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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.

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www.amcp.org
George Dunlop (G.D.) Leslie (1835-1921) was an English landscape and genre painter who trained at the Royal Academy of Arts in London. He painted scenes of everyday life, which was very popular during the 18th and 19th centuries.

He was the son of painter Charles Robert (C.R.) Leslie (1794-1859), who was born in London to an American family from Maryland. Both father and son were Royal Academician (RA) members of the Academy. (The Royal Academicians, which number among the greatest names in historic and contemporary British art, still govern the Academy and are responsible for its direction.)

G.D. Leslie, also born in London, studied under his father, a professor of painting at the Royal Academy, and later continued his studies at Cary's Art School and at the Academy. He exhibited at the Academy every year from 1859, becoming an RA in 1876.

Leslie was supported and helped by Edwin Landseer, famous for his pictures of horses, dogs and stags, and was a colleague of the highly regarded “social realist” illustrator Frederick Walker and the bird painter H. S. Marks. Leslie stated that his aim in art “has always been to paint pictures from the sunny side of English domestic life,” and this seems to summarize his work. Typical are pleasant interiors with pleasant people, as in Les Femmes Savants (Victoria and Albert Museum), and single figures such as Tea (1894), showing a pretty serving maid.

In Sun and Moon Flowers, Leslie has captured Victorian society's romantic idealization of nature, which reflected a growing interest in science, botany, and horticulture. Sunflowers have been called nature's “sun-dial” because their faces always follow the light of the sun.

Over the centuries, sunflowers were valued for their medicinal purposes in addition to their beauty. The Dakota Indians simmered the flower heads to make an infusion believed to alleviate chest pains, while the Zuni tribe claimed it cured snakebite. The Pawnee pulverized sunflower seeds with the roots of other plants and gave the resulting pulp to pregnant women to fortify their milk. And the sticky juice of the stem was prized for its curative powers by the Cochiti, who used it to dress and clean wounds, often using its large leaves as bandages.

Leslie cleverly composed the paintings female figures in a circular configuration, imitating the shape of the sunflower, and the sun itself. With a counter-clockwise motion, the woman on the right hands over the sunflowers to the woman on the left to be trimmed and inserted into the vases at her feet. It could be interpreted that the woman dressed in dark clothing represents death, as she surveys the sunflowers that have been plucked from their life source (the earth). They are given a brief new life, or rebirth, by the woman dressed in white, as she places them in water. Thus, Leslie has woven the theme of life and death's endless cycle into a casual scene of two women on a lazy summer afternoon. The painting’s composition further underscores man's close relationship with nature by the near proximity of the figures to the open window. Inside and outside seem to coexist in perfect harmony.

Another one of Leslie's paintings of women has recently received acclaim, according to a story by the BBC in November 2002. In an article titled “Victorian Painting Funds Science Block,” the BBC reported that “The sale of a Victorian painting, which had hung unnoticed in a south Wales school for more than 40 years, has helped fund three new classrooms. The Daughters of Eve [1883] by George Dunlop Leslie was sold for $170,000 after teachers at Llantarnam Comprehensive School, near Cwmbran, had the picture valued by auctioneers [at] Sotheby’s.” Ironically, another notable painting by Leslie is titled Kept in School (1876).

Leslie sold some of his paintings for commercial purposes, including This Is the Way We Wash Our Clothes, which was used for a soap advertisement. He also illustrated beautiful scenes for Victorian Christmas cards.

Sun and Moon Flowers is in the permanent collection of the Guildhall Art Gallery in London. It is currently part of the “Flower Power” exhibition at the Millennium Galleries in Sheffield, England. This exhibit, which demonstrates how different cultures have used flowers in art, runs through August 25, 2003.
Editorial Content and Peer Review

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

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

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

Original Research

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

Subject Reviews

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

Formulary Management

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

Contemporary Subjects

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

Editorials

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

Letters

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

Advertising Policy

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

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

The Journal of Managed Care Pharmacy is indexed by International Pharmaceutical Abstracts (IPA) and Iowa Drug Information Service.

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

Manuscript Preparation

Manuscripts should include, in this order, a title page; an abstract of no more than 400 words; text; references; tables, figures, and graphs; and financial disclosures and conflicts of interest (see Submission Checklist for details).

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

Original Research

An abstract is required in the format of:

- Objective
- Methods
- Results

Subject Reviews

An abstract is required, generally in the format of:

- Objective
- Conclusion
- Keywords

Formulary Management

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

Contemporary Subjects

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

Editorials

These submissions require no abstract.

Letters

These submissions require no abstract or title page.

Reference Style

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

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


2. No author given


3. Journal paginated by issue


4. Book or monograph by authors


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


6. Chapter in a book


7. Government agency publication


8. Dissertation or thesis


9. Paper (or Poster) presented at a meeting


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.

Submit the abstract and signed author attestation forms (available at www.amcp.org/jmcp/ep.pdf). All text should be in a word processing program (preferably Microsoft Word). Tabular material also should be in a word processing program using the tab function to create columns, not using “tables” or “cells.” Figures should be saved in Photoshop or Illustrator and may be re-created by us. We cannot accept PowerPoint graphics. Please identify the format (PC or MAC), all programs used, and all file names.

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

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

Submission Checklist

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

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

Reference Style

expanding the boundaries

ANNOUNCEMENT
for AMCP’s 2003 Educational Conference
October 15–18, 2003
Montréal Convention Center
Montréal, Québec, Canada
http://www.amcp.org

Register before September 15th to receive early-bird rates!
HIGHLIGHTS

Less than 30 years ago, pharmacists simply filled prescriptions, with little input to patient care. Vast networked computer databases were not yet available. Fax machines and photocopiers were not yet common. Pharmacy labels were produced on typewriters.

In the span of an average career, pharmacists have seen the boundaries of the profession expand exponentially — and the possibilities are tantalizingly immense. Today, pharmacists who practice in managed care are taking a front line position in patient health, designing systems and processes that will assure continued access to life-saving medications. Direct pharmacist interaction in disease management programs is growing increasingly prominent as an effective method for keeping not just a patient’s chronic conditions in check, but the cost of health care as well.

When Medicare was designed mid-century, pharmaceuticals were such a small part of the medical equation that they were overlooked in the plan — the consequences of which we struggle with today. The reform of Medicare will no doubt set a standard and a philosophy in medication management that will last well into this century, as the huge bubble of baby boomers enters the program. Additionally, the importance of designing a pharmacy benefit that is more than the provision of product has become apparent. A significant role for managed care pharmacy will be included in the future of Medicare.

The Academy is at the forefront of these many issues, taking a leadership role in the development of the pharmacy tools of the future: AMCP’s Format for Formulary Submissions, and Pharmacy’s Framework for Drug Therapy Management in the 21st Century.

Expand your boundaries — come to Canada in the fall and explore with us the new tools, technologies, theories and techniques of managed care pharmacy. Hear from experts in the policy debate and the research laboratories and learn from your colleagues. Join us for AMCP’s Educational Conference in Montréal, Québec, October 9–12, et bienvenue au Canada!

Michael Bailey, RPh
2003–2004 AMCP President

About the Academy’s 2003 Educational Conference

You will not want to miss the Academy of Managed Care Pharmacy’s (AMCP’s) 2003 Educational Conference, the largest assembly of pharmacy and health care professionals dedicated solely to the issues of managed care pharmacy. It will highlight a myriad of activities, initiatives, breakthroughs and partnerships that are shaping the future of managed care pharmacy. Join your colleagues for this premier networking and educational event. Refer to the Conference Overview in this brochure for a general listing of what will be happening each day. For a more detailed listing of educational sessions and activities occurring at the Conference, please visit AMCP’s website at www.amcp.org.

AMCP’s Managed Care Industry Forum

Friday, October 17, 12:30 pm–2:45 pm

A highlight of AMCP’s Educational Conference is the Managed Care Industry Forum. This unique event provides a setting in which to network with pharmacy colleagues in a relaxed, non-commercial environment. Every attendee is invited to attend this long-standing popular event, featuring many returning key players in pharmacy as well as some new faces representing innovative ways in which the managed care industry is evolving. The Forum serves as a separate but complementary event to AMCP’s Annual Showcase (our commercial exhibit show in the spring) by allowing both participants and exhibitors to network equally through the exchange of educational information only. Take advantage of this opportunity to discuss the latest issues and trends with other managed care pharmacy professionals. If your company would like to participate in the Forum, please call AMCP at (800) 827-2627 or visit www.amcp.org (click on ‘MCIF Prospectus’) to download the Prospectus. For a list of participants, please go to AMCP’s website at www.amcp.org.

Managed Care Pharmacy Residency Showcase

Friday, October 17, 2:45 pm–6:00 pm

AMCP’s 6th Annual Managed Care Pharmacy Residency Showcase features a focused and intimate forum for pharmacy students to meet one-on-one with representatives from managed care pharmacy residency and fellowship programs across the country in preparation for post-graduate activities. This event provides students with the opportunity to determine firsthand if a particular residency program meets their needs and expectations, while networking with fellow students and sharing ideas on their future career plans. The Residency Showcase is also an opportunity for promotion of programs to potential candidates as well as to foster new relationships and exchange valuable information. And again this year, AMCP will hold its Student/Resident/Fellow and New Member Reception in conjunction with the Residency Showcase to enhance attendance! If you are interested in showcasing your program, please call AMCP at (800) 827-2627 or visit www.amcp.org to download the Prospectus when it becomes available in late August.

Receptions

- AMCP’s Opening Night Reception ■ Thursday, October 16, 5:30 pm–7:00 pm
  The Academy of Managed Care Pharmacy will welcome you to Montréal and the 2003 Educational Conference at the Opening Night Reception. Join your colleagues for a relaxed evening of catching up and making plans for the days ahead. It’s a wonderful way to begin the 2003 Educational Conference!

- Student/Resident/Fellow and New Member Reception ■ Friday, October 17, 5:00 pm–6:00 pm
  Don’t miss this special reception where you’ll have an opportunity to mingle with AMCP Board of Directors, students from various schools of pharmacy, and new AMCP members in a relaxed, social environment. Make sure to stay for the drawing for your chance to win a free registration to AMCP’s 16th Annual Meeting & Showcase in San Francisco!
Opening General Session — From Homeless to Harvard
Thursday, October 16, 1:30 pm–2:30 pm
Liz Murray

Liz Murray’s life is a story of triumph over adversity. As the child of cocaine-addicted parents in the Bronx, her life was bitterly grim. There was never food in the house, her home was riddled in filth, drugs were everywhere and the welfare checks were spent before they arrived. By age 15, Liz’s mother had died of AIDS and she was left homeless, living on the streets, riding the subway all night, and eating from dumpsters. Amidst this pain, Liz always dreamed that her life could be much better someday.

“I started to grasp the value of the lessons learned while living on the streets. I knew, after overcoming those daily obstacles that next to nothing could hold me down.”

Determined to take charge of her life, Liz managed to finish high school in just two years while camping out in New York City parks and subway stations. She went on to earn a full college scholarship from The New York Times and entered Harvard in 2000.

Liz’s story is exhilarating and her delivery innocently honest, as she takes audiences on a very personal journey where she achieves the improbable. Lifetime Television produced a movie about Liz’s life story entitled From Homeless to Harvard, and Liz penned her own poignant memoirs in the book, Breaking Night. Come see Murray speak to AMCP attendees about her incredible true-life struggle to overcome overwhelming odds in an inspirational tale of the courage, determination and resolve of a young woman who will touch the lives of all who hear her speak during Thursday’s Opening General Session presentation.

Friday General Session
Friday, October 17, 11:00 am–12:30 pm
Keynote Speaker to be announced

AMCP Town Hall Meeting Session!
Thursday, October 16, 2:45 pm–3:45 pm

New this year, AMCP will feature a Town Hall Meeting educational session that will be focused on one “hot topic” of current interest to AMCP members. The topic will be selected based on its pertinence to managed care pharmacy and will be conducted in a town hall meeting format, enabling the audience to engage in conversation with an expert moderator and one another on the subject matter. This session will be held along with the concurrent educational sessions on Thursday, October 16th from 2:45 to 3:45 pm.

Please plan to attend this exciting forum for AMCP members to discuss a topic that is “hot” among managed care pharmacists this year!

The Academy of Managed Care Pharmacy is approved by the American Council on Pharmaceutical Education (ACPE) as a provider of continuing pharmaceutical education. Individuals may obtain up to 12.50 contact hours of credit (excluding satellite symposia) or 1.25 Continuing Education Units (CEUs) during AMCP’s 2003 Educational Conference. Attendees will be able to process their certificate online via AMCP’s website and immediately download a certificate of proof of attendance after the conference has concluded.

Audience
Health care professionals interested in, or who practice in, managed care, those who want to increase their knowledge of managing and coordinating pharmaceutical care programs, and those responsible for optimizing patient care and satisfaction within managed care.

Learning Objectives
By attending continuing education programming at AMCP’s 2003 Educational Conference, you will be able to:

- Describe successful collaborative practice models and their role in improving medication compliance, patient care, and outcomes.
- Make formulary decisions based on pharmacoeconomic and clinical analysis.
- Recognize how current data and market trends will shape the future practice of managed care pharmacy.
- Learn new developments in formulary methodology in Canada and the U.S.
- Examine legislative and regulatory action influencing managed care pharmacy.
- Cite new pharmacotherapies and technologies that will affect a patient’s quality of life and corresponding innovative disease management tools.
- Learn new professional development tools and trends in your career as a managed care pharmacist.
- Employ strategies to effectively design, administer, and manage the pharmacy benefit.

Contact hours include all Managed Care Essentials, Contemporary Issues, Pharmacy Partnership Briefings, Workshops and Closing Plenary Session. (Posters and the two General Sessions are not eligible for CE.) Your actual contact hours may vary depending on the number of sessions you attend. Please note that this is not yet a confirmed number of contact hours and CEUs.
Who Should Attend?

The Educational Conference attracts close to 2,000 attendees who are managed health care professionals interested in increasing their knowledge of the management and coordination of clinical, pharmacy benefit and pharmaceutical care programs. Those attending are comprised of practicing pharmacists from managed care organizations who are involved in the health management and research, outcomes management and pharmacoconomics; as well as representatives from pharmacy benefit management companies, professors of pharmacy studies throughout academia and representatives from the pharmaceutical industry.

The following professionals should plan to attend:

- Managed Care Executives
- Network Management Professionals
- Pharmacy Directors
- Professional Relations
- Staff/Clinical Pharmacists
- Formulary Management
- Students/Residents/Fellows
- Customer Service
- Medical Directors
- Marketing/Sales
- Professors/Academia

3 Easy Ways to Register!

- Online: www.amcp.org
  - When registering online, you must provide credit card information and e-mail information on your registration will not be processed.
  - When registering online, do not also send your registration by mail or fax.
- By fax: (800) 521-6017
- By mail: ExpoExchange/AMCP
  108 Wilmot Rd., Suite 400
  Deerfield, IL 60015

When registering by fax or mail, please complete the registration form included in this brochure or on the website and return it with the appropriate registration fees to the address or fax number listed above.

AMCP is an organization that represents individuals. In order to be eligible for the AMCP “member” registration fee, you must be an individual member in good standing.

If you have any questions about your membership, please contact the AMCP Membership Department at (800) 827-2627.

Please Note: AMCP Corporate Member employees must be individual AMCP members in good standing to be eligible for the “member” registration fee.

Take advantage of the reduced pre-registration fees by having your form and payment in full (by check or credit card) received on or before September 15, 2003. Registration forms received after this date are subject to the on-site registration fees. See the registration form in this flyer or on the AMCP website at www.amcp.org for fees. Confirmation notices will be sent to all confirmed attendees.

YOUR REGISTRATION FEE INCLUDES ...

All attendees of AMCP’s 2003 Educational Conference must register either in advance or on-site at the Conference to receive a name badge and program materials. Full program registration includes:

- Tote bag
- CD-ROM of presentations
- Final Program
- Faculty handouts

Admission to the following activities is also included: Contemporary Issues Sessions, Workshops, General Sessions, Poster Presentations, Pharmacy Partnership Briefings, Managed Care Essentials and Satellite Symposia. The Opening Night Reception, Managed Care Industry Forum, Lunch and the Managed Care Pharmacy Residency Showcase, as well as food and beverage functions associated with AMCP programming are included.
1. ATTENDEE INFORMATION

FIRST NAME LAST NAME

ADDRESS 1

ADDRESS 2

CITY STATE ZIP CODE

COMPANY

TITLE

MY AMCP MEMBERSHIP NUMBER (IF APPLICABLE)

2. REGISTRATION FEES

Pre-Registration (received on or before Sept. 15, 2003) On-Site (received after Sept. 15, 2003)

Full One Day* Full One Day*

RG01 Active Member (pharmacists) $340 $190 $445 $295
RG02 Associate Member (non-pharmacists) $550 $295 $650 $390
RG03 Government Employee (non-member) $345 $195 $450 $300
RG04 Non-Member $670 $435 $780 $540
RG05 Student Member $40 N/A $40 N/A
RG06 Resident/Fellow/Graduate Mbr $80 N/A $80 N/A
RG07 Student Non-Member $60 N/A $60 N/A
RG08 Press N/A N/A N/A N/A

*If registering for one day, please indicate which day you will be attending:

☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday

To become a member of AMCP, please visit AMCP’s web site at www.amcp.org.

3. METHOD OF PAYMENT

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

☐ Charge $___________ to my credit card (credit card will be charged immediately)

☐ Visa ☐ MasterCard ☐ American Express ☐ Discover

CARD NUMBER EXP DATE

CARDHOLDER PRINTED NAME CARDHOLDER SIGNATURE
TO ARRANGE HOTEL ACCOMMODATIONS, YOU MUST BE REGISTERED FOR THE CONFERENCE.

Please print or type. Please return this form with your conference registration.

ATTENDEE INFORMATION

FIRST NAME LAST NAME
TITLE
COMPANY
ADDRESS 1
ADDRESS 2
CITY STATE ZIP CODE
TELEPHONE FAX
E-MAIL ADDRESS

SHARING ROOM WITH (INCLUDE AGES IF UNDER 19)

HOTEL CHOICE

FIRST CHOICE
SECOND CHOICE
THIRD CHOICE

Type of room: (please check one) □ Single □ Double □ Triple

Special Requests: (Based on availability. Special requests will be made on your behalf, but cannot be guaranteed.)
(Non-smoking room, double/double beds, cribs, etc.)

Arrival Date: October ______, 2003

DEPARTURE DATE: October ______, 2003

METHOD OF PAYMENT

(Note: A valid credit card is required to confirm your hotel reservation. Please use a credit card with an expiration date of October 2003 or beyond as the hotel will be charging one night’s room and applicable taxes to guarantee your room reservation.)

□ Visa □ MasterCard □ American Express □ Discover

CARD NUMBER EXP DATE

CARDHOLDER PRINTED NAME CARDHOLDER SIGNATURE

INTERNET
Make your hotel reservations online through the AMCP web site at www.amcp.org. A valid credit card is required to confirm your hotel reservation. See Method of Payment at the bottom of this form.

FAX
When payment is by credit card, you may complete this form and fax it to ExpoExchange. All arrangements will be confirmed in writing. The fax number is: (800) 521-6017.

MAIL
Simply complete this form and return it to ExpoExchange. A valid credit card is required to confirm your hotel reservation. See Method of Payment at the bottom of this form. All arrangements will be confirmed in writing.

ExpoExchange/AMCP
108 Wilmot Road, Suite 400
Deerfield, IL 60015

HOTEL RATES

Le Centre Sheraton
• $248 Canadian single/double occupancy
• $182 (current US dollars) single/double occupancy

The Fairmont Queen Elizabeth
• $219/$239 Canadian single/double occupancy
• $157/$172 (current US dollars) single/double occupancy

Hotel Wyndham Montreal
• $208 Canadian single/double occupancy
• $149 (current US dollars) single/double occupancy

PLEASE NOTE:

□ You must be a confirmed registrant to obtain housing under AMCP’s block.

□ A valid credit card is required to confirm your hotel reservation. Please use a credit card with an expiration date of October 2003 or beyond as the hotel will be charging one night’s room and applicable taxes to guarantee your room reservation.

□ All new reservations, changes, and cancellations should be made directly with ExpoExchange by Monday, September 22, 2003. Starting Tuesday, September 23, 2003, please contact the hotel directly with any new reservations, changes, and cancellations. Room cancellations must occur by 14 days prior to your arrival.

□ Failure to cancel within the appropriate time frame will result in forfeiture of your entire one-night room deposit.

□ When cancelling a reservation by telephone with the hotel, record the date, cancellation number and the name of the person accepting the cancellation.

Please print or type and return one form per room. You may duplicate this form.
Hotel Rates [Please note that you will be charged the current exchange rate at the time of checkout. For a currency converter, please go to www.xe.com/ucc.]

- **Le Centre Sheraton**  
  - $248 Canadian single/double occupancy  
  - $182 (current US dollars) single/double occupancy

- **The Fairmont Queen Elizabeth**  
  - $219/$239 Canadian single/double occupancy  
  - $157/$172 (current US dollars) single/double occupancy

- **Hotel Wyndham Montréal**  
  - $208 Canadian single/double occupancy  
  - $149 (current US dollars) single/double occupancy

When cancelling a reservation by telephone with the hotel, record the date, cancellation number and the name of the person accepting the cancellation.  

All new reservations, changes and cancellations should be made directly with ExpoExchange by Monday, September 22, 2003.  

A valid credit card is required to confirm your hotel reservation.  Please use a credit card with an expiration date of October 2003 or beyond as the hotel will be charging one night’s room and applicable taxes to guarantee your room reservation.

All new reservations, changes and cancellations should be made directly with ExpoExchange by Monday, September 22, 2003.  Starting Tuesday, September 23, 2003, please contact the hotel directly with any new reservations, changes and cancellations.  **Room cancellations must occur by 14 days prior to your arrival.** Failure to cancel within the appropriate time frame will result in forfeiture of your entire one-night room deposit.

When cancelling a reservation by telephone with the hotel, record the date, cancellation number and the name of the person accepting the cancellation.

If you have any questions regarding registration or housing, please call AMCP at (800) 827-2627 if you have any questions.

Notes Regarding Hotel Accommodations

- You must first register for the 2003 Educational Conference before attempting to reserve a hotel room.  See the registration and housing forms in this brochure for details.  Please do not call the hotel or AMCP to make reservations for the conference.

- A valid credit card is required to confirm your hotel reservation.  Please use a credit card with an expiration date of October 2003 or beyond as the hotel will be charging one night’s room and applicable taxes to guarantee your room reservation.

- All new reservations, changes and cancellations should be made directly with ExpoExchange by Monday, September 22, 2003.  Starting Tuesday, September 23, 2003, please contact the hotel directly with any new reservations, changes and cancellations.  **Room cancellations must occur by 14 days prior to your arrival.** Failure to cancel within the appropriate time frame will result in forfeiture of your entire one-night room deposit.

- When cancelling a reservation by telephone with the hotel, record the date, cancellation number and the name of the person accepting the cancellation.

- If you have any questions regarding registration or housing, please call ExpoExchange at (847) 940-2155.

HOSPITALITY SUITES

Although reservations for hospitality suites are to be made directly with the hotel, AMCP requires that operating hours for hospitality suites — or any other special events — do not conflict with scheduled AMCP events or activities.  Please call AMCP at (800) 827-2627 if you have any questions.

CONFERENCE ATTIRE

‘Business Casual’ attire is encouraged for all AMCP 2003 Educational Conference functions.

RESERVATION OF MEETING ROOMS

AMCP is not releasing meeting space at the Montréal Convention Center.  If you wish to conduct a meeting in any of the AMCP-contracted hotels, AMCP must be notified in writing of your intent.  For a meeting space request form, you may access one on our website (click on ‘meetings’), or contact AMCP at (800) 827-2627 to have a form faxed or mailed to you.  You will be notified via fax or e-mail if your meeting space request has been approved/denied.  You may then contact the venue in which you would like the meeting to take place.

About the City

Montréal is truly an experience: old world charm, French joie de vivre and a modern style all its own.  World-renowned shopping, live jazz music, international cuisine, golf and ski resorts are just a few of the many reasons Montréalers take to the streets, theatres and clubs, hop on bicycles or stroll the city’s many parks year round.  The city’s airports accommodate 62 carriers with direct flights to 150 world destinations.  New York, Boston, Philadelphia and Washington, DC are only a one-hour flight.  Come see for yourself why this fabulous “European” city in continental America is one of the most popular destinations for conventions world-wide!

Montréal Convention Center

The Palais des Congrès de Montréal (Montréal Convention Center) is the centerpiece of the urban renewal and development in downtown Montréal, having just completed a $240 million expansion and renovation.

Architecturally designed to integrate naturally with the city sector it occupies, this ultra-modern facility offers state-of-the-art services while combining form and function in a harmonious and aesthetic union.  A commercial masterpiece, the four faces of the building’s exterior all have a common denominator: glass, illustrating a repeated theme of transparency in bold color.

A celebration of architectural achievement, the newly refurbished convention center accommodates large-scale conventions and exhibitions while offering an intimate and exclusive ambiance for AMCP attendees.

Did you know that...

- **Most Montréal vendors accept U.S. currency?**

- **The average temperature in Montréal in October is 53 degrees Fahrenheit?**

- **The city is officially bilingual?**

- **You will not need adapters for your electrical appliances in Canada?**

Photos courtesy of the Montréal Visitors and Convention Bureau
Visas are not required for U.S. tourists entering Canada from the U.S. for stays of less than 180 days. You will, however, need proof of your U.S. citizenship such as (a) your U.S. passport or (b) an original or certified copy of your birth certificate and photo identification. If you are a naturalized citizen and do not have a passport, you should travel with your naturalization certificate. A driver's license or Social Security card is not valid proof of citizenship.

All U.S. citizens entering Canada from a third country must have a valid passport. Alien permanent residents of the U.S. must present their Alien Registration Card, commonly called the “Green Card.” If you are a dual U.S./Canadian citizen you should always present yourself as a Canadian citizen when entering Canada. However, U.S. citizens should use their U.S. passports when entering or leaving the United States.

Due to international concern over child abduction, single parents, grandparents or guardians traveling with children should have proof of custody or notarized letters from the other parent authorizing travel. (This is in addition to proof of citizenship as explained above.) Any person under the age of 18 and traveling alone should carry a letter from his/her parent or guardian authorizing the trip. Travelers without such documentation may experience delays at the port of entry.

For further information, including information on student or business travel, visitors can contact the Embassy of Canada at 501 Pennsylvania Ave, NW, Washington, DC 20001, (202) 682-1740 or the nearest Canadian consulate.

If You Are Traveling on Air Canada Airlines:

To travel as a visitor from/to Canada, or to/from the U.S.A., a valid passport is the preferred document. For a Canadian or U.S. citizen, an original or certified birth certificate or a citizenship card/certificate plus a valid government-issued picture ID is accepted.

Landed immigrants in Canada from Commonwealth countries seeking to enter the United States as non-immigrants must possess a valid passport and non-immigrant visa in order to enter. For more information visit: [http://travel.state.gov/](http://travel.state.gov/).

Please Note:

Adults traveling with minor children are strongly advised to hold a letter of travel consent signed by the parent(s) or guardian(s) with legal custody. The letter must include the signer's address and phone details. It is recommended that this letter be notarized. If a parent/guardian is divorced or deceased, custody document or death certificate is required.

For Further Information: [http://travel.state.gov/passport_services.html](http://travel.state.gov/passport_services.html)
The following satellites are being held in conjunction with AMCP’s 2003 Educational Conference. Take advantage of the opportunity to attend these dynamic sessions while you are at the conference! Each will offer Continuing Education (CE) through an ACPE-approved provider. Statements of Credit will be handled by each satellite session. For general information and registration, please contact the respective satellite program contact. There are no additional fees required to attend these CE activities.

**Pre-Conference Dinner Symposia ■ Wednesday, October 15 3:00 pm–7:00 pm**
- **SS1** Presentation, Diagnosis and Treatment of Depression — Understanding the Impact of Symptom Variation, Age, Gender, Race and Ethnicity
  Deanna A. Kent • Eli Lilly and Company
  Phone: 317.276.0429 • Email: kent_deanna_a@lilly.com
  This program is supported by an unrestricted educational grant from Eli Lilly and Company

**Pre-Conference Dinner Symposia ■ Wednesday, October 15 3:00 pm–7:00 pm**
- **SS2** Demystifying Pharmaceoeconomics for the Practitioner
  C. Daniel Mullins, PhD • University of Maryland School of Pharmacy
  Phone: 410.706.0879 • Email: dmulllins@rx.umaryland.edu
  This program is supported by an unrestricted educational grant from AstraZeneca

**Breakfast Symposia ■ Thursday, October 16 6:00 am–8:00 am**
- **SS3** The Cost of Noncompliance in Children with Asthma
  Joan Fowler, PharmD • Creative Educational Concepts, Inc.
  Phone: 859.260.1717 • Email: jfowler@ceconcepts.net
  This program is supported by an unrestricted educational grant from AstraZeneca

**Breakfast Symposia ■ Thursday, October 16 6:00 am–8:00 am**
- **SS4** Biologic Therapy: Managing the Future
  Lee Termini • MediMedia Managed Care
  Phone: 267.685.2719 • Email: mdove@medimedia.com
  This program is supported by an unrestricted educational grant from Genentech, Inc.

**Lunch Symposia ■ Thursday, October 16 9:00 am–1:00 pm**
- **SS5** New Concepts in Diabetes: How Multihormonal Regulation Can Improve Glycemic Control
  Debbie Stern, RPh • Rxperts
  Phone: 949.788.2909 • Email: dstern@rxperts.net
  This program is supported by an unrestricted educational grant from Amylin

**Breakfast Symposia ■ Friday, October 17 6:00 am–8:00 am**
- **SS7** Value Based Management and Treatment of Depression: Key Measurements and Interventions
  Kelly Reddy-Heffner • Simpatico Resources, LLC
  Phone: 301.916.9433 • Email: kheffner@simpaticoresources.com
  This program is supported by an unrestricted educational grant from Forest Pharmaceuticals

**Breakfast Symposia ■ Friday, October 17 6:00 am–8:00 am**
- **SS8** The Impact of Insomnia in a Managed Care Environment
  Diana Brixner, RPh, PhD • University of Utah College of Pharmacy
  Phone: 801.581.3182 • Email: dbrixner@hsc.utah.edu
  This program is supported by an unrestricted educational grant from Sanofi-Synthelabo
ANNOUNCEMENT
for AMCP's 2003 Educational Conference
October 15–18, 2003
Montréal Convention Center
Montréal, Québec, Canada
http://www.amcp.org

Register before September 15th to receive early-bird rates!
Analysis of Cost and Utilization of Health Care Services Before and After Initiation of Insulin Therapy in Patients With Type 2 Diabetes Mellitus

MICHAEL S. ROSENBLUM, PharmD, MBA, and MICHAEL P. KANE, PharmD, BCPS

OBJECTIVE: This study analyzed the cost and utilization of health care services before and after the initiation of insulin in treating patients with type 2 diabetes mellitus (DM) to determine if disease-related and total health care costs decreased after patients were started on insulin therapy.

METHODS: 1,177 patients with type 2 DM between the ages of 18 and 65 years and continuously enrolled in a managed care organization for 9 months before and after their insulin start date were included in the study. Medical, facility, and pharmaceutical services in the preinsulin and postinsulin time period were examined along with a subanalysis of all types of medical service categories. Trending analysis was performed by dividing the postinsulin time period into mutually exclusive 2-month periods. The cost of total and disease-related services were studied over these intervals.

RESULTS: Analysis of the total 9-month preinsulin and 9-month postinsulin periods determined that average total and disease-related costs increased after insulin was started, with a mean difference of $2,220 ($0.001) for average total costs and $430 ($0.001) for disease-related costs. Trending analysis, though, demonstrated that much of the cost increase after the start of insulin occurred in the initial 2-month postinsulin period, after which both total costs and disease-related costs decreased by 57% ($0.001) and 49% ($0.001), respectively, throughout the remainder of the postinsulin time period. Facility costs decreased at all postinsulin measurement intervals, while pharmacy costs were the only treatment component to remain above the preinsulin period. Pharmacy services accounted for a greater proportion of the costs in treating patients with type 2 DM in the postinsulin time period, increasing from 19.8% of costs at baseline to 42.8% at postinsulin months 6 to 8.

