives based upon successful completion of the program.

Objectives:

1. List 4 reasons to explain the increase in over-the-counter drug sales in the last 10 years. ___

2. Describe the evolution of the regulatory changes that promoted the over-the-counter drug status in the United States. ___

3. Cite the 2 methods by which products are approved for OTC use in the United States. ___

4. List the 4 requirements for switching products from prescription drug status to OTC status in the United States. ___

5. Recognize at least 3 examples of successful prescription-to-OTC drug switches. ___

6. Recall and describe why some attempts to move prescription drugs to OTC status have failed. ___

7. Explain the role managed care has played in switching products from prescription status to OTC status in the United States. ___

8. Explain the managed care economic and health care issues for offering OTC coverage to beneficiaries. ___

Using the scale above for Questions 9–16, please indicate the number that best expresses your opinion.

9. What is your overall rating of this program? ___

10. How would you rate the pertinence of the program materials to your practice? ___

11. Please rate each of the following program aspects:
   a. Content  ___
   b. Clarity  ___
   c. Knowledge gained  ___

12. To what degree do you anticipate changes in patient care as a result of the material presented? (circle one)
    1 = No Change  2 = Significant change
    3 = 4 = 5 =

13. Please indicate the length of time it took to complete this program: (Circle selection)
    Hours: 1 2 3
    Minutes: 0 15 30 45

14. Please rate the difficulty factor for completing this CE program: (Circle selection)
    Easy  Moderate  Difficult

15. Please rate your willingness to recommend this program to colleagues: (Circle selection)
    Very willing  Willing  Not willing

16. Please indicate which venue you prefer for obtaining continuing education: (Circle selection)
    Written monograph  Slides  Videos  Internet-based
    Live sessions  Other: ____________________________

Your assistance in the evaluation process is greatly appreciated. Please return this form with the post-test answers.
Promotion of Prescription Drugs to Consumers: Case Study Results

CHRISTINA GLASGOW, PharmD; JON C. SCHOMMER, PhD; KIRAN GUPTA, MS; and KRISTA PIERSON, PharmD

ABSTRACT

OBJECTIVE: Identify key factors related to patients’ medication adherence and health outcomes after they received a prescription that they requested based on a prescription drug advertisement.

METHODS: During January 2002, 6 individuals who requested advertised prescription medications and received a prescription from their physician were interviewed. Qualitative analysis was employed to allow for preservation of individual findings and variances in effects for each subject.

RESULTS: In all, the 6 patients received 10 prescriptions. For 8 of the 10 requests (80%), the patients were given a prescription for the specific products requested. Of the 10 prescriptions granted to the patients, only one (10%) of the medications was discontinued by the patient due to lack of efficacy. In addition, one patient discontinued one of the products because it was withdrawn from the market. The results showed that individuals (a) may be willing to “just try” new therapies to see if they work better than their existing therapies, (b) appear to make decisions about the usefulness or value of the drug product after a short-term trial, (c) compare the value of the product with the out-of-pocket cost of the product after a short trial, (d) value and seek the advice of their physician about information they see in advertisements, (e) become extremely pleased when they find that the new product actually helps them, and (f) may develop favorable views about advertised prescription drug products, in general, if they had a favorable experience with the first product they requested. Some patients experienced disappointment, side effects, new challenges about how to fit the newly prescribed therapy into their lifestyle and existing drug regimen, the need for follow-up appointments with their physician, and the unwelcome challenge of how to pay for their newly prescribed therapy.

CONCLUSIONS: Each study subject had unique experiences and outcomes after asking his or her physician for an advertised prescription drug product. Both positive and negative experiences were noted. Asking for an advertised drug appears to be very quickly. Penetration, purchase frequency, consumer price, and price elasticity are all expressions of market share in the short term (i.e. measured in one-year increments or less). Over the long term, advertising also can be useful for building brand equity. Those who introduce new brands need to build the innate strength of the brand (brand equity) so that long-term momentum can be maintained when new competitors enter the market and during periods when promotional activities for the brand decline.

Due, in part, to its apparent success in the marketplace, spending on consumer-directed advertising for prescription drugs continues to grow. Figure 1 shows that spending on DTCA for prescription drugs reached $1.3 billion in 1998,
almost twice the $695 million level seen in 1996. In 1999, $1.9 billion was spent on DTCA and generated an estimated $9 billion in product sales. Expenditures for 2000 were $2.5 billion, or almost double that in 1998. It should be noted, however, that most promotion of prescription drugs in the United States still is directed toward professionals. For example, spending on DTCA in 2000 was only 2.2% of product sales compared to promotion to professionals that was 11.8% of those products’ sales.6

One of the largest and most important movements in the American marketplace is the shift toward self-care, and DTCA provides individuals with information necessary for meeting their self-care goals.7,8 In recent studies,9 consumer-directed ads were shown to help individuals make their own decisions about prescription medications and served to encourage individuals to talk with their doctors about the advertised products and the maladies they treat.

Another way DTCA may affect individuals is by encouraging people to remain compliant with their drug regimens.8,9 This implies that this type of advertising may achieve the “same kind of public health function as public health campaigns.”9 Compliance also may be impacted by the involvement of doctors in their patients’ therapies. In general, patients who have seen or heard their medication advertised and talked with their physician about the risks of the medication are more likely to take it.8

Although DTCA is seen as providing ways to build market share and brand equity for the ads’ sponsors and providing the kinds of information consumers need and want, little is known about how DTCA can affect patients’ experiences with these medications and resultant health outcomes. Some have described concerns about the effects DTCA can have on the use of prescription medications, the relationship patients have with their physicians, and the combination of these 2 factors on public health.7,10,11 For example, 49% of individuals surveyed reported that DTCA makes prescription medicine seem harmless, and 39% believed that the ads cause tension between patients and their doctors.7 In another survey, 58% of the respondents reported that advertisements make the drugs seem better than they really are, and 59% reported that the ads do not give enough information about the risks and negative effects of using the drug.11

Lisa Bero12 developed a model that outlines a number of steps where measurement of DTCA effects is needed (adapted model in Figure 2). The various steps consist of DTCA exposure, effects of advertising on the attitudes of patients and physicians, actions of patients and physicians, use of drugs and health services, and health outcomes.12 Bero identified where data already are available and areas where little or no data are available. In Figure 2, italicized items represent areas where little or no data exist. The bold-italicized areas represent the focus of our study. The lack of information and knowledge about effects that DTCA could have on patient adherence and health outcomes led us to conduct an exploratory study to look for insights that would help connect these components together and guide future research.

It is possible that patients who request and receive a prescription for an advertised drug are likely to have better adherence to this drug therapy than other drug therapies not requested. The thought is that if consumers are willing to spend time and energy on getting a prescription, then they may believe that the drug will help them in some way and be motivated to take it.9

**Methods**

During January 2002, 6 individuals who requested advertised prescription medications from their physicians were interviewed in depth to determine the type of effects their requests for the advertised drug product had on their medication adherence and health outcomes. The patients were required to meet specific criteria to be eligible for the study. Each individual...
needed to have (1) been exposed to a prescription drug advertisement, (2) requested a prescription from his or her physician as a result of exposure to the ad, (3) received a prescription based upon the request, and (4) filled that prescription and begun using it. Subjects were identified through fliers distributed at a community pharmacy in Minnesota calling for study volunteers. Only those individuals who volunteered and met all of the criteria for this study were interviewed. We estimate that the fliers were read by more than 100 individuals, but only 6 met the criteria and also were willing to participate in the study.

A list of interview questions was compiled to assist in obtaining information. We asked subjects questions to get their general impressions about prescription drug ads. More specifically, we asked them what drug or drugs they requested, what type of ad motivated them to request the medication, what their expectations were of the drug, how they are or were taking the drug, and what the outcome was of taking the medication. Subjects were given time to elaborate on any of the questions if they chose to do so.

Qualitative analysis was used to interpret the data obtained from the in-depth interviews. According to Maxwell,13 there are 5 specific “research purposes” that are well suited for qualitative analysis. These include comprehending the meaning of “events, situations, and actions” of study participants; understanding the context of people’s actions and the influence this has on them; discovering unexpected trends and effects; recognizing the process of events and actions; and developing underlying reasons for actions.13 Qualitative analysis was selected for this study to determine if and how DTCA may affect different people’s medication adherence and health outcomes related to the prescriptions they received. This type of design allowed for preservation of individual findings and variances in effects for each subject. It also permitted any unexpected trends to appear and helped to get a deeper understanding of each subject’s thoughts. Specifically, a qualitative interviewing approach was used to describe and interpret the results.14

### Results

A total of 6 people participated in the study: 5 were female (83%) and one was male (17%). All participants requested a prescription drug or drugs that they saw or heard about in an advertisement for the products. Specific drugs requested and received are listed in Table 1. The analytical approach we employed viewed each of the study subjects as a unique case for evaluation. The interview with each subject is described next. In such a case approach, both trends and unique aspects of the study subjects’ interviews are reported.

#### Study Subject 1

Subject 1 requested the drug Fen-Fen from her physician. The patient had seen a television ad for this product that promised to decrease appetite and help with weight loss. The patient stated that she hesitated to request the drug from her doctor because of uncertainty about whether the physician would
made the appointment to specifically ask about this product because her allergy symptoms were bothersome at the time. The patient described the relationship with her physician as “formal” and said that there was a definite sense that she was the patient and her doctor was the decision maker. Despite this, her physician wrote her a prescription for Claritin-D. She expected that the medication would eliminate her symptoms of itchy, watery eyes without making her drowsy. Her physician instructed her to take the medication only as needed, and she faithfully took it every day in the spring and summer when her symptoms were most bothersome. She reported that she is very compliant with her other medication regimens and that the Claritin-D greatly helped to reduce her allergy symptoms. If she were to run across an ad for another drug she felt would help her, she would feel comfortable requesting that drug, but she would seek advice from a different physician next time.

Study Subject 4

Subject 4 requested the drugs Ultram, Vioxx, and Ambien from her physician. She was introduced to these medications through ads and articles in a fibromyalgia newsletter and through television ads. Feeling that her fibromyalgia pain was well controlled and that she was not sleeping well, she made a follow-up appointment to address her pain and sleep issues and to ask about these products. The patient revealed that she feels very comfortable discussing her condition and medication issues with her doctor, so she did not hesitate to ask about the 3 drugs. Her physician gave her prescriptions for Ultram and Vioxx but not for Ambien, explaining that if her pain was better controlled at night, she would be able to sleep better without the need for a prescription. She expected Vioxx to help prevent pain during the day and Ultram to provide pain relief at night. She reports that she took Vioxx every morning for about 3 or 4 days. However, it did not seem to help as well as her previous pain therapies, and she felt very restricted in what she could take during the day since her doctor instructed her not to mix her other pain medications with Vioxx. Because of this, she resumed her previous daytime pain therapies, which she could take on an as-needed basis. As for Ultram, she was very pleased with its effects. She continues to take it as needed for pain at night and reports good relief. This patient also takes prescription medications for other conditions and denies forgetting or skipping doses of the other drugs.

Study Subject 5

Subject 5 requested Denavir and Effexor XR, one product from each of his 2 physicians. He learned about Denavir from an Internet ad and Effexor XR from a magazine ad. He has been seeing his primary physician for many years and called this doctor to request a prescription for Denavir over the telephone. According to this patient, his doctor knows his medical history very well, so the physician was happy to prescribe the cold sore medication. The patient stated that he had no expectations of actually prescribe it. However, she had made an appointment for a different purpose and thought that it was a good opportunity to ask about Fen-Fen. The physician prescribed the drug at this visit, and the patient began to take it along with her other prescriptions. The patient stated that she had expected to lose weight while taking this medication. However, she reported that it did not work because she was not able to take it long enough before the drug was withdrawn from the market. She stopped taking the medication and did not pursue any other alternatives.

