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JMCP

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Page

JMCP
Volume 9, No. 1

CONTENTS

ORIGINAL RESEARCH

FORMULARY MANAGEMENT

CONTEMPORARY SUBJECTS

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JMCP

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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AMCP/Pfizer Inc Managed Care Pharmacy Summer Internship Program

Twelve 2003 Summer Internship Positions Available

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- Work for eight weeks at a leading managed care organization under the supervision of a pharmacist preceptor.
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- Complete a one-week structured rotation through the managed health care division of Pfizer to gain a perspective on the pertinent issues in managed care pharmacy and how they impact the pharmaceutical industry.
- Present a poster at the AMCP 2003 Educational Conference in Montreal, Quebec, Canada.

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- Completion of a standard application postmarked by February 28, 2003.
- Full-time enrollment in an accredited school of pharmacy during the 2002–2003 school year with anticipated graduation in 2004 or 2005 with a PharmD degree. This internship may qualify as a specialty rotation, check with your school's clerkship coordinator.
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- Spend one week at a pharmacy benefits management company under the supervision of a pharmacist.
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To receive an application package, contact:

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This annual internship for pharmacy students reflects the commitment of the Academy of Managed Care Pharmacy and Pfizer to pharmacy education and to improving the quality of pharmaceutical care.

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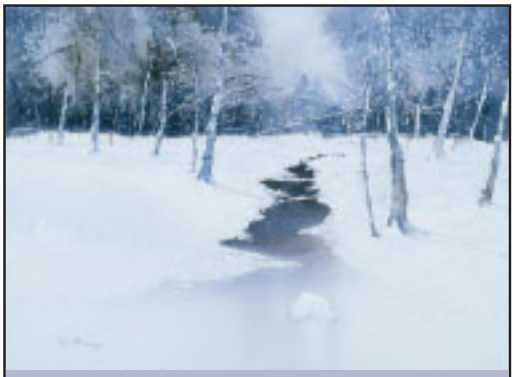
Pfizer

COVER IMPRESSIONS

About our cover artist

Winter Whisper (2002) ■ John W. Mauger, PhD

John W. Mauger, PhD, dean of the College of Pharmacy at the University of Utah, has successfully combined a rewarding career in the pharmacy field with a talent for painting. Although at first it would seem to be an unusual combination, it is certainly no surprise that a well-educated individual such as Mauger would be interested in the fine arts and appreciate the aesthetics of watercolor painting. His life-long interest in art grew as he began to visit art galleries and museums when he was an undergraduate student. He dabbled in oils before entering graduate school, but subsequently lacked the time to continue his painting. About 8 years ago, Mauger returned to painting using watercolors, and now he paints every night as a form of relaxation.



A silvery leaf,
Fluttering, floating, into
A small, silent brook.

He describes his style as mostly self-taught, but strongly influenced by contemporary watercolorists from the United Kingdom and Australia who follow the English watercolor tradition. He said, "They use a palette that achieves both depth and transparency, and their paintings convey a commanding sense of light. They achieve a luminous effect by using transparent rather than opaque, dark pigments. Following their tradition, I use a palette composed primarily of transparent watercolors. I have found that dilute washes of cobalt blue and cobalt violet create very beautiful glazes." He added, "Recently, I have become devoted to squirrel mop wash brushes that are used to gently apply the initial washes and final glazes. Australian artist Joseph Zbukvic, noted for his ability to create atmosphere and mood in his paintings, explains that 'mop wash brushes enable the artist to follow a bead of water across the paper as the washes are applied. The bead then allows the pigment to granulate and create a texture.' Another method I use to create texture is to mist the still-wet pigment with water, using a vintage glass DeVilbiss-brand atomizer originally marketed for medicinal purposes. In fact, I recall selling these atomizers when I was a pharmacy student."

Mauger paints most of his subjects from memory. He says that *Winter Whisper* is reminiscent of a brook found on the farm where he grew up in rural upstate New York, near Cooperstown. In this watercolor painting, he has effectively captured the beauty and peacefulness of a winter landscape. About the only sound one would expect to hear would be the soft rustling of a bird's wings as it takes flight from a treetop. His seamless blending of color is particularly evident in the meandering brook, as the glassy surface of the water progresses from a light wash of blue to a deeper blue-gray color. *Winter Whisper* displays a superb balance of light and dark, with the white blanket of snow in the foreground contrasting with the deeper tones of the vanishing horizon of trees in the background. A sense of mystery is suggested by the misty scenery of the backdrop.

Mauger's curriculum vitae lists his well-rounded pharmaceutical education and impressive professional credentials. He graduated from Union University, Albany College of Pharmacy, with a BS degree and then accepted a position as staff pharmacist at the University of Vermont Medical Center. While living in Vermont, he also worked in a rural community pharmacy. Next, came the opportunity to return to graduate school at the University of Rhode Island, where he earned both MS and PhD degrees in the pharmaceutical sciences. His interest in pharmaceutical research and education led to a career with a combined total of 23 years in academic pharmacy at West Virginia University and the University of Nebraska Medical Center, College of Pharmacy. He joined the University of Utah, College of Pharmacy, as dean in 1994. Mauger served as president of the American Council on Pharmaceutical Education from 1997 to 1999. He is currently a member of the U.S. Pharmacopoeia Biopharmaceutics Expert Committee and is on the editorial board of *Pharmaceutical Development and Technology*. He is also co-director of the Utah Addiction Center.

Mauger and his wife, Karen, reside in Salt Lake City. They have two grown sons, one of whom is, coincidentally, an art teacher.

Sheila Macho
JMCP Contributing Editor

COVER CREDIT

John W. Mauger, PhD, *Winter Whisper,* watercolor on paper. Salt Lake City, Utah. Copyright 2002.

SOURCES

Interview with the artist.

GENERAL MEETING INFORMATION

SCHEDULE AT-A-GLANCE

Wednesday, April 9

8:00 am–6:00 pm	Registration
1:00 pm–5:00 pm	Committee Meetings Pre-Conference Symposia
5:00 pm–6:30 pm	Opening Night Reception
7:00 pm–9:30 pm	Awards Dinner *(invitation only)*

Thursday, April 10

6:00 am–8:00 am	Breakfast Symposia
7:00 am–6:30 pm	Registration
7:30 am–5:00 pm	Committee Meetings
8:00 am–5:30 pm	Student Chapter P&T Competition
8:30 am–9:45 am	Round Table Discussions
8:30 am–12:00 pm	Managed Care Essentials
9:00 am–12:30 pm	Lunch Symposia
10:00 am–11:00 am	Educational Sessions
11:15 am–12:15 pm	Educational Sessions
11:30 am–12:30 pm	Student Session I
1:00 pm–2:30 pm	General Session
2:30 pm–6:30 pm	Exhibit Hall Open
4:00 pm–5:30 pm	Educational Sessions
5:30 pm–6:30 pm	Annual Showcase Reception in the Exhibit Hall

Friday, April 11

6:00 am–8:00 am	Breakfast Symposia
7:00 am–5:00 pm	Registration
8:30 am–10:00 am	General Session
10:00 am–2:45 pm	Exhibit Hall Open Poster Presentations
10:30 am–5:00 pm	Student Chapter P&T Competition
10:30 am–11:30 am	Educational Sessions
11:45 am–12:45 pm	Educational Sessions
2:45 pm–3:45 pm	Educational Sessions
4:00 pm–5:00 pm	Educational Sessions
5:00 pm–6:00 pm	Student and New Member Reception

Saturday, April 12

8:00 am–12:30 pm	Registration
8:30 am–9:30 am	Educational Sessions
9:45 am–12:00 pm	Plenary Session

schedule subject to modifications

WHAT IS AMCP'S 15TH ANNUAL MEETING & SHOWCASE ALL ABOUT?

AMCP's 15th Annual Meeting & Showcase will showcase a myriad of activities, initiatives, breakthroughs and partnerships that are shaping the future of managed care pharmacy. Join your colleagues for the premier networking and educational event for managed care pharmacy professionals. Refer to AMCP's website (**www.amcp.org**) for more details including an up-to-date listing of educational sessions and activities occurring at the Meeting!

WHO SHOULD ATTEND?

The Annual Meeting attracts almost 3,000 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 pharmacoeconomics; 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
- Staff/Clinical Pharmacists
- Students/Residents/Fellows
- Professional Relations
- Customer Service
- Network Management Professionals
- Pharmacy Directors
- Medical Directors
- Professors/Academia
- Formulary Management
- Marketing/Sales

3 EASY WAYS TO REGISTER FOR THE MEETING!

- **Online: www.amcp.org**
  - When registering online, you must provide credit card information and e-mail information or 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 on the next page 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 **March 10, 2003**. Registration forms received after this date are subject to the on-site registration fees. See the registration form on the next page or on the AMCP website at www.amcp.org for fees. *Confirmation notices will be sent to all confirmed participants.*

REGISTRATION FORM

AMCP's 15th Annual Meeting & Showcase
April 9–12, 2003 ■ Minneapolis Convention Center ■ Minneapolis, MN

DON'T WAIT! REGISTER BY MARCH 10, 2003 TO RECEIVE DISCOUNTED FEES.

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1. ATTENDEE INFORMATION

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MY AMCP MEMBERSHIP NUMBER (IF APPLICABLE) _____

TITLE _____

COMPANY _____

ADDRESS 1 _____

ADDRESS 2 _____

CITY _____ STATE _____ ZIP CODE _____

TELEPHONE _____ FAX _____

E-MAIL ADDRESS _____

3. REGISTRATION FEES (Please check the appropriate box below.)

	Pre-Registration (received on or before March 10, 2003)		On-Site (received after March 10, 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 contact the AMCP office at (800) 827-2627 for a membership application, or visit AMCP's web site at www.amcp.org and enroll online.

4. 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)*
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CARD NUMBER _____ EXP DATE _____

CARDHOLDER PRINTED NAME _____

CARDHOLDER SIGNATURE _____

Registration Cancellation/Refund Policy: *Cancellation of participant registration must be requested in writing and must be received by* ***March 19, 2003****. A* ***$150 administrative fee will be assessed on all cancellations.*** *No cancellation/refund requests will be granted after* ***March 19, 2003****. Registrant substitutions will be accepted with written notification from the original registrant. An administrative fee of $30 (other fees may apply) will be assessed. Only one substitution per registrant is allowed. No registration transfers to other AMCP national meetings.*

2. DEMOGRAPHIC INFORMATION

Please tell us:

I. Are you a pharmacist? 1A ☐ yes 1B ☐ no

II. What degrees/designations do you hold?
2A ☐ B.S. Pharmacy
2B ☐ M.P.A.
2C ☐ Ph.D.
2D ☐ M.B.A.
2E ☐ Other *(specify)* _____
2F ☐ Pharm.D.
2G ☐ M.P.H.
2H ☐ J.D.
2I ☐ R.Ph.

III. Which of the following best describes your employer? *(check one)*
3A ☐ Health Plan
3B ☐ Medical Group
3C ☐ Integrated System
3D ☐ Hospital
3E ☐ College or University
3F ☐ PBM/Mail Service
3G ☐ Home Care
3H ☐ Long-term Care
3I ☐ Retail Pharmacy
3J ☐ Consulting Firm
3K ☐ Pharmaceutical Manufacturer (MFR)
3L ☐ Government (VA, PHS, Military, State)
3M ☐ Not Currently Employed
3N ☐ Association
3O ☐ Other *(specify)* _____

IV. Which of the following best describes your job function(s)?
4A ☐ Director/President
4B ☐ Assistant Director/Vice President
4C ☐ Staff Pharmacist
4D ☐ Clinical Pharmacist
4E ☐ Clinical Coordinator
4F ☐ School/College Faculty
4G ☐ Student
4H ☐ Resident/Fellow/Graduate
4I ☐ Contract/Purchasing
4J ☐ Network Management
4K ☐ Professional Relations
4L ☐ Formulary Management
4M ☐ Distribution/Supply Chain
4N ☐ Customer Service
4O ☐ Consultant
4P ☐ Marketing/Sales
4Q ☐ Other *(specify)* _____

V. How many years have you been in your current role?
5A ____ year(s)

VI. Your reason for attending AMCP's national meetings? *(please choose all that apply)*
6A ☐ Obtain Continuing Education Credits
6B ☐ Enhance Knowledge and Skills
6C ☐ Opportunity for Networking
6D ☐ Develop Personal and Leadership Skills

VII. Is this your first AMCP meeting? 7A ☐ yes

Register:
- **Online: www.amcp.org**
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HOUSING FORM

AMCP's 15th Annual Meeting & Showcase
April 9–12, 2003 ■ Minneapolis Convention Center ■ Minneapolis, MN

TO ARRANGE HOTEL ACCOMMODATIONS, YOU MUST BE REGISTERED FOR THE MEETING.

Please print or type. Please return this form with your meeting 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 _____

FOURTH CHOICE _____

FIFTH CHOICE _____

Arrival Date:
April _____, 2003

Departure Date:
April _____, 2003

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.)

_____

_____

METHOD OF PAYMENT *(Note: All reservations require a $200 room deposit plus registration fee.)*

☐ Check deposit payable to ExpoExchange for $ _____ *(in U.S. funds drawn on a U.S. bank)*

☐ Credit Card to be charged *(credit card will be charged immediately)*

Charge to the following credit card (check one):

☐ Visa ☐ MasterCard ☐ American Express ☐ Diners Club ☐ Discover

CARD NUMBER _____ EXP DATE _____

CARDHOLDER PRINTED NAME _____

CARDHOLDER SIGNATURE _____

Please print or type and return one form per room. You may duplicate this form.

INTERNET

Make your hotel reservations online through the AMCP web site at www.amcp.org. Credit card deposit is needed to complete your reservation.

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. A $200 credit card room deposit is required. Please note that your credit card will be charged when this form is submitted.

MAIL

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HOTEL RATES

- Hilton Minneapolis
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  - $178 double occupancy
- Hyatt Regency Minneapolis
  - $162 single occupancy
  - $187 double occupancy
- Millennium Hotel Minneapolis
  - $151 single occupancy
  - $161 double occupancy
- Doubletree Guest Suites
  - $131 single occupancy
  - $131 double occupancy
- Embassy Suites Minneapolis - Downtown
  - $149 single occupancy
  - $159 double occupancy

PLEASE NOTE:

- You must be a confirmed registrant to obtain housing under AMCP's block.
- All reservations require a $200 room deposit. Please note that your credit card will be charged when this form is submitted.
- All new reservations, changes, and cancellations should be made directly with ExpoExchange by **Thursday, March 13, 2003**. Starting **Friday, March 14, 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 deposit of $200.
- When cancelling a reservation by telephone with the hotel, record the date, cancellation number, and the name of the person accepting the cancellation.

ORIGINAL RESEARCH

A Pharmacist-based Screening Program of Octogenarians Starting New Medications

EVAN SEEVAK, MD; DANIEL J. KENT, RPh, CDE; and EDWARD WAGNER, MD, MPH

ABSTRACT

OBJECTIVE: To measure the impact of clinical pharmacists in primary care practices who closely monitor patients older than 80 years after initiation of new medications.

METHODS: The study was an uncontrolled pilot trial performed at a group-model health maintenance organization in the Pacific Northwest between August and December 1999. Forty-eight patients who were older than 80 years and were prescribed at least one new medication in their primary care clinic were called at home 3 to 6 days after starting a new medication and asked questions focusing on compliance and potential adverse drug events.

RESULTS: More than 20% of patients (10 of 48) had a clinically important change made as a result of the pharmacist telephone monitoring; 42% of patients (20 of 48) either experienced an undesired medication effect (14 of 48) or an inadequate effect (6 of 48). Pharmacists spent an average 11.3 minutes at an estimated cost of $6.40 per patient.

CONCLUSION: A simple, inexpensive pharmacist-based program to screen for medication problems after initiation of new medicines may improve the care to a population older than 80 years.

KEYWORDS: Adverse drug reactions, Adverse drug events, Elderly, Clinical pharmacist, Pharmacist screening

J Managed Care Pharm. 2003(9)1: 13-18

Authors

EVAN SEEVAK, MD, is Assistant Clinical Professor of Medicine, University of California, San Francisco. (At the time of this study, Dr. Seevak was a fellow in the Division of Gerontology and Geriatric Medicine, Department of Medicine, University of Washington.) DANIEL J. KENT, RPh ,CDE, is Clinical Specialist, Diabetes/HIV, Center for Health Studies, at Group Health Cooperative, Seattle, Washington, and EDWARD WAGNER, MD, MPH, is Director, W.A. Sandy Mac Coll Institute for Health Care Innovation, Seattle, Washington.

AUTHOR CORRESPONDENCE: Evan Seevak, MD, Assistant Clinical Professor of Medicine, University of California, San Francisco, Alameda County Medical Center, 1411 East 31st St., Oakland, CA 94602. Tel: (510) 437-4886; Fax: (510) 532-0397; E-mail: eseevak@acmedctr.org

Adverse drug events (ADEs) and adverse drug reactions (ADRs) are quite common among older patients. The World Health Organization (WHO) has defined an ADR as "… any noxious, unintended and undesired effect of a drug after doses used in humans for prophylaxis, diagnosis or therapy…"[1] An ADE is a broader term that includes ADRs and has been defined as "an injury resulting from medical intervention related to a drug."[2] For example, an anaphylactic reaction to penicillin would qualify as both an ADE and an ADR, but an injury resulting from the use of an incorrect dose of penicillin would be an ADE only.