CONCLUSION: The initiation of insulin therapy in the management of type 2 DM involves an approximate 10% increase in total health care expenditures initially, although this is offset by the consistent and substantial 40% decrease in subsequent total health care expenditures 9 months following insulin initiation.

KEYWORDS: Type 2 diabetes mellitus, Cost and utilization analysis, Administrative claims data, Insulin, Retrospective cohort analysis

J Managed Care Pharm. 2003;9(4):309-16

The cost and utilization of health care services in the United States have demonstrated continued annual increases, with an estimated $1.3 trillion total national health care expenditure in 2000, including $175 billion on prescription drugs. Diabetes mellitus (DM) is representative of this phenomenon. The prevalence of diabetes increased by approximately 40% during the 1990s and currently afflicts an estimated 16 million Americans, 95% of whom have type 2 DM.

Trend analysis is a major contributor to cardiovascular disease. Approximately 50% of type 2 DM patients have diabetes-associated complications at the time of diagnosis. The economic cost of diabetes in 2002 was estimated at $132 billion, with an estimated $92 billion in direct costs. Much of the direct costs of diabetes is associated with the inpatient treatment of diabetes-related complications. Patients with diabetes have per capita medical expenses almost two-and-a-half times higher than their nondiabetic counterparts.

Most patients with type 2 DM eventually fail oral therapy, requiring insulin therapy for disease management. Initially, about one third of patients with type 2 DM require insulin injections to manage their disease. The long-term need for insulin in patients with type 2 DM is even greater since the use of sulfonylurea and metformin therapy is associated with an approximate 20% to 25% primary failure rate and a secondary failure rate of 5% to 7% per year.

In the United Kingdom Prospective Diabetes Study, at 9 years, fewer than 25% of patients receiving a sulfonylurea or metformin were adequately controlled (i.e., fasting blood glucose <140 mg/dL or hemoglobin A1C <7%). Due to factors such as increased risk of severe hypoglycemic episodes, the need to teach patients appropriate insulin use techniques, concern of weight gain, and concerns of the possible exacerbation of hyperinsulinemia and the dysmetabolic syndrome, patients and clinicians are often reluctant to initiate insulin therapy despite the success of insulin in significantly improving glycemic control.
in patients failing oral therapy. This study compared the utilization and costs associated with diabetes-related health care services and total health care services before and after the initiation of insulin therapy with type 2 DM.

Methods

Using administrative claims data, a retrospective cohort analysis was performed of the cost and utilization of health care services for patients with type 2 DM who were started on insulin. Two study perspectives were employed in this project: (1) an overall aggregate analysis using the entire preinsulin and postinsulin period as the time unit for the study, and (2) a postinsulin trending analysis. Short-term was defined as the 2-month time period immediately after the initiation of insulin and long-term defined as the 6- to 8-month period following insulin start.

Data Sources and Study Population

The study population was identified from a managed care database of 12,663,986 members with both medical and pharmacy claims data during a 4-year period between January 1, 1997, and December 31, 2000. The database included medical and pharmacy claims, demographic markers (such as age, gender, and geographic region), provider information (primary care, specialty care, and place of service), and member eligibility, the latter being critical to determining continuous enrollment status. The following inclusion criteria were applied to the entire population to identify the subset of patients with type 2 DM (ICD-9 CM and Generic Product Identifier [GPI: first 4 characters of the 14-character identifier] codes defined in Table 1):• ICD-9-CM 250, 250.x0, or 250.x2 exclusively in the database (excludes 250.x1 and 250.x3 codes); or• ICD-9-CM 250.xx with at least 2 prescriptions from the following GPI drug classes: 2720, 2723, 2725, 2728, 2730, 2750, 2760, 2799; or• ICD-9-CM 250.xx with no antidiabetic pharmacotherapy; or• Members with at least 2 or more prescriptions for oral antidiabetic drug therapy with no ICD-9-CM criteria.

Following the identification of patients with type 2 DM in the overall data set, the final study sample was defined from this population based on the following criteria:• patients between the ages of 18 and 65 years,• insulin initiated as part of the patient’s drug therapy,• eligible in the database for 9 months before and after insulin initiation (18 months of total continuous enrollment),• treatment with oral antidiabetic medications before insulin initiation, and• patient health coverage included medical and pharmacy benefits during the entire database eligibility period.

This population was subsequently used for data comparison and analysis. The following exclusion criteria were applied:• members not continuously enrolled in the database,• members with an ICD-9 CM diagnosis of 250 and receiving insulin exclusively,• members with ICD-9 CM diagnosis of 250.x1 and/or 250.x3 (type 1 DM) exclusively, and• members without medical and pharmacy benefits during their database eligibility.

The Hierarchical Coexisting Condition model, a diagnosis-based risk-assessment model, was used to identify patient comorbidities. Multiple regression analysis was performed using the identified comorbidities, patient age, gender, and region to evaluate the statistical power of these variables in explaining the differences in costs before and after the start of insulin.

Pricing Standardization

Medical and pharmacy costs were standardized across health plans. For professional and ancillary services, a uniform fee schedule was applied based on the resource-based relative value scale. Facility inpatient service pricing was based on an estimated per diem cost, taking into account the diagnostic service category of the facility, the presence of a major surgery, the presence of an ICU stay, and the length of stay. Inpatient price stan-
Comparison of cost and procedure utilization were analyzed during the admission was 250 were reviewed to determine which the admission diagnosis or any documented facility diagnosis during the admission was 250 were considered disease-related. All confinements in which medical costs were defined as all medical claims associated with diabetic supplies (referred to as inpatient facility) costs, with the insulin trigger event included in the postinsulin pharmacy category. Services provided to the study cohort were assigned to one of 29 mutually exclusive types of services (TOS) categories. Results are reported for unadjusted and truncated costs. Truncation was employed to examine the effect of outlier cases on average costs and was set at 3 standard deviations from the mean. Any costs that exceeded 3 standard deviations from the mean were truncated at that level. Aggregate costs and utilization before and after insulin initiation were compared, along with performance of a postinsulin cost-trending analysis. The aggregate cost and utilization analysis included the entire 9-month preinsulin and postinsulin time period (18 months in total). The trending analysis evaluated the costs of health care services in 60-day periods in months 0 to 2, 2 to 4, 4 to 6, and 6 to 8 after insulin initiation, compared to the 2-month preinsulin period. The final 30 days of month 9 were not included in the trending analysis since all comparisons were performed using mutually exclusive 60-day periods.

Diabetes-related drugs were identified using the Medispan 14-character GPI coding system. Medications with a GPI starting with “27” (representing the drug group category of antidiabetic agents of the 14-character code) were classified as antidiabetic drugs and included in the disease-related category, as were diabetic supplies with a GPI starting with 9720 (representing the drug class of diabetic supplies). Diabetes-related medical costs were defined as all medical claims associated with an ICD-9 CM diagnosis code of 250. All confinements in which the discharge diagnosis was 250 were considered disease-related for the purpose of this study. All other confinements in which the admission diagnosis or any documented facility diagnosis during the admission was 250 were reviewed to determine if the facility cost was diabetes-related.

Statistical Analyses
Comparisons of cost and procedure utilization were analyzed using paired t tests and calculated using the PRT option of PROC MEANS in SAS version 8.19 Statistical significance was set at P≤0.05. Multiple regression analysis was performed to test for differences in cost using patient comorbidities, age, gender, and geographic region as variables.

Results
The study identified 215,024 patients (1.7%) of the overall database as having type 2 DM, of which 1,177 patients (0.5% of the patients with type 2 diabetes) met all study eligibility criteria. Patients’ age, gender, and geographic region were similar for both cohorts (Table 2). Of the 9 geographic regions, the Pacific region had the lowest representation in the data set (1.7% in the overall type 2 DM cohort and 0.6% in the study cohort), primarily due to the high degree of capitation financing of medical services in the marketplace and the resulting poor capture of medical claims associated with this managed care operational model. The Middle Atlantic, New England, and South Atlantic regions accounted for 65% of the study cohort. The comorbidities most prevalent in the study population included cardiovascular disease (55.7%), musculoskeletal- connective tissue conditions (41.5%), endocrine and metabolic disease other than diabetes (39.1%), and minor dermatological disorders (29.1%).

Disease-related and Total Costs and Utilization
Pharmacy and medical costs were measured over the entire 9-month preinsulin and postinsulin time period, resulting in an 18-month longitudinal analysis. Disease-related and total pharmacy and medical costs increased in the aggregated 9-month period after insulin initiation compared to the 9-month period prior to insulin use (Table 3). The mean increase in disease-related pharmacy and medical costs were $144 (P<0.001) and $258 (P<0.001), respectively. Disease-related and total facility costs were not statistically different during these periods. Overall disease-related and total costs increased by a mean of $430 (P<0.001) and $2,220 (P<0.001), respectively. Mean differences in disease-related and total truncated costs were less than the unadjusted data, but remained statistically significant.

The overall increase in medications and prescriptions filled
Analysis of Cost and Utilization of Health Care Services Before and After Initiation of Insulin Therapy in Patients With Type 2 Diabetes Mellitus

between the preinsulin and postinsulin time periods were also statistically significant ($P<0.001$). This is consistent with the results for the disease-related and overall pharmacy costs in both measurement periods.

Table 4 shows the comparison of preinsulin and postinsulin cost and utilization of the TOS categories for the total and disease-related analysis, including average differences in procedure utilization and costs. These results were calculated during the 9-month preinsulin and postinsulin analytic time period. Statistically significant increases in disease-related cost and utilization were found in the ancillary service categories of home health/hospice visits and services and supplies, while increases in drug utilization were found in the total health care service analysis. Office visits increased in the disease and total health care service categories, as did laboratory; obstetrics; physical medicine; radiology; and vision, hearing, and speech exams, while facility costs were unchanged.

### Trending Costs

Table 5 compares disease-related and total health care expenditures preinsulin and postinsulin therapy. Average pharmacy, medical, facility, and total disease-related costs during the 2-month time period prior to insulin use were $125, $256, $250, and $631, respectively. Increases in pharmacy, medical, and total costs were noted in the 2-month period immediately after insulin initiation, although only increases in pharmacy costs were statistically significant ($P<0.001$). These cost increases began to reverse in postinsulin months 2 to 4, and fell below the preinsulin levels by months 4 to 6 in all categories except pharmacy. Facility costs decreased in all measurement periods. At months 4 to 6, medical ($P=0.003$), facility ($P=0.013$), and total costs ($P=0.002$) were all significantly below those of the 2-month preinsulin time period.

Comparisons of postinsulin measures at various 2-month intervals demonstrate a consistent decrease in most cost categories as a patient moved out from the insulin trigger event. Pharmacy costs were the only component cost to remain above that of the preinsulin time period, increasing from 19.8% of total costs at baseline to 42.8% at postinsulin months 6 to 8. The results for total costs parallel those for the disease-related category, with costs increasing in the initial 2-month period postinsulin initiation, then decreasing in the subsequent 2-month periods (Table 5). In the preinsulin period, pharmacy, medical, and facility components accounted for 10.5%, 28.0%,

### TABLE 4

<table>
<thead>
<tr>
<th>Differences in:</th>
<th>Preinsulin Mean Cost ($)</th>
<th>Postinsulin Mean Cost ($)</th>
<th>Mean Difference ($)</th>
<th>Standard Deviation of Differences</th>
<th>$P$ Value</th>
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</thead>
<tbody>
<tr>
<td>Pharmacy costs: disease-related</td>
<td>Truncated 508</td>
<td>652</td>
<td>144</td>
<td>504</td>
<td>$&lt;0.001$</td>
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<td></td>
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<td>Pharmacy costs: total</td>
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<td>Medical costs: total</td>
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<td>859</td>
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<td>Facility costs: disease-related</td>
<td>Truncated 286</td>
<td>314</td>
<td>28</td>
<td>3,072</td>
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<td>Untruncated 156</td>
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<td>6</td>
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<td>Facility costs: total</td>
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<td>3,967</td>
<td>450</td>
<td>15,959</td>
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<td>3,208</td>
<td>326</td>
<td>11,260</td>
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<td>Total costs: disease-related</td>
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<td>430</td>
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<td>Distinct drugs</td>
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<td>Number of prescriptions</td>
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<td>12.50</td>
<td>2.94</td>
<td>6.55</td>
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*Results derived for the entire 9-month preinsulin and postinsulin study period. NS = not significant ($P>0.05$).
and 61.5% of the overall total costs. This compares to 22.6%, 42.5%, and 34.9% at postinsulin months 6 to 8. Medical, facility, and total costs all decreased to levels below the 2-month preinsulin measurement period by months 2 to 4, while pharmacy costs continued to remain at levels above the preinsulin measurement period.

**Discussion**

The results of this study demonstrate that while the total health care costs of patients with type 2 DM initially increase when insulin therapy is started, insulin use is associated with an overall decrease in long-term health care expenditures. The initial increase in health care costs was primarily due to an increase in
Analysis of Cost and Utilization of Health Care Services Before and After Initiation of Insulin Therapy in Patients With Type 2 Diabetes Mellitus

Pharmacy and medical costs. Indeed, the number of drugs increased by 40% and the number of prescriptions increased by 31%. However, starting 2 months after insulin initiation, total costs and each component cost, except pharmacy, consistently decreased.

Insulin has been utilized for more than 80 years in the management of diabetes and continues to serve as the definitive treatment of this disease despite the availability of newer pharmacologic modalities. Insulin analogs (e.g., insulin lispro, insulin aspart, and insulin glargine) are the most recent advancement in insulin therapy, attenuating many of the common barriers to traditional insulin use. The use of insulin analogs has provided a more physiologic approach to insulin dosing, allowing a basal/bolus regimen of insulin delivery com-

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Rx</th>
<th>Medical</th>
<th>Facility</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>2-months prior with:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2 months after</td>
<td>51.24 (176.24)</td>
<td>&lt;0.001</td>
<td>49.45 (305.69)</td>
<td>NS</td>
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<td>2-4 months after</td>
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<td>&lt;0.001</td>
<td>-58.97 (197.28)</td>
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<td>4-6 months after</td>
<td>11.84 (136.84)</td>
<td>0.010</td>
<td>-79.26 (176.98)</td>
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<tr>
<td>6-8 months after</td>
<td>17.29 (142.29)</td>
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<td>-80.07 (176.18)</td>
<td>&lt;0.001</td>
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<tr>
<td>0-2 months after with:</td>
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<td></td>
<td></td>
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<tr>
<td>2-4 months after</td>
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<td>-108.42</td>
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</tr>
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<td>4-6 months after</td>
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<td>&lt;0.001</td>
<td>-128.71</td>
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<td>6-8 months after</td>
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<tr>
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<tr>
<td>6-8 months after</td>
<td>2.38</td>
<td>NS</td>
<td>-21.10</td>
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<tr>
<td>4-6 months after with:</td>
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<tr>
<td>6-8 months after</td>
<td>5.45</td>
<td>NS</td>
<td>-80.00</td>
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</tbody>
</table>

*Average costs shown in parentheses. NS=not significant (P>0.05).
parable to that of continuous subcutaneous insulin infusion (insulin pump theory). This “poor man’s” insulin pump method of intensive insulin therapy has allowed improved glycemic control, while lowering the risk of hypoglycemia, and improving patient convenience compared to traditional insulin therapy.20-23 The use of new insulin products, which lessen the clinical barriers to insulin use, may possess an even greater potential to reduce the overall economic burden associated with diabetes management.

Standardizing the pricing for all medical and pharmacy claims was necessary since the database contained members from different health plans with varying benefit designs. Professional and ancillary services were standardized to approximately 120% of the national Medicare payment level. Facility outpatient services were priced using cost-to-charge ratios. In order to create a standardized pharmacy cost, the average payment schedule (net plan after subtraction of member cost share) was applied to each pharmacy service, based on the National Drug Code and the metric quantity on each prescription claim.

An adequate amount of time was required in order to evaluate the cost and utilization of health care services before and after a patient with type 2 DM started insulin therapy. The 9-month data requirement used for defining this study population was adopted to ensure that a large enough population of patients was identified for the analysis while maintaining an adequate longitudinal study time frame. Member turnover in managed care is at such a rate that it is difficult to enroll a large study cohort with substantially more than 18 months of continuous enrollment when using administrative claims data. On average, 28.2% of a health plan’s membership disenrolls annually, according to the Health Plan Employer Data and Information Set national results.24 Of the 215,024 members with type 2 DM in our database, the number of enrollees with 6, 9, or 12 months of data available before and after the start of insulin were 2,254, 1,177, and 325 members, respectively. The 9-month cohort was therefore chosen for this analysis, though consistent results were found when the same analyses were performed on the 6- and 12-month cohorts (data not shown).

The trending analysis individually compared mutually exclusive 60-day postinsulin intervals with the 60-day time period immediately prior to the start of insulin. The authors chose to use the 60-day preinsulin period as a representation of the cost of health care services immediately prior to the initiation of insulin in patients with type 2 DM. These costs were then compared to the 4 postinsulin 60-day time intervals to trend costs after the initiation of insulin therapy (Table 5). Consideration was given to analyzing average monthly costs, but, due to the variability in costs on a month-by-month basis, interpretation of the trending results would have been unreliable. The 60-day intervals were selected to reduce the variation that occurs in a month-by-month analysis while still preserving the ability to analyze postinsulin trending information.

Multiple regression analysis was performed to assess the impact of patient age, gender, comorbid disease, and geographic location on the subsequent change in disease-related and total patient costs. Using unadjusted as well as truncated costs and analyzing each cost component (prescription, medical, and facility), no specific variable was found to be consistently significant in affecting health expenditures.

Spending on diabetes care has continued to increase in the United States, due, in part, to the epidemic increase in number of patients with DM. Cost-effective management of diabetes with insulin therapy has been shown to improve glycemic control in poorly controlled type 2 DM patients without adversely affecting quality of life.25 Using insurance claims data, the results of this study demonstrate the utility of insulin therapy in reducing long-term health care costs in the management of patients with type 2 DM.

## Limitations

Using claims data for retrospective analysis provides several advantages, including access to a large study population with geographic and demographic diversity. The study design attempted to address several potential limitations of using administrative claims data in evaluating patients with type 2 DM. The lower age limit of 18 years was used to restrict the analysis to adult patients, removing any treatment differences that may be present in the pediatric and adolescent patient populations. The upper age limit of 65 years was used to remove the Medicare patient population because their medical benefits are typically different from that of the commercial population, which can limit the ability to capture all relevant claims data. All patients in the study cohort were confirmed to have both medical and pharmacy benefits during the analysis period and were continuously enrolled.

This is a cost and utilization analysis only. The authors acknowledge that outcomes data would provide additional value to the study results. For instance, the ability to identify the patients who attained treatment goals could be helpful in analyzing the cost of effective treatment versus the overall treatment costs that were included in this analysis. Outcomes data, such as laboratory results, are not consistently available as an adjunct to administrative claims and therefore could not be included in this study. The ability to use hemoglobin A1C results, blood pressure measurements, body weight, and lipid levels would add to the results of this study. As most payers and insurers do not capture this information in their claims data, the authors could not report using these data. Other potentially valuable patient characteristics such as body mass index and vital signs at office visits were also unavailable. There is a trend toward more consistent and reliable capture of this information electronically, making efficient access to additional data elements a possibility in future research.

The authors chose to standardize medical and pharmacy costs across the database in an attempt to reduce bias in inter-
pretation of the results. Standardization of prices (health plan costs) might have masked some of the regional variation in preinsulin and postinsulin costs. Any differences uncovered are therefore driven by the utilization factors and the choice of therapy not by variation in health plan costs associated with geographic region or drug or medical benefit design.

The longitudinal time period used for the study was 18 months of continuous enrollment for each patient included in the analysis. This provided a 9-month preinsulin and 9-month postinsulin analytic window to study the differences in cost and utilization before and after the addition of insulin to the drug regimen. The authors recognize the value in using longer time periods, especially when studying chronic diseases such as DM. To expand the analytic time period, though, an alternate study design would be necessary that might impact the practical nature of performing this analysis.

**Conclusion**

Initiation of insulin therapy in the management of type 2 DM was associated with an approximate 10% initial increase in health care expenditures, followed by a consistent and substantial 40% decrease in subsequent total health care expenditures 9 months following insulin start. This, coupled with the clinical effectiveness insulin offers to many patients with type 2 DM and the progress that has been made in removing the barriers to its use, appears to add support for clinicians to consider insulin therapy earlier in the diabetes treatment algorithm.

To maximize the clinical and economic benefit that insulin can offer patients with type 2 DM, clinicians need to determine the optimal time to introduce this treatment option into each patient’s regimen. While insulin may be therapeutically superior to oral therapies, its use may also be cost effective by reducing the cost and utilization of health care services in patients with this disease.

**DISCLOSURES**

Funding for this research was provided by Aventis Pharmaceuticals and was obtained by author Michael S. Rosenblum. Rosenblum received financial support from Aventis, and author Michael P. Kane is a member of a speakers bureau for Takeda, Aventis, and Pfizer pharmaceutical companies. Rosenblum served as principal author of the study and was responsible for study concept and design. Analysis and interpretation of data and drafting of the manuscript were contributed by both authors. Critical revision of the manuscript was the work of Rosenblum. Statistical expertise was contributed by R. Alan Bowman, PhD, Associate Professor, Union College, Schenectady, NY. Administrative, technical, and/or material support was provided by Bowman and Integrail.

**REFERENCES**

Early Switch and Early Discharge Opportunities in Intravenous Vancomycin Treatment of Suspected Methicillin-Resistant Staphylococcal Species Infections

STEPHEN PARODI, MD; DAVID C. RHEW, MD; and MATTHEW BIDWELL GOETZ, MD

ABSTRACT

BACKGROUND: Patients with methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant coagulase negative staphylococci (MR-CoNS) infections are usually treated with intravenous (IV) vancomycin and remain hospitalized for the duration of IV therapy. Oral linezolid has excellent bioavailability and activity against MRSA and MR-CoNS and offers the potential for outpatient treatment of MRSA and MR-CoNS infections.

OBJECTIVE: To determine the potential for early switch (ES) from IV vancomycin to oral linezolid and subsequent early discharge (ED) in hospitalized, adult patients treated for an MRSA or MR-CoNS infection.

METHODS: We conducted a retrospective cohort study at the Veterans Administration Greater Los Angeles Healthcare System from January 1 through December 31, 2000. Potential reductions in vancomycin use, hospital length of stay (LOS), and economic savings were determined.

RESULTS: A total of 103 of 177 (58%) treatment courses for MRSA or MR-CoNS infections were potentially eligible for ES, with annual and mean decreases in vancomycin use of 535 defined daily doses and 5.2 days per event. Of the ES cohort, 55 of 103 (53%) courses were potentially eligible for ED, with an annual and mean reduction in LOS of 181 days and 3.3 days per event. The total potential savings was $220,181, at an average of $3,478 per event.

CONCLUSION: Early switch to oral linezolid for treatment of MRSA or MR-CoNS infections could reduce vancomycin use, hospital length of stay, and economic costs.

KEYWORDS: Oxazolidinone, Vancomycin, Length of stay, Methicillin resistance, Staphylococcal infections

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Methicillin-resistant *Staphylococcus aureus* (MRSA) is a virulent pathogen traditionally associated with severe nosocomial infections. Methicillin-resistant coagulase negative staphylococci (MR-CoNS) is occasionally associated with infection, usually catheter-related. With a few notable exceptions, epidemiologic studies in the United States and Western Europe have demonstrated increasing prevalence rates for MRSA and MR-CoNS over the past 2 decades. Data from the 1997 to 1999 SENTRY Antimicrobial Surveillance Program show that MRSA accounts for 34% of all U.S. nosocomial *S. aureus* isolates. Furthermore, data from the 2000 Healthcare Cost and Utilization Project Nationwide Inpatient Sample sponsored by the Agency for Healthcare Research and Quality show that *S. aureus* is implicated in 634 per 100,000 hospital discharges. These figures suggest that MRSA is implicated in 217 per 100,000 hospital discharges in the United States. Community-acquired MRSA infections are also becoming more common and represent a new threat to patients outside of the hospital setting.

A comparison of outcomes between MRSA and methicillin-sensitive *S. aureus* (MSSA) infections suggests a higher patient mortality rate with the resistant strains (21% versus 8%). Also, results from a cohort study show that MR-CoNS bacteremia is associated with a higher mortality rate and longer length of stay as compared to matched controls. At present, therapeutic options for reliably (with 99% to 100% activity) treating MRSA and MR-CoNS include vancomycin, teicoplanin, quinupristin-dalfopristin, and linezolid (Zyvox–Pfizer). Vancomycin has become the drug of choice for treating MRSA infections due primarily to its low cost and relatively low toxicity. However, reliance solely on vancomycin for control of MRSA is suboptimal because this antibiotic requires both therapeutic drug monitoring and intravenous (IV) administration, exerts selective pressure on a hospital’s microbial flora, and does not have comparable bactericidal activity when compared to β-lactam antimicrobials in the treatment of serious MSSA infections. Staphylococcal intermediate resistance and full resistance to vancomycin have also been reported.

The inpatient costs of treating MRSA infections with IV antibiotics are significant, and there is an increasing need to provide effective treatment of MRSA in the outpatient setting. The annual national pecuniary burden due to MRSA in a Canadian model approximates $42 million to $59 million. The excess expenditures for MRSA infections are a result of...
longer hospitalizations, isolation of infected or colonized patients, infection control screening programs, and administration of IV. 7,25,26 Oral linezolid (Zyvox) has excellent bioavailability and activity against MRSA and MR-CoNS. Linezolid is the first oxazolidinone antimicrobial approved for the treatment of MRSA and MR-CoNS infections. The efficacy of linezolid for MRSA and MR-CoNS infections when compared to standard therapy is favorable. Microbiologic and clinical cure rates with linezolid are equivalent to ß-lactam therapy of MSSA skin and soft tissue infections and vancomycin treatment of MRSA-related nosocomial pneumonia. 27,28 The 100% oral bioavailability of linezolid may allow for early switch (ES) to oral therapy for MRSA and MR-CoNS infections. 29,30 Several studies have affirmed the safety and efficacy of switching patients who are clinically stable to appropriate oral antibiotics in order to decrease hospital length of stay (LOS) for a variety of infections. 31-38 Data from a phase III clinical trial comparing the clinical efficacies of linezolid and vancomycin support the potential for linezolid ES for MRSA infections. This study shows that similar outcomes are observed with each agent, and a potential decrease in LOS is demonstrated for complicated skin and soft-tissue infection during the initial 2 weeks of hospitalization. 39 We have conducted a retrospective cohort study to evaluate the potential (not actual, as no intervention has been performed) opportunity for decreased vancomycin use, shorter LOS, and resulting economic benefits of linezolid oral switch therapy for patients with MRSA and MR-CoNS infections. Patient characteristics predictive of eligibility for ES and early discharge (ED) from the hospital are assessed.

### TABLE 1  Criteria for Early Switch (ES) and Early Discharge (ED)

<table>
<thead>
<tr>
<th>Early-Switch Criteria</th>
<th>Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afebrile</td>
<td>• No temperature &gt;37.8°C for 24 consecutive hours</td>
</tr>
</tbody>
</table>
| Ability to take oral medications | • Fulfillment of one of the following:  
  - Oral diet or feeds via a nasogastric/gastric feeding tube  
  - Taking oral medications |
| Clinical improvement  | • All infections: No evidence of hypotension or shock, clinician-documented impression of clinical improvement  
  - Pneumonia: At baseline O2 requirements, Po2>55mmHg or O2 sat >90%, stable or improved pulmonary infiltrates, improvement in cough, sputum production, hemoptysis if present  
  - Skin/soft tissue infection: Cessation of purulent drainage from a wound if present, improved edema/induration/erythema of the cellulitic area and/or wound  
  - Urinary tract infection: Improved dysuria, suprapubic pain, costovertebral angle tenderness, decreased pyuria  
  - Line infection: Resolution of purulent drainage from the catheter site, improved erythema/induration of the line site, resolution of bacteremia if repeat cultures were performed  
  - Primary bacteremia: Resolution of fever, chills, rigor, resolution of bacteremia with repeat cultures if performed  
  - Abscess: Adequate drainage with intravenous antimicrobials, radiographic and/or clinical improvement of the abscess if treated with intravenous antimicrobials alone |
| No non-MRSA or MR-CoNS infections requiring intravenous antimicrobials | • No resistant gram-negative infections requiring carbapenems, intravenous cephalosporins, aminoglycosides  
  - No fungal infections requiring amphotericin B or intravenous triazoles |
| Normal/normalizing white blood count (WBC) | • Normal: ≤11,000 WBC/µL  
  • Normalizing: Three consecutive decreasing WBCs on 3 separate days with the final value ≤12,000 WBC/µL |
| No linezolid contraindications | • No hypersensitivity to linezolid  
  • Absolute neutrophil count ≥1,000/µL  
  • Total WBC ≥1,500/µL  
  • Hematocrit ≥20%  
  • Platelets ≥75,000/µL |

<table>
<thead>
<tr>
<th>Early-Discharge Criteria</th>
<th>Requirements</th>
</tr>
</thead>
</table>
| Euvolemia                | • Serum sodium <150 mmol/L  
  • BUN/creatinine ratio ≤20:1 or at baseline if receiving renal replacement therapy  
  • Orthostatic blood pressure changes ≤20 mmHg |
| Stable mental status     | • At previous or new baseline mental status |
| Stable comorbid illness(es) | • All other medical conditions stable and not requiring further diagnostic workup or treatment which would necessitate hospitalization |
| Stable social situation  | • Discharge to home, acute rehabilitation, or a long-term care facility  
  • No homelessness  
  • Adequate support at the receiving home/facility for the patient's infectious disease diagnosis or comorbid conditions |
Early Switch and Early Discharge Opportunities in Intravenous Vancomycin
Treatment of Suspected Methicillin-Resistant Staphylococcal Species Infections

Materials and Methods

Patient Identification
The Veterans Administration Greater Los Angeles Healthcare System (GLA) inpatient facility is a 583-bed tertiary-care teaching hospital. All patients older than or equal to 18 years who were hospitalized during a full vancomycin treatment course of a microbiologically confirmed or presumed infection with MRSA or MR-CoNS were identified through a review of pharmacy and microbiology records from January 1 through December 31, 2000. A full treatment course was defined as the therapeutic administration of vancomycin for at least 7 consecutive days. A single dose of vancomycin was considered therapeutic for 7 days in patients dependent on hemodialysis. A defined daily dose was the amount of vancomycin required to achieve daily therapeutic trough levels (>10 µg/mL) for a given patient.

Microbiologic confirmation of MRSA or MR-CoNS infection required either 1 culture positive from a sterile body site or a nonsterile site supported by clinical evidence of infection. Presumed infection was defined as a clinical assessment of suspected MRSA or MR-CoNS infection without microbiologic confirmation. We included patients with presumed infection in our analysis because, in some instances (e.g., patients with MRSA colonization or prior MRSA infection or patients with clinical evidence of line sepsis, presumably due to MR-CoNS), the posttest probability for infection with MRSA or MR-CoNS remained high despite negative culture results. All isolates were identified with standard microbiologic methods, and susceptibility testing was performed according to the guidelines of the National Committee for Clinical Laboratory Standards.

The following conditions excluded patients from further analysis: transfer to another acute-care facility, death during hospitalization while on vancomycin therapy, or a diagnosis of microbiologically documented or presumed MRSA or MR-CoNS endocarditis or osteomyelitis. We excluded patients with MRSA or MR-CoNS endocarditis or osteomyelitis from our study because these patients would have required an extended course of antibiotics (often 4 to 6 weeks), and the safety profile of long-term use of linezolid has not been well established. In the absence of these safety data, we determined that we could not accurately determine the true cost savings of ES and ED with oral linezolid for these patients. Hospital acquisition of an infection was defined as isolation and initiation of treatment for MRSA or MR-CoNS greater than 48 hours after admission.