Study Subject 2

Subject 2 requested the medications Ortho-Tri Cyclen and Allegra-D from her physician. She had been exposed to these products from both television and magazine advertisements and was able to accurately describe phrases and specific characteristics of each ad. The patient felt very comfortable asking her physician for both products because she believed that she would benefit from taking them. She made an appointment specifically to request these medications and succeeded in receiving prescriptions for both drugs. The patient reported that she expected the Ortho-Tri Cyclen to regulate her menstrual periods and clear up her acne and the Allegra-D to decrease her allergy symptoms. She stated that she takes the Ortho-Tri Cyclen very regularly and only forgets “once in a while” and takes the Allegra-D only as needed for seasonal allergy symptoms, as directed by her physician. Both medications work well for her and have met her expectations of what they would do for her conditions. She was very satisfied with her health outcomes and would request a medication based on information presented in an advertisement again if she felt it would benefit her.

Study Subject 3

Subject 3 requested Claritin from her physician. She learned about this medication from a television ad, and she remembers the image of the actress “blowing dandelions” in the ad. She...
this medication. He just wanted to “try it” to see if it would help. He reported that he used it exactly as his doctor instructed, and it shortened the duration of his cold sore symptoms by approximately 3 days. The request for Effexor XR was directed to his psychiatrist. The patient read about this product in a magazine ad he found while in the waiting room at his doctor’s office. He showed the physician the ad and discussed the medication with him. After a thorough discussion with the doctor, the patient was given a prescription for Effexor XR to replace his prescription for Wellbutrin SR to treat his depression and anxiety. After he began taking Effexor XR each morning, he experienced a “groggy” or “cloudy” feeling. He spoke with his psychiatrist about this and was instructed to take the medication in the evening instead. This change greatly helped eliminate the goggy feeling during the day, and he has been faithfully taking this drug in the evening ever since. However, if his doctor had told him that he needed to take it in the morning, he felt that this unpleasant side effect could have decreased his adherence to this regimen, and he would have requested another change in therapy.

Study Subject 6

Subject 6 requested the drug Nexum. She saw the product advertised in magazines and on television and used a coupon in a magazine for a 7-day trial. She had been having problems with her “reflux disease” and thought that Nexum might help to alleviate it. In order to request this prescription, she called her doctor on the telephone since the physician knew her history very well. However, she stated that she would have made an appointment to specifically ask for the drug if the physician had required her to be seen. She expected this medication to reduce her heartburn symptoms, and after receiving a prescription for Nexum, she reported that it “completely eliminates” her heartburn. Her physician instructed her to take one capsule each day. However, since she did not have prescription insurance to reduce the high cost of this drug, she did not take any for about one week. Her symptoms returned, and she resumed her daily regimen despite the high cost. As for her other prescription medications, she seems to be rather compliant. This patient was extremely satisfied with her response to the medication, and she reports that she would ask for an advertised prescription drug again in the future if it seemed appropriate for her.

Insights Gained From Qualitative Analysis of the 6 Cases

In all, the 6 patients requested 10 prescriptions. For 8 of these requests (80%), the patients were given a prescription for the specific product they requested. Of the 2 remaining requests, one of the patients was given Claritin-D instead of Claritin, and the other prescription request for Ambien was denied (Subject 3). This request was refused because the physician felt that the other 2 medications that this patient requested would help control her pain at night so that she would not need a medication to help her sleep.

Some individuals in our study learned about advertised medications via multiple advertising sources, and others relied upon just one source of information. The most common sources of information were through television advertising and magazine/newsletter advertising. Only one of the prescription requests resulted from information discovered on the Internet.

Of the 10 prescriptions granted to the 6 patients, only one of the medications was discontinued by the patient due to lack of efficacy and because it did not meet her expectations (Subject 3, Vioxx). A patient discontinued one of the other prescriptions because the drug was withdrawn from the market (Subject 1, Fen-Fen). Another patient needed to adjust the time of day he was taking his requested medication (Subject 5, Effexor XR). This alteration increased the patient’s satisfaction with the drug’s effects. Four of the requested medications are taken only on an as-needed basis, and all patients taking these drugs understood when they needed to take them and were satisfied with their outcomes.

Discussion

This exploratory study serves to help understand consumer-directed advertising’s impact on consumers/patients. The results showed the complexity and unique characteristics each study subject presented. For some patients, consumer-directed advertising can help them find a prescription drug therapy that meets their health care needs extremely well. Quick diffusion of helpful therapies to patients who need them is useful to promote the health of individuals and society. Such positive experiences would lead these individuals to again request a medication based on information contained in an advertisement in the future.

However, all that glitters is not gold. In our case analysis, we found that some patients experienced disappointment, side effects, new challenges about how to fit the newly prescribed therapy into their lifestyle and existing drug regimen, the need for follow-up appointments with their physician, and the unwelcome challenge of how to pay for their newly prescribed therapy after price-related promotions (e.g., coupons) no longer applied. Also, for one of our subjects, it appeared that the process of requesting an advertised drug product revealed the formality of her relationship with her physician that would lead her to seek advice from a different physician in the future. These challenges are significant and serve to highlight the importance of not only drug product selection and utilization patterns that DTCA might influence but also aspects of drug product use by patients including adherence, clinical outcomes, affordability, new monitoring requirements, and the opportunity to change the new therapy if it is not satisfactory to the patient.

Other insights were gained through the in-depth interviews. Most of the patients were comfortable with asking their health care providers about advertised prescription drugs. It appears that patients had good relationships with their physicians and were encouraged to discuss various health issues. Also, it could be because consumers are taking a more active role in their own

Promotion of Prescription Drugs to Consumers: Case Study Results

516 Journal of Managed Care Pharmacy JMCP November/December 2002 Vol. 8, No. 6 www.amcp.org
health care. They may feel that if there is a chance that they could benefit from an advertised product, they will not hesitate to ask for it, no matter what type of relationship they have with their physicians. As one study subject put it, “I just wanted to try it to see if it would help” and then go from there. The cost implications of such an approach to prescription drug use are not known. More research is needed to understand if such trials of therapy lead to benefits that are worth the associated costs such as cost of the medications, follow-up, monitoring, and any costs associated with therapy failures.

Television and magazine advertisements were the principal sources for prescription ad exposure. This is not surprising since our society heavily utilizes these resources for entertainment and information purposes. Therefore, it is obvious why these sources may have the greatest ability to impact a larger proportion of consumers. It was interesting to note that one of the study subjects saw a print advertisement in his physician’s waiting room and decided to talk to the doctor about the medication since he was there anyway.

Our study was exploratory and utilized only 6 study subjects. Our goal was to use in-depth interviews with carefully selected cases to help us gain new insights and understanding about the effects consumer-directed advertising could have on individuals. The purpose of our study was to identify key factors related to patients’ medication adherence and health outcomes after they received a prescription that they requested based on a prescription drug advertisement. We learned that individuals (1) may be willing to “just try” new therapies to see if they work better than their existing therapies, (2) appear to make decisions about the usefulness or value of the drug product after a short-term trial, (3) compare the value of the product with the out-of-pocket cost of the product after a short trial, (4) value and seek the advice of their physician about information they see in advertisements, (5) are extremely pleased when they find that the new product actually helps them, and (6) may develop favorable views of not only the product they received (brand equity) but also about advertised prescription drug products, in general, if they had a favorable experience with the first product they requested.

The factors we identified, combined with the movement to more self-care by patients, could affect how patients will comply with prescribed therapies and evaluate the outcomes from these therapies. Patients might be willing to change therapies after a relatively short trial if they believe that there are other alternatives to try, based on information they receive through advertising. Quite often, new therapies may be advertised directly to consumers as a means to hasten the adoption of the new therapy. It is likely that there are patients who would like to try “what’s next” in therapy and would ask their physician if the new therapy might be an improvement over what they currently are taking. In marketing terms, these individuals are called “Innovators” or “Early Adopters”; they can play important roles in how new innovations are tried and adopted by the overall population (e.g. positive word-of-mouth endorsements to others).

These findings have practical implications for patient care and prescription drug use. Some patients take an active approach to their health care and ask their physician to prescribe a course of therapy that might benefit them. We interpret our findings to suggest that some patients and physicians work together to form a negotiated course of action that meets the patient’s needs and is deemed reasonable by the physician. Such an approach to the prescribing and taking of medicines has been called concordance.

In future research, concordance might be a more relevant perspective to take than the traditional notion of compliance. Concordance is an agreement reached after negotiation between a patient and a health care professional that respects the beliefs and wishes of the patient in determining whether, when, and how medicines are to be taken. Although reciprocal, this is an alliance in which health care professionals recognize the primacy of the patient’s decisions and perceptions about taking recommended medications. Concordance aims to help patients and prescribers make as well-informed a choice as possible about diagnosis and treatment and benefit and risk, and to collaborate fully in a balanced therapeutic alliance to optimize the potential benefits of medical care. The growth in consumer-directed advertising for prescription drugs might contribute to the use of this new approach to decision making about prescription drug therapy as it serves as an information source for patients and prescribers.

This was an exploratory study with the aim of gaining a better understanding of consumer-directed promotion for prescription drugs through the eyes of the consumer. Our approach allowed for preservation of individual findings and variances in effects for each subject. It also permitted any unexpected trends to appear and helped get a deeper understanding of each subject’s thoughts. However, such an approach has limitations. The small sample size provides no basis for generalizable conclusions. Also, we did not measure any health outcomes via quantitative means. All data were provided by the study subjects and represent their subjective assessments. The study participants were self-selected individuals and quite likely are individuals who thought that they had an interesting story to tell. Thus, the results most likely represent interesting case studies but do not represent generalizable data. Recall bias could be problematic in this study. It is not known how long ago the study subjects had asked for and received their prescription medications. For example, Subject 1 requested Fen-Fen, which was recalled in 1997 (at least 4 years before our study was conducted). However, it appeared that the experience she had was memorable, and she wanted to talk about it with the researcher. Such “critical incidents” can provide important insights.

**Conclusion**

DTCA has a variety of effects on consumers. It is difficult to gen-

www.amcp.org   Vol. 8, No. 6   November/December 2002  JMCP  Journal of Managed Care Pharmacy  517
eralize the type of effect it has on different populations. It has been shown to influence consumers to ask their health care providers about the advertised drugs and even encourage them to request a specific prescription product. As far as its effects on patient adherence and health outcomes, more research is necessary. What we learned from this exploratory study is that each study subject had a unique experience when he or she asked his or her physician for the advertised product. Consistent with previously reported research, it appears that physicians are willing to prescribe the products that patients request or, if more appropriate, similar products. However, our findings suggest that once the patient starts using those products, the patient’s experiences with the product and outcomes achieved are quite varied.

These results can serve as a guide for quantitative research. We propose that a useful next step for research would be to categorize patients who take selected drug products depending upon how they were prescribed those products (patient-initiated request or physician-initiated recommendation) and then compare patients’ characteristics, experiences, and outcomes to measure differences. Propensity scores, or other matching techniques, could be used to help assure that the 2 groups are similar on demographic and health care variables as comparisons in outcomes are made between the 2 groups.