While there is a large range in the medical literature of the incidence of ADEs and ADRs due to the variety of definitions used as well as differences in populations studied, the potential for ADEs and ADRs is a significant concern when providing medical care to the aged. A large study in Iowa of relatively healthy patients older than 65 years taking relatively few medications demonstrated a self-reported annual ADR rate of 10%.[3] In a group of veterans older than 65 years who were not as healthy and taking more medications on average, the annual rate of ADEs was significantly higher at 35%.[4]

The major risk for ADRs (and probably ADEs) seems to be the number of medications used.[5] Age does not appear to be an independent risk factor.[6] However, because age is a risk factor for a variety of chronic diseases (though this may be confounded by a survival effect), polypharmacy, and altered pharmacokinetics, frail older patients may be at increased risk for ADEs. According to data from the General Accounting Office, as many as 1 in 6 hospitalizations in older adults are due to ADRs.[7]

For any prescribing provider, there is tension between the increasing number of effective medical therapies for a number of chronic diseases and the known association between polypharmacy and ADEs. Health care providers who care for seniors are encouraged to actively screen for ADRs, inquire about noncompliance, and review whether prescribed medications are having their intended effect in an effort to minimize the risk of ADEs. Unfortunately, the effectiveness of such monitoring has not been well documented. Waiting for patients to actively complain of ADEs may be inadequate because elderly patients suffering from one or more chronic disease may become accustomed to suboptimal health and less likely to complain if they suspect a drug-related effect.[8] In settings where patients are at risk for an ADE due to polypharmacy or frailty, clinical pharmacists working closely with prescribing physicians may have a role in monitoring patients.[9]

In a variety of clinical settings, telephone contact has been

demonstrated to be a very effective tool in the management of several chronic diseases, including congestive heart failure, depression, and coronary artery disease, and among older men.[10-13] Von Korff et al. recommend that telephone contact can be a key element in efforts to improve the management of chronic illness.[14] Pharmacist-based telephone care also has been demonstrated to be effective in improving care. A study performed at the Palo Alto Veterans Administration Hospital demonstrated that having clinical pharmacists available to address medication concerns and refill requests resulted in a reduction in walk-in urgent-care visits when the pharmacist is able to satisfy patient needs through telephone assessment and appropriate prescribing as defined by protocol. Cost savings were demonstrated in this study due to fewer urgent-care visits. Six percent of the calls the clinical pharmacist received related to medication concerns (not a refill request), and two thirds of these medication concerns only required education.[15]

In this pilot study, the impact of proactive monitoring of high-risk seniors started on new medications was examined. Rather than waiting for patients to call with complaints, the clinical pharmacists called patients thought to be at risk for ADEs. The authors focused on patients older than 80 years because of a presumed level of frailty and medical complexity that might put them at high risk for polypharmacy and adverse events. Each patient received a phone call from a pharmacist working closely with his or her primary care physician in clinic. Based on the assumption that most adverse events occur soon after initiating a new medication, the phone calls were placed within 3 to 6 days of a new prescription.

Methods

Setting

The study was performed at 3 Group Health Cooperative (GHC) primary care clinics in Seattle, Washington. GHC is a group-model HMO serving approximately 500,000 enrollees. Six pharmacists who were employed by GHC in primary-care clinics participated. At the time of the study, their practices included a total of 12 physicians and 4 physician assistants with a patient base of 21,650. The Human Subjects Committee of GHC approved the study.

Patient Selection and Enrollment

Any patient older than 80 years who received a new prescription during the enrollment period was eligible. Clinical pharmacists enrolled patients at the time their new medication was dispensed between August 22, 1999, and December 1, 1999. Informed consent was obtained by the pharmacists at the time of enrollment. Pharmacists also asked patients for their phone number and the best time to reach them during the following 3 to 6 days.

Questionnaire

The clinical pharmacists used a script to conduct their phone interviews. The authors developed the script to elicit answers that would help determine whether potential adverse events were related to the medication that was recently started. They attempted to avoid using sophisticated medical jargon and reviewed the script with the participating pharmacists. The script asked several questions regarding the recently prescribed medication:

1. Have you been able to take the new medication?
2. Have you missed any doses?
3. Have you noticed any problems since you started taking it? If yes, then proceed to 4, 5, 6, and 7.
4. Did the problems start before or after you began taking the medication?
5. Do you think the problem is related to the medication?
6. Did you stop taking the medication because of the problems you were having?
7. If you stopped taking the medication, have the problems gone away?

Pharmacists recorded data on forms that corresponded to the script. They responded to questions, provided counseling on the effects of medications, and referred appropriate concerns to the prescribing physician. Pharmacists also recorded the number of attempts made to contact each patient and the amount of time spent, including the consent process. Phone calls were not taped or monitored.

TABLE 1 Characteristics of Enrolled Patients

Age	85.4 years (±3.4)
Sex	26 Females (54%)
Mean number of new prescriptions at time of new prescription	6 prescriptions (±2.7)

Evaluation of Reported Adverse Drug Events

Adverse events were reviewed by a geriatrician (Seevak) and pharmacist (Kent) and determined to be probable if the reaction was well known, if there was a temporal relationship between starting the new medication and the perceived effect, and whether symptoms resolved when the suspected medication was stopped. This assessment was based on criteria adopted by the WHO for assessing causality.[16] The 2 reviewers were in agreement on all suspected ADEs. With the exception of 2 patients, the authors did not have adequate follow-up to determine if symptoms resolved when medications were stopped. The authors were not involved in any rechallenges of suspected medications.

Results

Enrollment and Patient Characteristics

Fifty-four patients were asked to enroll in the study, and 48 patients agreed to participate. Several of the pharmacists commented that because of competing demands, they were

TABLE 2 *Actions Taken as a Result of the Intervention*

Medication	Age/Sex	Number of Concurrent Medications	Patient Concern	Action
Naproxen	87 M	10	Urinary retention	Urgent care visit/ urinary catheter
Amiodarone/ furosemide	86 F	5	Fatigue, poor sleep, and bradycardia	MD visit scheduled
Morphine SR	91 M	11	Grogginess	Changed to morphine/ MD appointment
Hydrocodone/ homatropine	86 F	4	Nausea	Stopped
Rofecoxib	93 M	3	Lightheadedness	Decreased dose
Furosemide	89 F	7	Not effective	Increased dose
Oxybutinin	90 F	4	Drowsiness	Decreased dose
Amoxicillin	81 F	10	Not effective	Changed to clarithromycin
Pantoprazole	86 F	7	Not effective	Changed to omeprazole
Hydrocortisone cream	81 F	3	Incorrect use	Pharmacist instructed patient on proper use

unable to enroll many patients who may have met entry criteria during the enrollment period. The mean age of participants was 85 years, and they were taking an average of 6 medications at the time of enrollment (Table 1). Women slightly outnumbered men. During the predetermined follow-up period of 3 to 6 days, 46 of 48 patients were contacted.

There were at least 15 patients who were not offered enrollment because they had dementia or hearing loss, had a caregiver who dispensed their medications, or were non–English-speaking. However, several patients with hearing loss, dementia, or a caregiver were offered enrollment.

Compliance With Physician Recommendations

Four percent of patients (2 of 46) who were contacted reported to the pharmacist that they had not started the recently prescribed medication. One of these patients had been prescribed 2 new medications and wanted to start one at a time so that she would be aware of any side effects. The second patient did not want to take the antidepressant she was prescribed because of a previous bad experience with antidepressants. She was not planning to tell her physician that she was not taking the antidepressant.

Undesired and Inadequate Effects

Forty-two percent of patients (20 of 48) either experienced an undesired effect attributed to the medication (14 of 48) or an inadequate effect (6 of 48).

Table 2 describes the actions that were taken after the pharmacist call. Three patients had their dose changed as a result of the pharmacist call. Three patients had a medication changed to another medication within the same class. One patient had her medication stopped by the pharmacist. As a result of the phone calls, 3 patients were scheduled to be evaluated by a physician within a day or two, including a patient seen in urgent care for urinary retention after starting naproxen.

The conversation between the patient and pharmacist revealed significant information for several patients. Actions taken as a result of the calls is described in Table 2. One patient taking nasal steroids developed epistaxis that resolved spontaneously. Six patients were encouraged by the clinical pharmacist to continue taking their recently prescribed medication despite a report of no benefit. One patient was reassured that the lightheadedness he was experiencing with an ACE inhibitor would resolve.

Pharmacist Effort and Cost

Pharmacists contacted 96% of patients (46 of 48) enrolled in the study after an average of 1.46 calls (Table 3). The pharmacists contacted the majority of patients on the first attempt. The pharmacists reported spending an average of 11.3 minutes per patient contacted, including time spent obtaining patient consent. Assuming a salary of $35 per hour, the estimated cost of this intervention was $6.40 per patient.

Discussion

This pilot study of telephone monitoring by pharmacists indicates that adverse effects commonly may appear in patients older than 80 years very soon after starting a new medication, and as a result of active pharmacist involvement, important clinical changes can be made in the medical regimen of a significant portion of these patients. These include changes due to ineffective medications, unwanted effects, and incorrect usage.

TABLE 3 Pharmacist Effort

Number of patients reached	46 (96%)
Average number of attempts	1.46 (±0.7)
Number reached on first attempt	30 (65%)
Average time spent per patient following enrollment	11.3 minutes (±5.1)

As a result of the simple intervention described in this pilot study, 21% of patients (10 of 48) had a significant change, and 30% of patients (14 of 48) described a problem with a new medication that met criteria for a probable ADR.

Because this is a small, uncontrolled pilot study with variable adherence to protocol, the results must be interpreted with some caution. In a relevant study by Hanlon et al., a group of veterans in North Carolina older than 65 years, each taking more than 5 medications a day, reported a one-year ADE incidence of 35%. Hanlon et al. defined ADEs as "noxious and unintended patient events…caused by a drug," and the ADEs were self-reported in a close-out interview.[4] The participants in Hanlon's study had a mean age of 69 and were taking 8 chronic medications compared with a mean age of 85 and 6 chronic medications in the pilot study described here. With a comparable degree of polypharmacy and significantly increased age, it should not be a surprise that participants in this pharmacist intervention experienced a high rate of adverse events. Unfortunately, Hanlon et al. did not report the timing of the ADEs in relation to when the offending medications were started. It would be interesting to learn if the majority of ADEs experienced in Hanlon's study occurred soon after initiation of a new medication. If so, that would reinforce the value of an early clinical pharmacist intervention.

Patients, in general, were very happy to receive a call from a pharmacist to see how they were doing with their new medication. Anecdotal reports from the clinical pharmacists regarding patient responses were very positive. Numerous patients expressed their pleasure when they received a call from their pharmacist. Several physicians initially expressed concern that this intervention might create more work for them by uncovering insignificant or factitious drug effects that would be brought to their attention. Physicians did not voice these concerns to their pharmacist colleagues during the study period, and it appears that the pharmacist interventions did not create more work for physicians. Whether or not this is true could be evaluated in greater detail in further studies with longer follow-up.

Whether the results of this study overestimate the problem of ADEs by soliciting feedback from the participants, as several of the participating physicians were concerned it might, is a reasonable concern. As with all studies reporting the incidence of ADEs and ADRs, it is important to view the data in the context of the study. Clearly, if the participants in this study were asked to call with problems instead of receiving an inquiring call from a pharmacist, the results would be less impressive and fewer actions would have been taken that altered patient care. The authors felt that the most significant result of this study was the number of actions (see Table 2) taken by the pharmacists as a result of the intervention, not the number of probable ADEs discovered.

A more rigorous approach to evaluating the criteria for causality in ADEs would require assessment of the benefit of a dechallenge (withdrawing the drug) and the consequences of a rechallenge, if performed.[16] Based on the response to question #7 in the questionnaire, it appears that several of the suspected ADEs, including the nausea experienced with hydrocodone/homatropine, the urinary retention with naproxen, and the dizziness with lisinopril, resolved with dechallenge. Though an attempt was made to assess the benefit of dechallenge with question #7, the follow-up was not adequate to fully assess the benefit derived from stopping potentially offensive medications. Ideally, the effect of stopping the potentially causative medication would have been reviewed later for each of the 14 patients with a suspected ADE.

Malone has described several threats to the reliability of studies of clinical interventions, including self-selection bias.[17] In our study, 89% of the patients who met the inclusion criteria agreed to participate in the study. However, there may have been some selection bias on the part of the pharmacists in enrolling patients. For example, several patients with dementia were not included in this study. While demented patients actually may be at increased risk of experiencing an ADE, they might require more pharmacist effort and time to enroll and then interview over the phone. A follow-up study should take this into account and establish strict entry criteria. A long follow-up period would be required to assess the benefit of this intervention. Measurable benefits might include decreased utilization, with fewer ER visits, hospitalizations, and clinic calls over the subsequent 12 months, attributable to better compliance, early detection of adverse reactions, and early detection of inadequate therapeutic effect. A larger study also might confirm the potential for cost savings that were demonstrated in a telephone-care pharmacy program at the Palo Alto Veterans Administration Hospital.[15] Of course, in addition to addressing biases and having a long follow-up period, a control group, as part of a randomized, controlled trial, would be needed to establish the value of this intervention in any follow-up studies.

The results of this study are promising enough to merit a larger, more rigorous study. Currently, the approach described in this pilot has been incorporated into a significantly larger, randomized, controlled study of an intervention employing team care for geriatric patients. Team care is a multidisciplinary, collaborative approach to providing health care that is patient-focused and includes physicians and pharmacists trained in geriatrics.[14] As in the pilot study, participants in this study will receive a phone call from a pharmacist screening for medication-related problems soon after receiving a new prescription from their health care provider. The primary goals of this larger

TABLE 4 List of Medications That Triggered Enrollment
(When a patient received more than one new prescription at the time of enrollment, both new medications are listed.)

1. Lisinopril	25. Pantoprazole
2. Lisinopril	26. Pantoprazole
3. Lisinopril and sertraline	27. Ranitidine
4. Lisinopril and levothyroxine	28. Cimetidine and triamcinolone nasal
5. Captopril	29. Triamcinolone nasal
6. Losartan	30. Triamcinolone nasal spray and triamcinolone inhaler
7. Furosemide/amiodarone	31. Triamcinolone nasal spray and triamcinolone cream
8. Furosemide	32. Triamcinolone nasal spray
9. Furosemide	33. Triamcinolone inhaler
10. Furosemide	34. Hydrocortisone cream
11. Hydrochlorothiazide/triamterene	35. Lorazepam
12. Atenolol	36. Morphine SR
13. Prazosin	37. Propoxyphene
14. Amoxicillin	38. Rofecoxib
15. Amoxicillin and guafenesin	39. Naproxen
16. Trimethoprim/sulfamethoxazole and tolbutamide	40. Choline magnesium trisalicylate and dienesterol
17. Trimethoprim/sulfamethoxazole	41. Sulindac and tylenol with codeine
18. Trimethoprim/sulfamethoxazole	42. Doxepin and sulindac
19. Cephalexin	43. Venlafaxine
20. Cephalexin	44. Donepezil
21. Doxycycline	45. Carbidopa/levodopa
22. Acyclovir	46. Promethazine
23. Cough syrup	47. Mesalamine
24. Hydrocodone/homatropine	48. Oxybutinin

study are improvements in resource utilization and functional outcome and improving physicians' comfort and competence in caring for elderly patients. Similar to the study described in this paper, the investigators in the larger intervention have chosen to focus on a population (patients older than 75 years) rather than a disease.

A follow-up study also may include the use of identifiers in the information system that would warn physicians and clinical pharmacists when high-risk drugs are prescribed for the first time, encouraging discussion among patients, pharmacists, and physicians. A recent study by Bieszk et al. used published guidelines for chronic disease management, including hypertension, diabetes, and congestive heart failure as a basis to develop a medication regimen review process to improve quality of care and reduce polypharmacy.[18]

Guidelines for prescribing in the elderly, such as the list of inappropriate medications that was developed by Beers with a panel of experts,[19] could have a role similar to chronic disease management guidelines. Instead of focusing on a disease, this set of guidelines, like the pilot study described in this paper, focuses on medication use among a population. Pharmacists could refer to this list of inappropriate medications when reviewing new prescriptions. If physician order entry is used, clinical decision support could identify and flag medications from this list, when they are ordered, that are considered inappropriate for seniors.[20] There were several medications (Table 4), including lorazepam, propxyphene, and doxepin, that were prescribed during the enrollment for this study that would have triggered such an alert.

Conclusion

This pilot study has demonstrated the potential benefit of using clinical pharmacists to actively monitor, via telephone, adverse events in elderly patients starting new medications. More than 40% of the patients (20 of 48) in our study had an undesired effect or lack of effect that they revealed to the inquiring clinical pharmacist. The inquiry resulted in a medication change or physician visit for at least 21% of the patients (10 of 48) called. Currently, the value of this inexpensive intervention is being tested more thoroughly on a larger scale.

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DISCLOSURES

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ORIGINAL RESEARCH

Prescription Drug Use Among Elderly and Nonelderly Families

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ABSTRACT

OBJECTIVE: This study augments existing literature by examining characteristics associated with prescription drug utilization and makes an in-depth assessment of family prescription drug economic burden within the United States. The objective of this study was to examine differences in prescription drug use and prescription drug characteristics among elderly and nonelderly families.