Demographic data, including age, gender, nursing home resident status, admit and discharge ward, requirement for intensive care unit (ICU) treatment, and comorbid conditions, were collected for all patients meeting the above criteria. A patient could have more than one vancomycin course included in the study if the additional treatments were indicated for an infection at a different site, a new infection at the original site occurring at least 7 days after clinical cure of the preceding infection, or continuous vancomycin administration through more than one hospitalization. Patients with positive MRSA or MR-CoNS cultures were evaluated for type of isolate (e.g. MRSA, MR-CoNS), site, and number of positive specimens. Cultures were clinically relevant if they correlated with the documented site of infection and were obtained in the 3 days prior to or 2 days after the initiation of vancomycin. Isolation of MR-CoNS was clinically relevant only with documentation of active infection regardless of the site and sterility of the specimen. MRSA or MR-CoNS isolation in the 30 days prior to hospitalization was considered chronic colonization. Infection or colonization with vancomycin-resistant enterococci (VRE) was also recorded. Duration and timing of vancomycin administration with respect to hospital admission, discharge, and clinically relevant MRSA or MR-CoNS positive cultures were obtained for each treatment course. Discharge disposition and duration of hospitalization were outcome measures. The GLA Institutional Review Board approved the study design and methods of data collection.

Early Switch and Early Discharge Criteria
Qualification for ES or ED required fulfillment of all respective criteria listed in Table 1 at least 1 day prior to recorded hospital discharge. All treatment courses were evaluated for ES; however, ED was assessed for only the ES-eligible cohort. Certain MRSA and MR-CoNS infections were ineligible for ES (but still eligible for inclusion in the study), including meningitis, septic arthritis, and septic thrombophlebitis. The reason for this was because, at present, linezolid is not approved for use in these areas, and we did not wish to promote directly or indirectly the unapproved usage of linezolid. Patients who were eligible for ES but who were not eli-
ble for ED on the same day as ES received a reevaluation of each subsequent hospital day to ensure that they remained eligible for ES while hospitalized. Patients who had a single relapse in their clinical condition (e.g., developed 1 episode of fever) but who otherwise fulfilled all other ES criteria remained eligible for continuation on oral therapy.

Two authors (Parodi and Rhew) reviewed the data for criteria for ES and ED and a third author (Goetz) served to resolve differences of opinion. Univariate and multivariate analyses were performed to determine the independent predictors of eligibility for ES and ED.

Cost Analysis
We performed a cost analysis using drug acquisition costs and specialty-based hospital costs (Table 2). Hospital costs were obtained from the GLA's computerized cost-accounting system called the Decision Support System. The individual costs for each patient's hospitalization were not readily available. Thus, the mean cost (not charge) per day of the hospital bed type (e.g., medical, surgical, ICU, etc.) occupied at the time of ED was obtained. The total bed cost consisted of the nursing, laboratory, pharmaceutical, radiological, surgical, and miscellaneous costs. The cost of isolation of MRSA patients was not calculated because patients on the regular medicine wards, who are either infected or colonized with MRSA, are not isolated or cohorted at GLA.

The potential economic impact of oral linezolid therapy on MRSA or MR-CoNS infections was calculated for patients eligible for ED only. The cost savings for ES without ED were not calculated because the difference in drug costs between generic vancomycin and linezolid was relatively insignificant as compared to the added expense of continued hospitalization.

Statistical Analysis
Statistical analysis was performed using EpiInfo version 6.04c and SPSS version 11.0 (Centers for Disease Control, Atlanta, GA, http://www.cdc.gov/epiinfo/epimanual.htm). The cohorts eligible and not eligible for linezolid ES were compared to identify the predictive variables of ES. ED predictors were calculated from the subset of vancomycin courses eligible for ES. All categorical variables were compared using the uncorrected \( \chi^2 \) or the Fisher exact test, as appropriate. Continuous variables were evaluated with Student's \( t \) or Mann-Whitney tests for normal and nonnormally distributed data, respectively. A conditional stepwise logistic regression model included all significant univariate ES and ED predictors. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated. A \( P \) value of less than 0.05 was considered significant.

Results
Patient Demographics
Of the 895 episodes of exposure to MRSA, MR-CoNS, or vancomycin, 177 (19.8%) met inclusion criteria for further evaluation. Reasons for exclusion are outlined in Figure 1. The 177 treatment courses were administered to 138 individual patients. The majority of patients received a single vancomycin course (111 of 138, 80.4%). The demographics and baseline characteristics of the patient population are listed in Table 3. Most patients (92.8%) had at least 1 comorbid condition, and 33 (23.9%) had 3 or more active medical problems. A wide range of MRSA or MR-CoNS infections were treated. Eighty-six (48.6%) of the treatment courses were for infections not hospital-acquired. Most of these patients had 1 or more underlying risk factors for MRSA or MR-CoNS infection, including the following: resident of a chronic care facility (34.8%), chronic indwelling catheters (e.g., intravenous or urinary, 32.6%), known previous hospitalization during the
Early Switch and Early Discharge Opportunities in Intravenous Vancomycin Treatment of Suspected Methicillin-Resistant Staphylococcal Species Infections

study period (30.2%), positive MRSA or MR-CoNS cultures within the antecedent month (16.3%), recent outpatient surgical procedures at GLA (10.5%), and history of intravenous drug use (9.3%). No clearly defined risk factors were found in 19 (22.1%) episodes.

Microbiologic Characteristics

The general microbiologic characteristics for the patient population are outlined in Table 4. Most (70.9%) of the clinically relevant cultures were positive for MRSA. One third of all infections were complicated by bacteremia, and 29 (49.1%) of these bacteremias were due to MRSA. Chronic MRSA or MR-CoNS colonization was documented in 35 (27.5%) of the cases. VRE colonization or infection occurred in 21 (11.9%) of the treatment events, with urine (52.4%) and blood (23.8%) comprising the most common sites of isolation.

Treatment

The mean duration of therapy with vancomycin was 16.6 ± 13.5 days. When a clinically relevant MRSA or MR-CoNS culture was present, vancomycin was started within 1.61 ± 1.70 days. Vancomycin was initiated an average of 9.72 ± 15.4 days after the admission date. Adjunct procedures aimed at removing the focus of MRSA or MR-CoNS infection were required in 65 (36.7%) of the treatment events, and 7 (4.0%) episodes necessitated a second intervention. Central venous catheter removal (43.0%), surgical procedures (26.2%), foley/suprapubic catheter changes (15.6%), and bedside abscess incision and drainage (13.8%) were the most common adjunct therapies.

Potential for Early Switch and Early Discharge With Oral Linezolid

The first and second investigators reached agreement with respect to ES and ED eligibility and timing in greater than 90% of the episodes. There were 12 (6.8%) and 8 (7.8%) conflicts regarding ES and ED qualification, respectively. The third investigator was able to resolve all differences of opinion utilizing the judgment made by either the first or second investigator.

A total of 103 (58.2%) episodes were potentially eligible for ES to oral linezolid and 55 (31.1%) for ED. The reasons for not qualifying for ES or ED are listed in Table 5. Presumed or confirmed infection with resistant gram-negative organisms in cases of nosocomial pneumonia (8 episodes), line infection (3), intra-abdominal abscess (1), urinary tract infection (1), and cellulitis (1) preempted ES to oral linezolid in 14 (7.9%) of the episodes. If a patient qualified for ES, the most common reason preventing ED was an unstable comorbid condition.

The significant patient characteristics predictive of eligibility for ES and ED are listed in Table 6. Independent predictors of ES were no complex primary diagnosis requiring continued intravenous vancomycin, lack of VRE colonization or infection, no diagnosis of pneumonia, the absence of a pulmonary comorbidity, having a culture positive for MRSA regardless of clinical significance, and shorter duration of vancomycin therapy. ED predictors included shorter hospitalization, younger age, and no requirement for ICU care. Comparisons between patients eligible and not eligible for ES and similar comparisons for patients eligible and not eligible for ED are presented in Table 7.

A sensitivity analysis for ES and ED predictors was subsequently performed that excluded treatment courses for complex MRSA or MR-CoNS infections (e.g., meningitis, infections

| Variable | n (%)
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Male</td>
<td>171 (96.6)</td>
</tr>
<tr>
<td>Age: mean years ± SD</td>
<td>67.9 ± 12.6</td>
</tr>
<tr>
<td>Nursing home resident</td>
<td>59 (33.3)</td>
</tr>
<tr>
<td>Number of comorbidities: mean number ± SD</td>
<td>1.85 ± 1.01</td>
</tr>
<tr>
<td>Comorbid conditions</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>80 (45.2)</td>
</tr>
<tr>
<td>Neurologic</td>
<td>64 (36.2)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>54 (30.5)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>36 (20.3)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>40 (22.6)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>34 (19.2)</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>17 (9.6)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>6 (3.4)</td>
</tr>
<tr>
<td>HIV</td>
<td>3 (2.2)</td>
</tr>
<tr>
<td>Mean (± SD) number of MRSA or MR-CoNS infections*</td>
<td>1.28 ± 0.64</td>
</tr>
<tr>
<td>One</td>
<td>111 (80.4)</td>
</tr>
<tr>
<td>Two</td>
<td>17 (12.3)</td>
</tr>
<tr>
<td>Three</td>
<td>8 (5.8)</td>
</tr>
<tr>
<td>Four</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Hospital-acquired infection</td>
<td>91 (51.4)</td>
</tr>
<tr>
<td>Primary diagnosis</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>53 (29.9)</td>
</tr>
<tr>
<td>Skin/soft tissue infection</td>
<td>31 (17.5)</td>
</tr>
<tr>
<td>UTI</td>
<td>28 (15.8)</td>
</tr>
<tr>
<td>Line infection</td>
<td>27 (15.3)</td>
</tr>
<tr>
<td>Primary bacteremia</td>
<td>8 (4.5)</td>
</tr>
<tr>
<td>Abscess any site</td>
<td>9 (5.1)</td>
</tr>
<tr>
<td>Other†</td>
<td>21 (11.9)</td>
</tr>
<tr>
<td>ICU data</td>
<td></td>
</tr>
<tr>
<td>Admit to ICU</td>
<td>62 (35.0)</td>
</tr>
<tr>
<td>Required ICU stay</td>
<td>91 (51.4)</td>
</tr>
</tbody>
</table>

* Methicillin-resistant Staphylococcus aureus (MRSA) and methicillin-resistant coagulase negative staphylococci (MR-CoNS).
† Meningitis (6), hemodialysis access infection (4), septic arthritis (2), septic thrombophlebitis (2), peritonitis (2), mastoiditis/otitis (2), infected pseudoaneurysm (1), empyema (1), neutropenic fever (1).
involving prosthetic materials, etc.). The multivariate model demonstrated not having MRSA or MR-CoNS pneumonia (OR 3.82, 95% CI 1.86-7.83) and lack of VRE colonization or infection (OR 3.80, 95% CI 1.33-10.8) remained independent predictors of ES, while all other variables were no longer statistically significant. ED predictors were unchanged from the primary analysis.

Subanalysis of the treatment courses was performed to define the characteristics of the population with hospital-acquisition of infection. Nosocomial MRSA or MR-CoNS infections were more likely to have a longer total hospitalization (39.9 versus 18.5 days, P<0.001), increased LOS after the cessation of vancomycin therapy (16.7 versus 12.0 days, P<0.001), greater requirement for ICU care (65.9% versus 36.1%, P<0.001), and more cardiovascular comorbidity conditions (54.6% versus 34.9%, P<0.001). There were no significant differences with respect to age, gender, primary diagnoses, and discharge disposition.

### Table 4: Microbiologic Data (177 events)

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA or MR-CoNS* culture positive</td>
<td>134 (75.7)</td>
</tr>
<tr>
<td>Number of MRSA or MR-CoNS positive cultures: mean ± SD</td>
<td>2.31 ± 1.53</td>
</tr>
<tr>
<td>Clinically relevant cultures</td>
<td>127 (94.7)</td>
</tr>
<tr>
<td>Number of clinically relevant cultures: mean ± SD</td>
<td>1.75 ± 0.92</td>
</tr>
<tr>
<td>Clinically relevant culture from sterile site</td>
<td>60 (47.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of clinically relevant isolate</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA</td>
</tr>
<tr>
<td>MRSA and MR-CoNS</td>
</tr>
<tr>
<td>MR-CoNS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Initial site of clinically relevant culture requiring vancomycin/patients with clinically relevant MRSA or MR-CoNS cultures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
</tr>
<tr>
<td>Sputum/bronchoscopy specimen</td>
</tr>
<tr>
<td>Urine</td>
</tr>
<tr>
<td>Deep wound</td>
</tr>
<tr>
<td>Vascular catheter</td>
</tr>
<tr>
<td>Skin/surface swab</td>
</tr>
<tr>
<td>Sterile fluid site†</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

| MRSA or MR-CoNS bacteremia at any time before/during vancomycin treatment course | 59/177 (33.3) |

* Methicillin-resistant Staphylococcus aureus (MRSA) and methicillin-resistant coagulase negative staphylococci (MR-CoNS).
† Pleural (1), synovial (1), peritoneal (1).

### Table 5: Potential Early Switch (ES) and Early Discharge (ED) for MRSA or MR-CoNS Infections*

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential events eligible for ES</td>
<td>103/177 (58.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reason for no ES (74 events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary infection required full-course of vancomycin</td>
</tr>
<tr>
<td>WBC did not normalize</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Presumed or confirmed non-MRSA or MR-CoNS infection—required IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobials</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Inability to take oral medications</td>
</tr>
<tr>
<td>Discharged on the day of ES</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Potential events eligible for ED (55/177, 31.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reason for no ED (122 events)</td>
</tr>
<tr>
<td>No ES</td>
</tr>
<tr>
<td>Unstable comorbid condition</td>
</tr>
<tr>
<td>Unstable social issues</td>
</tr>
<tr>
<td>Dehydration</td>
</tr>
<tr>
<td>Acute changes in mental status</td>
</tr>
<tr>
<td>Discharged on the day of ED</td>
</tr>
</tbody>
</table>

* Methicillin-resistant Staphylococcus aureus (MRSA) and methicillin-resistant coagulase negative staphylococci (MR-CoNS).

### Outcomes and Economic Analysis

More than half of the patients (98 of 177, 55.4%) required discharge to a long-term care facility or nursing home after their treatment course. The remaining cases were discharged to home (51 of 177, 28.8%) and acute rehabilitation (28 of 177, 15.8%). Table 8 illustrates the prospective potential savings affected by ES to oral linezolid followed by ED. The mean savings per eligible treatment course in vancomycin use and LOS were 5.2 and 3.3 days, respectively. The overall potential savings amounted to $220,181. The mean savings per treatment course was $4,003 ± $3,631. However, the 2 episodes with the largest decreases in hospitalization had estimated cost savings of greater than $15,000, which was more than 50% greater than the next set of data points. Thus, these outlying values were subsequently excluded from the calculation of the mean, leaving a final savings of $3,478 ± $2,392 per episode.

### Discussion

**Relevance of Findings**

We found that, in our facility, many patients with a broad range of MRSA or MR-CoNS infections often remain hospitalized to receive intravenous vancomycin after achievement of clinical stability. A significant number of these patients could avoid prolonged hospital confinement and subsequent morbidity by applying linezolid ES and ED. The potential economic savings due to this intervention are substantial (although the large standard deviations around our cost-savings calculations may...
potentially limit the economic benefits of applying ED). Other possible benefits from ES and ED include improved patient satisfaction with their care, removal of intravenous lines, and a reduction in the risk of acquiring new nosocomial infections.  

The advantages to ES and ED are not limited to the individual patient. Early discharge effectively diminishes the reservoir of MRSA or MR-CoNS-infected patients from the hospital population. This outcome is desirable for several reasons. First, the number of opportunities for transmission of MRSA or MR-CoNS to noncolonized patients or health care workers is reduced. Second, the concomitant decline in vancomycin use would decrease selective pressure for resistant organisms such as VRE. Finally, fewer hospitalized MRSA or MR-CoNS patients would free otherwise-committed human and financial resources for intensified infection control measures such as surveillance, contact isolation, personnel education, and improved antimicrobial utilization programs. 

Greater savings might be possible with disease processes requiring prolonged therapy such as MRSA or MR-CoNS endocarditis or osteomyelitis. Clinical experience using linezolid for either of these conditions is limited, and, to date, the agent does not have an approved indication for their treatment. For these reasons, we excluded such infections from our analysis. Even if such therapy was validated, long-term linezolid is not without risk because of the potential for emergence of resistance and development of drug toxicity. MRSA resistance to linezolid is difficult to induce in vivo but has occurred in a patient with an infected peritoneal dialysis catheter that was not removed during a month of continuous linezolid therapy. Discharge of such patients to long-term care facilities, where MRSA control measures may be limited, raises the possibility of transmission of linezolid resistant S. aureus strains in the community. Furthermore, approximately one third of patients experience reversible thrombocytopenia after 10 days of linezolid therapy. Anemia and pancytopenia are other adverse outcomes associated with prolonged treatment. The implementation of successful ES therapy for MRSA or MR-CoNS infections will require appropriate patient selection with respect to the type of infection, absence of prosthetic material or undrained foci of infection, and the ability to tolerate therapy.

### Limitations

Our study had several limitations. First, in our economic analysis, individual costs for each patient were unavailable, which required us to perform estimations rather than use patient-specific data. Second, we did not include the impact of ES with oral linezolid on subsequent hospitalizations, although we have no reason to believe that subsequent hospital admissions would either decrease or increase with the application of ES with linezolid. We also did not address the potential for adverse effects secondary to linezolid and the costs associated with treating these adverse events. However, in our study, we excluded patients from ES who had contraindications to linezolid. The potential for patient non-compliance with outpatient oral linezolid treatment was not incorporated into our economic modeling assumptions, although the once-daily dosing of linezolid is likely to enhance compliance with this medication. A formal cost-effectiveness analysis could...
Early Switch and Early Discharge Opportunities in Intravenous Vancomycin
Treatment of Suspected Methicillin-Resistant Staphylococcal Species Infections

TABLE 7: Comparisons Between Criteria for Patients Eligible and Not Eligible for Early Switch (ES) and Early Discharge (ED)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Eligible for ES (n=103)</th>
<th>Not Eligible for ES (n=74)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay</td>
<td>24.0 days</td>
<td>37.2 days</td>
<td>0.004</td>
</tr>
<tr>
<td>Duration of vancomycin</td>
<td>14.6 days</td>
<td>19.5 days</td>
<td>0.04</td>
</tr>
<tr>
<td>Eligible for ED (n=55)</td>
<td></td>
<td>Not Eligible for ED (n=122)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>65.2 years</td>
<td>69.1 years</td>
<td>0.03</td>
</tr>
<tr>
<td>Length of stay</td>
<td>14.6 days</td>
<td>36.3 days</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Days until initiation of vancomycin</td>
<td>5.91 days</td>
<td>11.4 days</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of vancomycin</td>
<td>15.5 days</td>
<td>17.1 days</td>
<td>0.08</td>
</tr>
</tbody>
</table>

TABLE 8: Outcomes and Economic Analyses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential decrease in vancomycin utilization (n=103)</td>
<td>535</td>
</tr>
<tr>
<td>Vancomycin days/year</td>
<td>3.20 ± 3.80</td>
</tr>
<tr>
<td>Fewer days of vancomycin/event</td>
<td></td>
</tr>
<tr>
<td>Hospital days/year</td>
<td>181</td>
</tr>
<tr>
<td>Fewer hospital days/event</td>
<td>3.30 ± 2.93</td>
</tr>
<tr>
<td>Potential economic savings (n=55)</td>
<td></td>
</tr>
<tr>
<td>Per year</td>
<td>$220,181</td>
</tr>
<tr>
<td>Per treatment episode*</td>
<td>$3,478 ± $2,392</td>
</tr>
</tbody>
</table>

* Potential economic savings per treatment episode = (cost of specialty bed + vancomycin AWP − linezolid AWP) x (decreased LOS). The 2 patients with cost savings exceeding $15,000 were excluded from the analysis.

have incorporated all of these factors as well as facilitated sensitivity analyses around our assumptions, but this was beyond the scope of our study objectives.

Finally, a randomized controlled trial (RCT) has demonstrated that patients with complicated skin and soft tissue infections who are treated with linezolid (IV followed by oral) experience a shorter LOS as compared to patients treated with IV vancomycin (9 versus 14 days, P=0.052). While not an RCT, our study evaluated the potential economic benefit of IV to oral switch with linezolid in a broader range of patients with MRSA and MR-CoNS infection. In fact, the greatest opportunity for cost savings occurred in patients with MRSA pneumonia, followed by MRSA skin and soft tissue infections. Our study also evaluated the potential for ES and ED for all eligible patients in a “real-world” setting and did not limit its evaluation to patients enrolled in a clinical trial.

Conclusion

Our study shows that oral switch therapy with linezolid appears to offer the potential for decreased vancomycin utilization, decreased LOS, and significant cost savings. Furthermore, we have shown that criteria for ES and ED can be developed and easily applied to identify ES and ED candidates. Validation of these results will require a prospective clinical trial of early switch to linezolid therapy that carefully assesses a variety of clinical outcomes, including relapse rates, emergence of resistance, and adverse events. Given the increased prevalence of MRSA and the limited treatment options available for this organism, new approaches are needed to diminish the impact of these infections on society and our health care system.

ACKNOWLEDGMENTS

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DISCLOSURES

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Early Switch and Early Discharge Opportunities in Intravenous Vancomycin
Treatment of Suspected Methicillin-Resistant Staphylococcal Species Infections

the study, the collection, analysis, and interpretation of the data, or the decision to submit the manuscript for publication. Funding was obtained by authors David C. Rhew and Matthew Bidwell Goetz. Rhew and author Stephen Parodi served as co-principal authors of the study. Study concept and design, analysis and interpretation of data, and drafting of the manuscript and its critical revision were the work of all authors. Statistical expertise was contributed by Rhew and Parodi.

REFERENCES


Pharmacoeconomic Modeling of Prior-Authorization Intervention for COX-2 Specific Inhibitors in a 3-Tier Copay Plan

JANE STACY, PharmD; ELIZABETH SHAW, MSIE; MICHELE D. ARLEDGE, PharmD; and DONNA HOWELL-SMITH, RPh, MBA

ABSTRACT

OBJECTIVE: To determine from a health plan perspective the cost-effectiveness of cyclooxygenase-2 (COX-2) specific inhibitors, with and without a prior-authorization (PA) process.

METHODS: A modeling exercise was employed, based on prescription drug claims for a managed care organization with 3.8 million health maintenance organization (HMO) and preferred provider organization (PPO) members. Drug claims revealed 96,154 members (2.9% of the 3.3 million members with a pharmacy benefit) who received either one or more prescriptions for a COX-2 drug or a nonspecific nonsteroidal anti-inflammatory drug (NSAID). These patients were stratified into 2 groups for further analysis, those having a concurrent proton pump inhibitor (PPI) and those without a concurrent PPI. Decision analysis was used to estimate the cost-effectiveness of COX-2 therapy. Actual health plan drug claims data were used to determine utilization and prescribing patterns of nonspecific NSAIDs, COX-2 specific inhibitors, and PPIs. Results from the literature from 8 clinical trials were employed to determine the probability of a serious gastrointestinal (GI) event. Cost-effectiveness analysis (CEA) was used to determine the cost of each therapy, including the predicted cost to treat a serious GI event in a drug benefit design with PA versus a benefit design without PA.

RESULTS: Cost-effectiveness analysis (CEA) showed that the cost per success (no serious GI event) for Cox-2 specific inhibitors with PA was $278 versus $422 without PA.

CONCLUSIONS: The one-year model predicted that costs associated with an increase in COX-2 utilization after removal of PA would exceed the costs to administer PA and treat NSAID-related serious GI events in the managed care population. Based upon this CEA, PA appears to be an effective tool to manage pharmacy costs. Further examination of the medical claims would be useful to validate the assumed GI event rates with or without PA and to further demonstrate more definitively the value of a PA program for COX-2 drugs.

KEYWORDS: Nonsteroidal anti-inflammatory drugs, COX-2 selective inhibitors, Prior authorization, Managed care, Serious GI events

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Prior authorization (PA) is a common tool within the managed care environment. Demand has increased for managed care plans to provide access to new and more costly drugs for their members. Many managed care organizations (MCOs) use the PA process as a way to control cost by assuring that members have tried less-expensive alternatives before meeting the criteria for use of the requested agent. With direct-to-consumer (DTC) advertising a mainstay in the current health care environment, some prescribers feel consumers have placed increased demands on physicians to prescribe advertised products. Health plans are continually looking for ways to control pharmacy cost trend through benefit design. To maintain optimal access to medications, it will become increasingly important to be cognizant of the effects of prescription drugs on total medical outcomes, including costs outcomes and the actuarial-underwriting process.

Benefit (re)design is likely the best way to address not only cost and access but also their impact on total medical outcomes. PA has historically been one benefit design feature frequently used by prescription benefit managers (PBMs) and health plans in the United States to control the use of higher-cost drugs. Today, one of these high-cost drivers is the cyclooxygenase 2 (COX-2) specific inhibitor class of drugs. COX-2 specific inhibitors cost an average of $80 more per month than their nonspecific nonsteroidal anti-inflammatory alternatives. For example, the average ingredient cost of a 1-month supply of a COX-2 specific inhibitor is $100, while the average ingredient cost of a generic nonspecific NSAID such as naproxen is $20 per month.

COX-2 specific inhibitors are indicated for treating osteoarthritis, rheumatoid arthritis, and acute pain. These medications may be alternatives for plan members who are intolerant to nonspecific NSAIDs or who have a high risk of developing gastrointestinal (GI) adverse events, particularly ulcers or GI bleeding. The main disadvantage of treatment with NSAIDs is the adverse effects that can be associated with their use, including GI discomfort and more serious events such as bleeding and ulceration. For serious GI events (defined as bleeding, ulceration, or perforation requiring hospitalization and/or additional treatment) the incidence is 2 to 4 times greater for those members who use NSAIDs chronically than for those who are not on chronic NSAIDs. The main clinical advantage for COX-2 specific inhibitors is the potential decrease in GI events. The efficacy for both COX-2 specific inhibitors and nonspecific NSAIDs in reducing pain caused by arthritis is similar, if not equal.
COX-2 specific inhibitors work by inhibiting prostaglandin synthesis by selectively inhibiting the cyclooxygenase-2 enzyme without inhibiting the cyclooxygenase-1 enzyme, unlike non-specific NSAIDs, which inhibit both COX-1 and COX-2 enzymes. Due to the selectivity of the COX-2 enzyme, this class of medications does not exhibit antplatelet activity, and a decreased incidence of GI effects has been reported. The side-effect profile of COX-2 specific inhibitors has been shown to produce a lower rate of GI events compared to traditional NSAIDs. At 2 to 4 times the indicated dose, celecoxib 400 mg twice daily had resulted in fewer ulcers, both symptomatic ulcers and ulcer complications, compared to NSAIDs. Results with rofecoxib showed significantly fewer GI events than with nonselective inhibitors, specifically naproxen.

Use of PA, in general, has been shown to result in a significant decrease in pharmacy costs for medications that have lower-cost therapeutic alternatives. There has been a documented drug-cost savings resulting either from use of lower-cost drugs or a decrease in drug utilization as an outcome of PA. PA could be a cost-effective method for use of medications that vary greatly in price but not in efficacy. Previous studies include work that found drug benefit design with PA reduced target drug costs by 49.8%.

Yet, PA may not be a popular cost-savings method among providers and patients because some find it burdensome. Therefore, it is important to evaluate not only cost savings but also how this intervention and process affects medical and service (e.g., satisfaction) outcomes. Kotzan et al. stated:

The long-term impact of PA programs has not been documented. If the drug programs are devised solely on the basis of economic consideration without regard for medical consequences, then it is possible that more expensive services will replace those expensive drugs removed from the formulary.

In the year 2000, the PA call volume in this MCO showed that the most requested class of medications was the COX-2 specific inhibitors. It accounted for 25% of the call volume, followed by proton pump inhibitors (PPIs), which accounted for 20% of the total calls (data not presented).

Historically, in this MCO health plan, PA on COX-2 specific inhibitors was associated with a lower use of COX-2 drugs and appeared to provide cost savings. The prescription drug market share of COX-2 specific inhibitors compared to all NSAID prescriptions in the MCO was 9%. This was lower than the national COX-2 prescription market share of 19%, as reported by IMS Health for July 1999.

The MCOs market share was also significantly lower compared to a 40% COX-2 market share for an unmanaged benchmark population with no restrictions on COX-2 specific inhibitors, based on information provided by the PBM. The calculated savings based on observed lower utilization attributed to the PA on COX-2 specific inhibitors was $0.31 per member per month (PMPM). Operating the PA call center is associated with many administrative costs. The administrative cost per call in 2000 was determined to be $0.07 PMPM for the entire call center. After paying the entire cost of the clinical pharmacy review call center, the PA on COX-2 specific inhibitors alone saved a net $0.24 PMPM ($0.31–$0.07). This equates to annual savings of almost $10 million for PA on COX-2 specific inhibitors in this MCO of 3.2 million members with a pharmacy benefit.

This study is a comparison between the utilization and predicted serious GI adverse event occurrence for members on non-specific NSAIDs versus COX-2 specific inhibitors, to permit determination of the cost-effectiveness of these medications with and without PA. The decision analysis takes into account the changes in utilization with and without PA as well as the cost of treatment for both benefit design options. Treatment cost will include not only drug costs but also the medical and hospital costs to treat adverse events, specifically serious GI events.

## Methods

### Data Source

Prescription drug claims from a health plan with 3.8 million HMO and PPO members were utilized for this study. At the time of the study, this MCO placed COX-2 inhibitors in the third copay ($30) tier and required PA. Generic NSAIDs were in the first copay ($5) tier, and brand-name NSAIDs (both single-source brand and multiple-source brand) were in the second copay ($15) tier. The review criteria used for this PA program included (a) failure or intolerance of 2 different NSAIDs or (b) evidence of adverse GI risk factors, such as concomitant use of steroids, proton pump inhibitors (PPIs), or prescription-strength histamine blockers, anticoagulant or antiplatelet therapy, bisphosphonates, or antineoplastic agents. Nondrug-related risk factors were also assessed, including either a history of or current GI bleed or ulcer. At the time of the study, no electronic step-therapy edit was in place; therefore, all criteria were assessed by physician-reported patient use of these medications and patient risk factors. Along with physician-reported patient use, drug claims history was assessed at the time of each request for PA.
to look for prior use of medications. Forty-five percent of requests were approved, which means that the member met both prior NSAID use and the risk-factor criteria. Of those denied, 66% failed to meet the NSAID prior-use criteria, 24% failed to meet the risk factor criteria, and the remaining 10% failed both criteria.

Table 1 shows the percent of claims approved based on each criteria level. The first criterion was failure of 2 different nonspecific NSAIDs. If the physician or the claims data verified use of 2 NSAIDs, a COX-2 specific inhibitor was automatically approved without any further check of criteria.

**Literature Evaluation**

A literature search was performed to determine the serious GI side-effect probabilities for each treatment option. The MEDLINE database was searched for clinical trials and review articles relating to nonspecific NSAIDs, COX-2 specific inhibitors, arthritis, and GI adverse effects. The search included human, adult studies from 1995 to 2001. Data were also gathered from American Hospital Formulary Source (AHFS) Drug Information, the package inserts of nonspecific NSAIDs and COX-2 specific inhibitors, and FDA transcripts from advisory committee meetings. Data compiled from the above literature sources provided the incidence for serious GI adverse events and/or reduction in incidence of serious GI events when a gastroprotective agent, specifically a PPI, is added to NSAID therapy. The probabilities were determined based on published literature. The sample size in this study was so large that we could assume that our population would experience side effects in both incidence and severity similar to those in the published reports.

Based on the published literature, several assumptions were made. The side-effect frequency was categorized by drug class and not by individual agent. These categories included COX-2 only, nonspecific NSAID only, COX-2 specific inhibitor plus a PPI, nonspecific NSAID plus a PPI, and no drug therapy. The probability of chronic nonspecific NSAID users developing upper GI ulcers, bleeding, and/or perforation within a 1-year period was assumed to be 2% to 4%. This decision analysis used a mean probability of 3%. The background probability of the general population experiencing a serious GI event is 0.4%. This incidence was used to estimate the probability of the COX-2 specific inhibitor population experiencing a serious GI side effect.