REFERENCES


DISCLOSURES

Funding for this research was provided by the University of Minnesota. All authors were either students or faculty at the university at the time of this study. Author Jon C. Schommer served as principal author of the study. Study concept and design and critical revision of the manuscript were the work of Schommer and authors Christina Glasgow, Kiran Gupta, and Krista Pierson. Drafting of the manuscript was the work of Glasgow, Schommer, and Pierson. Analysis and interpretation of data were contributed primarily by Glasgow and Schommer. Statistical expertise was contributed by Schommer.
EDITORIAL

Effective Cholesterol Management With Fewer Dollars

Employers, government, and health plans look to managed care pharmacists for ideas and programs to deliver the same or better outcomes at lower cost. Managed care pharmacists can look to the experience at Kaiser in Northern California in 2002 for a combination of methods to improve the efficiency of cholesterol reduction within coronary risk management. Kaiser and its 3 million members in North California use a computerized (electronic) medical record (EMR) and generic lovastatin to achieve superior clinical outcomes at lower cost for members with elevated cholesterol. In advance of the December 2001 introduction of generic lovastatin, Kaiser revised its cholesterol management strategy to start all new patients on generic lovastatin and dose lovastatin to target goal of low-density lipoprotein (LDL); atorvastatin is used only in patients who cannot tolerate lovastatin or cannot reach LDL target goal. Kaiser found that it can treat 5 patients with lovastatin for the same drug cost as just one patient on atorvastatin. The EMR and clinical practice guideline yield superior clinical results, with 60% to 70% of new patients still taking the statin at year compared to the national benchmark of about 30%. About 85% of Kaiser Northern California members on a statin drug have LDL cholesterol below 130mg/dL, nearly twice the national average of 45% and nearly 4 times Kaiser’s 22% rate in 1997. The value-for-money interventions at Kaiser extend to the use of generic beta-blockers and generic lisinopril in patients with or at high-risk of heart failure. Kaiser data also appeared to show that longer-term outcomes are superior, as measured by a 30% lower risk of death due to heart disease among Kaiser members compared to other Californians.

Tablet Splitting to Improve the Value-for-Money Equation in Cholesterol Management

In a previous issue of the Journal, Calabrese and Baldinger described a dose optimization program using pharmacy claims data to target patients in 15 drug categories to achieve $1.67 per-member-per-year (PMPM) or $0.14 per-member-per-month (PMPM) savings, in 2001 dollars, across the entire population of 234,000 members. This intervention included 3 statin drugs. In this issue of the Journal, Gee, Hasson, Hahn, and Ryono describe another value-for-money intervention involving tablet splitting of 3 statin drugs. Conducted prior to the market introduction of generic lovastatin, the researchers found that tablet splitting was associated with favorable clinical (laboratory) outcomes and humanistic-service outcomes while creating the opportunity to treat nearly twice as many patients for the same cost.

This work by Gee, Hasson, Hahn, and Ryono is at least the third published study of tablet-splitting interventions that has found favorable clinical or service outcomes attendant to significant improvement in cost outcomes. There are 2 studies that have measured the effects of tablet splitting on clinical outcomes. As noted by the authors, their work was preceded by a small study that found no significant difference in blood pressure among patients who took whole tablets of lisinopril compared to the same patients who crossed over to split tablets of lisinopril. A second study was conducted among patients who split tablets of the anticholesterol drugs simvastatin and atorvastatin, 2 of the 3 statin drugs studied by Gee, Hasson, Hahn, and Ryono. As with the current study, there was statistically significant but not clinically significant improvement in intermediate outcomes (i.e., serum lipid levels). However, unlike the work of Gee, Hasson, Hahn, and Ryono, the earlier study involved a small number of patients (N=125) and did not measure humanistic outcomes (e.g., service perception or patient satisfaction).

Another point regarding the study of Gee, Hasson, Hahn, and Ryono is remarkable. These authors recognize the important distinction between clinical analysis and statistical analysis. The relatively large study population, 519 patients in their Phase III analysis of laboratory values, contributed to findings of statistical significance for key intermediate clinical outcomes, lipid serum levels, for the tablet-splitting period compared to the prior period. Low-density lipoprotein (LDL) improved to an average 97 mg/dL in the tablet-splitting period from an average 102 mg/dL prior to tablet splitting, a relative improvement of 5% (P<0.001). While the authors correctly point out that this finding is not clinically significant, it could be of practical significance since the change could be described and construed as significant improvement according to internal and external reviews of health plan performance for quality-of-care measures. For example, the performance measure for “Cholesterol Management—Control” within the HEDIS (Health Plan and Employer Data Information Set) is defined as “the percentage of health plan members aged 18 to 75 who had evidence of an acute cardiovascular event (hospitalization for acute myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty) and whose LDL-C was screened and controlled to less than 130 mg/dL in the year following the event.” The Adult Treatment Panel III guidelines of the National Cholesterol Education Program of the National Heart, Lung, and Blood Institute released in May 2001 lowered the ideal LDL level to below 100mg/dL for “high-risk” patients. According to a standard of 100mg/dL LDL-C, the tablet-splitting intervention described by Gee, Hasson, Hahn, and Ryono, could make the difference between success and failure in the determination of a “high-performing” health plan and “failure” to manage cholesterol successfully.

Single-Patient Trial (SPT) Method—Substitute for Expert Opinion?

A remarkable 40% of patients with gastroesophageal reflux disease (GERD) treated with proton pump inhibitors (PPIs) were found by the single-patient trial (SPT) method to achieve the same or better outcomes as these patients treated with ranitidine. This work by Wolfe, del Rio, Weiss, et al. suggests that spending on drug treatment for GERD could be reduced by more than one third since histamine-2-receptor antagonists such as ranitidine cost managed care organizations (MCOs) $50 or less per day of therapy versus $45 or more per day of therapy with a PPI. All of the H2-antagonists (cimetidine, ranitidine,
famotidine, and nizatidine) were available from generic manufacturers by mid-2002. The availability of generic omeprazole, anticipated at year-end 2002 or early in 2003, would, of course, mitigate the impact of this SPT research on H₂-antagonists versus PPIs in 2003 and thereafter. However, the research method itself is intriguing and may have application for other disease conditions.

Readers will note that the authors used the Federal Supply Schedule to make their cost comparison for omeprazole versus generic ranitidine. While the prices in this schedule are not relevant to most MCOs, the relative cost difference is representative of the experience of most MCOs. Actual MCO cost-savings net of copay for the use of generic ranitidine versus (brand) omeprazole would generally exceed $2.50 per day of therapy or about $912.50 per year, greater than the $718.44 absolute savings per patient per year estimated by the authors.

Paying for Value in the Management of Multiple Sclerosis

In mid-May 2002, federal health officials announced that Medicare would cover interferon beta-1a (Avonex, Biogen) for multiple sclerosis (MS) but not 3 other commonly prescribed MS disease-modifying medications. The policy change was disclosed in a memo sent to the private health plans that are under contract to process Medicare Part B claims for the government. Effective August 1, 2002, Medicare would pay for injectable drugs that beneficiaries self-administer less than 50% of the time, according to the Centers for Medicare and Medicaid Services (CMS). The new guidance clarifies Medicare policy for determining whether a drug is “not usually self-administered” and therefore eligible for coverage under federal law. Up to this time, Medicare contractors had interpreted past guidance in varying ways, and, at the time of the announcement, CMS reported that fewer than half of Medicare carriers were paying for Avonex. The logic used by CMS in making the new coverage determination for Avonex but not the other 3 products was that Avonex is injected into muscle, allowing the presumption that it is usually not self-administered, meeting the criteria for Medicare coverage. Rival MS therapies, on the other hand, are not covered because they are administered subcutaneously and therefore eligible for coverage under federal law. Up to this time, Medicare contractors had interpreted past guidance in varying ways, and, at the time of the announcement, CMS reported that fewer than half of Medicare carriers were paying for Avonex. The logic used by CMS in making the new coverage determination for Avonex but not the other 3 products was that Avonex is injected into muscle, allowing the presumption that it is usually not self-administered, meeting the criteria for Medicare coverage. Rival MS therapies, on the other hand, are not covered because they are administered subcutaneously and could typically be self-administered by the patient. The competing products for treatment of MS at the time of the federal ruling included interferon beta-1a (Rebif, Serono SA), glatiramer acetate (Copaxone, Teva Pharmaceutical Industries, Ltd.), and interferon beta-1b (Betaseron, Chiron Corp., marketed by Schering AG's Berlex Laboratories).

There is no cure for MS, and the treatment goal centers on prevention of relapses and retarding progression of the disease. There are 4 categories of disease: relapsing-remitting (RRMS), secondary progressive (SPMS), primary progressive (PPMS), and progressive relapsing (PRMS). As with many diseases, MS patients respond selectively to drug therapy. Disease-modifying therapy available today is most effective for the RRMS form, the type of MS most common early in the disease process. All 3 of the beta interferons and glatiramer are approved by the U.S. Food and Drug Administration only for the RRMS form of MS.

In this issue of the Journal, Ollendorf, Jilinskaia, and Oleen-Burkey found a small but measurable advantage in clinical outcomes (i.e., incidence of relapse) and cost outcomes (i.e., drug cost and total direct costs of MS-related care) for glatiramer compared to 2 beta interferon products. Glatiramer requires daily dosing, while beta-1b is administered every other day, and beta-1a (Rebif) is administered subcutaneously 3 times per week. Beta-1a (Avonex) is dosed less frequently, just once per week, but is administered intramuscularly. The study by Ollendorf, Jilinskaia, and Oleen-Burkey appears to find some advantage in cost of care with glatiramer, but, interestingly, the cost savings did not stem from less laboratory testing for liver function, thyroid, and complete blood counts, an outcome that might be expected based upon product labeling. However, as the authors note, utilization of laboratory tests was low across all 3 disease-modifying agents in their study.

New Generic and OTC Drugs Provide Opportunities for Drug Benefit Managers

At year-end 2002, for the first time in history, the same strength and dose of a prescription drug was near approval by the FDA for over-the-counter (OTC) use. This milestone was made more significant by the coincident consideration of not one but 2 blockbuster prescription drugs. A decision from the FDA regarding OTC sale of loratadine 10 mg was expected on or before the end of November 2002, and the FDA was expected to approve omeprazole 20 mg for OTC sale late in 2002 or early in 2003. Both developments are significant. For loratadine, the OTC approval of the 10 mg strength could eliminate the prescription version, because under arcane FDA rules, a prescription drug cannot coexist with an OTC drug of the same dose and strength for the same indication. For omeprazole, the market effects could be presumably different since prescription omeprazole is indicated for gastrointestinal ulcers, gastroesophageal reflux disease (GERD), and “other symptoms associated with GERD,” while the OTC version of omeprazole has a narrow, tentative approval for short-term relief of “heartburn.” In the world of high-stakes marketing of prescription drugs, these are unprecedented events. At the same time, Congress was strenuously debating ways to reduce the burden of prescription drug costs for federal programs and the uninsured. The strategic acts by the maker of loratadine and desloratadine could have a negative impact on generic prescription drug competition. Harrington and Shepherd provide a comprehensive review of the regulations and developments in the marketing of OTC drugs that were previously available only by prescription.

Generic omeprazole was still not available to U.S. consumers in October 2002, one year after the patent on omeprazole expired. The manufacturer of omeprazole had reportedly invested 7 years in developing a strategy to negate the market erosion curve expected for omeprazole. The preferred method involved development of a replacement drug with superior...
properties, but the strategic planning process reportedly resulted in the creation of nearly 50 possible solutions, including legal challenges to the introduction of generic competitors. By the measure of influence on the market erosion curve of omeprazole, the investment in strategic planning was successful, as evidenced by the absence of generic omeprazole one year after the expiration of the patent on omeprazole. (The omeprazole patent expired in April 2001 but was extended to October 2001 by the conduct of a clinical study in pediatric patients.) The generic introduction of the first proton pump inhibitor (PPI) in the United States is much anticipated by pharmacy benefit managers, and the effects of the patent lawsuits are acutely obvious to managed care pharmacists. The legal challenges developed by the manufacturer of omeprazole began in 1985, 4 years before the drug was launched in the United States.\(^1\) Such legal challenges may not delay generic competition but have the minimum effect of ensuring that, when the patent lawsuits are resolved by the courts, one generic manufacturer has market exclusivity for the first 6 months. A 1984 federal law stipulates that a generic manufacturer that is challenged by a brand manufacturer in court is permitted 6 months of market exclusivity for the generic drug once the patent challenges are resolved.\(^1\)

Managed care pharmacists might be interested in some of the legal arguments made in the course of the 17-year history of patent challenges regarding omeprazole. For example, a patent complaint was filed by the manufacturer for the use of omeprazole in combination with antibiotics for the eradication of Helicobacter pylori. The argument was that physicians could not prescribe omeprazole in combination with the use of antibiotics for heartburn because this practice would violate the patent.\(^1\) A patent dispute in New York commenced in December 2001, and the trial was concluded in June 2002. Four months later, on October 11, 2002, the U.S. District Court ruled that 3 of the 4 generic manufacturers had infringed on patents related to the subcoating formulation for omeprazole.\(^1\) The court found that the fourth generic manufacturer had its own patented method for a subcoating formulation for generic omeprazole, and this manufacturer had FDA approval to market its generic omeprazole, but this was not the generic company that held the original abbreviated new-drug application and the 6 months of market exclusivity for generic omeprazole. Therefore, the U.S. District Court decision in October 2002 made the date for the introduction of generic omeprazole in the U.S. market uncertain.\(^2\) Every day that the legal dispute continued earned another $10 million in omeprazole sales.