METHODS: A measure of out-of-pocket prescription drug burden associated with family prescription drug utilization was constructed using data from the 1996 Medical Expenditure Panel Survey (MEPS). Families were designated as the unit of analysis and further divided by age (<65 and ≥ 65 years) of the reference person. The 1996 MEPS database provides medical expenditure data on a national sample of 8,917 families (22,601 individuals) and 147,308 drug episodes, i.e., prescription procurement. The ratio of family prescription out-of-pocket expenditures to family income was used to assign families to economic burden rank-ordered quintiles, each representing 20% of U.S. families in 1996.

RESULTS: Prescription size, price, and drug use were higher among elderly families. Their proportion of generic use was higher compared to nonelderly families. Additionally, out-of-pocket prescription expenditures represented 23.7% and 45.6% of the total out-of-pocket medical care burden for nonelderly and elderly families, respectively. The average prescription drug burden (total prescription out-of-pocket costs/family income) was 0.4% for nonelderly and 1.9% for elderly households.

CONCLUSION: The study results demonstrate an ability to identify populations with high economic burden for prescription medications. The presumption is that persons age 65 or older, lacking purchasing leverage, are more likely to pay full retail price and, consequently, higher prices. Our findings suggest that high prescription drug burden was a function of prescription size and cost per prescription, with prescription size showing more drastic differences between the high and low prescription drug burden subgroups. Future studies should continue to assess factors influencing families' prescription drug economic burden, and the information derived from these studies should be used by benefit planners in designing drug benefits within health insurance plans.

KEYWORDS: Out-of-pocket costs, Health status, and Generic drug use

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Perhaps one of the most enduring debates in social policy surrounds the addition of a prescription drug benefit to the Medicare program. These debates have been ongoing since the inception of the Medicare program some 35 years ago.[1] Advocates for prescription drug coverage argue that prescription medications should be covered to create a more comprehensive health care plan. Early opposition to prescription drug coverage was largely related to the minimal clinical benefits gained from the use of prescription drugs for treatment of chronic diseases during that time. However, today, the tremendous scientific breakthroughs in understanding the pathophysiology of diseases combined with the development of new pharmaceutical products make prescription drugs an effective form of treatment for acute and chronic conditions.[2] In this analysis, we examined characteristics of prescriptions associated with medication utilization among elderly and nonelderly families with different levels of prescription drug economic burden. We measured prescription drug economic burden as the ratio of out-of-pocket prescription drug expenditures to total family income.

Background

Experiences of receiving and paying for prescriptions are not the same for all consumers. For example, in 1997, uninsured persons aged <65 years spent an average $30.76 out-of-pocket per prescription compared to an average $9.96 spent by an insured person aged <65 years.[3] Miller and Moeller reported differences in the retail cost of medications to consumers across disease categories and insurance groups using the Medical Expenditure Panel Survey (MEPS), the same dataset that is examined in the extant study.[4] Uninsured individuals paid 16.5% higher prices for prescription drugs than did privately insured individuals. Particularly noteworthy is that 28.3% of prescriptions purchased by Medicare beneficiaries were not covered by insurance despite additional sources of coverage such as Medicare health maintenance organizations (HMOs). Poisal and Murray suggest that Medicare beneficiaries without prescription drug insurance often end up paying the highest price for drugs because they do not possess any bargaining power to gain discounts.[5]

The National Institute for Health Care Management Research and Educational Foundation reported that spending on retail outpatient prescription drugs increased by 18.8% in 2000, from $111.1 billion to $131.9 billion.[6] On average, in 1996, consumers purchased 6.94 prescriptions in that calendar year and paid about $35 per prescription. While prescription drugs were second to dental services in the proportion of cost borne by the consumer, 44.5% versus 51.5%, the burden of

prescription drug purchases is more economically significant among the elderly because pharmaceuticals represented a greater proportion of health care expenditures, 12.9% versus 7.8% for dental services.[7] A uniqueness of prescription drug expenditures is that in 1996, they represented about 13.0 % of total health care expenditures. Moreover, 45% of the prescription costs were out-of-pocket spending by the consumer through self-pay for the medication, and cost-sharing requirements, including deductibles, copayments, and prescriptions obtained after expenditure caps are exceeded. In contrast, approximately 18% of total medical expenses were borne by the consumer in 1996.[8] Cost sharing was disproportionately higher for prescription drugs. Prescription medication expenditures represent an extremely skewed distribution of costs borne by consumers since a small subset of the population incurs exceptionally high out-of-pocket expenditures.[9]

Several studies highlight the fact that persons aged >65 years are more vulnerable to medication costs. Older persons experience a greater prevalence of chronic diseases and, hence, consume more medications than their younger counterparts.[10-13] In a study of the financial burden of prescription drugs, persons aged ≥65 years with chronic conditions experienced a higher burden than those without chronic conditions. Those with diabetes spent an average of 4.1% of their household income, and persons with conditions such as heart failure, angina, and ulcers spent between 3.7% and 3.9% of their household income on prescription drugs.[14]

Crystal et al. analyzed out-of-pocket health care expenditures in relation to individual or couples income using data from the Medicare Current Beneficiary Survey (MCBS).[15] Total out-of-pocket health care expenditures averaged 19% of income for Medicare beneficiaries during 1995. Higher-burden subgroups included beneficiaries in poor health, spending 28.5% of income; beneficiaries older than 85 years, spending 22.4% of income; and beneficiaries with income levels in the lowest quintile, including those with Medicaid coverage, spending 31.5% of income. Medicare beneficiaries in fee-for-service programs averaged 23% of income in payment for health care services, and those with self-purchased supplemental insurance averaged 25.5% of income. Beneficiaries possessing employer-sponsored coverage or who were enrolled in HMO's experienced lower burden rates. The 2 highest out-of-pocket health expenditure categories were for medical services at 35.1%, followed by prescription medications at 33.9%.[15]

There is evidence that out-of-pocket prescription drug costs contribute significantly to the health care economic burden. Gross et al. evaluated out-of-pocket health care spending by poor and near-poor Medicare beneficiaries.[16] These consumers spent approximately half of their income on out-of-pocket health care expenditures. Beneficiaries with incomes between 100% and 125% of the federal poverty level spent an estimated 30% of their income on health care if they were enrolled in traditional Medicare and 23% if they were enrolled in a Medicare HMO. An interesting observation is that almost 60% of Medicare beneficiaries with incomes below the federal poverty level did not receive Medicaid assistance in 1997. Therefore, we cannot assume that Medicare beneficiaries with lower incomes have prescription drug coverage through Medicaid programs. The lack of Medicaid coverage would further exaggerate the influence of out-of-pocket expenditures for prescription drugs on overall health care economic burden.

Almost 2.5 million Medicare beneficiaries (30%) lacked prescription drug coverage and spent an average of approximately $546 out-of-pocket in 1998 compared to $325 spent by beneficiaries aged ≥65 years with private or public drug insurance.[5] Lillard, Rogowski, and Kington examined the effects of prescription drug insurance coverage on medication use and expenditures among the respondents aged ≥65 years.[17] Coverage significantly increased the likelihood of use, but not of total expenditures, among those who used prescription drugs. Insurance coverage also lowered out-of-pocket expenditures, consequently decreasing the financial burden on households with respondents aged ≥65 years. Insurance coverage for drugs significantly reduced the fraction of household income spent on prescription drugs by 50%, thereby reducing the family burden.[14]

The bulk of existing literature suggests that those persons aged ≥65 years are significantly burdened, i.e., a large percentage of their household income is dedicated to out-of-pocket prescription drug expenditures. One contradictory indicator of potential excessive burden is the proportion of persons leaving prescriptions unfilled for cost or affordability reasons. Data from the MCBS do not confirm the assumption[18] that elderly individuals are going without medications, and there is evidence suggesting that families with persons aged <65 years, rather than older families, are less able to afford prescription drugs than their counterparts aged ≥65 years.[19]

Methods

Unit of Analysis

Many studies treat economic burden as a measure of hardship, financial risk, or liability. In these studies, economic burden has been used to illustrate the vulnerability of individual consumers and their subsequent need for a prescription drug benefit.[14-16] However, health and medical benefits are generally available to dependents of insured employees, and out-of-pocket expenditures borne by an individual family member often draws upon family household resources. Based on this assumption, we posit that the burden associated with out-of-pocket expenditures is a family burden. In this research, family units were the primary unit of analysis for measures of out-of-pocket expenditures and resources available. (Burden and income for families with a reference person aged ≥65 years would differ from the combined income and burden for a couple aged ≥65 years since families could include dependents or income from family members aged <65 years.) Family was defined as any persons living together

and related to one another by blood, marriage, adoption, foster care, or self-identified as a single unit plus related students who are living away at postsecondary school.[20] In the analysis of prescription drug characteristics, individual prescriptions were the unit of analysis.

Data Source

Data from the Household Component and Prescription Drug Event public use files from the 1996 MEPS database were analyzed in this study. MEPS is a nationally representative survey of health care use including medications, expenditures, sources of payment, and insurance coverage for the U.S. civilian noninstitutionalized population.[20] All estimates are weighted to be representative of the U.S. population. The MEPS sample is a subsample of the 42,000 families included in the National Household Interview Survey. Families with missing data, such as age or income of the reference person, were excluded. Of the 8,917 family units in the 1996 MEPS sample, 418 (4.7%) were excluded by these criteria, resulting in a sample of 8,499 families, including 21,849 of the 22,601 individuals and 145,531 (99%) of the 147,308 prescriptions in the database. Rates of drug use are reported using the total sample, excluding 418 families with missing essential data. In other words, the denominator includes both prescription drug users and nonusers. A cross-sectional analysis was conducted using family-level data, and for some variables such as health status, individual level values were used to construct the family value.

The Prescribed Medication file is unique to MEPS because a pharmacy follow-back survey was used to verify prescription drug use. Prescription drug information was obtained from pharmacy providers frequented by household-sampled persons. The verification process attempted to obtain information for filled and refilled prescription medications. Each pharmacy was asked to provide the following information for each prescription: date the prescription was filled or refilled, the national drug code (NDC), medication name (generic or brand), medication strength, quantity dispensed, total charge, source of payment, and the amount of payment made by each source. Approximately 67% of the household patient-prescription pairs were verified. Further details of the verification methodology are described elsewhere.[21]

MEPS captures the NDC for prescriptions dispensed, while other surveys rely on self-reported descriptions of the medication used. By using NDC-coded data, we were able to explore the prescription characteristics such as generic versus brand name. Additionally, an advantage of the MEPS database over other national expenditure surveys such as MCBS is the availability of data for both individuals and households with persons aged <65 years and ≥65 years. Details on the database are described elsewhere.[20]

Measures

Family prescription drug economic burden. The economic burden of health care expenditures was measured as the ratio of family out-of-pocket health care costs to family income. Versions of this ratio, including individual burden rates, have been used to highlight the need for financial protection against high medical expenditures.[17,22] Prescription drug-specific economic burden scores were calculated by dividing the total family out-of-pocket prescription costs by total family income. Out-of-pocket costs consist of payments for prescription medications such as deductibles, copayments, and the costs for prescriptions obtained after the expenditure cap is exceeded. Prescription drug insurance premium payments were not included in the cost burden associated with prescription drugs.

The Consumer Expenditure Survey's (CES's) definition of family income was used.[23] The definition of family income includes wages and salaries; self-employment income; Social Security, private and government retirement; interest, dividends, rental income, and other property income; unemployment, workers' compensation and veteran's benefits; public assistance, supplemental security income, food stamps; regular contributions for support (including alimony and child support); other income (including cash scholarships, fellowships, or stipends not based on working, and meals and rent as pay).

Prescription drug characteristics. Prescription information such as number of medications was based on drug episodes reported. All prescriptions attributable to any individual with reported age were sorted in subgroups of persons aged <65 years and ≥65 years. Prescription-specific information was achieved by linking NDCs for each episode with U.S. Food and Drug Administration product identification using Multum,[24] a proprietary product used for assigning medications to generic/brand, "Orange Book," bioequivalency, and therapeutic categories.

Family health status. Family health status was assigned by examining each family member and flagging any member reporting fair or poor health status during the calendar year. Therefore, this value represents the percentage of families with at least one individual reporting fair or poor health status. The lowest health status score a person reported in any data collection rounds during a year was chosen regardless of the health status reported in other rounds. The health status variable was constructed using the lower values "fair" or "poor" to assign a low health status to the family.

Family economic barriers. Access to care for a family was determined if any member of the family answered "yes" to questions assessing whether cost was responsible for (1) having difficulty receiving care, (2) not being able to afford the care, or (3) if someone in the family went without care. The percentage of families with at least one person responding yes to any of the 3 economic barrier questions were analyzed for each burden quintile.

Family insurance status. Health insurance status of individuals within a family was determined based on mutually exclusive family coverage categories. The insurance categories were private, public only, and uninsured. Prescription drug insurance is not available in the MEPS public data file. As a result, a proxy measure of prescription drug insurance status

TABLE 1 Prescription Drug Use Among Families*

	All Family Units N = 8,499†	Family Units Age <65 N = 6,768	Family Units Age ≥65 N = 1,680
Drug Expenditures			
Family OOP‡ Rx expenditures	$247.72	$178.93	$524.11
Family income	$42,378	$46,242	$27,982
Family OOP Rx expenditures/income	0.58%	0.39%	1.87%
Family size	2.4	2.6	1.7
Age of household reference person	46.9	40.3	74.6
Families with at least one Rx	83.5%	81.9%	85.1%
Number of Rx's	16.1	13.2	28.0
Family Rx expenditures	$563	$448	$1,028
Share of Rx expenditures OOP	44%	40%	51%
Share of families with 100% Rx OOP§	15.6%	15.3%	16.6%
OOP Rx as % of total OOP Health care	29.5%	23.7%	45.6%
Rx Use‖	N = 147,308	N = 97,234	N = 48,297
Generic Rx¶	37.9%	38.1%	37.5%
Generic Rx expenditures	19.3%	18.7%	20.5%
Retail cost per Rx	$35.00	$34.38	$36.34
Rx Size (number of dose units)	56.8	55.4	59.6
Retail cost per dose unit	$0.62	$0.62	$0.61

Source: 1996 Medical Expenditure Panel Survey (MEPS) – April 2001 release.
** Where appropriate, the family average is reported.*
† Family units subdivided based on age of reference person; 51 families did not report a reference person with age.
‡ OOP: out-of-pocket.
§ Families with no evidence of Rx coverage.
‖ Unit of analysis for shaded values is prescriptions rather than family units.
¶ 2,177 prescription NDC codes did not match brand versus generic classification.

was constructed. Families with no evidence of payment by insurance companies for prescription medications (total cost = self pay) were categorized as lacking a prescription drug benefit, and those with any evidence of third-party payment of prescription drugs were categorized as having a prescription drug benefit.

Data Analysis

For the bulk of the analyses, the surveyed population was divided into 2 family subsamples based on the age (<65 years and >65 years) of the family reference person. Family-level weights provided by MEPS were used in the analyses. The use of weights allows us to project national estimates for the civilian noninstitutionalized U.S. population for 1996 for the variables of interest. The 2 subsamples, based on the age of the reference person for families and personal age for individuals, were ordered by prescription drug burden scores and assigned to one of 5 quintile categories. Those families with prescription drug economic burden scores in the 20th percentile or less were considered as the "low-burden" group. Families with economic burden scores between the 40th and 60th percentile range were considered to have a "middle burden," and those with prescription drug burden scores in the 80th percentile or higher range were considered to be families with "high burden." Comparisons were drawn of prescription drug characteristics between quintile groups.

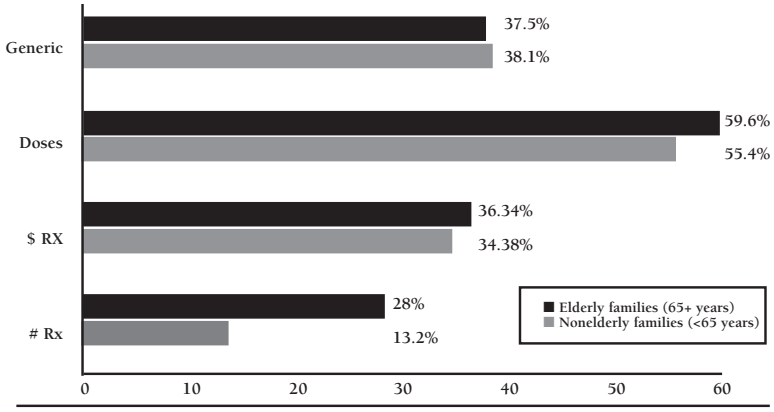
Results

The prescription drug use among families and prescription use characteristics are presented in Table 1 and Figure 1, respectively. This analysis examined 145,531 prescriptions used by 8,499 of the total 8,917 families in the 1996 MEPS database. Variables were weighted such that values represent estimates for slightly more than 4 million families with members aged ≥65 years in each of the quintiles and more than 16 million

families with members aged <65 years. For the 8,499 families in the final sample, the average prescription drug out-of pocket expenditure was $247.72 or 29.5% of total out-of-pocket expenditures for health care. As shown in Table 1, the elderly families' prescription drug expenditures represented 45.6% of the total out-of-pocket expenditures for health care versus 23.7% for the nonelderly families.

The average personal incomes were similar for persons aged ≥65 years and <65 years, $17,786 versus $17,386; however, household or family incomes differed substantially, $27,982 versus $46,242, respectively. The average family with the reference person aged 65 years and older spent $1,028 for medications, with $524 coming from family out-of-pocket resources. Elderly or families with members aged ≥65 years had higher prescription drug expenditures; their share of out-of pocket prescription drug expenditures was 51% versus 40% for the nonelderly families.