Adding a PPI for gastroprotection to either a nonspecific NSAID or COX-2 specific inhibitor reduces the risk of a serious GI side effect by approximately 50%. Therefore, we assumed the GI protective effect of a PPI combined with COX-2 specific inhibitor would be at least equivalent to a PPI combined with a nonspecific NSAID. Assuming an average 50% risk reduction with the addition of a PPI, the probability of a GI event with a combination of PPI and nonspecific NSAID therapy becomes 1.5%. The probability of a serious GI event for a PPI combined with COX-2 specific inhibitor is 0.2% based on the same risk reduction. A sensitivity analysis was performed for each probability to account for any assumptions made.

**Cost-effectiveness Analysis**

A cost-effectiveness analysis (CEA), using a decision tree, was used to evaluate the option of removing the PA on COX-2 specific agents. The tree was divided into 2 main branches: maintaining PA with the current criteria at the time of the study or removing PA. The subdivisions on each branch vary, including combinations of therapy and probability of serious GI side effects. The distribution of use of each medication combination is based on actual health plan data in pharmacy claims. The probabilities of a serious GI event came from published literature. Only those events defined as serious were shown in the model. For this CEA, we define all costs of therapy, including drug cost and cost of treatment for serious GI event, by cost per success. Success was defined as no serious adverse drug event.

All possible treatment combinations were analyzed, using the health plan pharmacy claims database, including COX-2, COX-2 with PPI, NSAID only, NSAID with PPI, and no prescription drug treatment. The cost and probability of each success and each adverse event were compared within the 2 different benefit models, which include the cost associated with maintaining PA on COX-2 specific inhibitors using the current PA criteria or eliminating the criteria-based PA requirement completely.

The cost in the model represents the actual cost of the claim to the health plan. Actual cost was calculated using the acquisition cost of the medication and the medical costs associated with a serious GI side effect. This cost is reported as annual cost and represents net health plan cost (i.e., cost after subtraction of member copay). No drug manufacturer rebates were factored since none were in place for COX-2 specific inhibitors at the time of the study. The cost of a serious side effect can include other required medications, physician visits, hospital costs, etc.

The cost of a serious GI side effect was classified as any cost associated with a medical claim correlating to a primary or secondary ICD-9 diagnosis code beginning with 531 (gastric or stomach ulcer). The data included all members with those ICD-9 codes, not just members receiving NSAIDs. ICD-9 codes include gastric ulcers with or without perforation or hemorrhage. These costs are an average of medical claims associated with these adverse events for a 1-month snapshot. The actual average cost to the health plan for a serious GI adverse event from medical claims data in November 2000 was $1,500 per event. There were just fewer than 1,000 medical claims per ICD-9 code for about 200 individuals, with total plan costs exceeding $300,000. The data were limited to just 1 month to minimize the probability that there was not more than 1 event per person. The “event” could include, but was not limited to, hospitalizations.

Previous studies have quoted treatment costs per event as high as $15,000. To account for the wide variability of the health plan’s actual cost of a serious GI event compared to reports in
published literature, a sensitivity and threshold analysis was performed. The sensitivity analysis showed that no change in study results was evident until the cost of a serious GI event was greater than $100,000. The costs in the model are based on 1 year of treatment and assume 100% compliance (12 fills per year) and not more than 1 serious event per member per year.

Table 2 lists each cost included in our CEA decision-tree model, including the cost of a serious GI event and cost of the drug for a 1-year time period. Figure 1 shows the decision tree used in the cost-effectiveness model. The tree is divided into 2 main branches. One branch includes the path when the PA is left on COX-2 specific inhibitors. This path shows percentages of members on each treatment branch and the percent probability of members in each path experiencing a serious GI event. The other branch depicts potential utilization when the PA is removed and how this shift in utilization affects the overall rate of serious GI events. Using the costs from Table 2, the cost for each branch was calculated, and, ultimately, the cost of each of the 2 major paths. It could then be determined whether it was cost effective to leave the PA on COX-2 specific inhibitors, taking into account both drug utilization and rate of serious GI side effects.

Population
The population of the cost-effectiveness model consisted of 96,154 members, or nearly 3% of the plan’s total membership with a drug benefit. This population was defined as all NSAID users and potential NSAID users. Potential NSAID users were defined as those members who tried to get a COX-2 specific inhibitor but whose claim was rejected at the pharmacy.

Figure 2 shows the percent of members who originally met criteria for PA and were approved for the drug, members who originally did not meet criteria and were rejected, and members who did not attempt to obtain a PA approval and alternatively used a nonspecific NSAID. The members who originally did not meet criteria were then analyzed the month following their original rejection to determine if they were approved on a future PA attempt, alternatively used a nonspecific NSAID, or filled no drug in the NSAID class. Specifically, each member included in the study population had received a nonspecific NSAID, received a COX-2 specific inhibitor, or tried to obtain a PA on a COX-2 specific inhibitor during January 2001. The percentage of members in each category was 71%, 8%, and 21%, respectively. Of 21% of members who tried to get a COX-2 but were denied by the crite-
ria, 12% received no NSAID, 5% were later approved for a COX-2, and 4% filled a nonspecific NSAID instead.

Actual health plan data were used to determine utilization and prescribing patterns of nonspecific NSAIDs, COX-2 specific inhibitors, and PPIs within the current benefit design at the time of the study. The alternate benefit design based on removal of prior authorization assumes no restrictions placed on prescriptions for COX-2 specific inhibitors. Therefore, utilization is estimated based on both current utilization of members with PA (15% of NSAID market share), rejection rate of COX-2 specific inhibitors (29% of population who tried to obtain a COX-2 specific inhibitor), and reported benchmarks of COX-2 utilization (IMS data of 19% market share).

The probabilities of having a serious GI event, obtained from the published literature (Table 3), were then placed in the decision-tree model. It was assumed that the published probabilities applied to the general population without restrictions, and, therefore, these numbers related to the branch without a PA. To determine the GI adverse events within the PA branch, it was assumed that those who receive a COX-2 specific inhibitor within the PA process are at a higher risk because they must meet risk criteria to receive approval for the medication. For this high-risk population, it was estimated that the population with a PA already in place for a COX-2 specific inhibitor is 5 times more likely to have a side effect. This was based on the 0.4% risk reported in the general background population and assumed a minimal 2% incidence of serious GI adverse effects from members taking chronic NSAIDs.

### Outcomes Measured

The primary outcome measure was the average cost per successful treatment. A successful treatment was defined as no serious GI event. This outcome was measured for both the prior authorization benefit and the proposed benefit without PA for COX-2 specific inhibitors. The costs associated with PA and without PA were calculated to determine if changes in utilization when PA is removed would have an impact on the number of successes and therefore decrease the cost of treating serious GI events enough to justify PA removal.

### Results

In the 3-tier copay design in this MCO health plan that required PA for COX-2 specific inhibitors, the average annual cost across all therapeutic possibilities for the study population was $271.04 per patient. This number is an average of all study treatment possibilities, including the cost of treating serious GI adverse effects. If the PA on COX-2 specific inhibitors was removed, and 100% of the study population who attempted to fill a COX-2 specific inhibitor received a COX-2 specific agent (i.e., all prescriptions presented to the pharmacy were dispensed), then the annual average cost of therapy would be $412.54 per patient, assuming 12 fills per year.

CEA compared the cost per success for COX-2 specific inhibitors with PA versus the cost per success without PA. The cost was $277.99 per success for PA and $421.82 per success without PA. Each additional 1% increase in the probability of having no serious GI side effect would cost the health plan an additional $47,167 per member per year for each member on a COX-2 specific inhibitor if the PA was removed. This equates to more than $13.6 million a year for the entire study population (N=96,154), assuming that all prescription claims for COX-2 specific inhibitors are no longer rejected and members are 100% compliant (12 fills per year).

---

### TABLE 2 Costs* in the CEA Model

<table>
<thead>
<tr>
<th>Medication</th>
<th>Probability of Serious GI Event, From Literature</th>
<th>Probability Used in the PA Arm of Model</th>
<th>Probability Used in the No-PA Arm of Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious GI Event</td>
<td>$1,500/event</td>
<td>2%</td>
<td>0.4%</td>
</tr>
<tr>
<td>COX-2 treatment</td>
<td>$691/12 monthly claims</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>NSAID treatment</td>
<td>$140/12 monthly claims</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>COX-2 &amp; PPI treatment</td>
<td>$1,755/12 monthly claims</td>
<td>1%</td>
<td>0.2%</td>
</tr>
<tr>
<td>NSAID &amp; PPI treatment</td>
<td>$1,204/12 monthly claims</td>
<td>1.5%</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

* Net plan costs after subtraction of member cost-share for claims with dates of service from November 2000 to February 2001.

### TABLE 3 Probabilities Used in the CEA Model

<table>
<thead>
<tr>
<th>Medication</th>
<th>Probability of Serious GI Event, From Literature</th>
<th>Probability Used in the PA Arm of Model</th>
<th>Probability Used in the No-PA Arm of Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>COX-2</td>
<td>2%</td>
<td>2%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Nonspecific NSAID</td>
<td>2% to 4%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>COX-2 and PPI</td>
<td>30% to 75% decrease risk of NSAID alone 10,13,23</td>
<td>1%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Nonspecific NSAID and PPI</td>
<td>30% to 75% decrease risk of NSAID alone 10,13,23</td>
<td>1.5%</td>
<td>1.5%</td>
</tr>
<tr>
<td>No NSAID</td>
<td>0.4%</td>
<td>0.4%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

### FIGURE 2 Population of the CEA Model
per year) with their treatment.

The national risk of serious GI event over the entire population is 0.4%. When the national population is compared to the study population, 13% of the study population exhibits some level of risk for GI complications. This is evident by the percentage of members who met the PA criteria and are therefore considered the higher-risk population. This higher-risk population in the study group could potentially sway results to make removal of PA seem more beneficial. In spite of this possible bias to PA removal, maintaining PA still proved to be a more favorable option.

To account for all assumptions in the model, a sensitivity analysis was performed on all probabilities and costs associated with serious adverse events. The predicted outcomes were not significantly changed even when probabilities and cost were adjusted for both sensitivity and threshold analysis. Removing the PA for the 3-tier benefit design was always a more costly decision (Figure 3).

There has been continued controversy around the exact GI risk reduction associated with COX-2 specific inhibitors versus nonspecific NSAIDs. The CLASS (Celecoxib Long-term Arthritis Safety Study) clinical trial and VIGOR (Vioxx Gastrointestinal Outcomes Research) study and other studies have brought up many questions around the potential risks and benefits of COX-2 specific inhibitors and the populations in which COX-2 specific inhibitors are most appropriate. These studies were published after the completion of this CEA but now provide a wonderful opportunity to reevaluate COX-2 specific inhibitor use and specifically evaluate actual rates of serious GI events that occurred within this health plan. A study by Bull et al. showed that prescribing patterns have begun to shift to higher-risk patients receiving COX-2 specific inhibitors and lower-risk patients receiving nonspecific NSAIDs based on a COX-2 risk score. As prescribing patterns and patient demand for these products begin to decrease and use is shifted to high-risk populations, the need and value of PA decreases.

The value of PA will continue to be discussed and debated. An analysis of the experience of a PA program in a Medicaid HMO showed that 95% of PA requests were approved, thereby questioning the value of PA. Nevertheless, Medicaid plans will likely maintain PA programs. A recent study from Hamer et al. suggested that the addition of PA for gabapentin could be used to decrease the prescribing of off-label uses of the drug. This fuels the debate on the use of PA to both reduce costs and achieve appropriate utilization.

Another factor to seriously consider when determining the value of PA is the effect on patient and provider satisfaction. The published studies that have examined the effects of PA programs have not measured either service outcomes (satisfaction with care) or health-related quality of life. Although our study showed a definite cost savings associated with PA on this particular class of drugs, the value may decrease when considering member retention, satisfaction, and the burden of use associa-
ed with the PA process.

Based on the results of our study, PA remains in place in this health plan for COX-2 specific inhibitors in the 3-tier and traditional drug benefit designs, but the PA program was removed due to concerns regarding member and provider satisfaction in the redesign of this health plan’s 4-tier drug benefit. When health plans consider a benefit design without PA, it is important that pharmacy managers and health plan actuaries take into account the predicted increased utilization of medications previously requiring PA and price the new benefit accordingly.

**Limitations**

There are several limitations of this study. While actual health plan data were used to measure utilization, cost of treatment, and population distribution, the probabilities of serious GI events were obtained from the published literature and not from actual events observed in our health plan. Further studies will be necessary to confirm the estimated rate (0.4% to 3%, depending on the drug) of adverse drug events in the health plan. Second, we assumed 100% compliance with drug treatment, since one objective of the study was to estimate the maximum cost to the health plan of discontinuation of the PA requirement. Cost of drug treatment could be overstated in this study if the population was not 100% compliant with the drug regimens.

This CEA focused solely on the PA process, and the influence of tiered copayments was not evaluated. It included only serious GI events; GI discomfort or any moderate or mild GI symptoms were not included. This study examined classes of drugs and did not evaluate specific drugs within the classes. Pharmacy claims data were used to calculate an average cost per therapeutic class, averaging the variation in cost by specific drug and dose. This method has limitations as well as potential value given the evolving body of knowledge regarding the relative differences among specific COX-2 drugs and NSAIDs in the incidence of adverse cardiac and renal effects, outcomes that were also not examined in this PA CEA.

**Conclusions**

Maintaining PA on COX-2 specific inhibitors can be a cost-effective tool to assure that target (higher-risk) members receive this treatment while those who are at low risk for adverse GI events use the nonspecific NSAIDs as first-line therapy. More than 15,000 members during the study period either did not meet risk criteria or their physicians did not try to obtain a PA. These members therefore received either a nonspecific NSAID or no therapy. Due to the variation of prescribing patterns for COX-2 specific inhibitors, significant DTC advertising, and the cost of COX-2 specific inhibitors compared to their equally efficacious NSAID alternatives, PA can be an effective tool to control costs in either a 3-tier copay design or a traditional drug benefit design. This CEA showed that the greater medication expense of COX-2 specific inhibitors versus nonspecific NSAIDs cannot be outweighed by the side-effect profiles of these 2 classes of medications. The risk factors for GI events are considered in the COX-2 inhibitor PA criteria, and, therefore, PA for COX-2 specific inhibitors remains a cost-effective managed care intervention when evaluating overall medical and pharmacy costs.


26. LaPensee KT. Analysis of a prescription drug prior authorization program in a Medicaid health maintenance organization. *J Managed Care Pharm.* 2003;9(1):36-44.


Original Research

Evaluation of a Monthly Coverage Maximum (Drug-Specific Quantity Limit) on the 5-HT1 Agonists (Triptans) and Dihydroergotamine Nasal Spray

LAUREN HOFFMAN, PharmD; GEORGE MAYZELL, MD; ALEX PEDAN, PhD; MAUREEN FARRELL, MPH; and THOMAS GILBERT, MS

ABSTRACT

BACKGROUND: Ensuring the appropriate use of migraine therapies is an important consideration for care providers, patients, employers, and managed care organizations (MCOs) because of the high cost of treatment for this fairly prevalent disabling disease. A review of utilization of serotonin 5-HT1 receptor agonists (triptans) in an MCO determined that about 24% of the patients who received triptan therapy exceeded the manufacturers’ recommendations regarding the maximum daily dose and safe treatment guidelines in a 30-day period. An initiative was designed to manage the coverage of migraine abortive therapies with the anticipated outcome of decreasing potential misuse or overuse of the medications.

OBJECTIVE: The objective of this retrospective, observational study was to determine the impact of a monthly drug-specific milligram coverage maximum (quantity limit) on serotonin 5-HT1 receptor agonists (triptans) and dihydroergotamine (DHE) nasal spray on the utilization and costs of migraine care in an MCO with approximately 600,000 covered members.

METHODS: A longitudinal, retrospective cohort analysis was conducted. All migraine-related services were analyzed, including outpatient medical visits, emergency department utilization, inpatient hospitalizations, and outpatient prescription drug use. The analysis was conducted using medical and pharmacy administrative claims. Analysis of data was performed for the period 12 months prior (October 1999 to September 2000) and 18 months postimplementation of the monthly drug-specific milligram coverage maximum (October 2000 through March 2002).

RESULTS: Imposition of a monthly coverage maximum for migraine abortive therapies was associated with a 26.1% reduction in overall per-patient-per-month (PPPM) medical costs for migraine care, from $55.52 PPPM to $41.02 PPPM (P<0.01). Utilization of serotonin 5-HT1 receptor agonists and DHE nasal spray declined by 16.7%, from 0.18 prescriptions PPPM to 0.15 prescriptions PPPM (P=0.039), and direct drug costs declined by 28.8%, from $29.18 PPPM to $20.78 PPPM (P<0.001). Utilization and costs of outpatient and inpatient migraine-related medical services declined by 40% from $16.58 PPPM in the preperiod to $9.94 PPPM in the postperiod (P<0.001).

CONCLUSION: A monthly drug-specific milligram coverage maximum was associated with significant reduction in drug costs and utilization of serotonin 5-HT1 receptor agonists (triptans) and DHE nasal spray. Utilization and costs of migraine-related medical services also declined after implementation of the coverage maximum for triptans and DHE nasal spray. The monthly drug-specific milligram coverage maximum appeared to have been successful in managing utilization of triptans and DHE nasal spray, including reduction of overall costs of migraine-related medical services and direct drug costs.

KEYWORDS: Migraine, Utilization, Costs, Serotonin 5-HT1 receptor agonists, Quantity limits, Drug therapies, Migraine-related medical services

J Managed Care Pharm. 2003;9(4):335-45

migraine is a fairly prevalent disabling disease resulting in high costs to managed care organizations (MCOs) and employers. The number of migraine patients in the United States in 1999 totaled 27.9 million.1-3 Nearly 75% of all migraine sufferers are women, and it is estimated that 1 out of every 4 households has someone who suffers from migraine headache.1,3 The economic burden of migraine in the United States, including physician visits, tests, pharmacologic therapy, and indirect costs, exceeds $14 billion annually.1 Evaluations of the economic impact have shown the indirect costs of migraine to be considerable.1-3

More than 60% of indirect costs have been attributed to lost work days. In fact, Hu and Markson et al. estimated the annual mean number of missed workdays for men and women with migraine to be 3.8 and 8.3, respectively.4 The cost of prescription drug therapy has been estimated to comprise 2.1% of the total cost and 30% of the direct treatment cost for migraine.4 In 1999, 41% of persons experiencing migraines used prescription drugs as treatment; now, with 7 marketed triptan agents, the percentage has likely increased.5

Preventive therapy for migraine is suggested for patients with (1) 2 or more attacks per month producing disability lasting greater than or equal to 3 days, (2) failure of acute therapies, (3) use of abortive therapies more than twice a week, and (4) existence of uncommon migraine conditions.7 Historically, only an estimated 3% to 5% of the migraine population is treated with prophylactic therapies.7 Ensuring appropriate management of the patient with a migraine diagnosis and proper use of the chosen drug therapies are important considerations for care providers, patients, employers, and MCOs.
Evaluation of a Monthly Coverage Maximum (Drug-Specific Quantity Limit) on the 5-HT1 Agonists (Triptans) and Dihydroergotamine Nasal Spray

### TABLE 1 Migraine Therapy Quantity-Limit Programs Reported in the Literature

<table>
<thead>
<tr>
<th>Migraine-related Utilization and Cost Measures</th>
<th>Culley et al. &amp; Wanovich PPM*</th>
<th>Lassen et al. PPM*</th>
<th>Goldfarb et al. % change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triptan Rx's</td>
<td>-0.028</td>
<td>-0.075</td>
<td>-17</td>
</tr>
<tr>
<td>Cost of triptans</td>
<td>-$12.33</td>
<td>-$21.24</td>
<td>-60.3</td>
</tr>
<tr>
<td>Migraineprophylaxis Rx's</td>
<td>+0.768</td>
<td>+0.042</td>
<td>+33.9</td>
</tr>
<tr>
<td>Cost of prophylaxis Rx's</td>
<td>-$0.08</td>
<td>+$4.62</td>
<td>+49.6</td>
</tr>
<tr>
<td>Number of office visits</td>
<td>+3.07</td>
<td>+0.008</td>
<td>+7.8</td>
</tr>
<tr>
<td>Cost of office visits</td>
<td>-$0.16</td>
<td>+$0.35 per visit</td>
<td>+29.1</td>
</tr>
<tr>
<td>Number of ER visits</td>
<td>-$0.00095</td>
<td>+$0.043</td>
<td>no change†</td>
</tr>
<tr>
<td>Cost of ER visits</td>
<td>-$0.12</td>
<td>+$21.49 per visit</td>
<td>+56.8†</td>
</tr>
<tr>
<td>Other acute pain medication Rx's</td>
<td>-0.610</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Other acute pain medication cost</td>
<td>-$0.32</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Migraine-related hospital admissions</td>
<td>+0.0017</td>
<td>NA</td>
<td>+66.7</td>
</tr>
<tr>
<td>Cost of migraine-related admissions</td>
<td>+$1.00</td>
<td>NA</td>
<td>-55</td>
</tr>
<tr>
<td>Total change or savings reported</td>
<td>-$12.25</td>
<td>NA</td>
<td>+1.5</td>
</tr>
</tbody>
</table>

* PPM=per patient per month.
† Urgent care results listed; emergency department utilization was not reported.

Headache management can be challenging. The complexities of patient care include accurate diagnosis, evaluation of triggers, choice of abortive therapy, and the need for and choice of preventive therapy. Patient education regarding triggers, treatment, prevention, management of rebound headache, and proper medication use is essential. Although numerous educational resources, including specialized Web sites (most sponsored by pharmaceutical manufacturers), are devoted to headache, specialty clinics and managed care-sponsored disease management initiatives specific to headache treatment are few. Overuse of analgesic medications can be a quality concern when managing the patient with a diagnosis of headache and may often be an issue that is overlooked in quantity-limit programs for migraine drugs.

Prevalence data indicate that 85.6% of migraine patients experience 4 or fewer headache occurrences per month. In addition, manufacturers’ dosing recommendations for the 5-HT1 receptor agonists indicate that the safety of treating an average of more than 3 to 4 headaches with these agents in a 30-day period has not been established. MCOs have reported pharmacy cost savings with programs that impose quantity limits on the triptan medications. These point-of-service edit programs typically allow for edit overrides after review of clinical information documenting a requirement for doses that exceed program limits.

Pharmacy utilization and cost-outcome measures include triptan, prophylactic therapies, and acute-pain medications. Medical utilization and cost-outcome measures include primary care physician (PCP) and emergency department or urgent care center visits (Table 1). These quantity-limit programs resulted in cost savings to these health plans. However, other researchers have reported different results. “Lifting of restrictions on triptan usage…” has been said by one to “produce significant reductions…” in physician visits and procedures. Another report from the employer perspective found that although triptan restrictions resulted in a total direct medical cost reduction of $0.38 per patient per month (PPPM), the cost reduction was offset by a loss of 1,830, workday equivalents, which resulted in an additional cost of $0.47 PPM.

The MCO in the extant study is located in the southeastern United States and is composed of 2 principal lines of business: health maintenance organization (HMO) and preferred provider organization (PPO), covering 600,000 lives (60% HMO and 40% PPO). A preliminary review of triptan medication utilization showed that in the final calendar quarter of 1999, there were 4,714 members (point prevalence=0.78) with a prescription claim for a triptan or dihydroergotamine (DHE) nasal spray; 1,140 (24%) were identified as receiving therapy in a 30-day period that exceeded treatment of 4 headaches per month at the maximum daily dosage. This initial analysis of utilization did not include an evaluation of the use of other analgesics.

In October 2000, based on this preliminary analysis, the health plan MCO designed and implemented a clinical pharmacy initiative to review and analyze, for coverage and payment purposes, the use of migraine medications. The principal intervention that evolved from the initiative placed a monthly drug-specific milligram coverage maximum at community and mail-order pharmacies on triptan medications and DHE nasal spray if prescribed in excess of the manufacturer’s recommended specifications for dosages, frequency of use, or duration of administration (Table 2).

Perhaps different from other managed care programs, this MCO coverage maximum initiative and intervention did not allow for medical exceptions or system overrides for additional coverage of medication quantities that exceeded the maximum quantities specified. The initiative was designed to manage the coverage of abortive therapies with the anticipated outcome of decreasing potential misuse or overuse of the medications. At the time of implementation, sumatriptan (Imitrex), rizatripan (Maxalt), and DHE nasal spray (Migranal) were included on the health plan’s preferred medication list (PML), or preferred drug formulary. The triptan medications and DHE nasal spray were not included in a prior-authorization program. No prescription benefit plans included a closed formulary design. All drug benefit plans were based on an open formulary design, and approximately 40% of members were enrolled in a 3-tier copayment structure (lowest copay tier for generic drugs, middle copay tier for brand drugs on the PML, and the third tier for drugs not listed on the PML).
Evaluation of a Monthly Coverage Maximum (Drug-Specific Quantity Limit) on the 5-HT1 Agonists (Triptans) and Dihydroergotamine Nasal Spray

Table 2: Medications Included in the Drug-Specific Milligram Quantity-Limit Intervention

<table>
<thead>
<tr>
<th>Drug Name and Milligram Strength</th>
<th>Community 30 days</th>
<th>Mail-Order 90 days</th>
<th>Milligram Maximum*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan tablets 25 mg</td>
<td>36</td>
<td>108</td>
<td>900 mg 2700 mg</td>
</tr>
<tr>
<td>Sumatriptan tablets 50 mg</td>
<td>18</td>
<td>54</td>
<td>900 mg 2700 mg</td>
</tr>
<tr>
<td>Sumatriptan tablets 100 mg</td>
<td>9</td>
<td>27</td>
<td>900 mg 2700 mg</td>
</tr>
<tr>
<td>Sumatriptan nasal spray 20 mg</td>
<td>9</td>
<td>27</td>
<td>180 mg 540 mg</td>
</tr>
<tr>
<td>Sumatriptan nasal spray 5 mg</td>
<td>36</td>
<td>108</td>
<td>180 mg 540 mg</td>
</tr>
<tr>
<td>Sumatriptan injectable 6 mg</td>
<td>9</td>
<td>27</td>
<td>54 mg 162 mg</td>
</tr>
<tr>
<td>Naratriptan tablets 1 mg</td>
<td>25</td>
<td>75</td>
<td>25 mg 75 mg</td>
</tr>
<tr>
<td>Naratriptan tablets 2.5 mg</td>
<td>10</td>
<td>30</td>
<td>25 mg 75 mg</td>
</tr>
<tr>
<td>Zolmitriptan tablets 2.5 mg</td>
<td>18</td>
<td>54</td>
<td>45 mg 135 mg</td>
</tr>
<tr>
<td>Zolmitriptan tablets 5 mg</td>
<td>9</td>
<td>27</td>
<td>45 mg 135 mg</td>
</tr>
<tr>
<td>Rizatriptan tablets 5 mg</td>
<td>24</td>
<td>72</td>
<td>120 mg 360 mg</td>
</tr>
<tr>
<td>Rizatriptan tablets 10 mg</td>
<td>12</td>
<td>36</td>
<td>120 mg 360 mg</td>
</tr>
<tr>
<td>Almotriptan tablets 6.25 mg</td>
<td>24</td>
<td>72</td>
<td>150 mg 450 mg</td>
</tr>
<tr>
<td>Almotriptan tablets 12.5 mg</td>
<td>12</td>
<td>36</td>
<td>150 mg 450 mg</td>
</tr>
<tr>
<td>Dihydroergotamine (DHE nasal spray)</td>
<td>1 kit (4 bottles of 4 mg each)</td>
<td>3 kits (12 bottles of 4 mg each)</td>
<td>16 mg 48 mg</td>
</tr>
</tbody>
</table>

* The coverage maximum was milligram-specific for each drug and strength; a maximum was not established for the 5-HT1 agonist drug category as a whole.

Implementation of the intervention provided the opportunity to study the effects of a drug-specific milligram coverage maximum on the overall utilization and cost of treating migraine patients in this MCO health plan. The goal of the study was to test the hypothesis that the implementation of a monthly drug-specific milligram coverage maximum for selected migraine-abortive drugs would have substantial favorable impact on direct drug cost without an adverse effect on total medical management cost for migraine.

Methods

A longitudinal retrospective cohort analysis of a health care claims database from the MCO was conducted. A total of 30 months of data were observed consisting of 12 months (October 1999 through September 2000) prior to and 18 months (October 2000 through March 2002) postimplementation of the monthly drug-specific milligram coverage maximum. A number of medical utilization and payment measures related to the treatment of migraine were analyzed in this evaluation. All migraine-related services were analyzed, including outpatient medical visits, emergency department (ED) utilization, and inpatient hospitalizations. Assignment to one of these groups was based on place of service, provider type, and ICD-9 coding. ED and inpatient claims were required to have a diagnosis of migraine (ICD-9=346.xx) as the primary diagnosis, located in the first position on the claim to be included in the analysis. Outpatient claims were allowed to have a migraine diagnosis in any diagnosis field on the medical claim. Cost measures for these services were based on the amount of payment to the respective providers from the health plan.

This evaluation included the analysis of outpatient prescription drug utilization and cost. Prescriptions for the following classes of drugs were included: triptans; non-triptans for migraine headache, which were defined as narcotic and non-narcotics analgesics; NSAIDs (including rofecoxib, meloxicam, celecoxib, and valdecoxib); ergotamines (with the nasal spray form of dihydroergotamine analyzed separately); migraine combination products; and prophylactic agents, including beta-blockers, calcium channel blockers, and tricyclic antidepressants. The specific agents included in these analyses are listed in Table 3. Medical and pharmacy claims were adjusted by a general inflation factor of 1.04 per annum.

Patient Inclusion and Exclusion

All members of the commercial HMO and PPO lines of business were included in the initiative, representing a potential eligible population of 600,000 members. Patients were excluded from the intervention if their employer group chose to not participate in the program that imposed the monthly drug-specific milligram coverage maximum for migraine-abortive drugs. Thirteen employer groups made this choice, resulting in an exclusion of 54,000 (9%) members from the intervention and these analyses.