**Direct-to-Patient Advertising (DTPA) and Direct-to-Consumer Advertising (DTCA) of Prescription Drugs**

A publishing company in St. Louis reported in mid-2002 that 17,000 community pharmacies were participating in “direct-to-patient-advertising” (DTPA) in 2002 compared to just 3,000 3 years earlier.\(^2\) The pharmacy chains that contracted with the company in 2002 included some of the largest chain drug stores in the United States. The practice of DTPA involves generation of a patient-specific “health newsletter” that is based primarily on the drug prescribed but is customized to the patient name, age, gender, and whether the patient has drug insurance coverage. While the fine print in the health newsletters identifies the drug company sponsor, this practice could undermine the ability of the pharmacist to provide unbiased counseling to patients. For the drug companies, the practice permits marketing messages to be wrapped in the patient-pharmacist interaction. Marketing promotions in the “health newsletters” sometimes included recommendations for patients using low-cost generic drugs to switch to higher-cost sustained-release versions of the same drugs. In other cases, these patient-specific newsletters targeted users of a competing company’s drug, urging patients to switch to the drug manufactured by the drug company that sponsored production of the newsletter. One billion such DTPA newsletters were expected to be produced in pharmacies in 2002, sponsored by 18 of the 20 largest U.S. drug companies, each paying as much as $10M to produce the health newsletters.

Eighteen months after the publication of federal rules that relaxed direct-to-consumer advertising (DTCA) of prescription drugs, IMS Health reported there were 40 brand-prescription drugs being advertised on television and about 100 brand drugs advertised to consumers in print and other media.\(^2\) TV advertisements accounted for $825M (55% of the total $1.5 billion) compared to $686 million for consumer-targeted print advertising. In this issue of the *Journal*, Glasgow, Schommer, Gupta, and Pierson report case-specific results of DTCA that support the results of consumer surveys.\(^3\) At least 5 consumer surveys conducted from 1998 through the first-half of 2002 have found a remarkably high reported rate of success in converting DTCA of prescription drugs into prescriptions written by physicians. By a measure that we might call the ad-to-Rx (ATR) ratio, DTCA of prescription drugs is very effective at generating new prescriptions. The ATR ratio ranges from 9% to 24%, with a modal value of about 15%.

An early study in 1998 found that 28% of the elderly who saw a drug advertised on television spoke to their physician about the drug, and 33% received a prescription for the requested drug, an ATR ratio of 9%.\(^4\) A telephone survey of 1,205 adults of all ages conducted in the first half of 1999 found that 81% of respondents had seen, read, or heard an ad for a prescription drug (versus 63% in late 1997), 28% of those who had seen, read, or heard an ad asked their physician for the advertised drug, and an amazing 84% who reported asking their physician for the drug claimed to have received the requested drug, an ATR ratio of 24%.\(^5\) A survey of 1,093 persons conducted in 2001 found that 32% of respondents had talked to their physician about an advertised drug, 26% had actually requested a prescription for the advertised drugs, and 71% reported receiving the requested drug, an ATR ratio of
about 18%. A particularly well-designed survey of 2,511 persons conducted in late 2001 found that DTCA television ads caused 30% of the respondents to ask their physician about the advertised drug, 29% actually asked for a prescription, and 44% received the prescription, an ATR ratio of 13%. A telephone survey of 943 adults in early 2002 found that 69% of the respondents who had asked their physician for a specific brand-name drug had received the drug. 5% said that a DTC advertisement had precipitated the physician visit, and 4% said they visited the physician because they wanted to obtain the advertised drug.

From a quality-of-care perspective, DTCA might have other effects. Among the aforementioned studies, about one third of respondents who had asked their physicians about a particular drug reported that they did not know the disease condition of the advertised and requested drug. Among 1,300 AARP members surveyed in May 2000, one third did not notice the small print in DTC advertisements regarding the side effects and risks of drugs. A survey of 1,601 persons conducted by Prevention magazine in September and October 2001 found that 49% believed that DTC drug advertising contributed to tension between physicians and patients. In the aforementioned survey of 2,511 persons sponsored by the Kaiser Family Foundation, 25% of the viewers of the television advertisement for montelukast believed erroneously that the tablet could be used to alleviate an acute exacerbation of asthma, and 70% of participants in the survey indicated that they learned little or nothing from watching the advertisements.

■ Measuring Outcomes of 3-Tier Copay Drug Benefit Plans

The dramatic increase in drug benefit costs in the period beginning in 1998 and continuing through 2002 caused a very rapid uptake of the 3- and 4-tier copay drug benefit plan designs among private health benefit plans, including Medicare+Choice plans. Languishing among 2-tier copay and closed formulary drug plans for 6 to 7 years, health plans, PBMs, and employers embraced these multi-tier copay plans with new vigor in 1999 and thereafter. But are these “new” drug benefit designs healthful for consumers and for the U.S. health care system? To begin to answer these questions, we first need a common nomenclature to use in defining these plans.

Single copay plans were used early in the administration of third-party prescription drug plans because the price (allowable charge in third-party payer vernacular) was not known. In the period before 1980, electronic claims processing of prescription claims and the precision and accuracy that we have come to expect today did not exist. The adoption of electronic processing for prescription drug claims in the early 1980s and its widespread implementation after 1985 permitted reconsideration of member cost-share in plan design. By the end of the 1980s, 2-tier copay plans were common, and percentage cost-share drug plans were feasible and even practical. Today, there exists a dizzying array of drug benefit designs among health plans and self-insured employers. Specified dollar copayments are overlaid with coinsurance, sometimes with deductibles or benefit (dollar) maximums. There are 3-, 4-, and even 5-tier plans. Research on the effects of these plans on cost, utilization, member satisfaction, and medication adherence, as well as other outcomes, demands that we have a nomenclature to define drug benefit plan design. Terms such as “multi-tier” or “3-tier” are not sufficiently specific to permit effective communication among managed care pharmacists and interested parties. For example, a 3-tier copay design may have 2 copay amounts (tiers) for brand formulary drugs while another 3-tier copay design may have only one copay amount (tier) for formulary drugs (i.e., nonformulary drugs would be assigned to the third-copay tier). Most 3-, 4-, and 5-tier copay designs assign the lowest (tier-1) copay to generic drugs, but even this is not always true.

Thus far, there have been few reliable results produced from efforts to measure clinical, service (humanistic), or cost outcomes of the multi-tier-copay drug plan designs. In this issue of the Journal, Nair, Ganther, Valuck et al., report that 3-tier drug plan members had less favorable attitudes toward their plans compared to those in 2-tier plans. This work advances our inspection of the effects of 3-tier copay drug benefit plans versus 2-tier plans, but the results should be interpreted cautiously and the discussion evaluated critically. While the authors attempted to measure the effects of age as an independent variable, their study groups were dramatically different. The 2-tier copay group (N=2,316) had 11.7% of its members over age 65 versus 54.7% for the 3-tier copay group (N=1,499). Not surprisingly, higher out-of-pocket copayment costs are incurred by persons over age 65 due to higher prescription utilization. Also, only 10% of the tier-2 plan members were enrolled in Medicare+Choice versus 61.4% of the tier-3 plan members. All Medicare+Choice members had a $1,000 annual benefit maximum, a variable that would be expected to affect member attitudes, particularly for the members with chronic diseases that were the subjects in their study.

Managed care strives to obtain the same or better outcomes at lower cost, thereby creating the ability to restrain the absolute amount and relative increase in health care premiums. Lower premiums make care affordable to more persons. Higher premiums make insurance coverage affordable to fewer persons. A significant increase in the cost of health care and health care coverage in 2002 and 2003 can be expected to result in an increase in the number of uninsured. U.S. Census Bureau figures, released September 30, 2002, showed that the nation’s uninsured population grew 3.5% in 2001, from 39.8 million in 2000 to 41.2 million. Free health care would make rationing necessary. Cost sharing at the point of care reduces the cost of health care premiums and can be employed in multi-tier copayments to influence member choice of care (e.g., drug). Therefore, multi-tier copay plans represent quintessential managed care, maximum choice. It is unfortunate, but reparable,
that many managed care drug plans overcharge members for generic drugs with copays of more than $5 per 30-day supply. For example, an announcement in mid-2002 trumpeted a program to promote generic drugs to physicians, pharmacists, and consumers but was associated with a 3-tier benefit design of $12 (generic), $20 (tier-2) and $30 (tier-3) copays for a 30-day supply. The study by Nair, Ganther, Valuck, et al. adds to a thin literature on health plan member attitudes, other than satisfaction, related to prescription drug benefit plans. The study methods and interpretation of results should be reviewed carefully and critically. For example, the authors report statistically significant results that often appear to be an artifact of the large sample size and may have little if any practical significance, but, nevertheless, be of interest to some readers. For example, the authors reported that 3-tier plan members compared to 2-tier plan members may be more likely to consult with friends or family members to obtain information related to the purchase of prescriptions, but not the pharmacist, or that 3-tier plan members may be more likely to obtain a second opinion from another physician. In all of these cases, the absolute differences in the mean scores are very small, less than 0.25 points on a 7-point scale. In survey research, ask 100 questions, and 5 will be statistically significant simply by chance, at an a priori P value of 0.05. Survey enough respondents, and small differences in mean scores will produce statistically significant results.

### JMCP Peer Review and Editorial Process

The quality of the Journal depends upon the collaborative work of authors, reviewers, and editors. Reviewers are often themselves authors, and more than 150 reviewers help to continuously improve the quality of the Journal. The bias management policy of the Journal is extensive and encompasses reviewers as well as authors. Members of the JMCP Editorial Advisory Board sometimes submit manuscripts for consideration, and these papers are treated no differently than any other manuscript. All manuscripts submitted for consideration in the Journal undergo a prereview screen to protect reviewers from work associated with a paper that, due to a fundamental flaw in research design or insufficient relevance to readers, cannot be revised sufficiently to earn publication in the Journal. This prereview process is generally completed within 2 weeks of receipt of the manuscript. After passing the prereview process, each manuscript is sent to at least 3 independent reviewers, selected based upon expertise in one or more areas that are the principal subjects of the manuscript. All reviews are conducted under masking of author names and affiliations. Anonymity is the cornerstone of critical, scholarly review.

The JMCP bias management policy applies to all persons, regardless of their affiliation. In this issue of the Journal, the chairperson of the Editorial Advisory Board, Marvin D. Shepherd, PhD, collaborated with another researcher, Patricia Harrington, to write a subject review on the very timely matter of the transition of drugs from prescription to availability over-the-counter (OTC). In this case, 3 expert peer reviewers agreed unanimously that the manuscript should be published, and the authors revised the manuscript according to all reviewer suggestions. The mission of JMCP is to provide reliable and timely information to assist managed care pharmacists in their efforts to maximize value for money and improve the quality of patient care.