FIGURE 1 Prescription Drug Characteristics



Source: 1996 Medical Expenditure Panel Survey (MEPS) – April 2001 release.

Overall, families with any form of public insurance averaged the highest number of prescriptions, 13.4 prescriptions compared to 11.9 prescriptions for privately insured and 6.9 prescription for uninsured families. The families with members aged ≥65 years accounted for a disproportionate share of prescriptions, with 12.6% of the sample accounting for slightly less than one third of all prescriptions. For elderly families, the average prescription was priced 5.7% higher and had 7.6% more doses. Cost per dose was approximately equivalent for elderly and nonelderly families when adjusted for prescription size. On average, the retail cost per dose was about 3% lower, which is a reflection of a larger prescription size, resulting in lower costs per dose, and higher proportion of expenditures represented by generic drugs.

Prescription Drug Burden

Prescription drug characteristics and expenditures across the low-, middle-, and high-burden quintile groups are presented in Table 2. The out-of-pocket prescription drug expenditures in the low- to high-burden quintiles ranged from $21 to $1,476. The corresponding prescription drug burdens ranged from 0.06% to 9.9% for the families with members aged ≥65 years and from 0.0% to 2.0% for families with members aged <65 years.

Prescription drug burden represented about 1% of income for the general population.[25] In this sample, this breaks down to 0.39% for households with persons aged <65 years and 1.87% for those with persons aged ≥65 years (Table 1). However, the distribution of almost all statistics is highly skewed, with a small proportion of individuals experiencing exceptionally high use and expenditures. For example, households with persons aged ≥65 years in the highest-burden quintile averaged 9.9%.[15]

After families were assigned to quintiles, total economic and prescription drug burden ratios were reported as the ratio of the means within the respective categories rather than the average of individual family means. In other words, the subtotal average expenditures were divided by the subtotal average income within each quintile. This mimics the methods used by Crystal et al. and minimizes the distortion caused by extreme scores in this skewed distribution of scores.[15]

In this analysis, the data were not censored and included extreme values that were excluded as outliers in other studies. For example, some researchers top capped expenses at 100% of income on the assumption that resources other than income were used to cover prescription drug expenditures.[15,16] In our analysis, there were 13 families with prescription drug burden exceeding 100% of income (one with only $20 annual income) who were legitimate families representing legitimate expenditures. These families would be dramatically impacted by maximum expenditure caps, and they also influence overall prescription drug burden rates, which were sensitive to extreme scores. Prescription drug burden rates for the highest quintile were higher than they would have been if families with extreme values were excluded. Different methods and the effect of calculating economic burden using ratio of the means versus average of the means are illustrated in Table 3. Based on the analyses, the economic burden was higher for elderly families than nonelderly families irrespective of calculation method.

In Table 4, the differences in medical expenditures, health status, and economic barriers by burden quintiles are summarized. An advantage of using the prescription drug-specific ratio, prescription drug burden, is the ability to examine prescription drug out-of-pocket burden in relationship to the total health care burden. Part of the explanation for the attention to prescription drug burden is the impact on the population older than ≥65 years. Because this population is covered by Medicare, which does not cover medications, the total medical

TABLE 2 Prescription Drug Use Among Families by Age and Burden Level*

	Age ≥65		
	Low Rx Burden§	**Middle Rx Burden‖**	**High Rx Burden¶**
Family Rx Burden			
OOP† Rx expenditures/income	0.06%	1.3%	9.9%
Rx expenditures	$142	$930	$2,131
OOP Rx expenditures	$21	$358	$1,476
Number of Rx's	4.3	27.2	55.4
Percent of Rx generic‡	47.1%	38.6%	43.1%
Percent of Rx expenditures generic	20.4%	17.1%	20.1%
Retail cost per Rx	$33.13	$34.33	$36.88
Rx size	52.7	55.4	62.7
	Age <65		
Family Rx Burden			
OOP Rx expenditures/income	0.0%	0.15%	2.0%
Rx expenditures	$20	$315	$1,263
OOP Rx expenditures	$0	$87	$619
Number of Rx's	0.7	10.6	33.5
Percent of Rx generic‡	61.1%	44.5%	39.2%
Percent of Rx expenditures generic	28.5%	20.5%	18.0%
Retail cost per Rx	$28.89	$29.78	$38.95
Rx size	58.5	58.8	63.3

Source: 1996 Medical Expenditure Panel Survey (MEPS) – April 2001 release.
* *Where appropriate, the family average is reported.*
† *OOP: out-of-pocket.*
‡ *Unit of analysis for shaded values is prescriptions rather than family units.*
§ *Low Rx Burden: Rx burden scores between 0 and the 20th percentile range.*
‖ *Middle Rx Burden: Rx burden scores between the 40th and 60th percentile range.*
¶ *High Rx Burden: Rx burden scores in the 80th percentile or higher range.*

economic burden decreases while the prescription drug burden increases, amplifying the significance of that burden.

Health status in the families with members aged ≥65 years was lower. Fifty-one percent of families had low health status in the high-burden quintile compared to 20% of families in the low-burden quintile. Families with 100% self-pay were used as a proxy for families with no prescription drug insurance. On average, 15.6% of families lacked prescription drug insurance. The incidence of no insurance was highest among the high-burden group for both elderly (19.6%) and nonelderly (15.2%) families. A similar relationship existed with barriers to health care in which a higher percentage of families in both the elderly and nonelderly high-burden groups responded "yes" to having experienced economic barriers to health care (Table 4).

Generic Drug Use

Generic use was highest among low prescription drug-burden families (61.1% of prescriptions), and differences between low- and high-burden families were greater in the families with members aged <65 years (Table 2). Generic expenditures for the elderly families were consistent across quintiles. In the low-burden families with members aged ≥65 years, this was 20.4% versus 20.1% in the high-burden families with members aged ≥65 years. However, the percentages of generic expenditures in the nonelderly families were dramatically different. In the low-burden families, 28.5% of expenditures were for generics compared to 18% in the high-burden nonelderly families. Generic drug use was highest for antimicrobial pharmaceuticals.[4] One possible explanation for highest generic drug use among families with members aged <65 years in the lowest prescription drug-burden quintile is that, in these families, medication use is less frequent and more often for acute care (for example, use of antibiotic drugs among children). Retail cost per prescription and cost per dose were lowest in this group.

TABLE 3 Comparison of Average Rx Burden Scores With the Ratio of the Means

		Total		Age < 65		Age ≥65	
	N	Average of Rx Burden Scores	Ratio of Average OOP* Rx/Average Income	Average of Rx Burden Scores	Ratio of Average OOP Rx/Average Income	Average of Rx Burden Scores	Ratio of Average OOP Rx/Average Income
Person	20,743	1.8%	0.59%	1.4%	0.39%	3.9%	2.1%
Family	8,499	1.16%	0.58%	0.63%	0.39%	3.19%	1.9%

Source: 1996 Medical Expenditure Panel Survey (MEPS) – April 2001 release.

** OOP: out-of-pocket.*

Generic drug use among family units with members aged ≥65 years did not differ across burden quintiles. The highest portion of generic drug use was in the lowest-burden group. The penetration of generic drug use in this population may be reaching the maximum opportunity level with all 3 burden groups using generic drugs to a greater extent than their younger counterparts. Generic drug use in the high-burden group with persons aged <65 years was lower than the low-burden group with persons aged <65 years in both proportion of prescriptions and proportion of expenditures (Table 2). Among those aged ≥65 years, the proportion of generic prescriptions was lower in the high-burden group compared to the low-burden group.

Discussion

Central to this research is the profile of prescription drug use contrasting families with reference members aged <65 years and ≥65 years and low, middle, and high prescription drug-burdened families. Consistent with previous research, consumers aged ≥65 years had higher average prescription costs and subsequent medication use.[12-14] Families in the high prescription drug-burden group purchased more prescriptions and had higher out-of-pocket expenditures and higher total prescription drug expenditures. Since prescription drug burden is the ratio of out-of-pocket prescription drug expenditures to income, the scores varied across quintiles, as expected, with expenditures increasing and income decreasing with higher burden rates. The method selected for computing burden in this analysis, the ratio of average out-of-pocket prescription drug expenses to average earned income, is comparable to that used in previous studies.[13,14]

The economic burden of prescription expenditures calculated at the family level is closer to reality than personal expenditures since discretionary household income is likely to be directed toward the needs of any individual member incurring health care expenses regardless of personal income. The prescription drug-burden ratio standardizes the out-of-pocket costs based on income and represents the relative significance of out-of-pocket prescription costs incurred by families. For example, high-income families with exceptionally high out-of-pocket medication expenses can be as heavily burdened as lower-income families with modest expenditures.

Using the prescription drug-burden ratio to group families dispels some assumptions believed to be associated with out-of-pocket burden. For example, the proportion of generic prescriptions among elderly families is relatively consistent across burden levels. However, the proportion of generics used in nonelderly families is related to burden levels with low-burden families using higher levels of generic prescriptions.

The relationship between health status and prescription drug burden is, as expected, inversely related. The proportion of family members indicating poor or fair health status is more than twice as prevalent in the high prescription drug-burden group compared to the low prescription drug-burden group (51% versus 20% among families with reference person aged ≥65 years). Finally, respondents were asked if they experienced an economic barrier to health care in general. This is not a direct measure of access to prescription medications but reveals an interesting disparity between elderly and nonelderly families, with the nonelderly experiencing higher levels of economic barriers, which is more pronounced in the high-burden families.

A notable observation is the escalation of average prescription cost across the prescription drug-burden quintiles. The number of prescriptions and share of prescription costs paid out-of-pocket for families were positively related to prescription drug burden. Insurance status was reported as medical insurance, in general, and not necessarily prescription drug coverage. Comparisons by insurance coverage were inconclusive. In an effort to assess prescription drug coverage, we counted the number of prescriptions paid entirely by the individual (total cost = self pay) as a marker for no evidence of insurance coverage. The proportion of prescriptions paid by families without evidence of coverage is smaller than what might be expected. Possible explanations are that individuals have alternative sources of help, including clinics or prescription assistance programs not perceived as insurers. The relationship of this variable to prescription drug burden is consistent with expectations in the nonelderly population but not related to prescription drug burden in the elderly.

With the exception of insurance status, this analysis supports the assumption that prescription drug burden is related

TABLE 4 Health Care Use Among Families*

	Low Rx Burden‡	Middle Rx Burden§	High Rx Burden‖
Age ≥65			
Medical Expenditures			
Medical care burden	1.2%	4.1%	14.7%
Total medical expenditures	$2,423	$6,894	$11,926
OOP† medical expenditures	$430	$1,158	$2,193
Share of total OOP expenditures attributable to Rx	4.9%	30.9%	67.3%
Perceived health status (fair or poor)	20.2%	28.0%	51.3%
Individuals responding "yes" to economic barrier to care	2.1%	3.3%	5.0%
Age < 65			
Medical Expenditures			
Medical care burden	.06%	1.3%	4.7%
Total medical expenditures	$1,105	$3,826	$6,874
OOP medical expenditures	$200	$727	$1,430
Share of total OOP expenditures attributable to Rx	0.0%	12%	43.3%
Perceived health status (fair or poor)	7.2%	8.1%	25.7%
Individuals responding "yes" to economic barrier to care	9.6%	9.1%	18.6%

Source: 1996 Medical Expenditure Panel Survey (MEPS) – April 2001 release.

* *Where appropriate, the family average is reported.*

† *OOP: out-of-pocket.*

‡ *Low Rx Burden: Rx burden scores between 0 and the 20th percentile range.*

§ *Middle Rx Burden: Rx burden scores between the 40th and 60th percentile range.*

‖ *High Rx Burden: Rx Burden scores in the 80th percentile or higher range.*

to income, number of prescriptions, health status, and total health expenditures. Prescription drug insurance coverage was not reported specifically, so inferences must be made from measures of medical insurance or evidence of self-pay.

Limitations

This is a cross-sectional research design and, consequently, contains no temporal ordering of information. Therefore, cause-and-effect relationships cannot be identified from the results. Additionally, with the cross-sectional design, trend analyses or forecasting cannot be conducted. The sample excludes institutionalized patients, and 418 families were excluded for missing data. These data include information for respondents who died during the calendar year, and we made no distinction for consumers insured for part of the year. Families insured for part of the year were categorized as insured. It is possible for a family to appear to have no health insurance coverage if they are enrolled in a plan with indemnity coverage and are reimbursed directly by the insurer. This is also true for families never reaching their deductible threshold. It is also possible that uninsured consumers have other than self-pay sources of payment if they are eligible for indigent programs or subsidies from charitable organizations.

In this study, the calculation of prescription drug economic burden did not include premium payments. MEPS, unlike the CES, does not collect information regarding prescription drug coverage premium payments, yet these clearly would be considered part of an overall measure of "burden." Additionally, a measure of prescription drug insurance coverage was constructed by identifying families with no evidence of payment from insurance companies. Our proxy measure for uninsured families was achieved by identifying families paying 100% out-of-pocket for prescriptions. This measure was derived from self-reports within MEPS. However, the probability of paying 100% out-of-pocket favors low-burden families who had fewer prescriptions and, consequently, a higher probability of not reaching their (insurance) deductible threshold.

Additionally, respondents were asked if they experienced an economic barrier to health care in general. This was not a direct measure of access to prescription medications but revealed an

interesting disparity between elderly and nonelderly families. Nonelderly families experienced higher levels of economic barriers that were more pronounced in the high-burden families.

Finally, unlike many other researchers, we did not censor the data but used ratios of the means within categories to accommodate extreme values. Our calculation of cost per dose also differs. Dose units as presented in Tables 1 and 2 do not necessarily represent a prescribed dose since multiple dose units are sometimes consumed. Cost per day of therapy may be a more appropriate and useful measure, but further work needs to be conducted linking MEPS data with a formulary compendium.

Conclusion

The often-stated purpose of a drug benefit is to alleviate beneficiaries of the hardship of out-of-pocket expenditures. Even consumers with drug benefits may have inadequate coverage and substantial out-of-pocket costs associated with prescription drug purchases. The value of insurance coverage is diminished if the drug benefit is designed such that significant hardship is borne due to cost sharing.

The study results demonstrate an ability to identify populations with high economic burden with respect to prescription medications. In this study, we used prescription drug economic burden to examine characteristics of prescriptions used by consumers with higher levels of out-of-pocket expenditures compared to income. The constructed prescription drug economic burden score could be used to compare prescription drug benefit proposals using simulation to calculate prescription drug burden for each proposal. The proposal having the most impact on overall average prescription drug burden would represent the more efficient proposal. The strongest argument for examining policy options using prescription drug economic burden is that it presents an opportunity to facilitate effective health care policy decisions by identifying those policy options that reduce average burden and protect consumers from extreme burden.

With no Medicare prescription drug coverage, the presumption is that the population aged ≥65 years, lacking purchasing leverage, is more likely to pay full retail price and, consequently, higher prices. These data suggest that high prescription drug burden was a function of prescription size and cost per prescription, with prescription size showing more drastic differences between the high and low prescription drug-burden subgroups. Future studies should continue to assess factors influencing families' prescription drug economic burden, and the information derived from these studies should be used by benefit planners in designing drug benefits within health insurance plans.

DISCLOSURES

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Ingonish, Nova Scotia *Photograph by Neil J. MacKinnon, PhD, RPh*

ORIGINAL RESEARCH

Risk of Myocardial Infarction With Combination Antihypertensive Regimens Including a Dihydropyridine Calcium Channel Blocker in Hypertensive Diabetics

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ABSTRACT

OBJECTIVE: The primary objective of this study was to determine if there was an increased risk of myocardial infarction (MI) in a high-risk hypertensive diabetic managed care population receiving combination antihypertensive therapy including a dihydropyridine (DHP) calcium channel blocker (CCB).

METHODS: A retrospective, population-based, case-control study design was used to determine the risk of MI versus the prescribed antihypertensive drug regimen. During 1997-1999, 6,096 diabetics with hypertension were identified. After exclusions, there were 131 "high-risk" study patients who suffered an MI during the study period. These were compared to an equally matched sample. High-risk patients were defined as those with a medical history of previous MI, angina pectoris or ischemic heart disease, or those who had undergone a coronary artery bypass graft and/or angioplasty procedure. Patients were then assigned to Group I cases and controls (DHP use) and Group II cases and controls (no DHP use). Odds ratios (OR) and 95% confidence intervals (CI) were determined for the independent variables and antihypertensive drug regimens. Logistical regression analysis was used to model age, ethnicity, and potential risk factors to identify any differences among calcium channel blockers.

RESULTS: After adjusting for age and gender, the OR for an MI in patients on a combination DHP regimen was 0.75 (95% CI, 0.44, 1.29). The OR for other regimens ranged from 0.52 to 1.16, with no significant difference between antihypertensive drug classes. In comparison to nondihydropyridines (NDHPs), the OR for DHPs was 1.38 (95% CI, 0.54, 3.54), but it was determined to not be statistically different (P=0.5065).

CONCLUSION: No increase in risk of MI could be determined with the use of a combination antihypertensive regimen including a DHP CCB when compared to other antihypertensive drugs in a matched high-risk population of patients with hypertension and diabetes. Choice of antihypertensive drug regimen may be less important than strategies that focus on achieving optimal disease outcomes to reduce the incidence of MI and hospitalization and lower health care costs in this high-risk population in managed care.