The inclusion criteria for this study were: (1) the patient was a member of an employer group with pharmacy endorsement language that included the drug-specific milligram coverage maximum contract limitation; (2) the patient had at least 1 medical diagnosis of migraine as evidenced by the presence in the medical claims history (outpatient office visits, emergency department visit, or inpatient hospitalization) of ICD-9 of 346.xx or a migraine-related Episode Treatment Group of 168 (common migraine), 169 (complicated migraine), or 906.3 (ongoing pharmacy treatment without provider intervention—migraine treatment), in both the preintervention and postintervention periods; and (3) the patient was enrolled at least 6 months prior to and 6 months postimplementation of the
TABLE 3  Medications Monitored in the Therapeutic Categories

<table>
<thead>
<tr>
<th>Triptan Therapy</th>
<th>NSAIDs</th>
<th>Prophylactic Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almortrip坦 (Axert)</td>
<td>Ibuprofen</td>
<td>Verapamil</td>
</tr>
<tr>
<td>Frovari坦 (Frova)</td>
<td>Flurbiprofen</td>
<td>Amitriptyline</td>
</tr>
<tr>
<td>Naratri坦 (Amerge)</td>
<td>Fenoprofen</td>
<td>Desipramine</td>
</tr>
<tr>
<td>Rizatri坦 (Maxalt)</td>
<td>Nabumetone</td>
<td>Doxepin</td>
</tr>
<tr>
<td>Sumatri坦 (Imitrex)</td>
<td>Ketoprofen</td>
<td>Imipramine</td>
</tr>
<tr>
<td>Zolmitri坦 (Zomig)</td>
<td>Naproxen</td>
<td>Nortriptyline</td>
</tr>
<tr>
<td>Ergotamines:</td>
<td></td>
<td>Protriptyline</td>
</tr>
<tr>
<td>Dihydroergotamine (DHE)</td>
<td>Sulindac</td>
<td>Trimipramine</td>
</tr>
<tr>
<td>Migranal (nasal DHE)</td>
<td>Tolmetin</td>
<td>Amoxapine</td>
</tr>
<tr>
<td>Ergots, Ergotamine</td>
<td>Meclofenamate</td>
<td>Clomipramine</td>
</tr>
<tr>
<td>Methysergide</td>
<td>Etodolac</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Ergot combinations</td>
<td>Bromfenac</td>
<td>Divalproex</td>
</tr>
<tr>
<td>Midrin, etc.</td>
<td>Ketorolac</td>
<td>Felbamate</td>
</tr>
<tr>
<td>Non-Triptans</td>
<td>Melenamic acid</td>
<td>Gabapentin</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>Meloxicam</td>
<td>Lamotrigine</td>
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<td>Buprenorphine</td>
<td>Phenylbutazone</td>
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<tr>
<td>Butorphanol</td>
<td>Diclofenac</td>
<td>Ethosuximide</td>
</tr>
<tr>
<td>Codeine</td>
<td>Oxaprozin</td>
<td>Methysuximide</td>
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<tr>
<td>Dezocine</td>
<td>Pipoxicam</td>
<td>Phosphonytin</td>
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<td>Dihydrocodeine</td>
<td>Celecoxib</td>
<td>Triamethadone</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Rofecoxib</td>
<td>Phencamidone</td>
</tr>
<tr>
<td>Hydrocodeone</td>
<td>Diclofenav</td>
<td>Mefenoxam</td>
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<tr>
<td>Hydromorphone</td>
<td>Mefenamic acid</td>
<td>Diazepam</td>
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<td>Levomethadyl</td>
<td>Gabapentin</td>
<td>Citalopram</td>
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<td>Meperidine</td>
<td>Lamotrigine</td>
<td>Fluoxetine</td>
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<td>Methadone</td>
<td>Oxycarbazepine</td>
<td>Fluvoxamine</td>
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<tr>
<td>Morphine</td>
<td>Oxycarbazepine</td>
<td>Sertraline</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>Ethosuximide</td>
<td>Ethotoxin</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Methanesulfon</td>
<td></td>
</tr>
<tr>
<td>Oxymorphone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentazocine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propoxyphene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remifentanil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sufentanil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salicylates and combinations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen and combinations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ergotamines:
- Sulindac
- Tolmetin
- Meclofenamate
- Etodolac
- Bromfenac
- Ketorolac
- Melenamic acid
- Meloxicam
- Phenylbutazone
- Oxycarbazepine
- Diclofenac
- Oxaprozin
- Pipoxicam
- Celecoxib
- Rofecoxib
- Diclofenav
- Mefenamic acid
- Gabapentin
- Lamotrigine
- Oxycarbazepine
- Ethosuximide
- Methanesulfon
- Oxycarbazepine
- Ethotoxin

Drug-specific milligram quantity allowances were determined according to a preset rolling “time period” of 29 days at retail or 67 days at mail-order. The 67-day time period at mail-order was established to allow the member time to mail the prescription, prescription processing by the mail-order pharmacy, and return mail of the drug to the patient. If a prescription required copayment charge.) The final study population of patients, with at least 1 medical claim for migraine and receiving 5-HT1 receptor agonist or DHE nasal spray therapy, consisted of 6,766 subjects, 1.1% of covered members in this MCO.

**Intervention**

The drug-specific milligram coverage maximum was implemented as a maximum milligram quantity of medication doses of triptan medications and DHE nasal spray covered for a 1-month time period. The intervention was drug-specific (not drug-class) and milligram-specific. Highlights of the intervention were as follows:

- A per-month maximum milligram quantity limit was placed on specific medications (Table 2).
- The maximum quantity covered was based on FDA and manufacturer dosing recommendations.
- All members, physicians, and pharmacy providers were sent notification via plan newsletters about the pharmacy initiative and maximum quantity-limit intervention (Letters A and B).
- Patients and physicians could receive notification about the drug-specific milligram coverage maximum at the time of prescription dispensing at a dispensing pharmacy. When a prescription was presented at the pharmacy with a quantity that exceeded the maximum coverage, the pharmacist would inform the patient that the prescription quantity exceeded the amount that the health plan would cover and offer the remaining quantity to the patient to be paid by the patient in out-of-pocket costs.
- Patients could (if they desired) purchase the total quantity prescribed by their physician by paying the full cost of the quantity prescribed that exceeded the maximum coverage quantity.
- Claim-system overrides or other medical exceptions were not allowed for medication quantities that exceeded the maximum drug-specific milligram coverage limits per month.

The intervention imposed the drug-specific milligram per month coverage limit across all pharmacy providers, mail-order as well as community pharmacy. Claims for drugs included in the intervention would reject at point-of-service (POS) at the pharmacy. When a pharmacist received a prescription for a triptan or DHE nasal spray and the prescription was entered into the POS system, the claim would pass the eligibility edits and proceed to a Plan File edit (the Plan File contains a description of benefits such as covered drugs, days supply limits, and coverage maximums). Prior claim history was used to trigger the coverage evaluation process.

Drug-specific milligram quantity allowances were determined according to a preset rolling “time period” of 29 days at retail or 67 days at mail-order. The 67-day time period at mail-order was established to allow the member time to mail the prescription, prescription processing by the mail-order pharmacy, and return mail of the drug to the patient. If a prescription...
**LETTER A**  
**Physician Notification: MCO Physician Newsletter—“Blueline”**

**Pharmacy Benefit Initiative: Migraine Medications**

Medications have a potential to cause harm and result in increased health care costs if used in excess or incorrectly.

Blue Cross and Blue Shield of Florida and Health Options are introducing Responsible Rx, a new quality improvement initiative that focuses on the maximum recommended dosage of specific medications. This initiative, which begins September 5, 2000, may help to assist patients by educating them on the use of certain drugs.

Initially, only five medications used in the treatment of migraines will be affected. Responsible Rx places a monthly coverage limit on the quantity of these medications. The maximum monthly quantities covered for the specific drugs included in this initiative are based on the manufacturer's recommended dosage and duration of therapy approved by the Food and Drug Administration (FDA) or supported by clinical literature.

It is anticipated that physicians will gain valuable information about the quantity of medications used during a month that may be useful in future patient management decisions for persons afflicted with migraines. Additional drug classes may be added to Responsible Rx in the future.

**Components of Responsible Rx:**

- A pre-set maximum quantity for coverage will be placed on some drugs dispensed per month. (Greater quantities can be prescribed and dispensed within one month; however, coverage will not be available.)
- Your Blue Cross and Blue Shield of Florida and Health Options patients will have prescription drug coverage for a pre-set maximum for one copayment per month.
- Members’ pharmacists are aware of this initiative and will inform your patients if it applies to their prescriptions.

**Drugs with Pre-set Maximum Coverage Quantities**

<table>
<thead>
<tr>
<th>Drug Brand Name</th>
<th>Dose and Pre-set Maximum Coverage Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imitrex</td>
<td>25 mg=36 tablets; 50 mg=18 tablets; Nasal spray=9 inhalers; Injectable=4 kits (8 syringes)</td>
</tr>
<tr>
<td>Amerge</td>
<td>1 mg=25 tablets; 2.5 mg=10 tablets</td>
</tr>
<tr>
<td>Zomig</td>
<td>2.5 mg=18 tablets; 5 mg=9 tablets</td>
</tr>
<tr>
<td>Maxalt, Maxalt MLT</td>
<td>5 mg=24 tablets; 10 mg=12 tablets</td>
</tr>
<tr>
<td>Migranal</td>
<td>1 kit (4 bottles)</td>
</tr>
</tbody>
</table>

**LETTER B**  
**Patient Notification: Member Newsletter—“Florida Blue”**

**For Your Good Health**

**Coverage Maximums on Some Drugs Begin**

If used in excess or incorrectly, medications are potentially harmful. Responsible Rx, a new program launched September 5, 2000, affects the maximum quantity of a medicine that will be covered in a 30-day period.

Responsible Rx currently includes five medicines prescribed for migraine headaches. Under this program, your plan will cover quantities of medication based on dosing guidelines established by the manufacturer of the medication and approved by the Food and Drug Administration. The quantities cover a typical course of treatment or therapy. You may fill or refill a prescription up to the quantity covered by one copayment each month. Amounts prescribed over the maximum may be filled but will not be covered under plan benefits.

The drugs currently covered under the Responsible Rx program are: Imitrex, Amerge, Zomig, Maxalt or Maxalt MLT, and Migranal. Other drugs for various conditions may be added in the future.

Your doctors and pharmacists have been informed of the program. We believe Responsible Rx may offer health care providers and patients valuable information about the quantity of medications used during a month. If you have any questions about the program, please feel free to speak to your doctor or pharmacist, or call the customer service number on your ID card.

**Outcome Measures**

A number of cost and utilization measures were used to observe outcomes in the study population over the entire study period and in comparing preintervention to postintervention periods. The following utilization measures PPPM were employed: (1) number of prescriptions, (2) quantity [units] dispensed, (3) days supply, (4) medical office visits, (5) emergency room visits, and (6) inpatient hospitalizations. The financial measures PPPM included payments for (7) prescription drugs, (8) total migraine-related prescription care, (9) medical visits, (10) emergency room visits, (11) inpatient hospitalization, (12) total migraine-related medical services, and (13) total migraine-related care. Total migraine-related prescription care was the calculated cost PPPM based on the sum of all prescription drugs used to treat migraine (Table 3).

The drug cost was based on the “amount paid” field on the prescription claim record and was defined as the total amount paid to the pharmacy (average wholesale price [AWP] per metric unit x quantity [metric units] dispensed) less the contractual discount [with the pharmacy] + dispensing fee – patient copay = amount paid). All financial measures (such as those analyzed related to medical utilization) were based on plan-paid amounts, defined as the amount paid by the health plan to the respective providers, after subtraction of the patient copayment or other applicable cost share.

**Statistical Analysis**

The goal of the study was to test the null hypotheses that the implementation of a monthly drug-specific milligram coverage maximum for selected migraine-abortive drugs would have no...
impact on direct drug costs for migraine therapy or total medical care costs. The alternative hypothesis was that the intervention would have a significant effect on direct drug cost and total medical care costs for members with migraine. Because claims data were used to obtain cost information, total costs did not include patient copayments, coinsurance, deductibles, or negotiated discounts with providers. Therefore, the total (health plan) paid amount from claims data served as a proxy for the actual total cost of migraine care.

Due to the skewed nature of the data (i.e., having variance that increases with the mean), the treatment differences in paid amounts and utilization counts were estimated using a generalized linear model (GLM) with a log-link function and gamma and negative-binomial distributions, respectively.21 Because patients may not be observed for equal amounts of time, the length of follow-up for each patient in each period was included in the models as an offset variable. Since total paid amounts for the preintervention and postintervention periods for each patient tend to be correlated, Generalized Estimating Equations (GEE) with compound symmetry of variance-covariance matrix was applied to account for these correlations.22 GEE was developed as an extension of the GLM to accommodate correlated data and is widely used by researchers in a number of fields.

A dummy variable (1=postperiod, 0=preperiod) was introduced to the models to estimate the effect of implementation of the quantity-limit intervention. All models were adjusted for age and sex. Due to the strong nonlinear relationship between age and total paid amount, the age variable was transformed into 5 dummy variables corresponding, respectively, to the following 5 age groups:

\[
\begin{align*}
&\leq 30, \\
&31 \text{ to } 40, \\
&41 \text{ to } 50, \\
&51 \text{ to } 60, \\
&>60 
\end{align*}
\]

In addition, the impact of disease severity, captured in terms of comorbidity, was assessed by adding the Charlson Comorbidity Index (CCI) as an independent predictor to the models.23 The CCI assigns weights for a number of major conditions present among secondary diagnoses. The index score is the total of assigned weights and represents a measure of the burden of comorbid diseases. CCI was used to ensure that the population carried the same illness burden in the preperiod and postperiod.

The analyses of costs and utilization of specific migraine-related medical services such as management (professional [physician] component of claims including physician office visits), facility, surgical, office visits, and pharmacy were complicated by the fact that a significant number of patients incurred no costs for particular services within the period. For this reason, 2-part models were employed to estimate the total paid amount for each service group. First, logistic regression was used to estimate the probability of incurring some costs or utilization within a specific time period (preperiod and postperiod), given the aforementioned independent predictors.24 Second, a generalized linear model with log-link function and gamma distribution (costs) or negative binomial distribution (utilization) was used to estimate the treatment differences, conditional on incurring any costs or utilization for migraine and

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**TABLE 4 Characteristics of Migraine Patients**

<table>
<thead>
<tr>
<th>Age</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-18 years</td>
<td>286</td>
<td>4.2</td>
</tr>
<tr>
<td>19-34 years</td>
<td>1,322</td>
<td>19.5</td>
</tr>
<tr>
<td>35-44 years</td>
<td>1,949</td>
<td>28.8</td>
</tr>
<tr>
<td>45-54 years</td>
<td>1,712</td>
<td>25.3</td>
</tr>
<tr>
<td>55-64 years</td>
<td>632</td>
<td>9.3</td>
</tr>
<tr>
<td>65+ years</td>
<td>865</td>
<td>12.8</td>
</tr>
<tr>
<td>Total</td>
<td>6,766</td>
<td></td>
</tr>
</tbody>
</table>

**Gender**

<table>
<thead>
<tr>
<th>Gender</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>5,484</td>
<td>81.1</td>
</tr>
<tr>
<td>Male</td>
<td>1,282</td>
<td>18.9</td>
</tr>
</tbody>
</table>

---

**FIGURE 1 Number of Triptan Prescriptions Per Patient Per Month**

**FIGURE 2 Number of Prescriptions Per Patient Per Month**

---
pharmacy services and prescriptions. The expected values were then calculated by multiplying these 2 estimates together. Due to the correlation of the data in the preperiod and postperiod for each patient, the GEE method was used in both stages of the 2-part model.

In all models, interactions between covariates (age, gender, CCI) were evaluated and found to be nonsignificant. A 2-sided P value of <0.05 was considered to indicate statistical significance. All analyses were performed using the UNIX-based SAS v.8.2 software system.

Results

A total of 6,766 patients (1.1% of eligible health plan members) met the criteria for inclusion in the study. All migraine-related health care claims for these patients, preintervention and postintervention, were reviewed and analyzed. Patient characteristics are shown in Table 4. During the study period, total enrollment in the MCO remained stable, with a mean of 602,892 members (SD=38,563). The number of patients eligible for inclusion in the study who utilized services each month remained fairly constant at 4,863 (SD=293). The majority (81%, n=5,484) of patients were female, which is perhaps slightly higher than national estimates (75%). In the study population, 54% (n=3,661) were between the ages of 35 and 54 years; 4% (n=286) were under age 18 years, and nearly 13% (n=865) were 65 years or older.

The number of prescriptions PPPM for triptans and all non-triptans (narcotic and nonnarcotic analgesics) was steadily increasing in this MCO between October 1999 and September 2000, the preintervention period (Figures 1 and 2). From October 2000 through March 2002, the postintervention period, utilization of these 2 groups of medications began to steadily decline. As of March 2002, the rate of prescription utilization PPPM for these groups of medications was below the lowest levels seen at any time during the preintervention period.

Similar findings were evident when analyzing utilization by means of quantity, or units, PPPM (Figure 3). Utilization of the drugs included in the quantity-limit intervention, as measured by days of drug therapy supplied, indicated a consistent rise in the 12 months prior to implementation. Postimplementation, this days supply utilization measure decreased in retail prescriptions and increased in the mail-order pharmacy component. Overall, postimplementation, the days of therapy supplied of triptans and DHE nasal spray remained stable (Figure 4).

Table 5 depicts the aggregate utilization and cost measures preimplementation (12 months) and postimplementation (18 months) of the monthly drug-specific milligram coverage maximum for the 6,766 patients identified. The intervention resulted in a reduction in utilization of the agents included in the monthly coverage maximum (triptans and dihydroergotamine nasal spray) from 0.18 prescriptions PPPM in the preperiod to 0.15 prescriptions PPPM in the postperiod (P=0.039). During the postintervention evaluation period, there were also fewer prescriptions dispensed for migraine combination products, ergotamines, and non-triptan agents (Table 5).

The analysis of payments PPPM for the prescription drug measures showed a significant decline in the postintervention period for the triptan agents and DHE nasal spray ($29.18 versus $20.78, P<0.001). The decline began in September 2000 at the time of member notification about the initiative (Figure 5). The decline in payments for the medications included in the drug-specific milligram coverage maximum initiative resulted in a decrease in the total migraine-related prescription care PPPM ($38.95 versus $31.08, P<0.001).

The utilization of migraine-related outpatient office visits fell steadily after the implementation of the drug-specific milligram coverage maximum initiative (Figure 6). Outpatient office visit PPPM utilization fell postimplementation (0.08 PPPM versus 0.05 PPPM, P<0.001). Migraine-related ED visits also declined (0.012 PPPM versus 0.009 PPPM, P=0.013) as did inpatient hospitalizations (0.0014 PPPM versus 0.0007 PPPM, P<0.001).
Evaluation of a Monthly Coverage Maximum (Drug-Specific Quantity Limit) on the 5-HT1 Agonists (Triptans) and Dihydroergotamine Nasal Spray

The analysis of medical service payments showed a significant decrease in office visit payments ($15.41 PPPM versus $9.32 PPPM, \( P < 0.001 \)) and inpatient visit payments ($1.15 PPPM versus $0.62 PPPM, \( P < 0.001 \)) (Figure 7). A slight decrease was noted in emergency department payments. Total migraine-related medical service payments PPPM declined over the 18-month postintervention period ($16.58 versus $9.94, \( P < 0.001 \)) (Table 5). Finally, the decreases in payments PPPM for migraine medications coupled with the decreases in medical management payments over the 18-month period (Figure 8), contributed to significant reduction in total migraine-related care payments PPPM ($55.52 versus $41.02, \( P < 0.001 \)).

The MCO health plan desired to measure the impact of imposition of the drug-specific milligram coverage maximum on the cost and utilization of migraine-abortive therapies, alternative medication use, physician visits, or ED visits. All medication categories related to migraine therapy decreased in the number of prescriptions PPPM after imposition of the quantity limit. Only the measures of triptan prescriptions PPPM and days supplied obtained at mail order increased (Figures 1 and 4). These findings were likely the result of an increase in the number of contracts containing a mail-order pharmacy option and the realization by some health plan members of the ability to obtain a greater quantity of migraine medication in 1 prescription fill (i.e., 3-month quantity; 90-day supply). The rise in the total days supplied for triptan medications overall was fueled by the increase in days supplied in the mail-order environment. Although days supply was evaluated, it was felt to be a poor measure of utilization for this drug category due to the variability in the value entered at POS in the days supply field on the prescription claim for drugs that are acute therapies and often prescribed to be used “as needed.”

Utilization and Cost Measures for Preimplementation and Postimplementation of the Monthly Drug-Specific Milligram Quantity Limit

<table>
<thead>
<tr>
<th>Measures</th>
<th>Drug Payments PPPM*</th>
<th>Pre</th>
<th>Post</th>
<th>( P ) value</th>
<th># of Rxs PPPM*</th>
<th>Pre</th>
<th>Post</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triptans + DHE nasal spray†</td>
<td>$29.18</td>
<td>$20.78</td>
<td>(&lt;0.001)</td>
<td>0.18</td>
<td>0.15</td>
<td>0.039</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine combos</td>
<td>$0.24</td>
<td>$0.18</td>
<td>0.085</td>
<td>0.04</td>
<td>0.03</td>
<td>(&lt;0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ergotamines</td>
<td>$0.34</td>
<td>$0.25</td>
<td>0.480</td>
<td>0.01</td>
<td>0.00</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Triptans</td>
<td>$5.61</td>
<td>$6.07</td>
<td>(&lt;0.001)</td>
<td>0.34</td>
<td>0.28</td>
<td>(&lt;0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td>$0.45</td>
<td>$0.48</td>
<td>0.739</td>
<td>0.02</td>
<td>0.02</td>
<td>0.632</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylactic agents</td>
<td>$3.13</td>
<td>$3.33</td>
<td>0.221</td>
<td>0.10</td>
<td>0.09</td>
<td>0.617</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine-related Rx care</td>
<td>$38.95</td>
<td>$31.08</td>
<td>(&lt;0.001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* PPPM = per patient per month
† dihydroergotamine nasal spray (DHE nasal spray)

Note: Payments were obtained for preperiods and postperiods from claims for the drugs and services listed. Total costs in each period were calculated per patient per month (PPPM). Total patient months preimplementation=12; postimplementation=18. The same patients were followed pre and post, N=6,766.

Discussion

This 660,000-member MCO located in the southeastern United States implemented a monthly drug-specific milligram coverage maximum (quantity limit) for triptan agents and DHE nasal spray in an effort to encourage patients and prescribers to review therapeutic goals and management strategies for migraine. The utilization of the triptan agents and other pain therapies in the migraine population was increasing prior to implementation of the quantity-limit intervention, and potential misuse of the triptan medications, in particular, was presumed as the quantity of units dispensed per month increased.

The MCO health plan desired to measure the impact of imposition of the drug-specific milligram coverage maximum on the cost and utilization of migraine-abortive therapies, alternative medication use, physician visits, or ED visits. All medication categories related to migraine therapy decreased in the number of prescriptions PPPM after imposition of the quantity limit. Only the measures of triptan prescriptions PPPM and days supplied obtained at mail order increased (Figures 1 and 4). These findings were likely the result of an increase in the number of contracts containing a mail-order pharmacy option and the realization by some health plan members of the ability to obtain a greater quantity of migraine medication in 1 prescription fill (i.e., 3-month quantity; 90-day supply). The rise in the total days supplied for triptan medications overall was fueled by the increase in days supplied in the mail-order environment. Although days supply was evaluated, it was felt to be a poor measure of utilization for this drug category due to the variability in the value entered at POS in the days supply field on the prescription claim for drugs that are acute therapies and often prescribed to be used “as needed.”

Utilization of serotonin 5-HT1 receptor agonists and DHE nasal spray declined by 16.7%, and the costs for these agents declined by 28.8%. The relative cost of the drugs included in the quantity-limit intervention during the preimplementation period (triptans and DHE nasal spray) among total migraine-related drug costs was 74.9%; that percentage declined in the postimplementation period to a share of 66.8%. Importantly, the decline in utilization of the abortive agents included in the quantity-limit intervention was not associated with an increase in the number of prescriptions PPPM for migraine prophylaxis.
agents or migraine combination therapies. In fact, utilization decreased in all drug categories, and there were no increases in any other medication category. This evaluation did not measure the utilization of alternative therapies such as over-the-counter (OTC) analgesics that could have increased during the postimplementation period. Changes in utilization of OTC therapies could not be measured using available prescription claims data.

The decrease in prescription utilization was accompanied by reductions in payments for triptans and DHE nasal spray that resulted in a reduction in total payments for prescription drugs. In the 18 months following implementation of the quantity-limit intervention, the only other significant change in medication-related payments was found in an increase in payments PPPM for the “non-triptan” agents, which included largely the narcotic analgesic medications. This finding may have been due to a change in utilization favoring some popular and costly therapies in the narcotic medication category such as long-acting oxycodone products. There was no increase in either the payments for nonsteroidal anti-inflammatory agents ($0.45 PPPM versus $0.48 PPPM, \( P=0.739 \)) or payments for drugs for migraine prophylaxis ($3.13 PPPM versus $3.33 PPPM, \( P=0.221 \)).

These findings contrast with other studies that reported increases in migraine prophylaxis prescriptions PPPM after implementation of a quantity-limit program.\(^{16-18}\) The previously reported programs included medical exception opportunities through prior-authorization procedures. A prior-authorization process offers the opportunity for interactions between clinicians that could have an impact (potential increase) on the prescribing of migraine prophylaxis therapy. Our quantity-limit intervention did not allow for overrides of quantity maximums, and no clinical interaction with prescribers took place to encourage the prescribing of migraine prophylaxis therapy. Changes in prescription drug copayments and expansion of 3-tier prescription benefits in response to the rising cost and utilization of prescription drugs were common in the MCO health plan at the end of 2000 and in 2001. These changes could have impacted the utilization of medications monitored in this analysis; however, overall, utilization as measured by prescriptions PPPM for this health plan during the 30-month evaluation period increased by 11.8%, from 0.657 prescriptions PPPM to 0.734 prescriptions PPPM (data not presented here).

The reductions in prescription utilization and costs for these migraine patients subject to the drug-specific milligram quantity limit were not associated with an increase in utilization or costs in medical claims. Outpatient office visit utilization was the largest component of all medical service utilization measures (Figure 8), and in October 1999, the rate of outpatient office visit utilization for migraine was 0.41 PPPM. By September 2000, outpatient office visits for migraine had risen to 0.81 visits PPPM. Just after implementation of the quantity-limit intervention, the outpatient office visit utilization rate fell to 0.44 by December 2000, a rate similar to that observed in
October 1999, in the preimplementation period. By the end of the postimplementation period, the utilization rate appeared to stabilize at approximately 0.3 outpatient medical office visits PPPM. ED utilization also declined in the 18 months postimplementation. There were no significant medical service utilization management programs implemented by this MCO health plan during this time period that had the potential to mask an increase in utilization of services by the patient population. However, the implementation of this quantity-limit intervention occurred coincident to a change in physician reimbursement, from capitation to fee-for-service, that was expected to result in a measurable increase in physician office visits. The decrease in medical utilization is therefore difficult to explain and would appear to be fairly robust given the coincident change in physician reimbursement. Overall, migraine-related medical service utilization declined by 37% and payments to medical providers declined by 40% during the postintervention period. There was a significant reduction (26.1%) in overall payments associated with migraine care PPPM.

The impact of quantity-limit interventions for migraine abortive drugs on prescription and medical service utilization have been previously reported to be associated with overall cost reductions due to decreases in utilization and direct drug cost of triptans. These cost reductions in triptans observed by others were often associated with increases in physician office visits and, in some cases, inpatient hospitalizations or ED visits. Our analysis found significant decreases in all medical service utilization, all categories of drug utilization, total migraine-related services (either medical or pharmacy), and in payments for triptans and DHE nasal spray during the 18-month measurement period following implementation of the quantity-limit intervention for triptans and DHE nasal spray.

**Limitations**

This study had several limitations. The monthly drug-specific milligram coverage maximum was not inclusive of all abortive therapies for the treatment of migraine. For example, butorphanol spray is sometimes used for the treatment of acute migraine. It is indicated for the treatment of pain syndromes other than migraine, and the dosage maximum is unclear, making it difficult to assign a 1-month drug-specific milligram coverage limit. In addition, since this intervention did not include prior-authorization criteria, indications for the use of an agent like butorphanol could not be considered. Finally, establishment of the quantity-limit intervention as a drug-specific milligram amount, and not drug class-specific, could have permitted patients to obtain multiple triptan therapies to circumvent the coverage maximums. This analysis was not constructed to determine use of duplicative therapies within the triptan or other therapeutic classes.

Another limitation was the inclusion of only administrative claims data to determine diagnoses and to serve as principal measures of utilization and cost. Therefore, prescription quantities for triptans and DHE nasal spray that exceeded the monthly drug-specific milligram coverage maximums (i.e., paid for in cash by health plan members) were not measured. This data source does not include analgesics and other medications purchased OTC. In addition, the clinical severity of the patient’s migraine, level of disability, and other variables such as weight, smoking habits, and race are not recorded in medical and pharmacy claims data and thus were unavailable for analysis. The exclusive use of claims data also did not permit an evaluation of clinical outcomes such as work performance, absenteeism, quality of life, and other migraine-related, disease-related measures that could have been impacted by the monthly drug-specific milligram coverage maximums in this intervention.

This study included analysis of the payments for migraine-related care and did not examine other factors that may have had an impact on the total cost of health care in this population of patients identified by medical claims with diagnostic codes for migraine. For example, there could have been an association between use of larger quantities of abortive therapies and adverse effects prior to the implementation of the monthly coverage maximum, which could have contributed to higher preinitiative medical visits. The cost impact of the quantity-limit intervention on patient use of OTC analgesic or other alternate therapies also was not measured. In addition, during the 30-month study period, there were changes made in payment structures and reimbursement agreements with providers (for example, the payment structure for primary care physicians was changed from a capitation to fee-for-service reimbursement) that may have had an impact (upward or downward) on the health care costs of managing these specific patients. This analysis was not expressly designed to explore these possibilities, and analysis of the impact of payment structure changes was not finalized at the time of preparation of this manuscript.
This was a longitudinal preanalysis and postanalysis that included no control group. Use of the same patient population in the preperiods and postperiods allowed the patients to serve as their own controls, decreasing prevariability and postvariability. Culley and Wanovich reported the impact of a quantity-limit program using a preintervention and postintervention evaluation, but no statistical analysis was reported; that study did not involve a single cohort, and the groups in the preperiods and postperiods were not comparable. Goldfarb et al. analyzed the effect of a triptan quantity-limit program in a retrospective claims evaluation, but these authors did not report statistical significance for the impact of the intervention. Our evaluation found significant predifferences and postdifferences in many of the outcome measures reported.

Lastly, the total clinical and economic significance of the decrease in utilization of the migraine medications in the absence of an increase in medical utilization is not known. This evaluation did not include an examination of cost-effectiveness or the cost of changes in work performance, productivity, or absenteeism.

Conclusion

A monthly, drug-specific milligram coverage maximum (quantity limit) on the triptan medications and DHE nasal spray was associated with a significant reduction in costs and utilization of abortive agents for migraine. The relative cost of the drugs included in the quantity-limit intervention (triptans and DHE nasal spray) declined from 74.9% of all migraine-related drug therapy to 66.9% after implementation of the quantity limits. Migraine-related medical services in the outpatient and inpatient service areas decreased when compared to the 12-month period prior to implementation of the quantity-limit intervention. Overall, the quantity-limit intervention appeared to have been successful in managing apparent overutilization of triptans and DHE nasal spray.

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20. “Episode Treatment Groups, ETGs, and ETG” are owned by Symmetry Health Data Systems, Inc. and are used under a grant of license. Episode Treatment Groups (ETG) is protected under United States patent #5,835,897. U.S. and foreign patents pending.
ABSTRACT

BACKGROUND: Prescription review by pharmacists prior to dispensing is an important step in an overall strategy for preventing medication errors. Contacts with prescribers may be required to clarify missing, unclear, or inconsistent information. While essential to reduce the likelihood of potential patient harm, clarification contacts are time-consuming for pharmacists and prescribers. The scope of the issue and the factors that contribute to it are not well understood.

OBJECTIVE: To quantify the frequency of contacts with prescribers that were necessary to obtain clarification of prescriptions and to identify the factors that made these prescriber contacts necessary.

METHODS: An analysis was conducted involving new prescriptions received by a national mail-order pharmacy that required clarification contacts with prescribers for quality reasons (i.e., those potentially impacting the accuracy of dispensing). Excluding refills and renewals, the percentage of new prescriptions requiring clarification contacts was calculated and categorized by incoming delivery channel (mail, fax, telephone, etc.). The quality problems that prompted these contacts were categorized according to the problem identified.

RESULTS: Among the total of 295,378 new prescription orders received during the 1-week study period (from April 7 to April 13, 2002), 8.7% contained quality problems that necessitated clarification contact with prescribers. Prescriptions received by fax transmission and mail were most likely to require clarification as compared with direct telephone conversation and miscellaneous (including electronic) channels. Among prescriptions that required a clarification contact for quality problems, an average of 2.4 problems per prescription was observed. The most common problems were: directions unclear or missing (24.3%); refill quantity unclear, missing, or incorrect (24.3%); dosage unclear (20.2%); drug name or strength unclear (13.2%); missing physician or patient data (11.4%); and missing prescriber signature (3.2%).

CONCLUSION: Prescriber clarification contacts are frequently needed to reduce the potential for medication error in the current prescription fulfillment process. While these contacts are necessary to clarify data elements essential to accurate medication dispensing, they are time- and resource-intensive. These study results suggest that alternate prescription order channels, including electronic, could reduce the sizable burden of prescription order clarification in mail-order pharmacy.