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

### REFERENCES


24. Beatty S. TV gets most drug-ad spending, but magazines have equal impact. Wall Street J. January 14, 1999: B8.


28. O’Connell V. Drug requests are more specific—FDA survey says doctors often prescribe the brands consumers name from ads. Wall Street J. April 15, 2002: B4.


30. O’Connell V. Drug requests are more specific—FDA survey says doctors often prescribe the brands consumers name from ads. Wall Street J. April 15, 2002: B4.


36. Data were released by the U.S. Census Bureau on September 30, 2002, and reported in: Tieman J. Uninsured hits 41.2 million. Mod Healthcare. September 30, 2002: 4.

The Human Genome Project—Pharmacogenomics: How Will It Affect the Role of Pharmacists?

Dear Editor:

The Human Genome Project (HGP) is expected to have a major impact on the field of medicine and revolutionize the delivery of drugs.1,2 With the power to identify the error in the gene and correct the same, the focus of medicine may shift from treatment to prevention. The impact of the HGP could also affect the pharmacist and the practice of pharmacy.3–5 The advent of the HGP may lead to the development of drugs tailor-made to each patient's genetic profile. The applications of the HGP to pharmacy and pharmacy practice are numerous. It is imperative that pharmacists keep up with the ever-increasing pool of knowledge regarding the HGP and pharmacogenomics.2

In the July/August 2002 issue of this Journal, Zachry and Armstrong presented data regarding health care professionals' perceptions of the role of pharmacogenomic data.4 They concluded that participants in their study were optimistic about the benefits and uses of pharmacogenomic data. The study participants were those who had recently attended a conference titled “Pharmacogenomics: Implications for Patients, Providers and Payers.” Clearly this information may have affected the views of the respondents, as discussed by the authors.4 However, there are many questions about the HGP. Are practicing pharmacists aware of the advances in the HGP, and do they have knowledge of pharmacogenomics? Do they have information about the impact of the HGP on pharmacy practice? Do pharmacists have the knowledge necessary to counsel patients on the correct use of the drugs? These and several other questions that involve the pharmacist role with the advent of the HGP and the increasing impact of the drugs?1,2 With the power to identify the error in the gene and correct the same, the focus of medicine may shift from treatment to prevention. The impact of the HGP could also affect the pharmacist and the practice of pharmacy.3–5 The advent of the HGP may lead to the development of drugs tailor-made to each patient's genetic profile. The applications of the HGP to pharmacy and pharmacy practice are numerous. It is imperative that pharmacists keep up with the ever-increasing pool of knowledge regarding the HGP and pharmacogenomics.2

The answers to some of these questions were the bases of a study we conducted to evaluate the impact of the HGP on the professional role of community pharmacists.3 Preliminary results of our study mimic those reported in the article by Zachry and Armstrong.4 In our study, we also ascertained the knowledge pharmacists presumed they possessed regarding the HGP and pharmacogenomics.5 In this study of 376 pharmacists working in a community setting, we found that the pharmacists' confidence in their knowledge regarding HGP and pharmacogenomics was around 40% on a scale from 0 to 100.5

Pharmacists in our study indicated that all patients should have access to their genetic profile (3.78±1.05, range 1-5). In addition, they agreed that health care providers should have access to patients' genetic information to help patients improve their health (3.40±1.11). They disagreed that health insurance plans should have access to patients' genetic information (1.98±0.99) and agreed that health plans would discriminate against potential customers if they had access to such information (3.92±0.96). They also disagreed that such data should be available to employers (1.68±0.97).

Continuing education credits in the field of pharmacogenomics should keep pharmacists abreast of the current advances of the HGP and their implications. Conferences such as those described in the article by Zachry and Armstrong should be encouraged.4 Pharmacists in our study agreed that they should be required to take at least 2 CE credits on human genetics (3.53±0.96). The community pharmacists were also of the opinion that colleges of pharmacy should include topics on the advances of the HGP in their curriculum (3.71±0.88) and that this information would prove highly advantageous to future pharmacists. The pharmacists believed that this information would not only help them learn about the HGP but also help them tremendously in patient counseling (3.71±0.85).

New developments in the HGP necessitate training pharmacists in handling drugs developed as a result of advances in the HGP. The community pharmacists we surveyed believed firmly in this fact (3.92±0.71), further agreeing that the role of the pharmacist will change in the future due to advances in the HGP (3.41±0.96). The mapping of the human genome is a monumental discovery in the field of medicine, but in the absence of adequately disseminated knowledge regarding this project, the magnitude of the HGP will not be fully realized.

Amit S. Kulkarni, MS candidate
Department of Clinical Sciences and Administration, College of Pharmacy,
University of Houston, Texas Medical Center

Sujit S. Sansgiry, PhD, Assistant Professor
Department of Clinical Sciences and Administration, College of Pharmacy,
University of Houston, Texas Medical Center

REFERENCES

Pharmatopia

Dear Editor:

All stakeholders within the pharmaceutical supply, distribution, and consumption chain have their own agenda. The stakeholders—patients, health professionals, plan sponsors, pharmaceutical companies, and governments—may learn from each other's point of view. What would Pharmatopia, the fictional land where the drug system favors the inhabitants, look like from the perspective of each constituent?

Pharmaceutical manufacturers in Pharmatopia see all research results in salable compounds. The FDA approves all compounds. Patents do not expire. Physicians write prescriptions for brand-name drugs only. No restrictions are placed on advertising to consumers or physicians. There are no formularies. Plan sponsors do
not restrict access to any drug or class.

The FDA in Pharmatopia finds that all drugs are safe, effective, and can be used over-the-counter. Manufacturers make no unsubstantiated claims. Congress does not second-guess FDA rulings.

From the prescribers’ view of Pharmatopia, all drugs work. No drug has a side effect or harmful interaction. Any drug on the market is appropriate for all patients and may be used without restriction. Patients do not ask for specific drugs when they visit. Pharmacists need not call for prior authorizations or formulary alternatives.

For patients in Pharmatopia, all drugs are accessible without restriction or copayment. All drugs work and have no side effects or harmful interactions. Their employers have plenty of money after paying for health care and offer large, annual raises.

For pharmacists in Pharmatopia, physicians write legibly or submit all prescriptions electronically. There are no drug shortages or recalls. All drugs are available generically. There is no shortage of pharmacists. Dispensing fees are adequate, and prescription volume allows time for extensive patient counseling.

Pharmatopia for plan sponsors (state, federal, and private employers) is quite intricately woven. The FDA is shut down so that no new blockbuster drugs make it to market. All members from the CEO/governor/president on down are on a single drug-benefit plan. Members take only the medications that they need to maintain their health and insist on having premiums and copayments. Members with chronic problems take the medications needed to maintain health and avoid deterioration.

Pharmacy Benefit Managers (PBMs) and other providers of pharmaceutical care have an ambitious view of Pharmatopia. All citizens work and have a pharmacy benefit. Pharmaceutical spend trend can be managed to the negative side. Members understand their pharmaceutical benefit and use it appropriately. All plan sponsors appropriately implement every clinical program. All claims adjudicate, resulting in no call volume. Pharmacists are satisfied with their reimbursement. Pharmaceutical manufactures offer large discounts without regard to volume.

The Congressional view of Pharmatopia includes the availability of all drugs from Canada. The elderly use fewer drugs as they age and use their savings to purchase the drugs that they consume. Pharmatopia can be legislated. Everyone votes for the incumbent.

A Dose of Reality
The chemical and pharmacological properties of drugs are examples of natural trade-offs: effects versus side effects. Within the delivery system, one constituency’s Pharmatopia is another’s bane. The system cannot simultaneously have only brand-name drugs and only generics. New chemical entities are expensive to bring to market and must support those that never become approved. The FDA exists to protect citizens from ineffective or toxic substances and unsubstantiated claims. Drug interactions play a major role in prescribing decisions.

Drug spend trend continues in double digits even with aggressive management. Formularies continue to be used as a tool to steer drug use to the safest, most cost-effective therapy and promote rational therapeutics. Generic drugs lower the cost of drugs to patients, health plans, and governments. Patients ask for drugs that they see advertised whether or not they are appropriate. Sponsors are unwilling to spend money on lifestyle drugs in order to conserve resources for life-saving therapies.

Universal Pharmatopia
If stakeholders receive some of the items from their personal Pharmatopia and the system runs most efficiently, then Universal Pharmatopia might take the following shape.

Drug companies keep doing research and enjoy, but don't abuse, the normal patent life. The FDA assures that safe and effective medications reach the market in a timely manner and does not compromise effective prescription drugs into ineffective OTCs by halving dosages. Prescribers take the time to briefly explain why an older drug really is best when patients ask for a particular brand. Practitioners write prescriptions for generics whenever they have the opportunity and embrace the technology that replaces the prescription pad. Patients follow their physicians' advice and use generics or over-the-counter drugs when available. People get used to paying a larger portion of their own medication expenses instead of looking for someone else to pay for what they consume. Patients resist incessant direct-to-consumer advertising of new drugs. Pharmacists negotiate a fair reimbursement contract—and then perform. Technology is adopted to streamline the entire drug delivery system, especially at the point of service. Plan sponsors promote or mandate generics and use quantity limits and prior authorization judiciously. Other clinical programs are tried; success is rewarded. PBMs and other providers of pharmaceutical care continue to offer value in management of drugs to enhance the well-being of members. The plans prosper and the providers share in the success. The U.S. Congress does not buy into the reimportation scam for short-term benefit but reduces direct-to-consumer advertising. If a Medicare prescription drug benefit is enacted, it is means-based and does not produce undue burdens on future generations.

Drugs provide huge health and societal benefits when used properly. The pharmaceutical supply chain must remain profitable for the producers and affordable for consumers. While each constituency brings its own needs and biases, the goal is to wring the waste out of the system while assuring progress against the real viliains—disease and suffering.

A system of checks and balances in which everyone wins something may be all that can be expected, but innovations may still add to efficiencies and bring us all closer to Pharmatopia.

Steven M. Pepin, PharmD, BCPS
Principal
PHARMWORKS, LLC
“Forging Drug Thought”
spepin@PHARMWORKS.com
Article Index by Subject Category

JMCP – July/August 1995 through November/December 2002

Adherence, Compliance, and Persistence
- Adherence, compliance, and persistence in drug therapy. 2002; May/Jun:177-78.
- Measuring adherence and persistence in drug therapy. 2002; May/Jun:204-46.
- Patient adherence with HMG reductase inhibitor therapy among users of two types of prescription services. 2002; May/Jun:186-91.
- A team approach to address antiretroviral therapy adherence barriers in a managed care organization. 2001; May/Jun:214-18.
- A study on the characteristics of prescription transmittal processes and the effect of a patient prescription reminder system on patient compliance. 1998; Mar/Apr: 174-78.

Adverse Drug Events
- Medical errors, adverse medical events, and PDRM. 2002; Sep/Oct: 400.
- Evaluation of resources used to treat adverse events of selective serotonin reuptake inhibitor use. 2001; Sep/Oct: 402-06.

Behavioral Health

Biotechnology
- Biotechnology as a pharmacy specialty. 1998; Sep/Oct: 465, 468-70.

Capitation Financing Methods
- Managing pharmacy risk in physician groups. 1999; Sep/Oct: 382-84.

Clinical Pharmacy Interventions—Quality, Service, and Cost Outcomes
- Determining the value of pharmacy services—the search for rigorous research designs. 2002; Mar/Apr: 152-53.
- Factors affecting pharmacist consultation services in a university health insurance plan. 2002; Jan/Feb: 53-56.
- Community pharmacists and diabetes health care. 2002; Jan/Feb: 56-57.

Clinical Pharmacy—Patient Consultation
- Factors affecting pharmacist consultation services in a university health insurance plan. 2002; Jan/Feb: 32-40.

Clinical Pharmacy—Payment for Services
### Article Index

**Clinical Pharmacy Quality Improvement**
- Cost-benefit analysis of pharmaceutical care in a Medicaid population—from a budgetary perspective. 1998; May/Jun: 303-08.