KEYWORDS: Calcium channel blockers, Dihydropyridines, Nondihydropyridines, Myocardial infarction, Diabetes mellitus, Hypertension

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Cardiovascular (CV) disease is the leading cause of morbidity and mortality in the United States. More than 30% of patients who suffer a myocardial infarction (MI) do not survive. Diabetic patients have an increase in the risk of coronary heart disease and MI mortality. Recent data suggest that even without a history of heart disease, type 2 diabetics have as high a risk for an MI as nondiabetics with a prior MI.[1] Additional risk factors such as age, gender, obesity, smoking, hypertension, and hyperlipidemia can further increase this risk. More aggressive treatment of diabetes mellitus, hypertension, and hyperlipidemia is recommended.

It is estimated that there are more than 11 million diabetics with hypertension in the United States who often require combination drug therapy to control their blood pressure. Though an angiotensin converting enzyme inhibitor (ACEI) is considered the initial drug of choice in patients with diabetes mellitus and hypertension because of its nephroprotective effect, the calcium channel blockers (CCBs) are also recommended by the Joint National Committee VI and are used extensively in combination therapy because of their favorable metabolic side-effect profile.[2] A concern about the safety of CCB agents in coronary heart disease has been the focus of recent clinical research. Several meta-analyses demonstrated a dose-related increase in MI risk with short-acting[3-5] and possibly intermediate-acting dihydropyridine (DHPs).[6]

Follow-up studies have focused on assessing the risk of long-acting DHPs on adverse cardiovascular outcomes with mixed results. Alderman et al.[5] found no increase in CV risk with long-acting CCBs in a matched case control study (adjusted odds ratio (OR) = 0.76, 95% confidence interval (CI), 0.41, 1.43). Two clinical studies in a hypertensive diabetic population suggest no adverse effects of DHPs, but perhaps even a beneficial one.[7,8] One study[9] and a meta-analysis[10] suggest that aggressively lowering the blood pressure may be more important than the choice of the antihypertensive agent(s).

In contrast, 2 prospective, randomized controlled studies suggest that hypertensive type 2 diabetics given the newer long-acting CCBs may be at a higher risk of an MI compared to other antihypertensive medications.[11,12] Pahor et al.[13] completed a meta-analysis from 9 randomized clinical trials with an aggregate population of more than 27,000 hypertensive patients. After an average 2-year follow-up period, there was a 31% increase in the risk of MI with DHP CCBS compared to other antihypertensive agents. The average increase in MI risk in diabetics was 51%.

These are unexpected findings since CCBs have been shown to have a favorable effect on atherosclerosis and stroke, exclusive of their blood pressure-lowering effect.[10,13] If there is an adverse CV effect with the DHPs, the mechanism is unknown but may be related to sympathetic activation caused by the reflex tachycardia. Are there different therapeutic effects on different CV risk factors? These disparate findings suggested the need to reevaluate the benefit versus risk of CCBs, specifically the DHPs, in hypertensive diabetics with coronary artery disease.

The primary objectives of the study were to (1) compare the risk of MI in high-risk type 2 diabetics receiving combination antihypertensive therapy with a DHP CCB versus other therapies for hypertension in a matched population of high-risk patients; and (2) assess the impact of such variables as age, gender, ethnicity, vital signs, laboratory tests, previous history of CV events, and concurrent medications on the relationship between CCBs and MI. A secondary objective was to compare the risk of MI between DHPs and nondihydropyridines (NDHPs).

Methods

This study followed a retrospective, case-control, matched analysis design. Data were collected from the membership, pharmacy dispensing, and claims database contained in the computerized Kaiser Permanente-Georgia (HMO) data warehouse. Information concerning ethnicity, smoking history, vital signs, and laboratory data was collected from patient chart review when available.

The primary outcome measurement was the incidence of MI. The null hypothesis for this study was that there was no difference in the incidence of MI in high-risk diabetic patients maintained on therapy with a combination antihypertensive regimen including a DHP CCB for hypertension compared to those patients on alternate antihypertensive treatment. Odds ratios and 95% CIs were computed. The null hypothesis was accepted if the OR and CIs were ≥1.0. Statistical significance was defined as a *P* value less than .05.

Patients with diabetes and hypertension were classified into cases with an MI (by ICD9 code 410) or matched controls without an MI diagnosis. The diagnosis of diabetes was consistent with criteria used by Health Plan Employer Data and Information Set (HEDIS) and by the HMO's Diabetes Population Care Registry. Hypertension was defined by a minimum of 2 documented encounters and a minimum of 3 months of continuous use of any antihypertensive medications during the time that the member was also identified as having diabetes.

Inclusion criteria for the case-study patients was as follows: aged 30 to 75 years at the time of MI who were members of the HMO for a minimum of 6 months prior to the MI and had a diagnosis of both diabetes mellitus and hypertension (information was in the database) during the 3-year period from January 1, 1997, through December 31, 1999. Controls were identified from the database as patients aged 26 to 79 years as of December 31, 1999, with a diagnosis of diabetes mellitus and hypertension, but without an MI diagnosis during the study period.

Cases and controls were further divided into "high-risk" patients, defined by ICD9 code as all patients with a prior history of ischemic heart disease, angina pectoris, percutaneous transluminal coronary angioplasty, (PTCA) coronary artery bypass graft (CABG), or prior MI. We assumed that an adverse cardiovascular effect associated with a DHP medication regimen would most likely be seen in this population.

Controls were then matched to cases based on the enrollment eligibility of high-risk controls compared to the MI date of each case. For each case-MI date, a pool of controls was generated such that each possible control had to be enrolled in the HMO for the 6 months prior to the MI date. From this pool, one control patient was randomly selected without replacement and assigned the MI date as the index date. This process was repeated for each case. Index date is thus defined as the date of the MI for the cases and the assigned date for the matched controls. Controls were matched 1:1 with MI cases because of resource limitations on patient chart review.

The following patients were excluded from selection for cases and controls: patients with less than 6 months of continuous enrollment prior to the index date, patients treated for hypertension for less than 3 months prior to the index date, and noncompliance to prescribed treatment for hypertension. Patients were considered noncompliant if, according to the pharmacy dispensing records, their refill rate was less than 67% for any antihypertensive prescription.

All patients were then assigned to one of 2 arms of the study, based on their antihypertensive regimen: Group I cases and controls—which included any regimen (monotherapy or combination therapy) with a DHP; all DHPs were grouped in cases and controls to determine a class OR. Group II cases and controls—which included any other antihypertensive drug regimen that did not include DHPs such as diuretics, beta-blockers, ACE inhibitors (ACEIs), angiotensin receptor blockers (ARBs), NDHPs, alpha adrenergic blockers, and clonidine. Although most patients were on combination therapy, the use of DHP was excluded from the Group II comparison group. NDHPs consisted of verapamil and diltiazem and were initially included in Group II.

Covariates for all matched cases and controls included age at the time of the event, gender, and medication use. Documentation was made separately for insulin therapy, oral hypoglycemics, estrogen replacement therapy, lipid-lowering therapy, and antiplatelet therapy (aspirin, ticlopidine, or clopidrogel). In order to better define disease control in the matched cases and controls, information from the patient medical record such as ethnicity, smoking status, vital signs (body mass index, systolic/diastolic blood pressures), and laboratory data (lipid profile, HbA1c, microalbuminuria) was collected for up to 12 months prior to the index date. Vital signs and laboratory data were averaged for statistical analysis.

Statistical analysis, utilizing SAS software, included determining the *P* values of potential covariables and an OR of having an MI among cases and controls on therapy with DHPs compared to other antihypertensive therapies. Contingency tables with chi-square analysis were computed on the covariables to determine the level of significance (*P* value) of any differences in the OR utilizing observed versus expected frequencies of the primary outcome, controlling for age and gender.

Mantel-Haenszel ORs adjusted for age and gender were used to measure the association between independent variables and the incidence of MI. A forward, step-wise, logistical regression model utilizing MI as a function of ethnicity, CV risk factors, and antihypertensive drug use was performed to test for independent risk factors as well as the OR of MI in DHP and NDHP cases and controls.

Results

From the Kaiser Permanente database, 10,399 patients (Figure 1) with a diagnosis of diabetes mellitus were identified for the 3-year study period. Of these, 6,096 (58.6%) were identified as having a diagnosis of hypertension. The initial data sample consisted of 299 patients (4.9%) with an MI diagnosis and 5,797 controls who did not suffer an MI during the study period.

Of this sample, 272 cases were considered "high-risk" by previously stated ICD9 criteria, and 961 controls were likewise considered "high-risk."

After exclusions for drug noncompliance, 135 cases and 876 controls were identified. From the controls, 135 patients were randomly selected based on the index date of the MI of the matched case. Two patients from the cases and 2 patients from the controls were prescribed more than one CCB during the 3-month time frame prior to the index date and were excluded (along with their matched cases/controls) from further analysis, resulting in a matched-pair sample of 131 patients in each group.

For a high-risk population, the blood pressure, hemoglobin A1c, and lipid profile were reasonably well controlled among the cases and controls (Table 1). These values and other variables were converted to dichotomous variables for chi-square analysis. Insufficient sample size or missing data and/or charts eliminated smoking, microalbuminuria, antiplatelet drug, and hormone use from further analysis.

As seen in Table 2, there was a higher percentage of whites with an MI versus African Americans in the cases (*P*=0.011). As expected, there was a higher incidence of prior MI (*P*<.001), CABG (*P*<.001), and PTCA (*P*=0.004) among the cases. There was no statistical difference in other variables for the cases and controls, including the use of insulin, oral hypoglycemics, and lipid-lowering medication. In the univariate analysis, Group II cases were less likely than their controls to be on an NDHP (*P*=0.023). For statistical analyses, ARBs were combined with ACEIs, and clonidine and alpha-blockers were combined into an "other" category.

Of the 131 cases with MI, 35 patients were on combination therapy with some type of DHP (Group I). The Group I cases consisted of nifedipine (18 patients), felodipine (8 patients), amlodipine (6 patients), isradipine (2 patients), and nicardipine (1 patient). Though considered an intermediate-acting DHP, isradipine was included in the cases and controls. Due to small sample size and patients on multiple DHPs, analysis of dose was not completed. As expected, few Group I cases (8.6%) were on monotherapy; 77.1% (n=27) were prescribed a beta-blocker (n=10), an ACEI (n=10), or both (n=7).

Of the Group I controls, 42 patients were on a DHP, including nifedipine (21 patients), felodipine (13 patients), amlodipine (7 patients), and isradipine (1 patient). For the Group I controls, 11.9% (n=5) were on monotherapy; 71.4% (n=30) were prescribed a beta-blocker (n=6), an ACEI (n=16), or both (n=8).

There were 96 Group II cases and 89 Group II controls consisting of patients who were not taking a DHP within 3 months prior to the index date. For the Group II cases, 87.5% (n=84) were prescribed a beta-blocker (n=18), an ACEI (n=47), or both (n=19). For the Group II controls, 80.1% (n=72) were prescribed a beta-blocker (n=18), an ACEI (n=34), or both (n=20).

The ORs for the difference in variables and the risk of MI after adjusting for age and gender are listed in Table 3. As expected, the OR for an MI increases with the presence of a prior MI, PTCA, and/or CABG. The calculated ORs among the various antihyperten-

TABLE 1 Age, Gender, Ethnicity, Laboratory Data, and Vital Signs Among MI Cases and Controls

	Cases	Controls
Patient Demographics		
Age (years)	58.3 (±9.1)	59.9 (±9.7)
Males	69%	63%
Females	31%	37%
White	68%	49%
African American	29%	47%
Clinical Characteristics		
BMI*	31.7 (±5.9)	32.8 (±6.6)
HgbA1c†	8.6 (±2.3)	8.6 (±2.0)
Total cholesterol‡	213.2 (±65.1)	213.9 (±48.7)
HDL‡	41.0 (±11.7)	44.8 (±12.8)
LDL‡	125.9 (±53.9)	122.4 (±42.2)
SBP§	134.8 (±17.2)	142.3 (±17.4)
DBP§	78.1 (±9.9)	81.5 (±9.5)

* *Body mass index (BMI) values in kg/m2.*
† *HgbA1c values in %.*
‡ *Total cholesterol, HDL, LDL values in mg/dL.*
§ *Systolic blood pressure (SBP) and diastolic blood pressure (DBP) values in mm Hg.*

sive drug classes were not statistically significant and ranged from a low of 0.52 with NDHPs to a high of 1.16 with ACEIs. The OR of drug regimens containing a DHP was 0.75 (95% CI, 0.35, 1.62). No Group I or Group II antihypertensive drug class or combination appeared to increase the risk of MI.

A summary of the combination therapies for the cases and controls is listed in Table 4. To test for concurrent antihypertensive medications as a confounding variable, 2 x 2 contingency tables were developed for Group I and Group II cases and controls on beta-blockers, ACEIs, diuretics, and other antihypertensives. This analysis demonstrated that there was not a significant difference between groups on all combinations, at the 95% confidence level. Thus, these drugs, especially the beta-blockers and ACEIs, did not appear to attenuate the risk of recurrent MI among those patients on DHP combination therapy for their hypertension.

To test for multiple CV events as a confounding variable, 2 x 2 contingency tables were developed for Group I and Group II cases and controls for patients with prior MI plus additional CV events/risks, CABG, and/or PTCA (excluding MI), and ischemic heart disease (excluding MI, CABG, PTCA). These were chosen as surrogate markers for the extent of CV disease. As seen in Table 5, this analysis demonstrated that there were no differences between groups with various CV events and risks at the 95% confidence level.

A logistical regression model was then developed to test for differences between Group I DHP and Group II NDHP cases and controls. The results of the modeling are listed in Table 6. The model could not incorporate laboratory values or vital signs because of subset sample size. Variables that significantly increased the risk of an MI on a CCB included ethnicity (whites) and those patients with more than 2 CV risk factors. When compared to the NDHPs, the DHPs were less protective (OR 1.38, 95% CI, 0.54, 3.54), but the difference did not reach statistical significance.

Discussion

CCBs consume a high percentage of the antihypertensive drug budget of most managed care organizations. These medications are widely prescribed due to their convenient once-daily dosing, neutral effect on glucose and lipid profiles, relatively low incidence of side effects, and high efficacy in elderly and African American populations. Beta-blockers and ACEIs continue to be preferred drugs because of their cardioprotective and nephroprotective effects in patients with heart disease and diabetes. However, many patients need combination therapy to reach the aggressive blood pressure goals (<130/80 mm Hg) required for a high-risk diabetic hypertensive—is it safe to add a DHP CCB to a diuretic, an ACEI, or beta-blocker regimen?

Our results did not identify a significant difference in the incidence of MI in this high-risk population between DHP combination therapy and other antihypertensive drug regimens. These results are in agreement with some previous studies.[5,7,8] In

TABLE 2 Statistical Comparison of the Frequency of Variables in Patients for Myocardial Infarction in Group I (DHP Exposure) and Group II (No DHP Exposure) Cases and Controls

Variable	Chi Square	*P* value
Age (≤50 vs. >50)	1.315	0.252
Gender (male vs. female)	1.083	0.298
Ethnicity (white vs. African American)	6.539	0.011
BMI (<28 vs. ≤28)	1.038	0.308
Hgb A1c		
<7.0	0.697	0.404
7.0-7.9	2.336	0.126
>7.9	0.271	0.603
HDL (<35 vs. ≥35)	1.120	0.290
LDL		
<100	0.050	0.823
100-130	1.302	0.254
>130	1.790	0.181
Systolic blood pressure (<130 vs. ≥130)	0.018	0.893
Diastolic blood pressure (<80 vs. ≥80)	2.391	0.122
Insulin (yes vs. no)	0.790	0.374
Oral hypoglycemics (yes vs. no)	0.382	0.537
Lipid-lowering drugs (yes vs. no)	0.268	0.605
Prior MI (yes vs. no)	14.672	<0.001
PTCA (yes vs. no)	8.264	0.004
CABG (yes vs. no)	11.905	<0.001
Angina pectoris	0.00	1.000
Ischemic heart disease	3.47	0.063

TABLE 3 Measurement of Association Between Significant Independent Variables and Myocardial Infarction, Adjusted for Age and Gender

Independent Variable	Odds Ratio (Mantel Haenszel)	Confidence Interval (95%)
Prior MI	2.70	1.61 - 4.54
CABG	3.93	1.71 - 9.02
PTCA	2.46	1.25 - 4.83
Dihydropyridines	0.75	0.44 - 1.29
Nondihydropyridines	0.52	0.28 - 0.97
Beta-blockers	1.01	0.62 - 1.64
ACEIs	1.16	0.70 - 1.91
Diuretics	0.92	0.56 - 1.51
Others	0.88	0.47 - 1.65

TABLE 4 Number of Patients on Combination Antihypertensive Therapy* in Group I (DHP Exposure) Cases and Controls Versus Group II (No DHP Exposure) Cases and Controls

	Group I		Group II		
Medication	Cases (N=35)	Controls (N=42)	Cases (N=96)	Controls (N=89)	*P* value
Nondihydropyridines	0	0	20	35	N/A
Beta-blockers	10	6	18	18	0.593
ACEIs	10	16	47	34	0.130
Diuretics	15	25	55	49	0.142
Others†	6	12	18	15	0.248

* *Columns do not add to sample size due to multiple combination drug therapy.*
† *Other drugs include clonidine and alpha adrenergic blockers.*

TABLE 5 Number of Patients With Major Cardiovascular Events in Group I (DHP Exposure) Cases and Controls Versus Group II (No DHP Exposure) Cases and Controls

	Group I		Group II		
CV Event/Risk	Cases (N=35)	Controls (N=42)	Cases (N=96)	Controls (N=89)	*P* value
Prior MI+*	13	9	48	20	0.459
CABG and/or PTCA†	10	4	18	12	0.691
Ischemic heart disease‡	9	23	29	52	0.577

* *Includes MI plus CABG and/or PTCA and/or ischemic heart disease.*
† *Excludes MI.*
‡ *Excludes MI, CABG, PTCA.*

addition, some studies[11,12] have reported that patients receiving a DHP CCB may have an increased risk of MI.