KEYWORDS: Pharmacy benefit management, PBM, Prescriber contacts, Clarification contacts, Mail-order pharmacy, Prescription dispensing, Prescription order channels

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to professional practice, health care products, procedures, and systems, including prescribing, order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.12

In this context, the pharmacist’s review of each prescription continues to play an integral role in preventing medication errors. Pharmacists are uniquely positioned to identify potential quality and safety issues before the medication is dispensed.3 Pharmacy practice standards exist to ensure quality along the entire spectrum of pharmacy tasks and responsibilities, including, but not limited to, training, prescription review, dispensing, patient counseling, drug utilization review, and record keeping.11 Encompassed within the prescription review standard is the requirement to clarify any missing or ambiguous elements of the prescription.11

If information on a prescription order is unclear or missing, pharmacists typically contact the prescriber via telephone or fax for clarification.4 These clarification contacts are distinct from other types of contacts related to pharmacy practice. Clarification contacts focus on the completeness and accuracy of the prescription order (i.e., that it contains all the required elements and the dosage is appropriate for the drug administration route). Other types of reviews performed by the pharmacist, which differ from clarification contacts, include drug utilization review (checking for drug interactions, potentially dangerous usage patterns, and other contraindications), therapeutic interchange (promoting compliance with the formulary of the patient’s pharmacy benefit plan), and prior authorization (requesting coverage approval from the patient’s pharmacy benefit plan).

The necessity for clarification contacts with prescribers affects the entire prescription fulfillment process.7 Inefficiencies produced may include rework (faxing copies of prescriptions to prescribers for completion or correction), data reentry, and telephone calls to the prescriber to obtain the correct information. These activities may lead to dispensing delays, poor customer service, and increased staffing costs.7 Additionally, distractions and interruptions have been shown to increase dispensing errors.5

While the cost of the pharmacist’s time may be offset by the medical savings associated with the avoidance of adverse drug events (ADEs), an opportunity clearly exists for improving the efficiency of the entire system.12 Managing quality by downstream inspection (such as evaluating the quality of prescriptions after they reach the dispensing stage) creates the potential for mistakes, and this may be more costly overall than managing quality earlier in the prescribing-dispensing process.13

There is little published data on the frequency with which prescriptions require clarification contacts in the outpatient setting. In a 1988 study of 9 community pharmacies in Indiana, 2.6% of new prescriptions were found to contain prescribing errors.14 The cost of the pharmacists’ interventions, including labor and operations costs, was estimated to be $1.75 per prescription. The average savings in avoided medical care was estimated to be the $7.15 per prescription from the potential drug-related complications that were presumed to have been avoided by making the interventions. In a larger study of 89 community pharmacies in 5 states, 1.9% of new prescriptions required a pharmacist’s intervention (including clarification of unclear or missing data as well as discussion of potential drug-drug interactions and patient allergies).3

The extant study was undertaken to quantify the prescriber clarification contacts made by a large home delivery (mail-order) pharmacy service operated by a nationwide pharmacy benefit management (PBM) company. The primary objective was to assess the types and frequency of prescription issues requiring clarification contacts with prescribers. Such data can then be leveraged to serve as a basis for process improvement initiatives, to ultimately reduce the likelihood of medication errors.

Methods

Study Sample

The data sample was drawn from prescriptions processed by a national home-delivery pharmacy service operated by a PBM company with dispensing operations involving 12 mail-order pharmacies located throughout the United States. Prescriptions were processed and dispensed from these pharmacies for patients nationwide who had been provided with prescription benefit plans by their employers, unions, managed care organizations, insurance plans, and government employee programs.

The sampling interval for this study was the 7-day period from April 7 to April 13, 2002. The sampling interval was chosen to exclude major holidays and other significant events that might have affected the submission or processing of prescription orders. During this time frame, a total of 1,732,389 prescriptions were received.

From this total number of prescriptions, a subset was identified that reflected all new prescriptions, excluding refills or renewals. For the purpose of this study, new prescriptions were defined as those for which there was no history of the same medication at the same strength being dispensed for the same patient within the prior 365 days. Aside from prescriptions that did not satisfy this definition of being new, no other exclusion criteria were applied.

Analysis of Clarification Contacts

Throughout the process for new prescription dispensing from this PBM network, information is recorded electronically in a proprietary, comprehensive, system-wide prescription fulfillment database at each of the various process steps. Such information includes data on the incoming delivery channel (mail, fax, telephone, etc.), the initial prescription review, clarification contacts (if needed), outcomes of the contacts, and final dispo-
Mail-Order Prescriptions Requiring Clarification Contact With the Prescriber: Prevalence, Reasons, and Implications

Upon reviewing each prescription prior to dispensing, the pharmacist renders a professional judgment as to whether the prescription requires clarification of any component with the prescriber. If a clarification contact is required, the pharmacist reviewing the prescription documents the reason(s) for the contact in the same database described above. Some clarification contacts are prompted by factors related to the drug being prescribed (e.g., unclear or missing drug name, strength, or directions). Contacts are also prompted by unclear or missing prescriber information, patient information, or signature. For certain prescriptions, multiple issues exist that necessitate a clarification contact.

Two different analyses were conducted on the set of new prescriptions identified. The first assessed the percentage of prescriptions that required clarification contacts. This was computed in aggregate as well as for each of the delivery channels through which the mail-order pharmacy received the prescription (e.g., mail, fax, telephone, voice message). Mail includes hard-copy prescriptions received by standard post or express service, and are almost entirely handwritten (data on file). Fax includes prescription facsimiles sent by prescribers. Telephone prescriptions are verbal orders called in directly to a pharmacist. Voice-message orders are prescriptions communicated via telephone with an audio recording device for prescription data elements. A Miscellaneous category was also created, which includes a variety of delivery channels that were infrequently used during this time period, such as file transfers from electronic prescribing devices. This final Miscellaneous category was collected and reported in aggregate because of the relatively small numbers of prescription flowing through each of these channels and because data limitations prevented confident subgroup analysis within it.

The second evaluation assessed the types of issues requiring clarification contacts. For all contacts, the reasons were tabulated and issues categorized by frequency of occurrence. The relative frequency of each issue was computed as a percentage of the total issue count among the sampled prescriptions.

As discussed above, the quantification and analysis of these clarification contacts were distinct from, and exclusive of, other prescriber contacts related to pharmacy practice, such as drug utilization review, therapeutic interchange, and prior authorization.

Results

During the period of this study, a total of 295,378 prescriptions met the criteria for inclusion in the study sample of new prescriptions, as defined above. Among these, 8.7% contained quality problems that required clarification contacts with prescribers. Examples of the types of prescriptions that required clarification can be found in Figures 1, 2, and 3. The prevalence of prescriptions having such issues varied, depending on the delivery channel (Table 1). Prescriptions received by fax and mail required relatively high rates of clarification as compared with direct telephone conversation and miscellaneous (including electronic) channels.

Prescriptions necessitating a clarification contact contained an average of 2.4 issues per prescription. The relative frequency of each type of issue is summarized in Table 2. The most common issues requiring clarification were related to directions for use and administration (directions unclear or missing), prescribed number of refills (refill quantity unclear or missing), dosage (dosage unclear), and drug identity and strength (drug name or strength unclear).

Discussion

Clarification contacts with prescribers play an important role as part of a comprehensive patient-safety program. Clarification contacts can help to ensure the accuracy and safety of the medications dispensed, but these important benefits require signifi-
cant investments in time and impact a pharmacy’s operational efficiency.1 In this study, a significant percentage of new prescription orders (8.7%) contained issues that required follow-up with prescribers for clarification. While these follow-up contacts place additional workload on both pharmacists and prescribers, they are critical for achieving safety objectives and satisfying legal requirements for dispensing. In fact, some of the most frequently identified issues in this study have a significant potential to affect patient health and safety. Those issues, which include lack of clarity in drug name or drug strength, dosage, and instructions for use, account for 57.7% of all issues identified in this study.

Efforts by individual pharmacies to improve the quality and safety of prescription dispensing fit within a broader set of initiatives that have been proposed and, in some cases, developed at the national and local levels, with the goal of reducing medication errors. In 2000, the U.S. government funded the Center for Quality Improvement and Patient Safety to serve as a clearinghouse for medical error reporting within the Agency for Healthcare Research and Quality. The federal government also instituted mandatory and voluntary reporting systems for medical errors, promulgated safety performance standards for the Medicare program, and funded premarketing and postmarketing surveillance by the U.S. Food and Drug Administration. In U.S. Veterans Health Administration facilities, medication safety has been improved through the use of automated order-entry systems.1 Similar systems are in place in other large and small hospitals, spurred in part by organizations like the Leapfrog Group that have placed computer order-entry near the top of their quality improvement agendas.15,16 The pharmaceutical industry is also developing drug names, labels, and packages to reduce the likelihood of dispensing errors associated with human factors (e.g., confusion, inattention, forgetfulness).1,17,18

Many of the efforts to reduce medication errors focus on the roles of the prescriber and pharmacist. For the prescriber, educational sessions are employed to improve awareness of potential errors during the prescribing process and to recommend ways to avoid them, such as printing clearly and using abbreviations with great caution. For the pharmacist, increasing emphasis is placed on clinical consultations with prescribers.12 Other changes include computerized pharmacy systems to identify questionable prescriptions, check for drug allergies, and flag potential drug-drug interactions; electronic prescribing systems; unit dose dispensing and distribution; standardization of processes and equipment; bar-coding of medication bottles; and automated dispensing systems.12

In the context of these activities and initiatives, clarification contacts by pharmacists with prescribers play a key role in promoting patient safety. This study found an overall clarification contact rate of 8.7% for new prescriptions received by a national home-delivery pharmacy, which is higher than the rates reported in earlier studies of community-based pharmacies. The exact reasons for this disparity are unclear, although a variety of factors likely contribute. Many potential differences between the 2 settings could affect clarification contact rates, including the demographics of the customers served, the types...
of prescriptions filled (maintenance medications versus medications for acute illness or injury), and differences in pharmacy operations related to pharmacy size. The relative frequency of certain delivery channels for prescription orders is another significant variable, with mail-order pharmacies receiving relatively few prescriptions by telephone (1% in this study) versus retail pharmacies where the percentage may be considerably higher. Furthermore, in a community setting, the pharmacist may have experience with a local prescriber’s practice style, handwriting, and prescription drug preferences that enable resolution of an issue through professional judgment without a clarification contact. A community pharmacist also may be able to obtain clarification of some information such as patient demographics directly from the patient or his or her proxy at the pharmacy counter, whereas this option is not as readily available to a home-delivery pharmacist. Recognizing all of these issues, mail-service pharmacists may tend to clarify prescriptions more often than their retail counterparts in order to assure safe and accurate dispensing.

Clarification contacts are time consuming for both pharmacists and prescribers. For pharmacists, these contacts may interrupt and delay dispensing and may also reduce the pharmacist’s availability to counsel patients. These contacts also introduce new opportunities for errors in dispensing, especially when issues on multiple prescriptions are being pursued and documented simultaneously. For prescribers, clarification contacts may interrupt face-to-face patient care and reduce the time they have available for other responsibilities. These contacts also increase demands on office staff and reduce overall office efficiency.

The workload associated with clarification contacts is a significant contributor to pharmacy staffing requirements and operating costs. As prescription volumes continue to increase (from 3 billion prescriptions dispensed in 2000, projected to reach 4 billion by 2004), the magnitude of this impact will only grow. A related concern is that staffing shortages, overwork, and job stress may further contribute to increased medication errors.

This study found that the need for prescription clarification contacts varies considerably based on the incoming delivery channel of the new prescription order, and the subgroup that included electronic channels demonstrated significantly less need for clarification. In this context, electronic prescribing may provide a means to reduce the inefficiencies associated with the current prescription ordering and fulfillment processes.

While this study did not specifically measure the comparative difference between electronic prescribing and other channels of prescription orders, this study did identify the potential need for a method of prescription ordering that requires less clarification contacts with prescribers. An electronic tool would permit a prescriber to transmit a legible prescription electronically to a pharmacy without the inherent opportunities for unclear, confusing, and missing information that is related to handwritten prescriptions. Electronic prescribing technology provides the potential to review and check the prescription against a variety of drug safety criteria (e.g., allergies or interactions), prompt the prescriber with appropriate warnings and options, and present clarification request to the prescriber before being transmitted to the pharmacy. Other advantages include the ability to handle renewal requests, support interactive messaging with pharmacists, maintain a history log on prescription processing, and provide dose calculators for specific medical conditions or age groups. Optimal integration of this technology requires immediate access to a wide range of patient data, including demographic information, lab results, allergies,
prescription benefit plan formulary, and current medications.\textsuperscript{24} It also requires access to detailed information on available drugs and formulations, dosage and administration guidelines, interactions, and contraindications. Many of these functions have already become available for electronic prescribing systems or are being tested in the marketplace.\textsuperscript{13,22}

Opportunities also exist to educate prescribers about the prevalence of the prescription issues described here and the associated risk of ADEs associated with them. As the total number of U.S. prescriptions continues to increase by approximately 150 million each year,\textsuperscript{23} efforts to inform prescribers about the critical elements of safe prescribing become even more important. Through direct outreach efforts to prescribers as well as initiatives involving medical organizations and health care delivery systems, opportunities exist to reduce the number of prescription issues that pharmacists are required to clarify.

\section*{Limitations}
One limitation of this study is its exclusive focus on new home-delivery (mail-order) prescriptions, so the results cannot be generalized to home-delivery refill or renewal prescriptions or to prescription fulfillment in other settings such as community pharmacies or hospitals.

A second limitation is that this is a descriptive study that was not designed to quantify clinical outcomes. We did not study the relationship between clarification contacts and the ADEs that may have been avoided and did not quantify the types and frequency of ADEs that are averted by clarification contacts with prescribers. Some of the issues identified in the extant study (e.g., unclear drug name, strength, or dosage) have the potential to cause dispensing errors and adverse events unless they are first clarified with prescribers. Based on pharmacy data alone, the likelihood, type, and severity of avoided ADEs could not be quantified.

A third limitation relates to the relatively small number of electronic prescriptions that were received during the analysis period. The clarification rate for the miscellaneous category (which included electronic prescriptions) was considerably less than most other channels and about one half the incidence of clarification contacts needed for mail-prescription orders, the most common channel for new orders to mail-order pharmacy. However, a more-detailed analysis of the issues related to the electronic subgroup of prescriptions requires a significantly larger sample, which may be more likely in a future period when electronic prescribing becomes more prevalent.

Finally, study design and limited data availability prevented the inclusion of the specific costs of performing the requisite clarifications with prescribers. Therefore, the overall economic impact of these activities was not quantified and provides an opportunity for future analysis.

\section*{Conclusion}
Traditional prescription-ordering processes offer many opportunities for miscommunication and mistakes and may contribute to the high rates of outpatient medication errors that have previously been reported. At a national home-delivery pharmacy, 8.7\% of prescriptions had incomplete, unclear, or missing information related to elements that are essential to accurate medication dispensing. Although clarification contacts with prescribers can help avoid these potential dispensing errors, these contacts are time consuming and reduce operational efficiency.

Future efforts might be directed toward improving the quality of prescription communication for those prescription order channels that are currently associated with higher rates of clarification contacts as well as shifting prescription communication away from these channels and toward those that require fewer clarification contacts.

Emerging electronic prescribing technologies may offer a better long-term approach to the problem of unclear or incomplete prescription orders.\textsuperscript{24} Electronic prescribing would presumably include electronic edits to verify the prescribed drug name, strength, dosage, etc., against valid data elements for these and other prescription order fields. Electronic edits can also help to ensure that prescription orders are populated completely and that the data are consistent with patient information and available medications. These technologies can also provide a more efficient means for pharmacists to receive and process prescriptions. Improving the quality of the initial prescription order will improve pharmacy and physician office efficiency by reducing the need for clarification contacts with prescribers.

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\section*{REFERENCES}


Acute exacerbations of chronic bronchitis (AECB), as the name suggests, is acute inflammation of the bronchial airways in the presence of underlying chronic bronchitis. AECB is generally accompanied by bacterial infections for which standard treatment is antibiotics. Approximately 13 million persons in the United States (almost 5% of the adult population) have chronic bronchitis and experience acute exacerbations. As such, in addition to its clinical effects, AECB is likely to have a substantial economic impact.

A variety of studies have been performed to assess the costs associated with AECB and its treatment. These studies can be grouped into 3 main categories: cost-of-illness studies, which evaluate the baseline resource utilization and costs associated with AECB; comparative cost studies, which assess the difference in costs resulting from different AECB treatments; and cost-effectiveness studies, which determine the incremental change in cost per incremental improvement in patient outcomes for different AECB treatments. Each of these types of studies provides unique information on the impact of AECB. Cost-of-illness studies, also known as burden-of-illness studies, provide an assessment of all costs associated with a condition and may include societal as well as direct and indirect medical costs. Comparative cost studies are important in the evaluation of the relative costs of treatments and may be important to treatment selection. Cost-effectiveness studies, by providing a common metric such as cost per quality-adjusted life-year (QALY) or symptom-free day, allow for comparisons across conditions and are most appropriate for societal or health plan allocation decision making.

Methods
To better understand the economic impact of AECB, we reviewed the economic literature for this condition. A MEDLINE literature search was conducted to identify articles with the MeSH headings “Pulmonary Disease, Chronic Obstructive,” “Pulmonary Emphysema,” or “Bronchitis, Chronic” and headings involving the term “Cost.” There was no time or language limitation to the search, and we did not limit the search to articles with abstracts available online. Only articles providing information on medical care costs for AECB in the United States or Canada were selected. Reference lists of identified articles were reviewed for additional relevant information.

Literature Search Results
A total of 8 published studies on the medical care costs of AECB in the United States and Canada were identified. Two of these are cost-of-illness studies, in that they provide information only on
the medical care costs (either inpatient only or inpatient plus outpatient) for the broad population of AECB patients. One of the identified studies is a comparative cost study, presenting differences in medical care costs for AECB patients treated with differing antibiotic therapies. Finally, 5 of the studies are cost-effectiveness studies, in that they compared both the costs and clinical outcomes for patients treated with a number of specified antibiotics. (See Table 1 for a summary of reviewed studies.)

Cost-of-Illness Studies

We identified 2 studies that assessed total costs associated with AECB in the United States and Canada. Both studies included data on inpatient treatment; one also included estimates of costs associated with outpatient care for AECB.

Niederman et al. conducted a retrospective analysis using claims and survey data to assess resource utilization and health care system costs for patients treated for AECB. Medicare

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<th>Reference</th>
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<td>Destache et al.</td>
<td>United States</td>
<td>Retrospective</td>
<td>Patient data obtained from medical records between January 1990 and January 1994. Patients were older than 36 years with mild-to-moderate acute infections and diagnosed chronic bronchitis documented in records. Three antibiotic groups were selected for comparison and were categorized as first-, second-, and third-line agents.</td>
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<tr>
<td>Niederman et al.</td>
<td>United States</td>
<td>Retrospective Analysis of claims data for patients treated for AECB. Medicare was the primary data source for patients &gt;65 years; data from the National Healthcare and Cost Utilization Project, the National Ambulatory Medical Care Survey, and the National Hospital Ambulatory Medical Care Survey were used for patients aged ≤65 years.</td>
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<td>Grossman et al.</td>
<td>Canada</td>
<td>Randomized, multicenter, parallel-group, open-label study; n=240 (120 ciprofloxacin, 120 usual care)</td>
<td>Outpatient adult men and women aged 18 years or older with chronic bronchitis and a recent history of frequent exacerbations (3 or more within the past year) were randomized to receive either oral ciprofloxacin (500 mg bid) or usual care. Patients were seen at months 3, 6, 9, and 12 for regular visits. Patients completed 3 self-administered questionnaires at regular and follow-up visits.</td>
</tr>
<tr>
<td>Smith and Pesce</td>
<td>United States</td>
<td>Retrospective analysis of data from published reports (published 1972-1989) ($Canadian1992)</td>
<td>Clinical and utility data were derived from published accounts. Cost data were from Medicare reimbursement rates. The model compared cost/QALY for treatment of AECB with PAC versus no PAC, given assumptions about life expectancy following hospitalization.</td>
</tr>
<tr>
<td>Saint et al.</td>
<td>United States</td>
<td>Retrospective</td>
<td>Analysis of claims data for patients treated for AECB. Medicare was the primary data source for patients &gt;65 years; data from the National Healthcare and Cost Utilization Project, the National Ambulatory Medical Care Survey, and the National Hospital Ambulatory Medical Care Survey were used for patients aged ≤65 years.</td>
</tr>
</tbody>
</table>
### TABLE 1: Summary of Reviewed Studies* (continued from previous page)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Days of therapy</th>
<th>First-line Agents</th>
<th>Second-line Agents</th>
<th>Third-line Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Destache et al.7</td>
<td>8.9 ± 3.3</td>
<td>8.3 ± 2.3</td>
<td>7.5 ± 2.5</td>
<td></td>
</tr>
<tr>
<td>Grossman et al.8</td>
<td>Not presented</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halpern et al.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemifloxacin</td>
<td>2.3%</td>
<td>0.20</td>
<td>0.79</td>
<td>5.67</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>6.3%</td>
<td>0.37</td>
<td>0.78</td>
<td>6.14</td>
</tr>
<tr>
<td>Niederman et al.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quenzer et al.12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saint et al.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University of Michigan</td>
<td>101</td>
<td>3.98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>University HealthSystem Consortium</td>
<td>12,379</td>
<td>5.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All acute and chronic bronchitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University of Michigan</td>
<td>154</td>
<td>3.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>University HealthSystem Consortium</td>
<td>13,904</td>
<td>5.07</td>
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</table>

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of Discharges</th>
<th>Mean Lengths of Stay (Days)</th>
<th>Physicians' Office</th>
<th>Emergency Dept.</th>
<th>Outpatient Dept.</th>
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<tbody>
<tr>
<td>Destache et al.7</td>
<td>207,540</td>
<td>6.3</td>
<td>89%</td>
<td>8.9%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Grossman et al.8</td>
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<td></td>
<td></td>
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<tr>
<td>Niederman et al.1</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference</th>
<th>Costs</th>
<th>Cost-effectiveness and Cost-Utility Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Destache et al.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics for AECB</td>
<td>$188 ± $122</td>
<td>$116 ± $99</td>
</tr>
<tr>
<td>Concomitant medications</td>
<td>$742 ± $1,364</td>
<td>$789 ± $1,352</td>
</tr>
<tr>
<td>Outpatient resources</td>
<td>$544 ± $544</td>
<td>$475 ± $485</td>
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<tr>
<td>Hospitalizations</td>
<td>$1,329 ± $6,064</td>
<td>$459 ± $2,169</td>
</tr>
<tr>
<td>Time lost from work</td>
<td>$291 ± $1,161</td>
<td>$628 ± $1,716</td>
</tr>
<tr>
<td>Out-of-pocket expenses for patient and caregivers</td>
<td>$100 ± $136</td>
<td>$150 ± $278</td>
</tr>
<tr>
<td>Total</td>
<td>$3,194 ± $6,575</td>
<td>$2,617 ± $3,300</td>
</tr>
<tr>
<td>Grossman et al.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>$188 ± $122</td>
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</tr>
<tr>
<td>Grossman et al.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemifloxacin</td>
<td>$138</td>
<td>$38</td>
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<tr>
<td>Clarithromycin</td>
<td>$258</td>
<td>$39</td>
</tr>
<tr>
<td>Total</td>
<td>$7,211</td>
<td>No NPPV</td>
</tr>
<tr>
<td>Niederman et al.1</td>
<td></td>
<td>Incremental cost-effectiveness ratio not calculated</td>
</tr>
<tr>
<td>Patients &gt;65 years of age</td>
<td>$5,497</td>
<td>Hospital Costs (mil)</td>
</tr>
<tr>
<td>Patients ≤65 years of age</td>
<td>$5,561</td>
<td>Physician Costs (mil)</td>
</tr>
<tr>
<td>All ages</td>
<td>$5,516</td>
<td>Total Treatment Costs (mil)</td>
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<tr>
<td>Drug cost</td>
<td>$1,703</td>
<td>$613</td>
</tr>
<tr>
<td>All other hospital costs</td>
<td>$7,760</td>
<td>$4,884</td>
</tr>
<tr>
<td>Total cost</td>
<td>$9,463</td>
<td>$5,497</td>
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claims data from 1994 were used to estimate inpatient and outpatient utilization rates and costs for patients aged >65 years. For patients <65 years, estimates were generated from the National Healthcare and Cost Utilization Project, the National Ambulatory Medical Care Survey, and the National Hospital Ambulatory Medical Care Survey. Inpatient resource utilization and charges for the <65 years group were inflated from 1994 to 1995 dollars (to have consistent inpatient and outpatient costs), while outpatient resource utilization rates and charge data were taken from the average of survey data from 1993 through 1995; 1995 costs were applied to both the inpatient and outpatient resource utilization rates.

In their analysis, Niederman and colleagues reported that the total direct treatment costs of AECB were largely attributable to costs of hospitalizations.\(^5\) The total annual AECB treatment costs for patients >65 years were $1.2 billion, while the cost for patients <65 years were $419 million. Total inpatient hospital costs for the >65 years group were $1.1 billion (92% of total costs) and $408 million (97% of total costs) for the <65 years group. The average hospital charges incurred, in 1995 dollars, were equal to $5,497 per patient aged >65 years and $5,561 per patient <65 years. Inpatient physician services account for an additional $32 million and $11 million for the >65 years and <65 years groups, respectively. Outpatient services data, although less reliable than inpatient data because diagnosis codes are often used interchangeably across respiratory diseases in outpatient data, indicated $24.9 million for the >65 years group and $15.1 million for those <65 years.

Based on 1998-1999 data from the University HealthSystem Consortium (UHC) Clinical Database (>100 U.S. academic hospitals) and the University of Michigan Health System (UMHS), Saint et al. calculated the average cost of a hospitalization for AECB (ICD-9 491.21) and for acute and chronic bronchitis (ICD-9 490, 491).\(^6\) Results were similar between the 2 data sources and comparable to the values reported by Niederman et al.\(^5\) The average cost of inpatient hospitalization for AECB was $6,285 for UMHS and $6,625 for UHC. Inpatient hospitalization costs for all acute and chronic bronchitis were $6,287 for UMHS and $6,524 for UHC.

### Comparative Cost Studies

Destache et al. used retrospective data to evaluate the efficacy and cost-effectiveness of antimicrobial therapy for patients with AECB.\(^7\) Data were obtained from medical records in the Pulmonary Department of Creighton University School of Medicine between January 1990 and January 1994. Patients with mild-to-moderate acute infections and a documented diagnosis of chronic bronchitis were eligible for the study. A total of 60 patients with 224 documented episodes of AECB were included in the analysis. Prior to data collection and review, a group of resident pulmonologists was asked to categorize the antibiotics prescribed for each documented episode of AECB into one of 3 groups. The antibiotics were categorized as first-line agents (amoxicillin, tetracyclines, erythromycin), second-line agents (cephradine, cefuroxime, cefaclor, cefprozil), and third-line agents (amoxicillin/clavulanate, azithromycin, ciprofloxacin). However, the AECB data analysis did not distinguish between antibiotics used for the initial presentation of
AECB and those used for subsequent presentations.

The costs associated with treatment for the initial and subsequent AECB episodes and the time between episodes were used to evaluate the efficacy and cost-effectiveness of each antibiotic treatment group. The total charges for treating AECB were determined by summing charges for laboratory work, office visits, radiology, antibiotics, and hospitalizations. The average total charges for treatment of AECB in each group, expressed in 1994 U.S. dollars, were $942 ± $2,173 for patients treated with first-line agents, $563 ± $2,296 for second-line agents, and $542 ± $1,946 for third-line agents (P<0.05, first- versus third-line). The average pharmacy costs associated with AECB were lowest for first-line agents; however, costs for other components of resource utilization for first-line therapy patients more than offset these savings. Treatment failure in patients receiving first-line agents occurred significantly more frequently than in those receiving third-line agents (19% versus 7%, P<0.05).

A significant difference was also observed in the hospitalization rate for AECB within 2 weeks of outpatient treatment for patients prescribed first-line agents compared to those prescribed third-line agents (18.0% versus 5.3%, respectively). In addition, the mean time between subsequent AECB episodes requiring treatment was significantly different among the 3 treatment groups: first-line agents, 17.1 ± 22.0 weeks; second-line agents, 22.7 ± 30.0 weeks; and third-line agents, 34.3 ± 35.5 weeks (P<0.005). The authors concluded that compared to first- or second-line agents, the use of third-line antimicrobial agents reduced the treatment failure rate, need for hospitalization, and overall costs of care as well as prolonged the time between AECB episodes.

Cost-effectiveness Studies

Five studies were identified as reporting on cost-effectiveness of treatments for AECB: 3 presented incremental cost-effectiveness, 2 reported on antibiotic treatments, and 1 reported on pulmonary artery catheterization. Two other studies presented costs and outcomes related to noninvasive positive pressure ventilation and cost per complication-free cure but did not present incremental cost-effectiveness ratios between treatments. Hospitalization and costs associated with treatment failure were the single largest cost driver in each of the studies, while drug costs were generally responsible for a smaller proportion of the total treatment costs.

Quenzer et al. developed a computerized pharmacoeconomic model to evaluate the impact of clinical response and adverse drug events on cost and cost-effectiveness of clarithromycin compared with those of 7 alternative antibiotics (amoxicillin/clavulanate, ampicillin, cefaclor, cefoxime, cephalosporin, clarithromycin, erythromycin) used to treat lower respiratory tract infections (LRTI). Cost data were obtained from 12 randomized, controlled, clinical trials conducted between 1987 and 1992 in outpatient clinics in the United States. A total of 2,377 patients, treated for acute exacerbations of chronic bronchitis (n=1,102), pneumonia (n=591), or a combination of the 2 conditions (n=201) were enrolled in the clinical trials from which data were used in the cost-effectiveness study.

The mean total costs per episode ranged from $137 to $267, depending on the starting medication. Drug acquisition costs accounted for a small percentage of the total treatment cost (4.3% to 32.4%) compared to clinical costs (including costs of treatment failure), which represented the largest percentage (45.9% to 62.2%) of the overall costs. The “cost-effectiveness analysis” was based on the proportion of patients with a complication-free cure (CFC), defined as a full course of therapy with a successful response and no adverse drug events (ADEs). It is important to note that this is not a true cost-effectiveness value, as it provides the overall cost per outcome for a single therapy rather than the incremental cost per incremental outcome as compared to another therapy. The mean cost per CFC ranged from $307 for clarithromycin to $612 for cefaclor. The ranked order of the 7 antibiotics from lowest to highest cost per CFC was: clarithromycin, cefixime, amoxicillin/clavulanate, erythromycin, cefuroxime, ampicillin, and cefaclor. Incremental cost per CFC ratios of all agents compared to the least expensive demonstrated additional costs per CFC that ranged from $145 for clarithromycin to $899 for cefuroxime. This study concludes that the costs associated with treatment failure and ADEs contribute substantially to the overall cost and “cost-effectiveness” of antibiotics used in the treatment of LRTI in the outpatient setting.

The Canadian Ciprofloxacin Health Economic Study Group conducted a prospective, randomized, open-label study to compare the annual “costs, consequences, effectiveness, and safety of ciprofloxacin versus standard antibiotic care,” for patients with AECB. The study population consisted of 240 patients (120 in each group), aged 18 years and older, with a history of 3 or more exacerbations within the past year. Patients were randomized to receive either oral ciprofloxacin (500 mg bid) or usual care, defined as “any antibiotic or combination of antibiotics other than a quinolone antibiotic (except under special circumstances).” Patient assessments occurred at 3-, 6-, 9-, and 12-month intervals. Annual cost estimates included antibiotics prescribed for AECB, concomitant medications, hospitalizations, emergency department visits, outpatient resources such as diagnostic tests and procedures, time lost from work, and patient and caregiver out-of-pocket expenses.