**Clinical Pharmacy Quality Improvement—Patient Safety and Prevention of ADEs**
- The case for pharmacy report cards. 1999; May/Jun: 176, 179-80, 182.
- Managing drug therapy decisions: pay me now or pay me later. 1998; May/Jun: 242, 245.

**Clinical Practice Guidelines (CPGs)**
- Crossing the quality chasm—incremental change through clinical practice guidelines (CPGs). 2002; Sep/Oct: 400-01.
- Relationship of clinical factors to the use of Cox-2 selective NSAIDs within an arthritis population in a large HMO. 2002; Jul/Aug: 252-58.

**Collaboration—Pharmacists and Others**
- Physician groups embrace pharmacists: collaborations that work. 1997; Sep/Oct: 526-28, 530.
- Pharmacy practice in the long-term care environment. 1997; Mar/Apr: 189-94.

**Collaboration—Pharmacy Education**
- A unique partnership: the Arkansas College of Pharmacy and the Arkansas PRO. 2002; Jan/Feb: 12, 14.
- Oregon State University partners with Medicaid and a managed care organization. 2001; May/Jun: 185-86.
- The University of Colorado School of Pharmacy and the University of Colorado Health Plan forge a PBM partnership. 1998; Sep/Oct: 478, 480.

**Collaborative Practice—Pharmacists as Prescribers**

**Database Analyses of Drug Utilization (see also Research Methods)**
- Claims data and drawing appropriate conclusions. 2002; Mar/Apr: 152.

**Decision Support Systems (DSS)**
- Understanding decision support systems. 2002; Mar/Apr: 96-101.

**Direct-to-Consumer Advertising (DTCA) (see also Drug Promotion and Advertising)**
- Direct-to-patient advertising (DTPA) and direct-to-consumer advertising (DTCA) of prescription drugs. 2002; Nov/Dec: 521.
### Article Index

- Responding to direct-to-consumer advertising. 2000;May/Jun:201-02.
- Direct-to-consumer advertising provides challenge to managed care. 1999;Mar/Apr:101-03,106.

### Disease Management—ALS (Amyotrophic Lateral Sclerosis)

### Disease Management—Angina, CHD, and CHF
- Managing congestive heart failure in a Medicare risk population. 1999;Jan/Feb:14-16.
- Direct medical costs of unstable angina pectoris in a defined population. 1999;Jan/Feb:39-44.

### Disease Management—Arthritis and Joint Pain
- Cost-effective use of Cox-2 drugs and NSAIDs. 2002;Jul/Aug:295-96
- Relationship of clinical factors to the use of Cox-2 selective NSAIDs within an arthritis population in a large HMO. 2002;Jul/Aug:252-58.
- Economic considerations in the management of arthritis. 1999;Nov/Dec:476-78,481-82,484.

### Disease Management—Asthma and Allergic Rhinitis
- Evaluating asthma medication use before and after an acute asthma-related event. 2001;Jul/Aug:303-08.

### Disease Management—Atopic Dermatitis
- The effect of atopic dermatitis on total burden of illness and quality of life on adults and children in a large managed care organization. 2002;Sep/Oct:333-42.

### Disease Management—Cancer

### Disease Management—Deep Vein Thrombosis

### Disease Management—Depression
- Utilization patterns of antidepressant medications in a patient population served by a primary care medical group. 1999;May/Jun:243-49.

### Disease Management—Diabetes
- Evaluating medication use for continuous quality improvement in diabetes care. 2002;Sep/Oct:378-82.
- Importance of blood glucose monitoring to achieve short- and long-term glycemic control. 1999;Nov/Dec:543-47.

### Disease Management—Heartburn
### Article Index

#### Disease Management—Helicobacter Pylori
- Gastroesophageal reflux disease in a managed care setting: charges by place and type of service. 1998;Jan/Feb:64-70.
- Peptic acid disorders: developing a disease management program. 1996;Sep/Oct:569-75.

#### Disease Management—Gastroesophageal Reflux Disease
- Peptic acid disorders: developing a disease management program. 1996;Sep/Oct:569-75.

#### Disease Management—Obesity
- A cost-effective analysis of appetite suppressants for obesity treatment in a managed care organization. 1998;May/Jun:293-300.

#### Disease Management—Osteoporosis

#### Disease Management—Otitis Media and Infectious Disease
- Fluoroquinolone-use evaluation by acute cystitis. 1996;Sep/Oct:564-68.

#### Disease Management—Seizure Disorders

#### Disease Pathology

#### Dose Optimization
- Dose optimization: an opportunity for pharmacy administrative services. 2002;Mar/Apr:81.
- Dose-optimization intervention yields significant drug cost savings. 2002;Mar/Apr:146-51.

#### Drug Benefit Management—Benchmarks and Measures
- Searching for drug benefit benchmarks—cost per day of therapy. 2002;Jan/Feb:54-55.

#### Drug Benefit Management—Efficiency
- Tablet splitting to improve the value-for-money equation in cholesterol management. 2002;Nov/Dec:519.

### Disease Management—Hypercholesterolemia
- Effective cholesterol management with fewer dollars. 2002;Nov/Dec:519.

### Disease Management—Hypertension

### Disease Management—Multiple Sclerosis

### Disease Management—Obesity
- A cost-effective analysis of appetite suppressants for obesity treatment in a managed care organization. 1998;May/Jun:293-300.

### Disease Management—Osteoporosis

### Disease Management—Otitis Media and Infectious Disease
- Fluoroquinolone-use evaluation by acute cystitis. 1996;Sep/Oct:564-68.

### Disease Management—Seizure Disorders

### Disease Pathology

### Dose Optimization
- Dose optimization: an opportunity for pharmacy administrative services. 2002;Mar/Apr:81.
- Dose-optimization intervention yields significant drug cost savings. 2002;Mar/Apr:146-51.

### Drug Benefit Management—Benchmarks and Measures
- Searching for drug benefit benchmarks—cost per day of therapy. 2002;Jan/Feb:54-55.

### Drug Benefit Management—Efficiency
- Tablet splitting to improve the value-for-money equation in cholesterol management. 2002;Nov/Dec:519.
Article Index

- Pharmacy cost reduction imperative at United HealthCare. 1999;Jan/Feb:19-20.
- Pharmacy benefit administration options. 1996;May/Jun:272-78.
- New generic and OTC drugs provide opportunities for drug benefit managers. 2002;Nov/Dec:520.
- Successful disease management programs for health and welfare fund union groups. 1998;May/Jun:269-70,272.
- Drugs, PPOs, tiered cost-share for beneficiaries, and consumer preferences. 2002;May/Jun:177.
- Consumer preferences for types of cost containment in prescription drug programs. 2002;May/Jun:192-98.
- Patient satisfaction with and knowledge of their prescription drug coverage. 2001;Jan/Feb:34-42.
- A comparison of satisfaction with mail versus traditional pharmacy services. 1997;May/Jun:327-37.
- Triptan quantity limits. 2002;May/Jun:182-84.
- Medical and pharmacy cost and utilization outcomes of a quantity limit on 5-HT1 agonists (triptans) by a managed care organization. 2001;Nov/Dec:468-75.
- Benefit maximums versus drug benefit needs for Medicare beneficiaries. 2002;Nov/Dec:402-03.
- Prescription use behavior among Medicare beneficiaries with capped prescription benefits. 2002;Sep/Oct:360-64.
Article Index

Drug Promotion and Advertising
(see also Direct-to-Consumer Advertising (DTCA))
- Information requirements of health systems as drug purchasers: does the FDA have a role in setting evidentiary standards? 1996;Nov/Dec: 593-98.
- Health care communications agencies respond to managed care. 1998;Jan/Feb: 9-12.

Drug Spending, Utilization, and Cost Trends
- Drug costs out of control—check your assumptions. 2002;Mar/Apr:81.
- Too much or too little? The role of pharmaceuticals in the health care system. 1999;Jul/Aug:296-97, 301-02.
- Local area market dynamics. 1998;Mar/Apr:115-17, 120.

Drug Therapy and Therapeutic Selection
- Clinical and economic impact of glatiramer acetate versus beta interferon therapy among patients with multiple sclerosis in a managed care population. 2002; Nov/Dec: 469-76
- A pharmacoeconomic model comparing two long-acting treatments for overactive bladder. 2002; Sep/Oct:343-52.
- The search for better antipsychotics continues. 2002;Jul/Aug:298.
- Safety and efficacy of a mandatory formulary switch from nifedipine GITS to amlodipine. 1999;May/Jun:225-29.
- Evaluation of blood pressure and adverse effects in patients converted from lisinopril to benazepril. 1999;Jan/Feb:52-54.
- Physicians’ perspectives of a therapeutic conversion with a staff-model HMO. 1997;Jan/Feb:35,56,65.

Drug Therapy—Natural Products

Drug Utilization Review (DUR) or Drug Utilization Management
- Gabapentin and indications of appropriate use. 2002;Jul/Aug:293-94.
- DUR messages—better data needed for making better decisions. 2002;May/Jun:178-79.
- Better data for making better decisions: finger-pointing or useful drug use review. 2002;May/Jun:208-10.
- High frequency of itraconazole prescriptions with potentially interacting medications in a large health care plan. 2002;May/Jun:199-203.
- The pharmacist’s assessment of second generation online prospective drug utilization review. 1998;Mar/Apr:183-191.

Ethics
- Ethics and the use of drug formularies. 1996;Mar/Apr:76,78,81-82.
Formulary Management—Methods and Effects—Pharmacoeconomics

- Exploring the methodological challenges of investigating comparison groups with different underlying characteristics: a case study. 2002;Sep/Oct:353-59.
- The role of pharmacoeconomic information in the formulary decision-making process. 2000;Mar/Apr:108,113-14,117-18,121.
- Outcome analysis of a formulary transition from nifedipine to felodipine at a Veterans Affairs Medical Center. 1999;Sep/Oct:425-28.
- DOD’s Pharmacoeconomic Center: translating research into good patient care practices. 1997;Nov/Dec:662-64,666.
- Pharmacoeconomic analysis of hormone replacement therapy—implications for managed care. 1997;Mar/Apr:200-09.

Formulary Management—P & T Committees


Health Care Delivery

- Pharmacy: looking back to see the future. 1998;Sep/Oct:454-55,459-60,462.
- International markets offer new opportunities for MCOs and PBMs. 1997;Jul/Aug:403-04,409-10.
- Integration takes managed care in different directions: horizontal, vertical, and beyond. 1997;May/Jun:260,263-64.
- Indian Health Service: paving the way for pharmaceutical care. 1997;Jan/Feb:36,41-43.
- Alternative medicine in managed care pharmacy. 1997;Jan/Feb:77-80,83-86.

Health Care Quality Improvement

- Information technology to cross the quality chasm. 2002;Sep/Oct:401-02.
- Quality improvement opportunities in health care—making it easy to do it right. 2002;Sep/Oct:394-99.
- Quality measures: looking in all the wrong places. 2001;Mar/Apr:88.
- Medical and medication errors: a partial summary of reports by the Institute of Medicine and the quality interagency coordination task force. 2001;Jan/Feb:62-68.
- Managed care and the quest for quality measures. 1997;May/Jun:255,258-89.
- How to evaluate disease state management programs. 1997;May/Jun:270,273-74,277-78.
- Successful CQI-based programs in a group-model managed care setting. 1995;Sep/Oct:134,137.

Health Care Spending and Health Economics

- Health economics II: some unique aspects of health economics. 2000;Mar/Apr:173-78.
Article Index


Health Insurance and Health Care Finance

- Direct contracting: the next purchaser strategy. 1996;Jan/Feb:11-12,14,16.

Institutional Managed Care

- Managed pharmaceutical care within a criminal justice system. 2001;May/Jun:182.