It is possible that the DHP MI cases may have had a shorter duration of hypertension or diabetes. The Group I DHP patients did not appear to have less severe CV disease compared to Group II (no DHP) patients on other antihypertensive drugs, but undetected differences in complex cases with more than one CV event and multiple combination antihypertensive therapy may have been present; i.e., one drug in the combination could offset the effects of another drug. The higher OR (1.16) detected for ACEIs may have been a surrogate marker for more advanced diabetes with renal complications.

In our study, NDHPs appears to be associated with a lower OR (0.54) than DHPs (0.75) though CIs overlapped, and the results did not reach statistical significance. Further comparative analysis of this group of patients in a larger sample is necessary. Unexpectedly, white patients were more likely to suffer an MI on a CCB than African American patients, based upon the results of the logistical regression analysis. Ethnic differences should be further explored in future studies.

The strengths of the study were (1) both study and control populations were well matched by eligibility criteria and comparable by age, gender, vital signs, and biochemical laboratory tests; (2) cases and controls were well controlled in terms of control of their diabetes, hypertension, and hyperlipidemia; and (3) compliance was assessed by checking pharmacy dispensing records, thereby increasing the reliability of determining whether the case and control groups were taking the prescribed antihypertensive medication(s).

Limitations

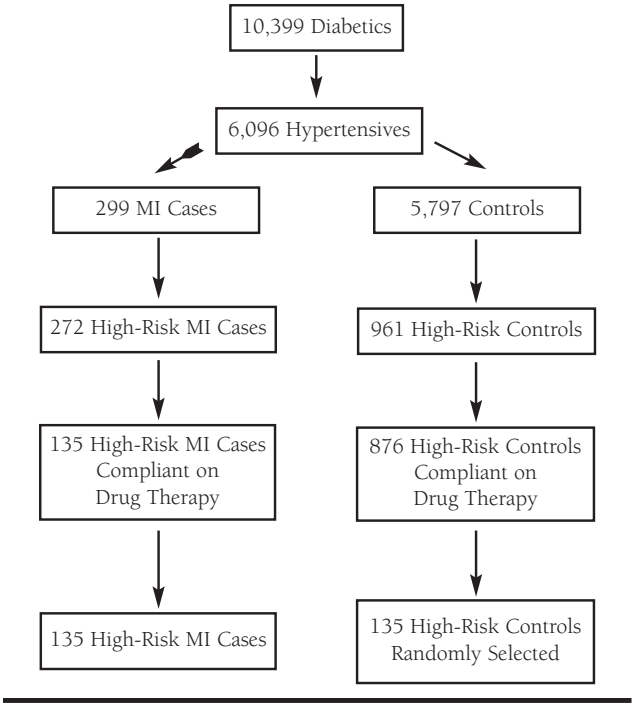
The limitations of our study are (1) the retrospective case-control design limits control of all covariables, and the sample size limits power; (2) most patients were on combination therapy and, therefore, the OR is reported in "marginal" as opposed to "absolute" terms, though no differences were noted on combination therapies; (3) the duration of drug exposure was variable from a minimum period of 3 months, and the effect of dose was not analyzed; and (4) there were both missing charts and data for variables such as ethnicity, smoking status, vital signs, and laboratory tests. For example, in 37 MI cases (and 48 controls), ethnicity could not be determined, thus it is possible that a disproportionate amount of minorities may have been in the missing data.

An unexpected finding was that almost 6 times as many

TABLE 6 *Logistic Regression Model for the Effect of Calcium Channel Blockers on the Subsequent Occurrence of Myocardial Infarction in High-Risk Patients*

Risks	Comparison	OR	CI (95%)	*P* Value
Age	>50 vs. ≤50	0.55	0.21 – 1.46	0.23
Ethnicity	White vs. African American	0.50	0.25 – 1.00	0.05
# CV risks	>2 vs. 1-2	5.22	2.34 – 11.64	<0.0001
Drugs	**Comparison**	**OR**	**CI (95%)**	***P* Value**
All CCBs	Yes vs. No	0.65	0.34 – 1.26	0.21
DHP CCBs	Yes vs. No	0.75	0.35 – 1.62	0.46
NDHP CCBs	Yes vs. No	0.54	0.23 – 1.28	0.16
Type CCB	DHPs vs. NDHPs	1.38	0.54 – 3.54	0.51

FIGURE 1 *Study Design*



high-risk "case" patients with an MI were excluded from the analysis (137 of 272, or 50.4%) due to noncompliance compared to "control" patients (85 of 961, or 8.8%) who did not suffer an MI (Figure 1). This suggests that identifying reasons for noncompliance (lack of patient education, high cost, side effects) and keeping high-risk patients out of the hospital should become a high priority for a managed care organization. Strategies to assure patient education and compliance may be important pharmacy initiatives in such a high-risk population.

While an increase in CV risk was not identified with the DHP CCBs in our study, it is possible that this class of agents may increase the long-term risk of diabetic complications by increasing proteinuria. Results from 2 recent studies suggest that ACEIs are much more nephroprotective than DHPs in both hypertension[14] and diabetes.[15] A comparison of the safety and long-term efficacy of CCBs with lower-cost alternatives remains an important issue for managed care organizations. The recently released results of the National Heart, Lung, and Blood Institute-funded Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial study may provide the necessary evidence-based medicine to address this important issue.

Conclusion

Combination therapy with a DHP CCB did not appear to have a deleterious effect on increasing the risk of an MI in a high-risk diabetic, hypertensive population. Further research in prospective, randomized, double-blind clinical trials with more patients is needed to determine if monotherapy or combination therapy with the various CCBs are safe and cost effective for long-term use. Strategies should continue to be focused on achieving optimal disease outcomes and maximizing patient compliance to more effectively reduce the incidence of MI and hospitalization and lower health care costs.

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ORIGINAL RESEARCH

Analysis of a Prescription Drug Prior Authorization Program in a Medicaid Health Maintenance Organization

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ABSTRACT

OBJECTIVE: To determine the factors important in approving prescription reimbursement under prior authorization (PA) in a Medicaid managed care organization (MCO).

METHODS: A cross-sectional statistical analysis was performed using administrative data for one month of PA requests to an MCO with more than 250,000 Medicaid recipients in the northeast United States.

RESULTS: More than 95% of PA reviews resulted in payment for the originally prescribed products. The most common treatments involved were atypical antipsychotics, antacids, antidepressants, antihypertensives, anticonvulsants, and Cox-2 inhibitors. The rejection rate for nonformulary products was 7.1% while that for formulary products was 3.7%. Nevertheless, most drugs requiring PA were formulary-listed, with protocols to reinforce prescription guidelines. Rejection of reimbursement was inversely related to patient age. Most likely to be authorized were drugs for smoking cessation, pain, and nausea, while those least likely to be approved were multivitamins, sleep aids, and high-cost antidepressants.

CONCLUSION: Although nonformulary products are more frequently subject to PA, 78.6% of PA procedures are performed in response to requests for formulary-listed products. The PA rejection rate for this Medicaid MCO was small; 4.4% overall and 7.1% for nonformulary versus 3.7% for formulary drugs.

KEYWORDS: Pharmaceuticals, Prior authorization, Managed care, Medicaid, Reimbursement, Formulary

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The purpose of this study was to determine whether and under what circumstances prior authorization (PA), a labor-intensive administrative procedure, results in approval of the PA. The specific research questions are: (a) How frequently does the PA procedure result in denying reimbursement for a prescribed drug, and (b) What are the factors that predict reimbursement denial in a PA intervention program?

Health plans and health policy analysts are interested in whether or not PA programs affect the original prescription rate and the actual utilization rate of affected drugs, given the expensive and administratively intensive nature of these procedures. The null hypothesis is that PA of drugs does not significantly affect the utilization rate of prescribed pharmaceuticals. Second, the vast majority of PAs are approved, regardless of therapeutic class or patient characteristic. A corollary to the null hypothesis is that no particular drug class or patient age and gender has any relationship to the outcome of PA.

Even if the null hypothesis is true, a PA program may give rise to a "sentinel effect" in preventing prescribing of drugs on the list of PA drugs. This effect could be well worth the cost of the administration of the program, but this question is beyond the scope of the present project and has been documented elsewhere.[1]

Background

The Prior Authorization Procedure for Pharmaceuticals

Since no two drugs are exactly alike in their efficacy and safety for particular patients, health plans with formularies use management tools such as PA to influence prescribing for certain drugs. In this procedure, physicians call the health plan to obtain authorization to prescribe a drug on the PA list for a particular patient because the prescriber believes that the drug is the most appropriate treatment for that patient. Health plan staff typically review patient characteristics, diagnosis, and prescription history and adjudicate the physician's request. A question of major importance is whether this procedure really changes the ultimate outcome in terms of the patient receiving the originally prescribed medication. A secondary question is whether there is a difference between formulary-listed drugs and nonformulary drugs in the frequency with which PA is used and in the frequency with which this procedure actually reverses prescription choice by denying reimbursement on the basis of formulary status.

In 1997, 87% of all managed care organizations (MCOs) used PA.[2] By 1999, this had increased to 88.3%. A breakdown of the use and results of PA by MCOs of various types is shown in Table 1.[3]

According to the 2000 Novartis Pharmacy Benefit Report,[3] plans with closed formularies, such as the extant

TABLE 1 Use of PA by Health Plan Lines of Business

	Commercial/ Group	Medicaid	Medicare	Overall	Research Site HMO
Use PA	94.1%	82.9%	81.4%	88.3%	Yes
Apply to select therapeutic classes	79.8%	67.9%	81.8%	77.9%	All classes
Average number PAs requested PMPM	0.08	0.03	0.14	0.08	0.09
Average % of approvals	74.0%	81.0%	69.0%	74.0%	95.6%

Sources for national figures: Novartis Pharmacy Benefit Report.[3]

research site health maintenance organization (HMO), a Medicaid MCO, report the highest number of PAs and the lowest percentage of approvals. In this regard, the extant research site HMO data from January 2001, analyzed in this report, appear to be in line with expectations in terms of the number of PAs but far above national figures in terms of the numbers of requests that are approved. As noted below, figures for the research site HMO reflect the final rejection rate after any appeals.

A pharmacy benefit manager owned by the PacifiCare Health Systems reported to a congressional subcommittee[4] that their data (which were not provided to the committee) showed that PAs for nonformulary products occurred in only 1% of claims, and 75% of these requests were approved. One may reasonably speculate that this low request rate for nonformulary products may illustrate a sentinel effect[1] in which physicians were "alerted" to either the formulary status of drugs in local health plans by their patients through health plan communication or through prior experience with PA denials. For example, IMS Health, a national vendor of prescription data, offers a proprietary service to pharmaceutical firms[5] based on the precept that managed care formularies exert an influence in local markets beyond their membership where they have a significant share of membership because doctors become used to prescribing according to their formularies. Off-formulary prescribing for members that comprise a significant portion of physician practices results in frequent patient complaints about lack of reimbursement, which usually leads to the prescribing of an alternative drug with better coverage under the patient's plan or PA procedures.[6] As mentioned below, health plans rely on the sentinel effect to reduce nonformulary prescribing to a point where PA approval rates are high but nonformulary claim volume is low. The latter consideration needs to be figured into cost-benefit calculations for PA justification.

Managed Care Organization Formularies and Prior Authorization of Pharmaceuticals

In recent years, pharmaceutical costs have outstripped most other aspects of health care in cost growth. MCOs have primarily used 2 tools in their efforts to control pharmaceutical budget growth: formularies and PA, which tend to work synergistically. The effect of PA in controlling utilization, the focus of this research, needs to be understood in the context of the health plan's formulary.

The PA of pharmaceuticals by health plans is controversial. Health plans maintain that PA helps to curb inappropriate drug use through its sentinel effects. Critics answer that it raises administrative costs for all affected parties. Health plans report costs of $10 to $25 per authorization request while more than 80% of the requests are approved.[2] Some doctors see PA as threatening to their independence and authority in diagnosis and treatment. Some patients may consider PA to be interference with their right to receive the best quality medical care. Pharmaceutical companies consider PA an unnecessary barrier to access to their products. Pending legislation in various states could influence procedures to overturn PA denials, the length of time in which a coverage decision must be rendered, disclosure of denials to patients and doctors, and many other rules that will drive up the cost of the PA procedure. It is reasonable to question whether cost savings from the procedure offset the administrative expense and whether drug PA in a litigious environment invites avoidable complaints and lawsuits by interfering with the practice of medicine by denying prescription reimbursement.

In spite of these doubts and pitfalls, the use of PA appears to be growing, attendant to the increased use of drug formularies by employers and health plans. In 2000, nearly all HMOs and the vast majority of preferred-provider organizations (PPOs) used drug formularies.[7] This observation is consistent with personal communications from various sources, including executives at CIGNA HealthCare, with a large commercial population, who claim that PA has restrained per-member-per-month (PMPM) costs for Cox-2 inhibitors (rofecoxib and celecoxib) in CIGNA programs that include PA.[8]

Effect of a Closed Formulary in a Commercial HMO

In a recent study, Motheral et al. reported on the utilization and financial impact of a commercial HMO's closed formulary.[9] In this retrospective cohort study with a pre-post design, formulary cases (patients) had a higher generic drug refill rate, lower total

TABLE 2 Frequencies of Variables

Variable	Value	Frequency	Percentage
Formulary status	Yes	17,308	78.6%
	No	4,701	21.4%
Reimbursement status	Paid	20,888	94.9%
	Adjusted	147	0.7%
	Rejected	974	4.4%
Patient age	Children (0 to 17)	2,581	12.4%
	Young adults (18 to 34)	2,870	13.7%
	Early middle age (35 to 50)	6,687	32.0%
	Later middle age (50 to 64)	5,215	25.0%
	Elderly (65+)	3,527	16.9%
Gender	Male	9,023	41.0%
	Female	12,986	59.0%

claims, and lower mean brand claims in the postformulary period than matched controls, controlling for age, sex, chronic disease score, and utilization in the preformulary period.

One of the study-dependent variables was the mean number of PAs per subject, defined as the total number of PAs divided by the number of months of eligibility during the research period. With the implementation of the formulary, the closed formulary group had a greater increase in the mean number of PAs per patient-month ($P<0.0001$). Not surprisingly, PAs tend to be more frequent under closed formularies. Because PA and formulary coverage can affect commercial HMO enrollment decisions, as noted above, but not Medicaid program enrollment, the effects of the application of the PA procedure in commercial and Medicaid programs may not be completely comparable.

Consumer Perceptions of Prior Authorization Programs

Another recent study by Momami et al. explored consumer perceptions of 4 drug management strategies, including PA.[10] This study used a cross-sectional mail survey design that targeted MCO enrollees residing in the mid-Atlantic region. Reporting on the results, the authors state:

> "…[R]espondents mildly agreed that PA limits their access to the best medications….They felt neutral that this policy results in less-effective medications, compromises the quality of their drugs, and affects their compliance with their drugs. Finally, respondents mildly disagreed that PA makes it more convenient to get the prescribed drugs. Respondents' overall attitude toward PA was somewhat negative."

Furthermore, the authors reported that PA was one of the factors that motivated members to join or leave an HMO, and members of more liberally managed plans such as PPOs were more likely to ask their pharmacists questions about PA.

These data suggests that many patients find the PA procedure at least moderately annoying and potentially a factor in member dissatisfaction and plan disenrollment. However, it was not viewed as negatively in this particular study as the imposition of a formulary itself, which of course often results in increased PA. As noted above, consumer perceptions of PA could effect enrollment in a commercial plan but not a Medicaid managed care program, and this could be a consideration in how the procedure is applied in the 2 types of programs.

Cost-Benefit Analyses of Prior Authorization

Some cost-benefit analyses of the PA procedure have recently been conducted. In one health plan that included both commercial and Medicaid members, the average administrative cost of a limited PA program covering bupropion (standard release formulation), the Cox-2 drugs, the glitazone antidiabetic drugs, antifungals, zafirlukast/montelukast, and sildenifil, was $17.87 per PA at a volume of 936 requests per month.[11] No cost savings for the Medicaid population were reported, although cost savings for the Cox-2 drugs, the glitazones, and sildenifil were reported for the commercial population. This study did not take into account any factor for a supposed sentinel effect. The administrative costs included employee salaries and indirect administrative costs. The savings calculation used in the study was: savings in drug spend = (# denied x $Rx) – ($ substitute Rx). The net savings to the health plan = (monthly PAs x administrative $) – reduction in drug spend.