Patients in the ciprofloxacin treatment group had lower costs for concomitant medications, time lost from work, and out-of-pocket expenses for patients and caregivers. Cost of antibiotics accounted for less than 6% of the total annual cost per patient in each treatment group. Hospitalizations represented 42% ($1,329 ± $6,064 [SD], Canadian $) of the total annual cost in the ciprofloxacin group compared to 18% ($459 ± $2,169 [SD]) in the usual care group. The only statistically significant predictors of hospitalizations were duration (P=0.004) and severity (P=0.004) of chronic bronchitis. The overall mean annual cost of AECB in the ciprofloxacin group was $3,194 ±
intubation by 37.5% and hospital mortality by 16.1%), suggesting that adjunct NPPV dominated standard therapy alone. Sensitivity analyses demonstrated lower costs for standard therapy alone only when the rate of intubation was greater for NPPV than for standard therapy.

Smith and Pesce (1994) evaluated cost-effectiveness of pulmonary artery catheterization (PAC) among patients with severe AECB requiring mechanical ventilation. Costs were obtained from Medicare reimbursement rates, and clinical probabilities were derived from published data. Utility values were estimated; the model assumed posthospital survival of 1.74 years. Sensitivity analyses were performed around all variables. The incremental cost per QALY associated with the use of PAC compared to standard care was $77,407 (1992, U.S.$). If survival were improved by 8.7% (base case estimate is 5%), the cost/QALY would decrease to $50,000, a value considered to be the upper threshold for acceptable cost-effectiveness in the literature.

Limitations

While most of the studies included in this review were recently published, a number of the studies contain data that are several years old. Further, the studies reviewed here were not consistent in their costing methodology; not all treatments evaluated are currently selected routinely as first-line therapy for AECB. However, inflating all costs to 2003 U.S. dollars would be misleading in that it would imply that the studies are directly comparable. In addition, these studies represent standard treatment patterns in North America but are likely not generalizable worldwide. For example, Miravitlles and colleagues’ analysis of costs from the Gemifloxacin Long-Term Outcomes in Bronchitis Exacerbations (GLOBE) study. This prospective double-blind, controlled, health outcomes study compared health economic and clinical outcomes after randomized treatment with either oral gemifloxacin or oral clarithromycin for AECB. This study included 386 patients at 46 centers in the United States and 52 patients at 10 centers in Canada. Treatment effectiveness was measured as the proportion of patients without recurrence requiring antibiotic treatment following resolution of the initial AECB.

Compared with clarithromycin, gemifloxacin treatment resulted in significantly more patients without AECB recurrence requiring antibiotic treatment after 26 weeks (73.8% [158 of 214] versus 63.8% [143 of 224], P=0.024). Fewer patients receiving gemifloxacin were hospitalized (5 of 214 versus 14 of 224, P=0.059) and they had less time until return to usual activities (8.3 versus 10.1 days, not significant [n.s.]). The mean direct cost per patient receiving gemifloxacin was $127 less than the comparable cost with clarithromycin ($247 versus $374, respectively, n.s.); mean per-patient total costs (direct plus indirect) were $329 less for patients receiving gemifloxacin ($1,413 versus $1,742, n.s.). Among direct costs, hospitalizations were the largest component, corresponding to 46% of total gemifloxacin costs and 60% of clarithromycin costs. Gemifloxacin dominated clarithromycin in cost-effectiveness analysis; that is, gemifloxacin treatment resulted in both improved outcomes and decreased costs (either direct or direct plus indirect) as compared to clarithromycin treatment.

The cost-effectiveness of 2 treatments associated with severe AECB has been reported. In the first, a meta-analysis of randomized, controlled trials was used to determine effectiveness parameters for a decision-analytic model comparing noninvasive positive pressure ventilation (NPPV) plus standard therapy versus standard therapy alone for severe AECB. Published literature and regional databases of health care resource utilization were used to provide costs for each node of the model. Clinical variables included probability of requiring early or late intubation, slow versus short wean, acquiring ventilator-associated pneumonia, length of intensive care unit and regular ward hospital stay, and probability of dying associated with various therapies. In the base case, the average cost for patients treated with NPPV was estimated to be $7,211 (1996 Canadian $) versus $10,455 for standard therapy only, and NPPV was superior on both outcome measures (decreased need for endotracheal intubation by 37.5% and hospital mortality by 16.1%), suggesting that adjunct NPPV dominated standard therapy alone. Sensitivity analyses demonstrated lower costs for standard therapy alone only when the rate of intubation was greater for NPPV than for standard therapy.
tion of total health care expenditure in patients with AECB.

Second, the choice of antibiotic can affect AECB costs. Cost-comparison and cost-effectiveness studies have reported that differing antibiotics have differing impacts on treatment failure rates and on the length of time between AECB episodes. By decreasing failure rates and increasing time between AECB episodes, effective therapies decrease hospitalization rates and duration of hospitalization. For example, in the Destache et al. study, while drug costs were lower for medications classified as first-line compared to third-line antibiotics, hospitalization rates were significantly higher among patients receiving first-line antibiotics, resulting in increased total costs for AECB.

Overall, the studies discussed in this review suggest that the least-expensive antibiotic is not necessarily the most effective or the overall least-expensive treatment. Even a slight increase in hospitalization rate or length of stay can more than offset costs resulting from more-expensive antibiotics. Further, as factors such as patient adherence to prescribed therapy and bacterial resistance patterns will influence treatment outcomes, characteristics of potential antibiotic therapies must be carefully evaluated. However, little is known about factors influencing a physician's choice of antibiotic.

A small number of studies have evaluated physician choice of antibiotics. Trevisani et al. surveyed 118 general practitioners in the Italian National Health Service to evaluate physician habits and antibiotic preferences in the outpatient management of acute bronchitis and acute exacerbation of chronic bronchitis. The findings suggest that quinolones and macrolides were the preferred antimicrobial agents for cases of AECB and that high-cost antibiotics were prescribed by 72% of general practitioners for AECB patients compared to 47.8% of general practitioners for acute bronchitis patients (P<0.001). Only a small number of physicians (9 of 118) reported taking into account cost prior to prescribing an antibiotic.

To a certain extent, the evaluation of cost-effectiveness of antibiotic treatment is a moving target. Long-term consequences of antibiotic use, particularly the development of resistance, are not addressed in these studies, yet they have a substantial potential impact on future costs and treatment patterns.

As managed care formulary decision makers require more information about cost-effectiveness, it is possible that physician-prescribing patterns will converge on the treatments that are most cost effective. However, other factors also influence physician treatment selections. Additional work is needed to evaluate factors influencing physician decision making for AECB treatments. Specifically, it will be important to understand how medication costs, overall treatment costs, and cost-effectiveness of alternate therapies affect treatment decisions. This information can then be used to help guide formulary decision-management programs and develop disease-management programs. Appropriate and cost-effective AECB treatments will result in superior patient outcomes that provide the greatest value for the use of limited health care resources.

DISCLOSURES
Funding for this research was provided by GlaxoSmithKline and was obtained by authors Mitchell K. Higashi and Alan W. Bakst, who are employed by GlaxoSmithKline. Author Michael T. Halpern served as principal author of the study. Study concept and design were contributed by Halpern, Higashi, and Bakst. Analysis and interpretation of data were contributed by Halpern and author Jordana K. Schmier. Drafting of the manuscript was primarily the work of Halpern and Schmier and its critical revision was the work of Schmier, Higashi, and Bakst. Administrative, technical, and/or material support was provided by Higashi and Schmier.

REFERENCES
Alternate Financial Incentives in Multi-tiered Formulary Systems to Improve Accountability for Outcomes

RICHARD S. CHUNG, MD; DEBORAH A. TAIRA, ScD; and CHARLES NOH, PharmD

ABSTRACT

BACKGROUND: Drug manufacturer rebates paid to health plans and pharmacy benefit management companies have come under increased public scrutiny. Over the past several years, numerous articles have appeared in the literature encouraging a shift to a more quality-based decision-making process for health plan drug formularies.

OBJECTIVE: To propose a new basis for formulary placement decisions that would include consideration of health-plan-specific measures (clinical outcomes, total cost, adherence, and appropriateness of care) and align incentives for health plans, physicians, pharmacists, and pharmaceutical companies to promote high-quality care.

SUMMARY: The proposed approach builds on key components of the Pharmacy’s Framework for Drug Therapy Management in the 21st Century and the Academy of Managed Care Pharmacy’s Format for Formulary Submission, including a focus on patient outcomes and evidence-based decision making. The proposed approach would lessen the influence of drug manufacturer rebates on formulary placement by shifting the focus to appropriateness of care, clinical outcomes, patient adherence, and total cost of care. Pharmaceutical manufacturers would benefit from the focus on adherence to drug therapy and total cost of care. Health plans and pharmacy benefit management companies would gain in that they may be able to reduce efforts in drug utilization review as pharmaceutical manufacturers are given incentives to market their drugs more appropriately. Physicians and pharmacists would benefit because the rebate money would be used to provide quality-based financial incentives related to adherence and appropriate use of drugs.

CONCLUSION: The implementation of this approach would be difficult and require cooperation from employers, pharmacists, pharmaceutical manufacturers, health plans, and pharmacy benefit management companies. Aspects of this approach could be incorporated into existing pharmacy benefit management processes to encourage the delivery of high-quality health care.

KEYWORDS: Financial incentives, Drug formulary, Outcomes assessment

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The practice of providing drug manufacturer rebates to health plans and pharmacy benefit management companies (PBMs) has recently come under greater public scrutiny. In April 2003, the Office of Inspector General (OIG), U.S. Department of Health and Human Services, issued a compliance program guidance for pharmaceutical manufacturers, which states (in part):

In particular, manufacturers should ask the following questions, among others, about any problematic arrangements or practices they identify: Does the arrangement or practice have a potential to interfere with, or skew clinical decision-making? Does it have a potential to undermine the clinical integrity of the formulary process? If the arrangement or practice involves providing information to decision-makers, prescribers, or patients, is the information complete, accurate, and not misleading?

Though not prohibited, discounts to purchasers, including rebates, need to be carefully reviewed to ensure they do not violate these OIG guidelines. The current process in drug formulary development and management tends to focus more on net drug cost than total (medical and pharmaceutical) costs and is therefore influenced significantly by the amount of drug rebates. This may be particularly true for PBMs that benefit financially from rebate revenues but do not share the risk for medical expenditures. The focus on drug rebates may lead to consequences that include inappropriate use and overuse of certain medications. Health plans respond to perceived misuse with drug utilization management strategies and interventions that may increase administration costs to the system.

The proposed (alternate) approach would realign incentives for pharmaceutical manufacturers, health plans, pharmacists, and physicians in an effort to improve the quality of care and clinical outcomes. This approach draws on suggestions from Pharmacy’s Framework for Drug Therapy Management in the 21st Century and the Academy of Managed Care Pharmacy’s Format for Formulary Submissions. Pharmacy’s Framework for Drug Therapy Management encourages a focus on patients and their clinical, service, and cost outcomes, while the Format for Formulary Submissions calls for comprehensive evaluation of documents that could be used in evidence-based decision making. Emphasis on outcomes and evidence-based decision making are key components of the approach proposed here, the specific goals of which include

1. lessening the influence of proposed rebates on formulary placement by shifting the focus to appropriateness of care,
clinical outcomes, patient adherence, and total cost of care; 
2. encouraging health plans and PBMs to develop effective 
   quality improvement programs, including incentive 
   programs; 
3. rewarding physicians and pharmacists for “best practices,” 
   including improvements in patient adherence and appro-
   priate use of drugs; and 
4. encouraging pharmaceutical manufacturers to promote 
   their drugs appropriately. 

This approach is based on the assumption that total cost of 

care will be reduced through the encouragement of the appro-

The Current System

Current procedures for managing formularies vary considerably 

based on market conditions and organizational structure. In 
general, for 2 drugs that are considered to be equally safe and 
efficacious, the dollar amount of proposed rebates may be the 

factor that determines level of formulary placement (Figure 1). 

Regardless of whether a pharmaceutical attains preferred status 
on a formulary, it may be promoted in the community by phar-

maceutical sales representatives. Because these representatives 

are often given volume-based financial incentives, their promo-

tion of the pharmaceutical may result in overuse or inappro-

priate use. This may lead to suboptimal clinical outcomes and 

unnecessary inflation of pharmaceutical costs. Managed care 

organizations respond to this cost inflation with mechanisms 

that attempt to control costs while maintaining high-quality 
care, including prior authorization, counter-detailing, and dif-

ferential copayment levels.5-11

Proposed System

Our proposed approach focuses on encouraging best practices 

for health plans, PBMs, physicians, pharmacists, and pharma-

cutical manufacturers within a formulary management system, 

particularly one tied to tier-copay benefit designs (Figure 2). 

Multi-tiered copayments in prescription drug benefits have 

increased in number over the past several years as managed care 

organizations have struggled to meet patient preferences for 

open formularies (choice) while containing costs.12 A survey of 

700 large employers found that 60% were using a multi-tiered 

copayment structure in drug benefit design in 2002, up from 

48% in 2001.13 Moving to a multi-tiered copayment structure 

results in cost savings to health plans and employers by encour-

aging members to shift to lower-cost generic and brand-drug 

alternatives, increasing member copayments for their more 

costly drug choices, decreasing drug usage, and increasing 

rebates to health plans from pharmaceutical manufacturers. 

Our proposed approach involves changing the basis for for-

mulary placement in a multi-tiered system. Rather than basing 

decisions for drugs with similar safety and efficacy on net drug 

price, the proposed approach would expand the focus to 

include appropriateness of care, clinical effectiveness, total cost 

of care, and patient adherence. Net drug price would be one 

component of total cost of care.

Appropriate Use of Pharmaceuticals

Many of the newer pharmaceuticals have been proven to be cost 

effective for specific types of patients. Health plans have imple-

mented preauthorization requirements to encourage appropri-

ate use of many brand-name drugs and step-therapy protocols 

that specify first-line use of generic alternatives. Under the pro-

posed system, fewer preauthorization requirements would be 

needed as pharmaceutical manufacturers would become more 

accountable for appropriate drug use. The drug makers would 

receive reports on the appropriate use of their drugs, relative to
competitors, and formulary placement would depend, in part, on the level of appropriate use.

Health plans and PBMs are already actively involved in developing prior-authorization requirements or system edits to encourage appropriate use of pharmaceuticals, particularly high-cost ones. Moreover, in the Pharmacy’s Framework for Drug Therapy Management’s self-assessment tool, pharmacists are encouraged to consider whether the patient has been effectively assessed and accurately diagnosed and whether appropriate drug therapy has been selected (Core Focus Area #3).4 Under the proposed approach, health plans would work with pharmacists and physicians to derive guidelines for appropriate use, based on evidence from the literature and/or analysis of claims data. The pharmacist’s self-assessment grid could be modified to include a component indicating whether the use of the drug was appropriate based on these guidelines. Once the criteria are approved, pharmaceutical manufacturers could be given a profile of the use of their drug compared to others in the same therapeutic category.

For example, Table 1 summarizes the appropriate usage of COX-2 inhibitors for 2 brand drugs according to appropriateness criteria developed by a health plan. Concomitant use was defined as use of another drug within 60 days of the COX-2 inhibitor prescription. History of comorbidities was defined as having at least one ICD-9 code for a given condition within 1 year prior to the COX-2 inhibitor prescription. The following ICD-9 codes were used in the analyses: rheumatoid arthritis 714.0-714.3x; osteoarthritis 715.xx; chronic spondylosis 721.xx; systemic lupus erythematosus 710.0; gastroduodenal ulcer 531.x, 532.x, 533.x; GI bleed 578.x.

### Table 1: Number of Patients Who Met the Criteria for Appropriate COX-2 Usage

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Total</th>
<th>Drug A</th>
<th>Drug B</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>16,391</td>
<td>9,680</td>
<td>6,711</td>
<td></td>
</tr>
<tr>
<td>Number of patients who meet any of the criteria 1 to 6</td>
<td>10,230</td>
<td>6,435</td>
<td>3,795</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Number of patients who meet none of the criteria 1 to 6</td>
<td>6,161</td>
<td>3,245</td>
<td>2,916</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1. Age &gt;60</td>
<td>6,583</td>
<td>4,330</td>
<td>2,253</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2. Medically significant chronic disease (rheumatoid arthritis, chronic spondylosis, systemic lupus erythematosus)</td>
<td>5,423</td>
<td>3,454</td>
<td>1,969</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3. History of gastroduodenal ulcer or GI bleed</td>
<td>976</td>
<td>600</td>
<td>376</td>
<td>0.1131</td>
</tr>
<tr>
<td>4. Patient is on concomitant glucocorticoid or anticoagulant therapy</td>
<td>1,359</td>
<td>866</td>
<td>493</td>
<td>0.0003</td>
</tr>
<tr>
<td>5. Patient is on concomitant misoprostol, proton-pump inhibitor, histamine2 antagonist, or misoprostol-diclofenac combination</td>
<td>1,859</td>
<td>1,161</td>
<td>698</td>
<td>0.0016</td>
</tr>
<tr>
<td>6. Patient is on chronic high-dose NSAID therapy</td>
<td>74</td>
<td>42</td>
<td>32</td>
<td>0.6867</td>
</tr>
</tbody>
</table>

*The sample population for this illustration was composed of patients in possession of a COX-2 inhibitor on March 31, 2002. Concomitant use was defined as use of another drug within 60 days of the COX-2 inhibitor prescription. History of comorbidities was defined as having at least one ICD-9 code for a given condition within 1 year prior to the COX-2 inhibitor prescription. The following ICD-9 codes were used in the analyses: rheumatoid arthritis 714.0-714.3x; osteoarthritis 715.xx; chronic spondylosis 721.xx; systemic lupus erythematosus 710.0; gastroduodenal ulcer 531.x, 532.x, 533.x; GI bleed 578.x. *
If a health plan or PBM wanted to go a step further, they could also ask physicians to rate the appropriateness of a manufacturer’s drug detailing in their community. Researchers in Canada developed the Assessment Instrument for Drug Detailing (AIDD) that asks physicians to score the quality of drug detailing provided by pharmaceutical sales representatives. Mean scores for each major pharmaceutical manufacturer could be calculated and used to support formulary decisions.

Although health plans might prefer to influence participating physicians without interference from drug sales representatives, the reality is that these representatives spend a considerable amount of time educating physicians about their products. The proposed approach would encourage pharmaceutical manufacturers to work with health plans and PBMs to develop appropriateness criteria and to reward sales representatives for promoting appropriate use. Giving preferred formulary placement to products that are marketed appropriately, through detailing and advertisement, would ultimately lead to more cost-effective care. Ideally, this would encourage sales representatives to make longer, more meaningful calls on physicians that would allow them to discuss appropriateness.

With the pharmaceutical manufacturers given incentives to improve appropriateness, health plans may need fewer preauthorization requirements. For instance, a health plan might agree to remove preauthorization requirements if a drug were to reach a certain level of appropriate use (e.g., 90%). In addition, a specific physician might not need to seek preauthorization when he or she reaches a certain threshold for appropriate usage. Appropriate-use criteria would be reviewed regularly to ensure continued cost-effective care.

Patient Adherence
Randomized controlled trials generally follow a strict protocol and have regular monitoring to insure high patient adherence. Part of the reason that efficacy demonstrated in clinical trials is not always evident in the community is that patients outside of clinical trials are much less likely to adhere to drug treatment plans. Under the proposed system, health plan or PBM staff would analyze retrospective claims data to assess differences in adherence between all drugs for a specific condition. These analyses would be based on possession ratios calculated from pharmacy claims. For instance, for each drug, one could compare the percentage of patients who had the drug in their possession at least 80% of the time. Adherence would not be examined for drugs taken as needed.

Clinical Effectiveness of Care
Under the proposed system, health plans or PBMs in partnership with health plans, would analyze retrospective claims data to determine which drugs demonstrated the best patient outcomes, including fewer side effects (e.g., bleeding) and adverse events (e.g., acute myocardial infarction). When available, health-related quality of life, attainment of goal lab values, and work days lost would also be examined.

There are several reasons why these outcomes analyses might be worth the effort. As stated above, efficacy data from clinical trials often do not mirror real-world experience, partly because adherence rates tend to be lower outside of clinical trials. Second, a health plan’s membership may differ from the clinical trial population in terms of age, severity of disease, ethnicity, or other important characteristics. Prior evidence suggests that drug efficacy differs with respect to patient characteristics.

Analysis of health plan data would reveal information on outcomes for the specific population that would be affected by any decisions. While this type of drug-specific outcomes analysis would only be possible for high-volume drugs, the analyses might be modified to look at outcomes by therapeutic class for other drugs with less volume. This review of health-plan-specific effectiveness data, in conjunction with evidence from the literature, would provide decision makers with a more comprehensive view of the potential impact of formulary decisions.

Total Cost of Care
Evidence from the literature clearly suggests that many drug therapies improve the health of patients, thereby decreasing hospital admissions and increasing productivity. When drug formulary placement decisions are made, however, medical service offsets are often not considered. Rather, the net drug cost, calculated from the price and potential rebates, is often the only cost figure taken into account. Under the proposed model, cost analyses would focus on total costs of care, including pharmaceutical, inpatient, outpatient, and physician fees. The goal of the proposed approach would not be to reduce drug expenditures but to increase expenditures on the most cost-effective medications, reduce expenditures on inappropriately used medications, and reduce medical costs through improved outcomes.

Rebates Replaced With Quality-Improvement Incentives
Rebates currently average between 2% and 20% of the drug’s wholesale price and are given to health plans by drug manufacturers based on market share and other factors. Under the proposed system, rebates from pharmaceutical companies would be replaced by payments tied to specific programs that promote high-quality care, including disease management and quality-based financial incentive programs for physicians and pharmacists. Use of incentives to promote quality in health maintenance and preferred provider organization health plans has become increasingly common. In September 2002, the Centers for Medicare and Medicaid Services announced a demonstration project that would reward physicians in group practices for improvements in the quality of care they provide to Medicare enrollees. The “bonus” money would be derived from savings achieved through improvements in patient management.

The concept of pharmacy incentives is a natural extension of the use of incentives for physicians. These incentive programs could include bonuses for improving patient adherence.
Underlying Assumptions

There are several assumptions that would need to be true for this approach to be effective. First, we assume that the measurement of clinical outcomes and appropriateness can be done accurately and effectively. This focus on outcomes will work best for high-use drugs. For drugs with low utilization or rare outcomes, a single health plan’s data would be unlikely to provide evidence of significant differences among treatment alternatives. However, groups of health plans, such as members of the Blue Cross and Blue Shield Association, could pool data to examine outcomes. Second, the quality of the outcomes analyses would depend on the quality of the data employed. Health plans would need to invest in data infrastructure prior to implementing this approach and would often need to collaborate with a PBM company to measure outcomes. Once algorithms were defined, the level of resources needed may diminish.

Discussion and Limitations

Over the past several years, numerous articles have appeared in the literature encouraging movement toward a more quality-based decision-making process for pharmaceutical formularies. Under the proposed approach, decisions regarding formulary placement would be based on evidence from the literature as well as health-plan-specific measures including appropriateness, adherence, clinical outcomes, and total cost. Incentives for health plans, physicians, pharmacies, and pharmaceutical manufacturers would be realigned to promote the delivery of high-quality care. Health plans would benefit from the improvement in the health of their members. They would also receive support for quality-improvement programs that have demonstrated positive outcomes, and they may be able to reduce the cost of their drug utilization review as pharmaceutical manufacturers are given incentives to market their drugs more appropriately. Pharmacists and physicians would be rewarded for increases in patient adherence to drug therapy and appropriate use of specific pharmaceuticals. Pharmaceutical manufacturers would see the rebate money being used to increase patient adherence. Drugmakers with relatively more effective products would also benefit from the focus on total cost rather than net drug price.

Health plans could also use the results to inform employers and members of the cost-effectiveness of pharmaceuticals. Employers are increasingly requesting this type of information as they make decisions regarding coverage options for their employees. One limitation would be lack of plan-specific outcomes for new drugs. The FDA approved an average of 38 new drugs per year during the 1990s. Because health-plan specific outcomes data would not be available for new pharmaceuticals, formulary decisions would need to be based on available evidence from trials and published studies.

Another limitation would be the lack of sufficient data, in terms of scope and timeliness, to compare specific drugs. With regard to scope, systems that do not have integrated medical and pharmaceutical data would have difficulty linking drugs with total cost of care or outcomes of care. This is a significant limitation but not an insurmountable one. It is possible to develop partnerships between health plans and PBMs that would facilitate the sharing of these data. In addition, although outcomes data might be limited, aggregation of data may sometimes be acceptable, such as comparing drug therapy outcomes at the therapeutic-class level rather than the trade-name level. PBMs may also combine data from several health plans to draw general conclusions on effectiveness. Moreover, while timeliness of data is an important issue, we believe that new technologies have permitted prompt processing of claims, spurred further by scrutiny from the National Committee for Quality Assurance.

This manuscript is largely hypothetical and does not address some of the unresolved issues in formulary placement. For example, should the market share of a drug affect formulary placement? While community physicians and members might prefer that the health plan offer preferred status to a drug they use most often, a purely evidence-based approach would not give preference to drugs with higher market share. Another question that remains is: Should a health plan attempt to strike business partnerships with all drug manufacturers by allowing each to have a “preferred” drug in at least one therapeutic class? By embracing all drug manufacturers in some fashion, a health plan might avoid encouraging one pharmaceutical manufacturer to initiate an aggressive marketing campaign to offset formulary decisions. While these issues are not addressed in this approach, they would need to be considered when making formulary decisions.

Conclusion

The proposed approach would retain a multi-tier copayment system but would base drug formulary position on health-plan-specific data concerning appropriateness, patient adherence, clinical outcomes, and total cost of care as well as evidence from the literature. Implementation of this approach would be difficult and require cooperation among employers, pharmaceutical manufacturers, pharmacies, physicians, and health plans. However, aspects of this approach have already been incorporated in pharmacy benefit management processes and quality-of-care initiatives across the country. For example, in 1998, Regence BlueShield of Seattle adopted formulary submission guidelines that focused on demonstrating the outcomes and
value of pharmaceuticals. These guidelines have become a model for health plans across the country. Moreover, researchers at the Department of Veteran’s Affairs Medical Center in Durham developed and validated a Medication Appropriateness Index for use in research, quality improvement initiatives, and clinical care. By integrating aspects of initiatives like these that have been successfully implemented across the country, the proposed approach seeks to encourage health plans, PBMs, physicians, pharmaceutical manufacturers, and pharmacists to help bridge the “quality chasm” documented in the Institutes of Medicine report.

DISCLOSURES

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Two events in the drug regulatory approval process in recent years warrant the attention of managed care pharmacists and should prompt reassessment of assumptions regarding drugs marketed in the United States. The first event, involving levothyroxine, received considerable public attention from 1999 through 2002. The second event involves an appellate court decision in May 1999 regarding combination product esterified estrogen and methyltestosterone (Estratest and Estratest HS, Solvay Pharmaceuticals). The circumstances of these events are noteworthy, and the social and market effects of each are sizable. Levothyroxine products (Synthroid, Levoxyl, Levothroid, Unithroid, and Thyro-Tabs) are the number one drug class in the United States by volume of prescriptions and number of patients.1 Estratest and Estratest HS, with combined volume of about 4 million units in community pharmacy in 2002, placed it at approximately rank number 100 among all brand-name drugs by unit volume (utilization). By dollar volume, the levothyroxine products collectively ranked in the top 25 drugs in the United States, with more than $1.2 billion in sales, and the Estratest products collectively rank in the top 200 drugs by sales volume.2,3

In 2000 and 2001, Abbott Laboratories, which had acquired Knoll Pharmaceuticals and its prescription drug Synthroid, engaged the U.S. Food and Drug Administration in a tug of war over the need for FDA review and approval of Synthroid (levothyroxine). The matter received considerable public attention since Synthroid was the number 3 drug by community pharmacy prescription volume in 2000 and one of the most commonly used drugs in the United States for many years.4 Unithroid (Jerome Stevens), formerly marketed as Thyrox, was approved by the FDA on August 21, 2000, as the first levothyroxine product approved through the New Drug Application (NDA) process. The FDA approval of Unithroid commenced a race for FDA approval of competing levothyroxine products by establishing the first “standard” levothyroxine product. At the request of Knoll Pharmaceuticals, the FDA had extended the deadline for levothyroxine approval until August 14, 2001, and said that manufacturers who marketed their drugs “without an approved application after that date would be subject to regulatory action.” Any levothyroxine product not approved through an NDA or Abbreviated NDA (ANDA) by August 14, 2001, would be subject to regulation as an unapproved new drug,5 Synthroid ultimately received FDA approval near year-end 2002, but not before precipitating a mandate from the FDA to scale down production of Synthroid and alarming physicians, pharmacists, and patients that Synthroid may become unavailable.6

A parallel matter involving the combination product, esterified estrogens and methyltestosterone (Estratest and Estratest HS, Solvay Pharmaceuticals), is equally important and instructive. A decision dated May 11, 1999, from the U.S. Court of Appeals, Eleventh Circuit, in Florida Breckenridge v. Solvay Pharm granted Solvay’s abrupt motion to dismiss with prejudice but found that attorneys for both parties engaged in conduct “designed to mislead and confuse the court regarding the regulatory status of Estratest and Menogen.” The appellate court judges condemned the conduct of the attorneys and found that “the adversarial parties both had an interest in hiding the fact that they needed FDA approval from the court. In Solvay’s case, admitting that Estratest was not legally on the market would be fatal to their claims because the Lanham Act only protects parties engaged in lawful commerce.” Since “use in commerce” was defined by the courts as “lawful use in commerce” and since Estratest had never been formally approved by the FDA for marketing in the United States, Solvay had no trademark rights to Estratest and no common-law protection from competition. The judges wrote also, “Breckenridge had an interest in hiding the FDCA [Food, Drug and Cosmetic Act] violations from the court. Since this litigation began, the FDA has taken action against Breckenridge for, among other things, marketing Menogen without FDA approval.”

The appellate court judges found in Florida Breckenridge v. Solvay Pharm that the lower court (U.S. District Court for the Southern District of Florida, D.C. Docket No. 97-8417-CIV-RYSKAMP) did not specifically address the legal effect of the unapproved sale of Estratest because “the attorneys misled the court into thinking that their clients did not need approval.” The appellate court decision included the finding “that there is no magical exception that allows Solvay or Breckenridge to opt out of the FDA approval process. As the government’s brief points out, both Estratest and Menogen are ‘new drugs’ under the FDCA and require approved NDAs or ANDAs before they may be lawfully marketed.” Since Estratest was marketed in 1964, 2 years after the 1962 amendments to the FDCA, and Menogen was introduced later (in 1997), neither drug was subject to the grandfather provisions of the FDCA.

This 11th Circuit Court of Appeals decision dissected the purpose of FDA’s “DESI” (Drug Efficacy Study Implementation) program, which was to subject drugs already marketed, and therefore found be safe by standards established by the FDA as required by the FDCA of 1938, to a determination of efficacy as required by the 1962 amendments. An independent (DESI) panel reviewed the data regarding efficacy of each drug and made a recommendation to the FDA. If the FDA concurred with the panel recommendation, a notice was published in the Federal Register and a supplemental NDA would be approved for the drug. The DESI program applied only to drugs that already had approved NDAs as of 1962. All other drugs were considered “new” drugs, requiring an approved NDA or ANDA before marketing. The only exception was a drug generally recognized as safe and effective, the “GRASE” exception. The appellate court found that “Estratest cannot satisfy the GRASE exception” because (a) “a drug must meet requirements at least as stringent as those for NDA approval” and (b) “Solvay has continually failed to obtain approval based on the evidence it

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**Prescription Drugs Marketed in the United States Should Be Approved by the FDA**

This editorial discusses two significant events in the drug regulatory approval process in recent years. The first event involved levothyroxine, which was a commonly used drug in the United States for many years. Abbott Laboratories, which had acquired Knoll Pharmaceuticals and its prescription drug Synthroid, engaged the U.S. Food and Drug Administration (FDA) in a tug of war over the need for FDA review and approval of Synthroid. The FDA extended the deadline for levothyroxine approval until August 14, 2001. Abbott was not able to secure FDA approval by this date, which subsequently led to the discontinuation of Synthroid’s production.