Internet Pharmacy

- Concern about foreign-source pharmacy Internet providers. 2001;Sep/Oct:335-36.
- The Internet and PBMs: new business model or business as usual? 2000;Mar/Apr:102,105-07.

Lifestyle Drugs

- Enhancing life or eradication ugliness?: lifestyle drugs. 2002;Jan/Feb:15-16,19-20.

Managed Care Pharmacy Practice

- John Ogden talks about managed care in the Veterans Administration. 2002;Mar/Apr:91-93.
- Career changes in managed care pharmacy. 2000;May/Jun:208,10,15.
- Managed care and the pharmacy profession revisited. 1999;Mar/Apr:78.
- The importance of communication skills for the managed care pharmacist. 1998;Mar/Apr:102.
- The changing face of managed care pharmacy and the role of PBMs. 1997;Sep/Oct:494,497-98.
- Managed care pharmacy: leading pharmaceutical care integration forward. 1997;Mar/Apr:139,141-42,143-47.

- Blue Cross and Blue Shield: making pharmaceutical care a key component of managed care. 1996;Jan/Feb:33-34,36,38.
- Professional opportunities in managed care pharmacy. 1995;Sep/Oct:80,82,86-87.

Managed Health Care

- Examining the managed health care continuum. 1997;Sep/Oct:511-12,515-16,518.

Manpower and Job Satisfaction

- Burnout in a sample of HMO pharmacists using the Maslach Burnout Inventory. 1998;Sep/Oct:495-503.

Medicaid


Medicare (see also Drug Benefit Management Methods—Benefit Design)

- Prescription coverage options for Medicare beneficiaries. 1999;May/Jun:250-54.
- Overview of Medicare for managed care professionals. 1996;Mar/Apr:165-72.
### Article Index

#### Pain Management

#### Pharmaceutical Industry
- India's pharmaceutical industry: a growing influential force in the world pharmaceutical market. 2002;May/Jun:211-15.
- Managed care and the University of Texas College of Pharmacy. 2001;Nov/Dec:490.
- University of Michigan College of Pharmacy and managed care partner to enhance drug therapy. 2001;Sep/Oct:345-46.
- An inside look at the benefits of a student pharmacy and therapeutics (P & T) committee competition from the University of Illinois at Chicago. 2001;Jul/Aug:259-60.
- Managed care concepts prominently featured in innovative management programs at Duquesne University. 2001;Mar/Apr:94,96.
- Managed care teaching and research in South Dakota. 2001;Jan/Feb:10,11.
- Synergy between the University of Louisiana at Monroe and the Louisiana Drug Utilization Review Board. 2000;Sep/Oct:420.
- College offers certified managed care pharmacist program. 2000;May/Jun:262-63.
- The University of Maryland's Center on Drugs and Public Policy. 2000;Mar/Apr:184-85.
- Managed care pharmacy practice at the Texas Tech University Health Sciences Center School of Pharmacy. 1999;Nov/Dec:556-57.
- Description of a formal affiliation between a school of pharmacy and a managed care organization. 1999;Sep/Oct:433-37.
- Improving efficiency and effectiveness in managed care: ongoing efforts at the University of New Mexico College of Pharmacy. 1999;Mar/Apr:111.
- Pharmacy internship offers real-world exposure to managed care pharmacy practice. 1996;Nov/Dec:605-06.
- First managed care pharmacy course at the University of Illinois at Chicago. 1998;Jan/Feb:80-81.
- Draft criteria for residency programs in managed care pharmacy. 1997;May/Jun:363-64,366,368,371.
- Internship takes classroom into the "real world." 1997;Mar/Apr:234,241.
- Linking the ivory tower and real-world practice: building a synergy bridge in managed care pharmacy. 1997;Jan/Feb:107-08,110.
- New degree program at Ole Miss: B.S. in pharmaceutical sciences/management major. 1997;Jan/Feb:112-113.
- Managed care pharmacy at the St. Louis College of Pharmacy. 1996;Jul/Aug:439,442.
- Managed care pharmacy education at the University of Washington School of Pharmacy. 1996;May/Jun:319-20.
- Managed care pharmacy education at MCP. 1996;Jan/Feb:53.

#### Pharmacogenomics
- Health care professionals' perceptions of the role of pharmacogenomic data. 2002;Jul/Aug:278-84.
- Driving market share in an integrated health system without therapeutic interchange. 2001;Jul/Aug:283-86.

#### Pharmacy Education
- Selection bias in physician education-intervention programs. 2002;Mar/Apr:82.
- Physician education-intervention influenced prescribing for otitis media. 2002;Mar/Apr:141-45.
- Linking the ivory tower and real-world practice: building a synergy bridge in managed care pharmacy. 1997;Jan/Feb:107-08,110.
- New degree program at Ole Miss: B.S. in pharmaceutical sciences/management major. 1997;Jan/Feb:112-113.
- Managed care pharmacy at the St. Louis College of Pharmacy. 1996;Jul/Aug:439,442.
- Managed care pharmacy education at the University of Washington School of Pharmacy. 1996;May/Jun:319-20.
- Managed care pharmacy education at MCP. 1996;Jan/Feb:53.
• UIC students mobilize first student chapter of AMCP. 1995;Nov/Dec:185-86.

Population Health—Interventions and Prevention of ADEs
• An employee influenza initiative in a large university managed care setting. 2001;May/Jun:219-23.
• Who bears responsibility for glucocorticoid-exposed patients in a large health maintenance organization? 2001;May/Jun:228-32.
• Public health, managed care, and pharmacy: an evolving trilect. 2001;Jan/Feb:12, 14-16.

Prior Authorization (PA)

Privacy of Health Information
• Privacy just took on a whole new meaning: what HIPAA means to pharmacists. 2001;Sep/Oct:342.
• Employer access to employee prescription records: dilemmas for pharmacists. 1997;Sep/Oct:504-05, 508.

Quality Assurance

Research Methods (see also Survey Methods)
• Statistical significance versus practical significance. 2002;Sep/Oct:404.
• Conjoint analysis in pharmaceutical research. 2002;May/Jun:206-08.
• Researching managed care pharmacy using Internet searches. 2001;May/Jun:201-04, 213.
• Research methodology: designing a research study. 1998;Sep/Oct:504-14.
• The vital role of pharmacy benefit management firms in health services research. 1998;Jan/Feb:23-24, 26-28.
• Epidemiological techniques. 1997;Jan/Feb:30-32, 35.
• Method is everything: evaluating results by study design. 1997;Jan/Feb:66-68, 71-72, 75-76.
• Interface between pharmacoepidemiology and pharmacoeconomics in managed care pharmacy. 1996;May/Jun:282-89.
• Outcomes research, pharmacoeconomics, and the pharmaceutical industry. 1996;Jan/Feb:48-52.

Safety—Health Care Worker

Safety—Patient Care (see also Drug Utilization Review (DUR))

Specialty Pharmacy
• The emergence of specialty pharmacy. 2000;Jul/Aug:280-84.

Survey Methods (see also Research Methods)
• Constructing mail survey questionnaires to maximize the rates of return and assure the validity and reliability of responses. 2002;May/Jun:225-31.
• Implementing mail survey questionnaires. 2002;Mar/Apr:157-61.

Technology—Automation
• Automated dispensing technologies: effect on managed care. 1995;Sep/Oct:212-17.

Technology—Education and Information
• Use of technology throughout the curriculum. 2002;Mar/Apr:86.
• The Internet: changing the managed pharmaceutical care environment. 1999;Sep/Oct:387-88, 390, 392.
• Technology and automation update. 1998;May/Jun:345-50.
• Automation aids prescription processing—but professional judgment remains indispensable. 1995;Sep/Oct:90,93-95.

**Technology—Electronic Prescribing**

• Extent of electronic prescribing implementation as perceived by MCO pharmacy managers. 2002;Jan/Feb:41-47.

**Therapeutic Interchange—Therapeutic Selection**

• Utilization of pharmacy claims data to evaluate therapeutic interchange programs. 1999;Jul/Aug:331-34.

**Value of Pharmacotherapy**

• RxHealthValue offers three recommendations and cost research. 2001;Jan/Feb:17-20.

**Women's Health**

• Estimating the relative cost effectiveness of four contraceptive methods in the prevention of unwanted pregnancies within the Department of Defense active-duty women. 1999;Mar/Apr:131-36.
All articles in JMCP undergo peer review. Letters are published without editing but may be peer reviewed to ensure accuracy. The fundamental departments for manuscript submission are:
- Original Research
- Subject Reviews
- Formulary Management
- Contemporary Subjects
- Editorials
- Letters

These articles are based upon 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. An abstract is required, generally in the format of Background, Objective, Methods, Results, Conclusion, Keywords.

These are well-referenced, comprehensive reviews of subjects relevant to managed care pharmacy. An abstract is recommended, generally in the format of Background, Objective, Summary, Conclusion, Keywords.

These are well-referenced, comprehensive reviews of subjects relevant to formulary management methods or procedures in the conduct of pharmacy and therapeutics (P & T) committees and may include description and interpretation of clinical evidence. These articles should include an abstract in the format of Original Research or Subject Reviews, depending upon the subject matter.

These submissions describe pilot projects or other subjects that are not intended to be comprehensive reviews of the subject. These manuscripts should be well referenced and include an abstract in the format of Original Research or Subject Reviews, depending upon the subject matter.

These submissions are peer reviewed but require no abstract.

These submissions may be peer reviewed for accuracy but require no abstract or title page.

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

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

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

■ Manuscript Preparation

Manuscripts should include, in this order, a title page, a separate page identifying all authors (including degrees, employers, titles, contact information, and financial disclosure and conflicts of interest), an abstract of no more than 300 words, text, references, figure captions, tables, and figures.

JMCP abstracts should be written narratives that contain the information described for each type of article shown below, where applicable:

Original Research

• Background
• Objective
• Methods
• Results
• Conclusion
• Keywords

Subject Reviews

These are well-referenced, comprehensive reviews of subjects relevant to managed care pharmacy. An abstract is recommended, generally in the format of Background, Objective, Summary, Conclusion, Keywords.

Formulary Management

These are well-referenced, comprehensive reviews of subjects relevant to formulary management methods or procedures in the conduct of pharmacy and therapeutics (P & T) committees and may include description and interpretation of clinical evidence. These articles should include an abstract in the format of Original Research or Subject Reviews, depending upon the subject matter.

Contemporary Subjects

These submissions describe pilot projects or other subjects and are not intended to be comprehensive reviews of the subject. These articles should be well referenced and include an abstract in the format of Original Research or Subject Reviews, depending upon the subject matter.

Editorials

These submissions are peer reviewed but require no abstract.

Letters

These submissions may be peer reviewed for accuracy but do not require an abstract or title page.

■ Reference Style

References should be prepared following AMA style. Shown below are examples of common types of references:

1. Standard journal article

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


2. No author given

Top 25 U.S. hospitals, ranked by admissions, 1992 Managed Healthcare. 1994(Sep);4(9):64.

3. Journal paginated by issue


4. Book or monograph by authors


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


6. Chapter in a book


7. Government agency publication


8. Dissertation or thesis


9. Paper (or Poster) presented at a meeting


■ Submission of Manuscripts

A paper copy of the manuscript, including originals of figures and tables, should be submitted to the JMCP Peer Review Administrator at the Academy of Managed Care Pharmacy at 100 North Pitt Street, Suite 400, Alexandria, VA 22314. Tel: (800) 827-2627 or (703) 683-8416 or FAX: (703) 683-8417. The paper copy is necessary to ensure proper presentation and placement of text, figures, tables, and graphs.