A recent study reported that step therapy for Cox-2 inhibitors was cost effective.[12] Step therapy requiring treatment failure due to gastrointestinal discomfort is the protocol commonly incorporated into health plan PA procedures for Cox-2 drugs. The study was reanalyzed because cost data for the products in the study (celecoxib, rofecoxib, naproxen sodium, and nabumetone) was inaccurate. The reanalysis confirmed that step therapy might be cost effective, but that a 3-tier copay plan in which the Cox-2 drugs are assigned to the third tier is more cost effective considering plan cost and member choice.

An international meta-analysis of studies of the impact on health care quality and cost of restrictive formularies[13] was unable to draw definitive conclusions but suggested that PA may be effective in controlling drug costs without increasing costs in other areas of medical expenditures. A study to determine whether PA of topical tretinoin for acne is in the best interest of health insurers and, if so, to determine the optimal member age for topical tretinoin PA, indicated that PA for topical tretinoin is of no great benefit to insurers.[14] The authors conclude that although they generally support the use of PA, elimination of prior authorization altogether for this condition treatment would result in at most a 12% loss, about one penny PMPM, that would be balanced by reduced inconvenience for patients and reduced expenditure of time for doctors.

A study in the hospital setting[15] of the PA of antimicrobial use determined that requiring preapproval for selected parenteral agents can decrease antimicrobial expenditures and improve susceptibilities to antibiotics without compromising patient outcomes or length of hospital stay. While the circum-

stances of this type of PA are very different from PA in the ambulatory setting, the findings of this study may have implications for PA of antibiotics in the ambulatory setting where considerations of antibiotic resistance and response to antimicrobial therapy can be somewhat similar.

A 1995 study described an evaluation of Medicaid HMO PMPM costs, preauthorization processes, drug utilization, and provider and member educational efforts. After one year of managing the pharmaceutical benefit of a former Medicaid population, plan PMPM pharmacy costs decreased, PA request and call activity decreased, and drug market shares shifted toward formulary agents.[16] Provider and member acceptance of the restrictive formulary grew as consistent interaction with the HMO increased HMO staff familiarity with specific patient cases, and providers grew more familiar with the HMO's criteria for decisions regarding PR.

Another 1995 study[17] concluded that PA requirements in a Medicaid population might be highly cost effective with regard to expenditures for NSAIDs, drugs that have very similar efficacy and safety but have substantial variation in cost.

The Research Site HMO Drug Formulary

The extant research site HMO uses a "closed" formulary that covers only certain brand drugs. Furthermore, some of the covered formulary drugs require PA for reimbursement, a practice common in other managed care plans. The PA procedure as described below is used by the health plan to screen prescriptions for medical necessity according to utilization guidelines that have been incorporated into the PA protocol and procedure.

TABLE 3 PA Statistics for the Top 20 Therapeutic Classes

Drug Class	Number PA Procedures	Percentage of PA
Atypical antipsychotics	2,696	12.2%
Antacids	1,916	8.7%
Antidepressants	1,830	8.3%
Antihypertensives	1,172	5.3%
Anticonvulsants	1,067	4.8%
Cox-2 inhibitors	825	3.7%
Hypnotics	802	3.6%
Nonsedating antihistamines	788	3.6%
Male sexual disorder	713	3.2%
Analgesics and narcotics	693	3.1%
Antifungals	599	2.7%
ACE Inhibitors	506	2.3%
Cholesterol-lowering	479	2.2%
HmG-CoA inhaled asthma steroids	460	2.1%
Analgesics and NSAIDs	439	2.0%
Oral hypoglycemics	403	1.8%
Antidepressant 5HT reuptake	294	1.3%
Reverse nucleoside for AIDS	250	1.1%
Electrolytes	248	1.1%
CNS stimulants	214	1.0%

The Research Site Formulary and Prior Authorization Process

The research site drug formulary has a closed design and was developed to cover medically necessary and cost-effective prescription products for self-administration in the ambulatory setting.

The goal of the HMO's PA process is to ensure that medication regimens that are high cost, high risk, or with narrow therapeutic indices are used appropriately in the care of members. The PA process is required for

- limited-use agents such as orphan drugs (payment for orphan drugs will be based on the "Office of Orphan Product Development" guidelines for medical necessity);
- all brand-name medications when there is an A-rated generic equivalent available, except as noted in the generic medications section;
- all nonformulary medications (for example, sildenafil, simvastatin, topiramate);
- medications and regimens under concurrent clinical review, regimens that are outside the parameters of use approved by the U.S. Food and Drug Administration (FDA) or accepted standards of care, for example, a longer than 14-day course of antibiotics;
- prescriptions that exceed $500;
- injectable medications other than insulin, epinephrine, and vitamin B-12 and injectables administered by physicians or other skilled professionals (certain injectables are available exclusively through the injectable program);
- all prescriptions that exceed plan limits, for example, prescriptions for the antiasthmatic drug montelukast in doses greater than the maximum dose of one tablet per day; and
- prescriptions processed by nonnetwork pharmacies.

Upon receiving a PA request, the research site HMO will ensure that the recipient "continues a course of treatment without interruption by (a) authorizing continued treatment from the current prescriber or (b) facilitation of an uninterrupted transition to an equivalent course of treatment received from providers within the HMO network." Protocols must comply with FDA-approved guidelines and not contribute to a pattern of fraud or abuse.

Physician and pharmacy providers receive regular communications detailing changes in the PA process. Doctors have the primary responsibility for obtaining PA of medications. When possible, the prescriber obtains PA before the member goes to the pharmacy. If a nonnetwork doctor writes a prescription and that prescriber refuses to contact the health plan for authorization, then it is the responsibility of the primary care physician to obtain authorization.

TABLE 4 Frequency of Requests for Individual Drugs (Frequency >1.0% of PAs)

Prescription Ranked by PA Frequency	Formulary Drug	Number of PA Requests	Percent of Requests	Disposition		
				Accepted	Rejected	Percent Rejected
Lansoprazole	Yes	1,350	6.1%	1,301	49	3.6%
Olanzapine	Yes	1,280	5.8%	1,242	38	3.0%
Risperidone	Yes	940	4.3%	912	28	3.0%
Bupropion SR	No	586	2.7%	533	53	11.1%
Metoprolol XL	No	545	2.5%	509	36	6.6%
Generic temazepam	Yes	449	2.0%	444	5	1.1%
Topiramate	No	379	1.7%	349	30	7.9%
Rofecoxib	Yes	287	1.3%	277	10	3.5%
Nephrocaps	Yes	239	1.1%	234	5	2.1%
Atorvastatin	Yes	230	1.0%	225	5	2.2%
Zolpidem tartrate	Yes	228	1.0%	224	4	1.8%
Fluoxetine	Yes	225	1.0%	222	3	1.3%
Sertraline	Yes	220	1.0%	212	8	3.6%
Tramadol	Yes	212	1.0%	205	7	3.3%
Paroxetine	Yes	212	1.0%	205	7	3.3%
Celecoxib	Yes	211	1.0%	202	9	4.3%

Prior Authorization Process for Physicians

To obtain a PA, the physician or his or her staff contacts the research site HMO. Requests should be reviewed within 24 hours of receipt. If the request fails to meet the research site HMO-approved criteria, a medical director reviews the request, relying upon accepted clinical and state guidelines. Arrangements are made for the patient to continue on therapy until the request is resolved.

Appeals are reviewed by the medical director's office. Prescribers should receive a written notice of the decision within 72 hours of receipt of the appeal. The physician, patient, and pharmacy should all be notified of the medical director's decision on the PA within 72 hours.

Methods

Analytical Technique

This study used a cross-sectional statistical analysis of health plan administrative data for one month of PAs submitted to the research site HMO by physicians. These data consisted of 22,009 PA records for the month of January 2001, the first month for which these data elements had been recorded for the health plan. Although this was the first month of recording, the PA program had been in existence at the research site HMO for more than 5 years. Thus, these data do not represent new or extraordinary circumstances for the program, although seasonality of claims may be a significant limitation of the study.

Data analysis consisted of calculating univariate frequencies, bivariate cross tabulations, and the calculation of a binary logistic regression model of the likelihood that a request for PA would be denied, given drug types and patient demographics. The binary multiple logistic regression technique was chosen for the main data analysis because it helps to identify which factors independently predict reimbursement denial under PA.

Administrative data were used in this project because they contain information about every request for PA. These data are limited since the diagnosis and reasons for the request are not recorded. The therapeutic class of the product requested was used as a proxy for the diagnosis.

Results

The majority (78.6%) of the drugs subject to PA are formulary-listed products. PA is thus used far more often to validate appropriate use of listed drugs for which the health plan likely receives financial discounts than it is used to review the use of nonformulary products. Still, the number of nonformulary reviews is substantial, with nearly 5,000 such reviews in one month.

Demographically, a majority (59%) of the patients who were subject to PA for prescription drugs were female, consistent with Medicaid enrollment demographics; 57% of the patients were between ages 35 and 65 years, and 17% were age 65 or older (Table 2).

Reimbursement Outcomes

The overwhelming majority (more than 95%) of PA reviews resulted in the payment of claims for the originally prescribed product. One flaw in these data is that there is no indication of whether the claim went through an appeals process prior to being paid. The PA process adjusted a small number of claims. An adjusted transaction occurs when a PA has been approved but the patient does not pick up the drug at the pharmacy. In this situation, the transaction is "reversed" (not "rejected") to adjust for the amount paid. However, in this paper, the calculation of the rejection rate includes consideration of reversed claims in the denominator: we consider them to be authorized and paid because that was the intention of the plan.

Only 4.4% of the requests were finally rejected. In one month, this amounted to fewer than 1,000 requests. If January is a typical month for the program, then in one year, about 10,000 to 12,000 requests will be rejected.

Therapeutic Classes

Twenty therapeutic classes accounted for 1% or more, each, of the PAs (Table 3). The top 6 therapeutic classes were atypical antipsychotics, antacids, antidepressants, antihypertensives, anticonvulsants, and the Cox-2 specific inhibitors. This list of drug classes mirrors the experience of many state Medicaid programs that have PA programs for pharmaceuticals.[18] The top 10 (of 83) therapeutic classes accounted for 56.5% of all PAs, and the top 20 accounted for 74.1% of all requests. Most of these therapeutic classes were represented in the PA file by only 3 or fewer drugs.

Individual Drugs

The great majority of PAs among the most frequently represented therapeutic classes discussed above were for branded pharmaceutical products (Table 4). Of 87 most requested products, accounting for nearly 64% of all requests, 70 were for branded pharmaceuticals (55.3% of all requests), 7 were for vitamins and minerals (4.8% of all requests), and 10 were for generic products (3.7% of all requests). The frequency of generics and vitamins requested increases when products of lower frequency are considered, but, overall, the majority of PAs are made for branded pharmaceuticals. Thus, one of the primary outcomes, and indeed an implicit function of the research site HMO's PA program, is to monitor and control the utilization of branded pharmaceuticals.

Since the research site HMO is a Medicaid managed care program, this roster of products reflects a mix that characterizes the treatment of Medicaid populations. For example, the high frequency of atypical antipsychotic drugs such as ziprasidone, risperidone, and quentiapine reflects the significance of Medicaid in the coverage of pharmacologic treatment of psychosis. However, other products listed seem fairly typical of those that might be subject to PA in a commercial HMO covering the general population. For example, heartburn medications such as lansoprazole and omeprazole and antidepressants such as fluoxetine, citalopram, and sertraline are among the most commonly used drugs in any health insurance plan.[19]

Since vitamins and minerals are generally not covered by health plans unless they are prescribed by a physician and are considered medically necessary, their coverage is always subject to PA. Given the predominance of PA for a limited number of branded products and the evident purpose of this administrative procedure to control the utilization of branded pharmaceuticals, the following presentation of results focuses on the PA process applied to the branded products listed in Table 4.

Bivariate Results: Prior Authorization and Formulary Status

It was noted earlier that PA is required for all nonformulary drugs and also to ensure the medical necessity for and proper utilization of certain formulary drugs. An example of the latter case is rofecoxib, a formulary Cox-2 inhibitor. A patient must first fail on 3 traditional NSAIDs before a claim for rofecoxib is accepted and reimbursable to the pharmacy.

One of the central questions of this research is whether the PA approval of formulary-listed products is proportionately more likely than that of nonformulary products. Although the vast majority of PAs of both formulary-listed and nonformulary products were approved, significantly more PA requests for nonformulary products were rejected than should be expected by chance alone ($P<.0001$). This seems reasonable because although the PA procedure is used to ensure appropriate medical utilization of formulary-listed drugs, PA for nonformulary drugs involves the additional step of first checking to see whether there is a "therapeutically equivalent" branded or generic formulary-listed drug, and then checking whether the patient has already failed to respond to the identified "equivalent" formulary-listed product. We were unable to obtain data regarding the percentage of treatments with branded formulary products that have failed, so we cannot determine the proportion of formulary-listed products that have turned out not to be truly equivalent to nonformulary products in the cases of specific patients.

This result appears to support the argument that PA is one of the tools by which the MCO enforces the use of brand formulary products since the probability of rejection of the prescription is higher when a nonformulary brand product is prescribed. Using a nonformulary product requires an extra burden of support for approval—not only must it be therapeutically appropriate, the same criterion as that for a formulary drug requiring PA, but the nonformulary drug must also be therapeutically superior to the brand formulary drug, for the specific patient. Showing superiority of the brand nonformulary product would require demonstration that the patient failed treatment on the formulary product.

Particular Drugs and Prior Authorization Rejection

The top 10 drugs in terms of reversed prescriptions include lansoprazole, olanzapine, topiramate, clotrimazole-betamethasone diproprionate, rofecoxib, quinapril hydrochloride tablets, celecoxib, sertraline, oxycodone-acetaminophen tablets, and citalopram. Although the numbers of rejections are small for all of the individual drugs and only 2 of the top 10 drugs were nonformulary products, the nonformulary products had considerably higher rejection rates than the formulary products. This is in line with the overall results showing that the rejection rate for all nonformulary products was 7.1% while that for formulary products was 3.7%.

The most common reason for reversing the prescription of formulary drugs was the application of quantity limitations per month. These limits are in addition to the general plan limits in which a "maximum of a 34-day supply or 150 units (whichever is less) of medication is eligible for coverage." The plan limits statement reads, "Prescribed medications of regimens that are for nonformulary drugs or over 34-days supply/150 units require PA."

Prescription Rejection by Patient Demographics

Age: The likelihood that a product will fail to be reimbursed under PA at this Medicaid HMO is inversely related to age, with the widest divergence in actual versus expected rejections in the youngest age group (0 to 17 years) and the oldest age group (65+ years). There is no hypothesis for this association at present, and its use in this study is simply as a covariate, controlled in the multivariate analysis.

Finally, the PA requirements on the products might be more likely to be met for the older patient. This association will be assessed again when multivariate analysis results are reported. (The age categories were 0 to 17, 18 to 34, 35 to 49, 50 to 64, and 65+ years [Medicare/Medicaid dually eligible patients]).

Gender: There does not appear to be any association between gender and the likelihood of having a prescription reversed under PA, and we know of no hypothesis that posits such an association.

Prescription Rejection by Therapeutic Category

Prescriptions from particular therapeutic categories are more likely to be reversed under PA. The top 10 categories in terms of impact on prescribing under the PA program are angina drugs, multivitamins and mineral formulations, sleep aids, antismoking drugs, antifungals, ACE inhibitors, anticonvulsants, anxiolytics, A-listed antiemetics, and nonsedating antihistamines. For most of these therapeutic classes, one or two drugs account for nearly all of the PAs as well as the rejections.

Multivariate Analysis Procedure

In order to determine which factors in the PA data independently determine the outcome of a PA, a binary multiple logistic regression analysis using the dependent variable "Rejected" was employed, signifying the rejection of approval for a particular request. Rejected is a categorical dummy-coded variable for which a case is scored 1 if reimbursement authorization is denied and 0 if the request is either adjusted or paid.

Based on the bivariate cross-tabulation results above, the therapeutic class dummy variables were entered in a preliminary model along with age group and formulary status. Of these, anxiolytics and the drug classes containing furosemide and multivitamin soft gels were discarded as not statistically significant in the preliminary modeling.

The remaining variables mentioned above were entered into the first block of a 2-block regression model. A second block of variables representing individual, commonly prescribed drugs was entered into the regression model. This was done to determine whether individual drugs added additional information about the results of PA over and above that provided by therapeutic classes. Only 2 of these drugs, the analgesic/narcotic (oxycondone/acetaminophen) and the drug for smoking cessation, depression, and anxiety (bupropion), added additional statistically significant information about the outcomes of PAs.

Model Results

The binary logistic regression results suggest that, for the most part, the covariates are not intercorrelated. The highest correlation was between the request for PA of angina drugs and age group of the patient. In line with the low intercorrelations, the results of multivariate analysis were similar in direction to the bivariate relationships discussed earlier.

Using the prior probabilities of group membership (Rejected [1,0]) of about 0.05, 0.95 in the analysis maximized the probability of correct case classification by the binary logistic regression procedure, but the classification power of the model was modest, at about 68% correct. The results of the Hosmer-Lemeshow goodness-of-fit test were not statistically significant. This finding implies that the model variables and, by extension, the data elements collected by the research site HMO are not highly predictive of the results of a PA. It is possible that an analysis of the specific reasons why the PA of products results in approval or rejection (eg., exceeding plan limits) would be more powerful in helping to prospectively classify the results of PA. However, these reasons are not recorded in the PA claims data system at present.