The second event involves an appellate court decision in May 1999 regarding combination product esterified estrogen and methyltestosterone (Estratest and Estratest HS, Solvay Pharmaceuticals). The circumstances of these events are noteworthy, and the social and market effects of each are sizable. Levothyroxine products and Estratest are ranked among the top 200 drugs in the United States, with more than $1.2 billion in sales.

The editorial highlights the importance of ensuring that prescription drugs marketed in the United States are approved by the FDA. The failure to obtain FDA approval for Synthroid and the legal challenges surrounding Estratest underscore the need for managed care pharmacists to reassess their assumptions about drug approval processes and the implications for patients and the market.
has provided the FDA."

The appellate court in *Florida Breckenridge v. Solvay Pharm* also chastised the FDA, stating that "It is incomprehensible that Estratest has been allowed on the market without approval for 35 years. It seems reasonable that most patients undergoing treatment for menopause fairly assume that any medication freely available and prescribed by their doctor has been proven safe and effective to the satisfaction of the FDA. They have a right to expect that the laws, as passed by Congress to protect them, are being enforced. To this date, Estratest has failed to satisfy the FDA that it is safe or effective as required by the FDCA, yet the FDA has taken no action to remove the drug from the market. We are accustomed to hearing arguments in situations like this bemoaning scarce governmental resources and the like, but there can be no good excuse for allowing a company to violate the law for 35 years. If the drug is not safe or effective enough to be approved, 35 years seems like sufficient time to get around to taking some action."

We think that the 11th Circuit Court of Appeals in its decision in May 1999 made a reasonable request of the FDA. Four years later, esterified estrogens with methyltestosterone are marketed by Solvay as Estratest HS and Estratest and by Syntho Pharmaceuticals (Farmingdale, NY) as Syntest HS and Syntest DS in equivalent strengths, respectively,* but not interchangeable since no standard has been established through the NDA process. To add an additional challenge to managed care pharmacists, the drug clearinghouses such as Medispan list Estratest and Estratest HS as brand innovators (“O” drugs) and Syntest HS and Syntest DS as “generic” (“Y”) drugs, resulting in brand and generic copayments for members, respectively, in multi-tier copayment drug plans.

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**REFERENCES**


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**Mooney Falls**  
*at Havasupai Canyon in Grand Canyon National Park*  
"In a desert may be an oasis. So also in life."

Photograph by John P. Barbuto, MD, Sandy, Utah
Managed care pharmacists are often called upon by health plans, pharmacy benefit managers (PBMs), or medical groups to educate physicians about prescription drug prices and therapeutic alternatives. Managed care pharmacists who work in these roles find that physicians are not well informed about absolute and relative prescription drug prices. A survey of physicians in 2000 found that 20% reported being “aware of actual drug costs” and 80% reported lack of such knowledge; only 13% reported receiving “formal education” about drug costs.1 Physicians were more sensitive to the cost of prescription drugs when patients had no health insurance. Physicians gave “strong consideration” to the cost of drugs when patients were self-paying (94%) versus 68% when patients had Medicare and 30% when patients had either Medicaid or private health plan coverage of prescription drugs. Physicians’ estimates of the cost of a month’s supply of 33 commonly used drugs were accurate in 45% of cases, too low in 40% of cases, and too high in 15%.

Evidence of the magnitude of the challenge in educating physicians about prescription drug prices can be found in the results of an educational intervention that involved (a) an interactive teaching conference and (b) distribution of a pocket guide, which listed the average wholesale prices of more than 100 medications commonly used in primary care.2 The study involved 146 internal medicine physicians in a before/after survey research design. Physicians after the intervention were more likely to ask patients about their out-of-pocket drug costs (22% before versus 27% after, P<0.01) and less likely to feel unaware of drug costs (78% before versus 72% after, P=0.02). After the intervention, physicians also reported more concern about the cost of drugs when prescribing for patients with Medicare (58% before versus 72% after, P<0.01) or no insurance (90% before versus 98% after, P<0.01). Knowledge of the costs of 33 drugs was more accurate after the intervention than before (P<0.05). Yet, remarkably, after the intervention, 72% of physicians still felt “unaware of drug costs.”

Physician profiling (“report cards”) that includes information about the relative cost of therapeutic alternatives can affect average prescription drug costs. In a previous issue of the Journal, Yokoyama, Doan, Godley, et al. found that physician prescribing profiles combined with academic detailing that included relative price information for selective serotonin reuptake inhibitors (SSRIs) were associated with a reduction in the average cost per day of therapy of at least 11% over a 2-year period.3 The combination of physician report cards and financial incentives can be influential in reducing prescription drug costs. A medical group in Michigan reported in 2003 that an incentive program that involved physician report cards for proton pump inhibitors (PPIs) and SSRIs was associated with a 6.8% reduction in prescription drug costs.3 Baseline data, differentiation of the effects of price versus utilization, and inflation-adjusted results were not presented, but the medical group reported that 73% of physicians who participated decreased their average costs in each of the 2 drug categories. The intervention involved prizes awarded to physicians who (a) recorded the lowest average drug cost for the 2 drug categories or (b) decreased their average overall drug cost by the largest percentage. The focus of the intervention was PPIs, SSRIs, overall generic drug use, and “judicious use of antibiotics.”

Like the lyrics of a popular song—“What have you done for me lately?”—drug plan sponsors and governmental agencies want to know what pharmacy benefit managers do to help manage care and cost outcomes. The penultimate goal of PBMs and managed care pharmacy is to demonstrate the value of interventions in the delivery, administration, and management of prescription drug and medical benefits. Two articles in this issue of the Journal measure the effects of pharmacy benefit management interventions on clinical, service-humanistic, or cost outcomes.

In a preliminary analysis to determine need for intervention, Hoffman, Mayzell, Pedan, Farrell, and Gilbert found that 24% of health plan members who received a prescription for either a serotonin 5-HT1 receptor agonist (e.g., sumatriptan [Imitrex]) or dihydroergotamine (DHE) nasal spray (i.e., Migranal) received a quantity sufficient in a 30-day period to exceed treatment of 4 headaches per month at the maximum daily dosage.3 The authors subsequently measured the utilization and cost outcomes of a program that imposed limits on coverage of migraine- abortive drugs, specifically, the triptans and DHE nasal spray. The authors found a 17% reduction in utilization of these target drugs and a 29% reduction in direct drug costs of the target drugs. Presumably, the difference in reduced utilization versus cost was due, in part, to the use of prescriptions as the measure of utilization rather than days of therapy or units.4 The cost reduction is more remarkable since the authors used an inflation adjustment factor of only 4% per annum. The combined effects of drug price inflation and drug mix were about 10% to 11% per year during the 30-month time period of this study, and drug utilization increased about 6% to 7% per year during this time.4,5 In this context of rising drug “price,” the combination of price increases and the mix of drugs, and rising drug utilization in general, the utilization and financial effects of the drug coverage limits studied by Hoffman, Mayzell, Pedan, Farrell, and Gilbert are more dramatic.

The extant study by Hoffman, Mayzell, Pedan, Farrell, and Gilbert did not measure clinical or service outcomes of the intervention, and it would have been valuable to know what happened to the nearly one quarter of triptan and DHE users who exceeded maximum dose guidelines. However, the effects on utilization and cost outcomes were significant. Overall costs of migraine-related drug therapy declined by 20%, from $38.95 per patient per month (PPPm) to $31.08 PPPm. Total migraine-related medical costs, also unadjusted for inflation, declined by 40%, from $16.58 PPPm to $9.94, contributing to a reduction of 26% in the total (drug and medical) cost of migraine-related

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**EDITORIAL SUBJECTS—IN THIS ISSUE**

- **Effects of Physician Report Cards, Knowledge of Drug Prices, and Financial Incentives in Prescription Drug Costs**

- **Clinical, Service, and Cost Outcomes of Drug Coverage Edits and Quantity Limits**
care, from $55.52 to $41.02 PPPM.

With regard to the intervention itself, the coverage limit on migraine-abortive drugs was applied specifically and solely to triptans (5 were on the market at the time) and DHE nasal spray, and there was no prior-authorization (PA) or medical exception process. The coverage limit was applied as a drug-specific milligram quantity per month of therapy (30 days). A coverage limit applied to a class of drugs (e.g., triptans) rather than to individual triptan drugs would presumably result in a larger decline in drug-class costs as well as better address the clinical outcomes reportedly sought by the authors. In the 18-month period after implementation of the drug-specific milligram limit per month (30 days), the PPPM cost of triptans and DHE nasal spray declined from 75% to 67% of total migraine-related drug costs, $29.18 PPPM and $20.78 PPPM, respectively.

Stacy, Shaw, Arledge, and Howell-Smith estimated that a PA requirement for cyclooxygenase-2 (COX-2) specific inhibitors was associated with utilization and cost reduction of COX-2 drugs of $0.31 PMPM in 2000 dollars or $0.24 PMPM after subtraction of the administrative costs of the call center, producing aggregate savings of $10 million per year in their MCO of 3.3 million members with a pharmacy benefit. The authors predicted from a cost-effectiveness model that the cost per success, defined as no serious gastrointestinal (GI) event (i.e., upper GI ulcers, bleeding, or perforation), was $278 with a PA requirement for COX-2 drugs versus $422 per success without the PA requirement. This difference translates into $13.6 million in additional cost per year in 2000 dollars or about $0.35 PMPM if the PA requirement for COX-2 drugs was removed from the pharmacy benefit.

Current research published elsewhere found that COX-2 drugs become cost effective compared to the nonselective nonsteroidal anti-inflammatory drug naproxen (Naprosyn, Aleve) only if the estimated average cost of $2.66 per COX-2 tablet is reduced by 90%. Using a COX-2 drug instead of a nonselective NSAID in average-risk patients had an incremental cost of $275,809 per year to gain 1 additional quality-adjusted life-year (QALY), which dropped to $55,803 for each QALY gained when the analysis was limited to the subset of patients with a history of bleeding ulcers. Readers might note that both studies recognize a 50% relative risk reduction for serious GI event for COX-2 drugs compared to nonselective NSAIDs in treating chronic arthritis pain, and both studies employed a factor of 1% for the absolute risk reduction in serious GI events for COX-2 drugs versus NSAIDs. Collectively, the 2 studies suggest that a PA requirement for COX-2 drugs may be appropriate and cost effective when measured by clinical and cost outcomes.

Pressure on Pharmacy Benefit Managers for Disclosure and Demonstration of Value—Rebates and Drug Benefit Cost Savings

The Bush administration issued a press release in late April 2003 warning pharmaceutical manufacturers and pharmacy benefit managers that payments to health plans or PBMs for increasing the market share of a drug could be illegal under the antikickback statute of federal law. The guidance provided by Janet Rehnquist, inspector general of the U.S. Department of Health and Human Services, defined “legitimate discounts” as a reduction in the price of a prescription drug “properly disclosed and accurately reported.” The Office of the Inspector General (OIG) advised drug manufacturers and PBMs to disclose their financial arrangements to payers, including employer-sponsored health plans, in order to escape prosecution under the antikickback laws. The OIG guidance also warned drug manufacturers that (a) research and education grants must be divorced from marketing and (b) “to the extent the manufacturer has any influence over the substance of an educational program or the presenter, there is a risk that the program may be used for inappropriate marketing purposes.”

PBMs have also come under pressure to demonstrate value in promised drug benefit cost savings. A survey of 543 U.S. employers, representing about 6 million benefits-eligible employees, found 42% of the employers felt that involvement by PBMs contributed to higher drug benefit costs versus 28% who said that PBMs decrease overall drug benefit costs. There was also interest in making changes in drug benefit management in the future, including (a) mandatory disclosure of rebate income received by PBMs (40%), (b) mandatory refills at mail-order for maintenance drugs (28%), and (c) pairing physician networks with pharmacy networks to prescribe lower-cost alternatives (22%). Federal legislation to restrict patent extensions on brand-name drugs was favored by 75% of employers.

The requests for more disclosure of financial arrangements are not new but became more vociferous in 2003. A forum on PBM practices in late 1998 suggested full disclosure as a standard of practice in the PBM industry, including full disclosure of all manufacturer relationships. For example, there was a charge that some PBMs are being paid “to keep drugs off the Maximum Allowable Cost list [by some manufacturers] at the expense of the customer.” The forum on PBM practices also recommended the ability to audit the actual reimbursement rates and amounts paid by PBMs to participating pharmacies, with no margin retained by PBMs. One PBM officer stated at a forum in mid-1999 that “repricing” by PBMs (in which the plan sponsor is billed a higher amount than what is actually paid to the pharmacy provider) was probably only illegal when the practice is not disclosed to Employee Retirement Income Security Act (ERISA) clients but may be illegal for (non-ERISA) government agencies and municipalities (non-ERISA plans) that do not fall under the ERISA regulations.

Lawsuits filed by plan sponsors against PBMs for not disclosing the practice of repricing date back to at least as early as 1998. A Wall Street Journal investigation in March 2003 revealed that a PBM had charged a Westport, Connecticut,
employer $215 for a prescription claim for 90 tablets of ranitidine (generic Zantac) for which the PBM had paid the community pharmacy $15, a $200 gross margin for the PBM on a single prescription. The PBM reported that such practices helped to push its net income up 63% in 2002, and this business practice of taking the “spread” between reimbursement paid to pharmacies and the amount billed to drug plan sponsors, including government employers, had replaced revenue otherwise available in administrative fees for claims processing and other services. Another PBMs senior officer told attendees at an investors’ conference on January 8, 2002, that PBM margins and profits came from claims processing fees in 1995, but in 2001 and 2002, “We receive payments from pharmaceutical manufacturers that are not shared with our clients…in the form of administrative fees, what we call therapeutic class partners.”

PBMs include the U.S. General Accounting Office. In a report in January 2003, the GAO found that PBMs saved customers an average of 18% compared to what customer would pay in community pharmacies without third-party coverage administered through the PBMs and 27% discount through mail-order pharmacy. The GAO found additional discounts negotiated with mail-order pharmacy resulted in lower out-of-pocket costs for drug plan members, reduced costs for drug plan sponsors, and “helped to lessen rising premiums.” The GAO did acknowledge that community pharmacies were forced by PBMs to accept discounted reimbursements while performing additional administrative tasks. In addition to pricing, the GAO estimated that drug manufacturer rebates “reduced plans’ annual spending on prescription drugs by 3% to 9%.” No evidence of the value of rebates was presented in the GAO report in January 2003. The GAO report does include the following statement, with a footnote and references to U.S. Securities and Exchange Commission (SEC) filings, “Public financial information suggests that manufacturer payments are important sources of earnings. For example, in financial reports submitted to the SEC, the 2 of the PBMs we reviewed stated that manufacturer rebates and fees were key to their profitability.”

The GAO report in January 2003 was not a resounding endorsement of the value of PBMs. In addition to the uncompensated workload pushed upon community pharmacists and difficulty in quantifying “rebate savings,” the GAO examined other PBMs “intervention techniques” such as drug utilization review (DUR), prior authorization (PA), generic substitution, and therapeutic interchange, and concluded that “their full impact on savings is not easily quantifiable.” The GAO found that the 3 PBMs that it reviewed reported savings for individual intervention techniques ranging from less than 1% to 9%, but a footnote in the report states, “While plans reported savings from therapeutic interchange, concerns have been raised that in some cases, PBMs’ relationships with manufacturers and retail pharmacies influence PBM interventions, such as substituting higher-cost drugs when lower-cost therapeutic equivalent drugs are available. Medco Health Solutions and Advance PCS filings with the SEC indicated that the U.S. Department of Justice is undertaking an industrywide investigation to examine PBM relationships with pharmaceutical manufacturers and retail pharmacies and PBMs’ programs related to drug formulary compliance, which includes rebates and other payments made by manufacturers to PBMs. The SEC filings show that the Department of Justice is also investigating payments made by PBMs to retail pharmacies or others in connection with PBM interventions.”

In late June 2003, the U.S. Department of Justice joined a whistleblower lawsuit alleging inappropriate prescription processing and dispensing practices in mail-order pharmacies owned by a PBM.

Another arm of the federal government has a history of skepticism of the business practices of PBMs in their relationships with pharmaceutical manufacturers. As noted above, the Office of Inspector General released its Compliance Program Guidelines for Pharmaceutical Manufacturers in April 2003, including guidance on “educational grants” and “payments to PBMs.” For educational grants, even if the educational or research purpose is legitimate, the OIG states that there is risk of violation of the antikickback statute if “the manufacturer has any influence over the substance of an educational program or the presenter.” For the latter, regarding drug manufacturer payments to PBMs, “Any rebates or other payments by drug manufacturers to PBMs that are based on, or otherwise related to, the PBMs customers’ purchases potentially implicate the antikickback statute. Protection from violation of the antikickback statute is available by structuring such arrangements to fit in the GPO (group purchasing organization) ‘safe harbor’ at 42 CFR 1001.952 (j). That [GPO] safe harbor requires, among other things, that the payments be authorized in advance by the PBMs customer and that all amounts actually paid to the PBM on account of the customer’s purchases be disclosed in writing at least annually to the customer.” While this is a guidance and not a list of explicit demands, it is clear that customers, including the federal and state governments, will continue to seek and demand more complete disclosure of revenues and profits earned by PBMs from drug manufacturer payments, and the OIG will scrutinize professional education and grant making by pharmaceutical manufacturers to ensure that these functions are divorced from drug product sales and marketing.

In this issue of the Journal, Chung, Taira, and Noh propose an alternate paradigm for drug manufacturer payments to PBMs and health plans based upon the notion that these dollars could be better spent on measurable long-term rather than short-term outcomes or other objectives. While this concept may not be new, and some may argue that it is not even profound, the authors have made a useful attempt at describing the framework for such a proposal. By doing so, the authors permit managed care pharmacists to criticize details and assumptions in the
proposal, creating the opportunity for informed and scholarly debate about alternate scenarios to the present situation. Chung, Taira, and Noh point to an example in which only 62% of 16,391 patients who received 2 COX-2 drugs were found to meet at least 1 of 6 criteria that would establish appropriate use of these drugs, as established by the health plan, and there was a significant difference between the rate of appropriateness for drug A (66.5%) versus drug B (56.6%, P<0.001). The authors suggest that this sort of information should be used by health plans and PBMs in making formulary placement decisions; i.e., drug A might earn placement in tier-2 copayment while drug B might be placed in formulary as tier-3 copayment or excluded from the health plan drug formulary. The manufacturers of COX-2 drugs A and B could be presented the results of periodic assessments of appropriate use, according to the criteria established by the health plan, in an effort to improve intermediate (appropriateness of use) outcomes. It is not a large leap to imagine that drug manufacturers could allocate rebate dollars for specific purposes such as the measurement and periodic reporting of key intermediate and long-term outcomes and pay-for-performance in quality measures for providers, physicians, and pharmacists. And so, we are back to the beginning, back to a fundamental concept of paying for performance of health care providers, PBMs, and other vendors that provide support to those who deliver the care to health plan beneficiaries. The data requirements, in volume and quality, for this alternate method of allocating drug manufacturer price discounts and rebates will be large.

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

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Dear Editor,

Pharmacy students at the University of Houston are taking advantage of a unique organization devoted to raising interest in the field of industrial pharmacy and managed care. The organization is SIPS—the Society of Industrial Pharmacy Students—which came into being in 1998, the brainchild of a few pharmacy students who desired more information about the business side of pharmaceutical care. The mission of SIPS is to create an environment and provide opportunities for students and the pharmaceutical industry to interact and collaborate on mutually beneficial projects. The organization’s goal is to provide students with detailed information regarding career opportunities within the pharmaceutical industry.

For the past 5 years, the officers of this very active organization have invited eminent individuals from across the country to visit the University of Houston and expound upon their life experiences to SIPS members. Over the years, SIPS has expanded its focus from providing a platform to learn about pharmaceutical companies to also learn about the areas of managed care and drug distribution. Some of the past speakers have been from companies such as Pfizer, Eli Lilly and Company, Merck, Pharmacia-Upjohn, Wyeth, AstraZeneca, Cardinal Health, McKesson, and Kelsey-Seybold Clinics.

The SIPS organization was the first at the College of Pharmacy to devote its efforts specifically to understanding issues facing the pharmaceutical industry and to delve into the effects managed care has on a pharmacist’s professional responsibilities and growth. Special attention is given to recognizing that pharmacy is undergoing a controversial evolution and plays a pivotal role as drug and health care costs rise at exponential double-digit rates.

The University of Houston College of Pharmacy has an advanced pharmacy management program consisting of 4 semesters of didactic coursework devoted to bringing students “up to speed” on issues that affect the current pharmacy environment. The College also has a very active masters program in pharmacy administration. The addition of a joint PharmD/MS program that the College plans to offer further indicates that the progressive growth of managed care anticipated within pharmacy is recognized by academicians.

Why was it necessary to form such an organization? First, the lack of a strong industry presence on most pharmacy campuses, compounded by the lack of exposure to career opportunities within the pharmaceutical industry, triggered the need for a greater understanding of this growing area of pharmacy. Students in pharmacy schools across the country spend up to 6 years preparing to be pharmacists, with little interaction with prospective employers in the pharmaceutical industry. Most students opt to select traditional community (retail) or institutional (hospital) careers because of their constant exposure to them in their pharmacy training. The SIPS organization felt that students’ exposure to the pharmaceutical industry would interest them in lucrative positions available in managed care.

Another main focus of the organization has been to clarify opportunities offered by the pharmaceutical industry. A misconception that SIPS tackled was that the pharmaceutical industry only offers sales representative jobs that utilize very little of the students’ pharmacy education. In addition, students posed the question of why they should struggle in industry if all they had to do was dispense medications in a retail pharmacy and be more highly compensated for their time. Many students also believed that the pharmaceutical industry only offered better positions if students furthered their education and became research scientists. Since drug discovery and pharmaceutical research is traditionally not highly emphasized in most pharmacy schools, students are not even aware of what research entails. Thus, the SIPS organization addressed these misconceptions. The SIPS organization not only provides this industry exposure but is also a platform for communication between the students and the pharmaceutical industry.

The SIPS organization also strives to help students understand the fundamental reasons for rising health care costs and the importance of managed care in this process. It addresses this issue by inviting pharmacists from managed care environments to visit the University of Houston. As health care costs increase and baby boomers age, managed care plays a vital role in the evolution of health care. It does so by taking on more responsibility and reining in costs in order to provide a broader range of services to a greater population of people. PricewaterhouseCoopers published a report in April 2002 that investigated what fuels the rising cost of health care. Several reasons for an increase in costs were identified, including drug and provider costs and inflated legal expenses. The report also projected the impact managed care will have over the next 5 years in controlling costs. These are some of the topics that are discussed by presenters at the SIPS monthly presentation seminars.

Other SIPS seminar topics include the role of the pharmacist in managed care formulary development, drug approval by pharmacy and therapeutic committees, the pharmacist’s role in drug protocol development, and promotion of evidence-based medicine. By participating in formulary selection and guideline implementation, pharmacists can have a profound influence on patient outcomes and health care costs.

What are SIPS students doing to further prepare themselves for entry into the field of managed care? As Society members, students can explore the various opportunities available to them via informal meetings and lunches with pharmaceutical companies. Students who want to learn about the business side of pharmacy now have a formal process in which to be mentored by fellow pharmacists in the industry. The SIPS organization is now collaborating with managed care and industry to develop company partners for future collaborative efforts that further the goals of SIPS members.

Since 1998, the SIPS organization has hosted many events, including arranging industry field trips, promoting representation at conferences, inviting eminent speakers for presentation, developing career workshops, and endorsing the overall posi-
Dear Editor,

I read with great interest the article by Meyer and colleagues in the March/April, 2003 issue of the Journal. I am very concerned that the authors may not have used complete information and may have made inappropriate assumptions in their research. My concerns are as follows:

1. While the Evidence for Interferon Dose Effect: European-North American Comparative Efficacy (EVIDENCE) trial showed a 12% greater number of relapse-free patients for interferon beta-1a (Rebif—referred to as IB1a2 by the authors) versus Interferon beta-1a (Avenex—referred to as IB1a1 by the authors) at 24 weeks, the data showed a 1% greater number of relapse-free patients favoring IB1a1 at 48 weeks. Inferring long-term clinical effectiveness, especially with a lifelong disease like multiple sclerosis, from short-term study findings can be fraught with difficulty.

2. No consideration is given by the authors to the costs of treating the increased number of side effects attributable to use of IB1a2 versus IB1a1 as demonstrated in the EVIDENCE trial. These include higher frequency of occurrence of injection site disorders, liver abnormalities (including elevated ALT and AST), and white blood cell abnormalities (including leukopenia).

3. In estimating the incremental cost to a plan of adopting IB1a2, the authors deduct administrative costs related to managing multiple products on formulary. The assumption is that IB1a2 is adopted in place of other approved products, not in addition to these products. As such, the savings in question are attributable to the plan’s decision to adopt an exclusive formulary, not to IB1a2 per se. Similar savings would accrue to the plan if exclusive status were awarded to IB1a1 or to any other approved product. The true incremental cost to a health plan of placing a new patient on IB1a2 versus other products in a nonexclusive formulary setting is therefore significantly higher than the $0.05 PMPM cited by the authors.

4. Incidence of neutralizing antibodies was much higher in IB1a2-treated patients. While the clinical significance of antibodies has not been completely elucidated, many clinicians are now testing for neutralizing antibodies and discontinuing interferon beta therapy when the antibody titer increases to greater than 20.

5. IB1a1 is the only interferon beta product to have shown positive effects on brain atrophy and cognitive dysfunction in clinical trials. These findings may correlate to better long-term treatment success.

6. The claim in the article that assumes 80% of newly diagnosed multiple sclerosis patients would utilize IB1a2 appears to have no basis in fact. Market share in this category has not changed appreciably since IB1a2’s entry. Due to mounting concern over neutralizing antibodies, it is highly doubtful that its market share will attain the projections reported by the authors.

In conclusion, pharmacoeconomic modeling is based upon certain assumptions, and the pharmacy-budget impact analysis in the article by Drs. Meyer, Phipps, Cooper, and Wright did not properly represent the known clinical evidence for the treatment of multiple sclerosis or common practices used in drug benefit administration.

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Shortcomings in Pharmacy Benefit Forecasting—Interferon Beta Products

Dear Editor,

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DISCLOSURES

There was no specific funding for the preparation of this letter. Dr. Rich has served as a consultant to Biogen, Inc; Berlex, and Teva.

REFERENCES


The Authors Respond

Dear Editor,

We appreciate Dr. Rich’s careful review of our manuscript, which appeared in the March/April 2003 issue of JMCP.1

As we clearly outlined in the introduction, our objective was to suggest a method for using administrative claims to evaluate potential direct population costs of pipeline therapies prior to the availability of full cost-effectiveness analyses. This analysis was undertaken before the launch of the product in order to provide preliminary information to those with direct responsibility for the pharmacy budget alone. The study was published after the drug was approved.

The majority of Dr. Rich’s points (points 1, 2, 4, and 5) focus on costs related to clinical outcomes, side effects, and patient functioning that would be included in a full cost-effectiveness or budget impact analyses. These types of analyses are critically important to evaluate the true value of therapies, but formulary dossiers containing the information may not be available until after the drug is marketed.2 However, payers frequently require customized proactive information prior to marketing to anticipate potential blockbuster drugs and possible cost-containment strategies. The proposed claims analysis is an attempt to bridge that early information gap.

When more information becomes available through detailed cost-effectiveness and completed phase III and IV studies, the true budget impact on both the pharmacy and medical budgets would indeed take precedent over preliminary assessments. For instance, the 63-week extension of the EVIDENCE study demonstrated a 17% reduction in relapse rates for 44 µg tiw interferon beta-1a (Rebif-IB1a2) compared to 36 µg cw interferon beta-1a (Avonex-IB1a1), indicating a sustained impact on relapse over time.3 With regard to side-effect management, a statistically significant higher rate of flu-like symptoms were also reported in the IB1a1 group (53.4%) compared to the IB1a2 group (44.8%).3 Information from the trial shows that neutralizing antibodies are not related to clinical impact on relapse rates; therefore, the influence of neutralizing antibodies is still unclear.3

We did include administrative costs of prior authorization related to costs that plans may incur by implementing a prior-authorization program (point 3). We assumed in the base analysis that the new product would compete with existing therapies and IB1a2 would be used in place of other similar products. The model is flexible to incorporate a variety of scenarios, but we chose a share-shift analysis approach in the base case where there was some decline from the other products.

The 80% share estimate in new users was indeed aggressively set forth by the manufacturer (point 6). We specifically performed sensitivity analysis around this estimate as presented in the manuscript. However, a reduced market-share estimate would only reduce the anticipated impact of interferon beta-1b.

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REFERENCES


Patient-Reported Utilization Patterns of Narcotic Drugs

Dear Editor,

I read the article on the above subject in the May/June 2003 issue of JMCP with interest. A perhaps far more interesting topic could be explored by the authors: the topic of “the rest of the story,” when patients choose to take themselves off of such medications. In the treatment of chronic nonmalignant pain, it is important to recognize that this category is a hodge-podge. We cannot assume that there is only one situation or pathophysiology involved. So, any commentary on the “group” needs to recognize that there will be variation in applicability.

However, with that said, it is fascinating to observe the patients with “chronic nonmalignant pain” who become fed up with taking all the pills (or patches) and simply take themselves off. They may go from high doses of very expensive medications to use of nothing more than ibuprofen. Yet, this may occur with no observable change in the underlying condition. The only thing that changes is their desires. This is a very, very revealing outcome when it happens.

Perhaps these authors would care to look at “the rest of the story.” They must certainly have some patients who eventually go off of all the narcotics. When this happens, what leads to the outcome? What evidence exists that underlying pathology changed? Or is the change simply one of choice? If so, what do we learn from this?

Obviously, there are many countries in the world that do not
have the economic situation to support the use of chronic high-grade narcotics (particularly very expensive ones). What do their citizens do? And have you ever seen an animal that needed chronic narcotics? The lessons I’m obviously implying are easily available for anyone who simply wishes to look at pain behavior across the world. However, ethnocentrism seems to lead many investigators to turn a blind eye to the rest of the world.

While full understanding of pain behavior in humans requires looking at all humans, we may still learn a great deal from examination of selected subgroups. In regard to the subgroup of patients with chronic nonmalignant pain, there is much to learn about pain from an examination of desires.

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REFERENCES

Common Industry Practices and OIG Compliance Guidance

Dear Editor,

I read the Office of Inspector General (OIG) Compliance Program Guidance for Pharmaceutical Manufacturers published May 5, 2003.1 In my opinion, the key to the “guide” is contained in the introductory discussion under kickbacks. The OIG states that what people may regard as common industry practices (for example, relationship-building activities such as taking customers to entertainment or sporting events, dinners, or seminars) are not necessarily legal when viewed under the antikickback laws. This is a somewhat disingenuous statement, as there is a lot of discretion involved in determining these matters, and it is a very technical reading of a very vague statute.

The antikickback statute is so broadly written, everything seems illegal. We’ve raised, and now seem to celebrate with large legal fees, a generation of technocrats: compliance experts that sanctimoniously opine on what’s legal, etc., based on literal readings, without understanding or caring about the impact from a substantive or industry standpoint.

The biggest trap in the guidelines is the reliance on the so-called “one purpose” test: If one purpose of a program can be considered to be inducing referrals, then the whole program structure fails. What is it that the drug manufacturers do that isn’t based on the motivation to sell their product or induce referrals? Does anyone think the education and research programs, even divorced from sales, are charitable? If the OIG wants price competition, it seems to me that it should try to adapt its rules to common industry practices and focus on obvious abuses and outright fraud or inappropriate conduct. Doesn’t price competition require manufacturers to follow, not disregard, “common industry practices?”

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REFERENCES
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- [ ] Home Address

**Work Telephone**

**Home Telephone**

**E-mail Address (Primary)**

**E-mail Address (Secondary)**

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- [ ] Secondary E-Mail

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### 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**

### Demographic Information

**Please tell us:**

1. Are you a pharmacist?  
   - [ ] yes
   - [ ] no

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

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

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

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

   ___ year(s)