Please send an electronic version of the manuscript, either on a disk or via e-mail, to jmcp@amcp.org. All text should be in a word processing program (preferably Microsoft Word). Tabular material also should be in a word processing program using the tab function to create columns not using “tables” or “cells.” Figures should be saved in Photoshop or Illustrator and may be recreated by us. We cannot accept PowerPoint graphics. Please identify the format (PC or MAC), all programs used, and all file names. In a cover letter, the corresponding author should:

• Briefly describe the importance and scope of the manuscript;
• Certify that the paper has not been accepted for publication or published previously and that it is not under consideration by any other publication;
• Suggest names of possible reviewers when appropriate; and
• Identify the nature and extent of any financial interest or affiliation that any author has with any company, product, or service discussed in the manuscript.

One of the following statements must be signed by all authors and submitted with the manuscript:

• “In consideration of the Academy of Managed Care Pharmacy (AMCP) taking action and reviewing and editing this submission, the author(s) undersigned hereby transfer(s), assign(s), or otherwise convey(s) all copyright ownership to AMCP in the event that this work is published by AMCP”

• “I was an employee of the United States Government when this work was prepared for publication; it is therefore not protected by the Copyright Act, and there is no copyright that can be transferred.”

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

REFERENCES

AMCP Members receive many benefits, including:

▲ **AMCP Publications . . .**
  Numerous publications including AMCP News, the *Journal of Managed Care Pharmacy* (JMCP), *Who’s Who in Managed Care Pharmacy*, and the Catalog of Pharmacy Quality Indicators are only a few that are available to AMCP members.

▲ **Registration Discounts . . .**
  A valuable benefit that provides AMCP members with reduced registration fees to all of AMCP’s continuing educational (CE) programs.

▲ **Career Information Services . . .**
  A service that provides AMCP members with the opportunity to advertise their availability for employment, and employers the opportunity to advertise their positions that are available within their organizations.

▲ **Fax-on-Demand . . .**
  A popular service that offers quick answers to questions about AMCP and managed care pharmacy.

▲ **Member-Only Access to Information on the AMCP Web Site . . .**
  An important link to the latest updates on clinical, market, legislative and regulatory, and administrative issues shaping the practice of managed care pharmacy.

▲ **Weekly News . . .**
  An e-mail service that reviews the week’s events of importance to the pharmacy profession.

▲ **Legislative and Regulatory Updates . . .**
  An essential information service that provides our members with key information on issues that affect managed care on a national and a state-by-state basis.

▲ **Meetings With Congressional Leaders . . .**
  Each year, AMCP coordinates and assists our members to meet directly with policy makers to discuss concerns and issues affecting managed care.

▲ **AMCP Committee Involvement . . .**
  Opportunities exist through AMCP’s leadership to become involved, network with peers, and influence the direction of managed care pharmacy.

**Join AMCP today.**

**No other organization offers you the same depth of information and influence in managed care pharmacy.**

A membership application is on the reverse side for your convenience. After completing, please mail or fax to AMCP.
Membership Application

Please print or type.

Member Information

☐ Mr.  ☐ Ms.  ☐ Mrs.  ☐ Dr.

FIRST NAME ___________________________________________ LAST NAME ___________________________________________

TITLE ________________________________________________

ORGANIZATION NAME: ___________________________________________

ORGANIZATION ADDRESS ___________________________________________

CITY ___________________ STATE _______ ZIP CODE _____________

HOME ADDRESS ___________________________________________

CITY ___________________ STATE _______ ZIP CODE _____________

Address all mailings to my:  ☐ Company Address  ☐ Home Address

WORK TELEPHONE ___________________ FAX ___________________

HOME TELEPHONE ___________________

E-MAIL ADDRESS ___________________

REFERRED BY ___________________

Demographic Information

Please tell us:

I. Are you a pharmacist?  ☐ yes  ☐ no

II. What degrees/designations do you hold?

☐ B.S. Pharmacy  ☐ Pharm.D.
☐ M.P.A.  ☐ M.P.H.
☐ Ph.D.  ☐ J.D.
☐ M.B.A.  ☐ R.Ph.
☐ Other ____________________________

III. Which of the following best describes your employer?  (check one)

☐ Health Plan  ☐ Medical Group
☐ Integrated System  ☐ Hospital
☐ College or University  ☐ PBM/Mail Service
☐ Home Care  ☐ Long-term Care
☐ Retail Pharmacy  ☐ Consulting Firm
☐ Pharmaceutical Manufacturer  ☐ Government (VA, PHS, Military, State)
☐ Not Currently Employed  ☐ Other ____________________________

IV. Which of the following best describes your job function(s)?

☐ Director/President  ☐ Assistant Director/Vice President
☐ Staff Pharmacist  ☐ Clinical Pharmacist
☐ Clinical Coordinator  ☐ School/College Faculty
☐ Student  ☐ Resident/Fellow/Graduate Member
☐ Contract/Purchasing  ☐ Network Management
☐ Professional Relations  ☐ Formulary Management
☐ Distribution/Supply Chain  ☐ Customer Service
☐ Consultant  ☐ Marketing/Sales
☐ Other (specify) ____________________________

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

______ year(s)

Annual Membership Rates

☐ Active Member (pharmacists who support the mission and goals of AMCP) ______$195 per year
☐ Associate Member (non-pharmacists) ____________________________ $395 per year
☐ Student Member ____________________________ $25 per year

Required: Graduation date (mo/yr) ___________ School ___________

☐ Resident/Fellow/Graduate Member ____________________________ $75 per year

Required: Resident/Fellow/Graduate completion date (mo/yr) ___________

Site ____________________________

Method of Payment

☐ Check made payable to AMCP for _______ (in U.S. funds drawn on a U.S. bank)

☐ Charge $___________ to my credit card  ☐ Visa  ☐ MasterCard  ☐ American Express

CARD NUMBER ___________ EXP DATE ___________

CARDHOLDER PRINTED NAME _________________________________________

CARDHOLDER SIGNATURE ___________________________________________
NOTICE

Facts and Comparisons Owns the MDDB Product Line

Pursuant to a federal court order, First DataBank (‘FDB’) has sold to Facts and Comparisons the Medi-Span business that it acquired in 1998. Accordingly, all customers who had been receiving MDDB products from FDB will now receive them from Facts and Comparisons. Facts and Comparisons will provide all customer support, and sales services regarding MDDB products. Facts and Comparisons is prepared to offer MDDB integrated drug database products to both current and new customers.

Questions about MDDB products should be addressed to:

Robert E. Brown
Director of Sales, Marketing and Customer Service
Facts and Comparisons
1-800-223-0554 ext. 2196 or 314-216-2196
rbrown@drugfacts.com

FDB is required to ensure that the transition of the MDDB product line to Facts and Comparisons preserves the integrity, accuracy and timeliness of the MDDB products. FDB will fulfill its responsibilities by transferring to Facts and Comparisons all of the data systems related to MDDB products and knowledgeable employees to operate those systems. Until Facts and Comparisons has developed its own production system, however, FDB will continue to provide production services for the MDDB products to Facts and Comparisons. In addition, FDB is required to supply to Facts and Comparisons, for two or more years, data for the MDDB drug information database that is just as timely and accurate as the data that is in FDB’s NDDF drug information database.

You should have complete confidence that the transition of the MDDB products will preserve their integrity. In addition to the commitment of FDB to make this transition faultless, a court ordered Monitor will continuously review FDB’s compliance with its obligations and United States Federal Trade Commission has the power to enforce the court order.

Thanks to JMCP Peer Reviewers, 2002

The following peer reviewers made one or more contributions to the editorial process for the Journal of Managed Care Pharmacy in calendar year 2002. We are indebted to these professionals for their assistance in continuous quality improvement of the content of JMCP—Editor.

Earlene Lipowski, PhD
David Lourwood, BS, PharmD
Alan Lyles, DSc
Neil MacKinnon, PhD, RPh
Suresh Madhavan, BS, MBA, PhD
Daniel Malone, PhD, RPh
Donna Marshall, PharmD, MS
Karen Martin, PharmD, MBA
Bradley Martin, PharmD, PhD
William Martin, PharmD, MA, MS
Gina Matter, BS Pharmacy
Dennis McCallum, PharmD
Kimberly McGuigan, PhD
Eric Millheim, PharmD, MBA
Anthony Morrallie, PharmD, MBA, BCPS
Brenda Motheral, PhD, MBA
Daniel Mullins, PhD
Marko Mychaskiw, RPh, PhD
Robert Navarro, PharmD
Suzanne Novak, MD
Francis Palumbo, PhD, JD
Steven Pepin, BS, PharmD
Eleanor Perfetto, PhD, MS, BSM
Steven Peskin, MD, MBA
Andrew Peterson, BS Pharm
Ryn Pitts, MS RPh
Carol Pugh, PharmD
Mark Pugh, BS Pharm, PharmD
Gene Reeder, PhD
Kristin Richards, PhD
Cathlene Richmond, BS Pharm D
Michael Sax, PharmD
Kenneth Schafermeyer, PhD
Michael Schmidt, Pharm D
Fadia Shaya, PhD, MPH
Marv Shepherd, BS, MS, PhD
Judith Shinogle, PhD, MSc.
Denise Sokos, PharmD, BCPS
Emery Spaar, BS Pharm, MBA
Andy Stergachis, PhD
Tara Storjohann, PharmD
Rosy Suleman, RPh, PharmD
Robert Valuck, PhD
Randy Vogenberg, PhD
Linda Wagner, BS PharmD
John Watkins, RPh, MPH
William Waugh, PharmD
Albert Wertheimer, BS, MBA, PhD
Rhonda Wroble, PharmD
David Yoder, PharmD, MBA
Winnie Yu, PharmD, BCPS
Richard Zabinski, PharmD
John Zevzavadjian, BS

Robert Anderson, PharmD
Kurtis Andrews, PhD, MSPH
Otto Bacon, RPh
Daniel Baker, PharmD, FASHP, FASCP
John Barbuto, MD
Loren Baskin, PharmD
Dea Belazi, PharmD, PAHM
Shannon Benedetto, PharmD
Joshua Benner, PharmD, MS
John Bentley, MBA, PhD
Stuart Berney, BS Pharm, PhD
Melanie Bishop, PharmD
R. Wayne Blackburn, PharmD, MBA
Sandra Blake, PhD, MBA
Sallie Bowden, PharmD, BCPS
Diana Brixner, RPh, PhD
Crystal Bryner, RPh
Scott Bull, PharmD
David Calabrese, RPh, MHP
Michael Callahan, PhD
Daniel Canafax, PharmD
Jeffrey Casberg, MS, RPS
James Chan, PharmD, PhD
Donna Chieffari, BS Pharmacy
Erin Conley, PharmD
Liesi Cooper, BS, MBA, PhD
Deborah Cooper
Eric Culey, BS, PharmD
Joan Deady, MS, PharmD
Nicole Devita, RPh, MHP
Kristin Devlin, PharmD
Joseph DiCesare, BS Pharmacy, MPH
Arjun Dutta, PhD
Bruce Fallick, MS, RPh
Patrick Finley, PharmD
Leslie Fish, PharmD
Jean Paul Gagnon, PhD, RPh
Kimberly Galt, BS, PharmD
David Gettman, PhD, MBA, BS
Peg Glessner, PharmD
Jeffery Graham, MD
Mark Greg, PharmD, RPh
Matt Grissing, BS in Pharmacy
Butch Habegeer, BS, MBA
Zafar Hakim, PhD
Richard Hammel, PhD
Patrick Hardigan, PhD
Catherine Harrington, PharmD, PhD
Joel Hay, PhD
Ryan Haynes, RPh, MBA
Alan Heaton, BS Pharm, Pharm D
Edwin Hedblom, PharmD
Jan Hirsch, RPh, MS, PhD
Janice Hoffman, PharmD
David Holdford, RPh, MS, PhD
Tom Hughes, PhD
Peter Hurd, PhD
Michael Johnsruud, PhD, MS, BS
Sejal Jonas, PharmD
Eric Klein, PharmD
Katherine Knapp, PhD
Pamela Koerner, PharmD
Stephen Kogut, BS MBA PhD
Ken Lawson, PhD