The prescription of multivitamins, sleep aids, and the psychotropic drug bupropion (prescribed for smoking cessation) resulted in significantly *higher* odds of having a PA rejected. The prescription of angina, smoking cessation (other than bupropion), antifungals, ACE inhibitors, antiemetics, formulary drugs, in general, and the pain drug oxycondone/acetaminophen resulted in significantly *lower* odds of having a PA rejected. Drugs for smoking cessation and drugs to control pain and nausea were the most likely to be approved by PA. *Greater* patient age was associated with significantly *lower* odds of having a PA rejected.

Discussion

The finding that the formulary status of a prescribed drug influences the outcome of PA, with formulary drugs more likely to be authorized, was anticipated and is consistent with the work of others cited above (Motheral et al., 2000; Momami et al., 2000).

The association of age group with approval of PA was not anticipated and has not been reported in the literature. This association of PA approval with older patient age is apparently over and above that which is due to the tendency of older people to use any particular class of drugs that were retained in the model. At present, there is not a hypothesis regarding this association.

The relative ease of getting approval for smoking-cessation drugs at the research site HMO appears to be part of a general emphasis at the health plan on primary prevention of smoking-related disorders. In view of the recent settlements between the tobacco industry and state Medicaid programs, this emphasis may reflect a broader policy of encouraging smoking cessation within Medicaid programs.[20]

The relative ease of getting approval for pain and nausea drugs would understandably be associated with a general policy within

managed care of increasing quality of life for patients with serious illness such as cancer and, perhaps, AIDS.

On the other hand, multivitamins are not generally covered by health plans, with only special exceptions, and the tendency of a PA program to reject requests for reimbursement of these products should be expected. The only basis for approving such a request would be in the rare case of malnutrition, extremely poor diet, or some sort of physiological abnormality such as enzyme deficiency.

The prescription of sleep aids causes a review of patient diagnosis and raises the question of why over-the-counter products cannot be used. Admittedly, this is a very poorly understood medical area, and much more precision in the targeting of sleep products and the diagnostic criteria for prescribing them is needed.

Bupropion sustained-release is the first representative of a new class of psychotropic drugs called the serotonin-norepinephrine reuptake inhibitors. This drug commands a price premium over the more established selective serotonin reuptake inhibitors such as fluoxetine and citalopram. Health plan officials report that it is often prescribed as a smoking cessation aid. In this application, the drug is subject to PA.

More than 95% of PA reviews in the study sample resulted in payment for the originally prescribed products. The most common treatments affected by the PA process were atypical antipsychotics, antacids, antidepressants, antihypertensives, anticonvulsants, and Cox-2 inhibitors. The rejection rate for nonformulary products (7.1%) was nearly double that for nonformulary products (3.7%). Nevertheless, most drugs requiring PA were formulary-listed, but with protocols to reinforce prescription guidelines related to standards of appropriate utilization.

Our model variables and, by extension, the data elements collected by the research site HMO, are not highly predictive of the results of a PA. It is possible that an analysis of the specific reasons why the PA of products results in approval or rejection (eg., exceeding plan limits) would be more powerful in helping to prospectively classify the results of PA. These reasons are not recorded in the PA claims data system at present, but it seems that there would be value in recording them to better determine why physicians prescribe nonformulary drugs and why they prescribe in ways that are at variance with PA criteria. In fact, this could be a basis for the review of PA criteria in terms of their conformity with local medical practice.

The administration of the research site HMO PA program requires considerable resources. The pharmacy director has devoted considerable time to the creation of the program and monitors its continuing development. Two full-time RNs adjudicate the PA claims, which number between 70 and 100 per day. Many of these claims are easily adjudicated because the PA criteria are simple, although some go through an appeals process that involves interacting with physicians. These RNs are also involved in helping to set PA policy for particular drugs and ongoing research to maintain the currency of PA criteria. A programmer/analyst devoted about one-half time to the PA claims data system provides computer programming and statistical analysis for routine and special reports of PA claims. An administrative assistant devotes approximately one-quarter time to supporting this RN team for PA administration.

Drug PA programs reflect the desire of payers to reduce prescription drug costs and channel utilization toward formulary-listed drugs but also often represent an attempt to reinforce health plan or community standards of medical practice and treatment guidelines to encourage appropriate utilization. For example, a course of antibiotics longer than 2 weeks is more than health plan guidelines allow and would be unusual in terms of recommended utilization. Another example would be that biologics for rheumatoid arthritis would not generally be prescribed until a patient had failed to respond to methotrexate. Although nonformulary products are more subject to PA more frequently, by proportion, the majority of PA procedures are performed in response to requests for formulary-listed products. In a commercial health plan, many products for which the health plan receives a rebate may be prior-authorized for conformance to plan guidelines. A major unanswered question is the extent to which PA protocols truly reflect the standard of care in medical practice and significant public health concerns. There is a need to verify that the clinical basis for the PA criteria are grounded in sound, evidence-based medicine.

The predominant use of PA for nonformulary drug prescribing could support the assertion by Medicaid programs that while PA may have some financial motivation, its basic rationale is the medically appropriate use of pharmaceutical products. This question is all the more significant in view of the Pharmaceutical Manufacturers Association (PhRMA) lawsuit against the state of Maine regarding the imposition of PA under the state's Medicaid program for drugs not listed on the state's formulary. PhRMA contended that the PA program was financially motivated and not in the interest of beneficiaries. In March 2001 and again in June 2001, the U.S. Circuit Court of Appeals found that "although PA is triggered by a manufacturer's refusal to participate in the Maine prescription program, testimony from the court record indicates that the final decision to require PA for a particular drug is based primarily on clinical criteria applied by health care professionals."[21] Specifically, placement of a drug on the PA list may only be decided by the state's Medicaid Drug Utilization Review Committee, composed of physicians and pharmacists licensed in Maine. PhRMA is appealing this decision to the U.S. Supreme Court.

PA seems likely to remain a widely used tool for Medicaid and non-Medicaid managed care programs because its wider use suggests that health plan sponsors believe that drug-benefit PA reduces costs.[20] However, the ultimate fate of PA in commercial health insurance in pharmacy benefit programs will probably not be decided through litigation regarding interference in medical practice but by the growing emphasis on consumer cost sharing in recent health insurance benefit design, exemplified by tiered formularies. Some health plans contend that if patients are required to pay extra for particular drugs, they should not be

forced to undergo restrictive administrative procedures to be reimbursed. On the other hand, PA will probably continue to find use in reinforcing standards of care. If the trend toward greater consumer cost sharing continues, PA will probably become unnecessary as a way to increase the utilization of formulary products since plans will rely on patient out-of-pocket cost sensitivity to channel utilization toward preferred products.

Limitations

Population: The research site HMO is a Medicaid MCO. Its covered population is, therefore, discontinuously eligible for benefits as people lose and gain income or assets. On the other hand, if a state has a Medicaid managed care program under a Section 1115 waiver from the U.S. Department of Health and Human Services, a beneficiary has no other coverage option. This could make it somewhat different from private HMOs that cover commercial populations since enrollment patterns in a commercial HMO generally depend on the stability of their employer customers and on employee health plan choices when employers offer multiple options. In a commercial HMO, employees sometimes have the option of joining another health plan during an open-enrollment period or even opting out of the employer plan in favor of participation in a spouse's health plan. An employer might change health plans based on complaints about a drug formulary, or a beneficiary might change health plan options. Thus, a drug formulary might have implications for enrollment and disenrollment, if, for example, a patient's preferred drug is not covered under a closed formulary. In considering the results of the present study, we must keep in mind that the differences between commercial and Medicaid populations might limit the generalizability of our conclusions.

Sampling: For administrative reasons, we were only able to access one month of claims data in a timely fashion. Since a Medicaid population may be seasonal in that beneficiaries may be better able to find employment at some times during the year than others, and many illnesses are seasonal, the limitations of a single month's data are significant and can limit the generalizability of our conclusions.

Conclusion

In this 250,000-member Medicaid HMO, 78.6% of drug PA procedures in January 2001 were performed in response to requests for formulary-listed products. The PA rejection rate for this Medicaid MCO was small: 4.4% overall and 7.1% for nonformulary versus 3.7% for formulary drugs. The generalizability of these conclusions may be limited because a Medicaid population has significant differences from commercially insured populations in terms of socioeconomic status and enrollment choice.

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ORIGINAL RESEARCH

Meta-analysis of Oral Triptan Therapy for Migraine: Number Needed to Treat and Relative Cost to Achieve Relief Within 2 Hours

JAMES U. ADELMAN, MD, and JONATHAN BELSEY, MBBS

ABSTRACT

OBJECTIVE: To determine the cost-effectiveness of the 5-HT$_{1B/1D}$ agonists, or triptans, in the acute treatment of migraine.

METHODS: To determine the cost-effectiveness of the triptans, a meta-analysis was conducted of the efficacy data from 27 oral triptan trials, using the endpoint of "pain-free" status within 2 hours after initial dosing as the indicator of efficacy. Efficacy data were used to determine the number needed to treat (NNT) to achieve pain-free status in 1 patient within 2 hours postdose and then applied the per-dose costs for each triptan to the NNT values.

RESULTS: Rizatriptan 10 mg and almotriptan 12.5 mg were the most cost-effective of the triptans, costing $48.34 and $48.57, respectively, to achieve pain-free status in 1 patient within 2 hours postdose. Frovatriptan 2.5 mg was the most costly, with a cost-effective ratio of $162.49. All other triptans fell between these extremes: zolmitriptan 5 mg ($65.18), sumatriptan 100 mg ($70.83), sumatriptan 50 mg ($75.67), zolmitriptan 2.5 mg ($78.74), and naratriptan 2.5 mg ($141.43), in decreasing order of cost-effectiveness.

CONCLUSION: Using an NNT analysis, the least-costly drugs to achieve migraine cure within 2 hours are rizatriptan 10 mg and almotriptan 12.5 mg. From a population health perspective, the lower acquisition cost of almotriptan 12.5 mg allows for effective treatment of more patients than rizatriptan 10 mg for no additional medication cost.

KEYWORDS: Cost-effectiveness, Efficacy, 5-HT$_{1B/1D}$ agonist, Triptan, Migraine

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Migraine is a common condition in the United States, affecting approximately 18% of women and nearly 7% of men.[1] This chronic, episodic disorder is characterized by moderate to severe, usually unilateral head pain that is typically accompanied by other symptoms, including nausea, vomiting, photophobia, and phonophobia.[2] Without treatment, a migraine attack can persist for several days,[2] significantly compromising a person's ability to work or perform everyday tasks.

Migraine not only adversely affects the "migraineur's" quality of life but also, when an attack strikes, affects his or her ability to function in society. Because of the severity of the pain and the accompanying symptoms, migraineurs often must retire to quiet, dark rooms until the headache resolves. Consequently, the costs of migraine are measured not only in terms of direct medical costs but also in terms of indirect costs from missed work days or reduced productivity while on the job.

Direct costs for treating migraine include prescription drug costs and physician, hospital, and emergency room services.[3] In 1999, Hu et al. estimated the direct medical costs of migraine at $1 billion per year, with about $100 spent per diagnosed patient.[3] Physician office visits accounted for about 60% of these costs, and prescription drugs for about 30%. Emergency room visits accounted for less than 1% of the total direct costs.[3] The indirect costs of migraine include lost work days, losses related to reduced productivity, lost productivity of caregivers attending to them, and families made dysfunctional by a member disabled by migraine. In his 1998 review of the economic burden of migraine to society, Ferrari, citing data from the American Migraine Study, noted that 50% of female and 30% of male migraineurs missed 3 or more days of work per year because of migraine, and 31% of female and 17% of male migraineurs missed 6 or more days per year.[4] Even when migraineurs are able to remain at work during a migraine attack, they are much less productive when experiencing migraine symptoms.[5] Published estimates of the indirect costs of migraine vary widely, but they lie somewhere between $1.4 billion and $17.2 billion per year.[4]

Given the social and economic impact of migraine, effective treatment of this disorder can have a profound effect. Until the early 1990s, migraineurs relied primarily on over-the-counter analgesics such as aspirin or nonsteroidal anti-inflammatory drugs to relieve their headache. Those who consulted a physician for migraine might have been prescribed stronger pain relievers or preparations containing ergotamine. Although ergotamine and its analog, dihydroergotamine, are

TABLE 1 Comparison Profile of Oral Triptans

	Sumatriptan	Zolmitriptan	Naratriptan	Rizatriptan	Almotriptan	Frovatriptan
Brand name	Imitrex	Zomig	Amerge	Maxalt	Axert	Frova
Source	GlaxoSmithKline (formerly GlaxoWellcome)	AstraZeneca (formerly Zeneca Pharmaceutical)	GlaxoSmithKline (formerly GlaxoWellcome)	Merck & Co., Inc.	Almirall Prodespharma Pharmacia Corporation	Vernalis plc Elan Corporation UCB Pharma
T_{max} (time to peak plasma concentration)	2.5 hrs. (acute pain period); 2.0 hrs. (nonpain period)	2.5 hrs. (acute pain period); 2 hrs. (non-pain period); 2 to 3 hrs. overall	3 to 4 hrs. (acute pain period); 2 to 3 hrs. (nonpain period)	1.0 to 1.5 hrs. (standard tablets); 1.6 to 2.5 hrs. (orally disintegrating tablets); not affected by pain status	1 to 3 hrs.	2 to 4 hrs.; increased by 1 hr. in the presence of food
Mean	2.5 hrs.; MAO-A	3 hrs.; active N-	6 hrs.; moderate	2 to 3 hrs. (plasma half-life)	3 to 4 hrs. (plasma)	26 hrs.
Elimination half-life (drug and active metabolites)	Inhibitors cause unpredictable increases in oral sumatriptan bioavailability, increasing elimination half-life by 40%	Desmethyl metabolite has two-thirds potency of parent compound and contributes to half-life	Renal impairment increases elimination half-life to 11 hrs.; moderate hepatic impairment increases elimination half-life to 8 to 16 hrs.		Clearance 40% reduced in moderate renal impairment and 60% reduced in severe renal impairment	Unaffected by impaired renal or hepatic function
Dosage	25 mg, 50 mg, or 100 mg every 2 hrs. as needed; maximum dose not to exceed 200 mg in 24 hrs.	2.5 mg to 5 mg every 2 hrs. as needed; maximum dose not to exceed 10 mg in 24 hrs.	1 mg to 2.5 mg every 4 hrs. as needed; maximum dose not to exceed 5 mg in 24 hrs.	5 mg to 10 mg every 2 hrs. as needed; maximum dose not to exceed 30 mg in 24 hrs.	6.25 mg to 12.5 mg, repeated after 2 hrs. if necessary. Maximum dose not to exceed 25 mg in 24 hrs.	2.5 mg, repeated after 2 hrs. if necessary. Maximum dose not to exceed 7.5 mg in 24 hrs.
How supplied	Oral tablets of 25 mg, 50 mg, 100 mg	Oral tablets and orally disintegrating tablets (wafers) of 2.5 mg, 5 mg	Oral tablets of 1 mg, 2.5 mg	Oral tablets and orally disintegrating tablets (wafers) of 5 mg, 10 mg	Oral tablets of 6.25 mg, 12.5 mg	Oral tablets of 2.5 mg

Data from Amerge[6]; Drug Infoline[7]; Drug Infoline[8]; Goadsby et al.[9]; Imitrex[10]; Maxalt[11]; Axert[12]; Frova[13]; Muir et al.[14]; Napier et al.[15]; Parsons et al.[16]; Pharmalicensing[17]; VanDenBrink et al.[18]; Zomig.[19] Revised labeling information on sumatriptan from Winner et al.[20]; Zoler.[21]

migraine-specific drugs, their use is associated with a range of adverse effects, including nausea, vomiting, and vasoconstriction of systemic and coronary arteries. The most recent advance in the acute treatment of moderate to severe migraine has been the introduction of the 5-$HT_{1B/1D}$ agonists, a migraine-specific class of drugs known as triptans. The first triptan, sumatriptan, became available in the United States in 1993 as an injectable formulation. Later, it became available as an oral tablet and a nasal spray. Since then, 5 other triptans—zolmitriptan, naratriptan, rizatriptan, almotriptan, and frovatriptan—have been introduced, each in an oral tablet formulation; rizatriptan and zolmitriptan are also available as orally disintegrating tablets (Table 1).[6-21] New-drug applications have been filed with the U.S. Food and Drug Administration for eletriptan.

For many patients with moderate to severe migraine, triptans effectively relieve the migraine and its associated symptoms. Although triptans cost more per dose than do other migraine drugs, for patients with disabling migraine, triptans are becoming the drugs of choice. To compare the cost-effectiveness of the various triptans, we conducted a meta-analysis of efficacy data from oral triptan studies. We then extrapolated these data to determine the true cost-effectiveness of each triptan. Our goal was to generate data that would enable providers to make appropriate, effective prescribing decisions and assist health care insurers in making informed formulary inclusion decisions.

Methods

Randomized, double-blind, placebo-controlled trials of oral triptan treatment for migraine were identified through electronic searches of MEDLINE and EMBASE databases and a manual search of reference lists from primary or benchmark papers and review articles. The time period searched was from January 1990 through February 2002. Studies were included in the meta-analysis if they met the following criteria: (1) were a randomized, double-blind trial, with a placebo control arm; (2) had a single-dose triptan treatment, with no rescue medications or repeat doses of triptan allowed for 2 hours after initial dosing; (3) data was available from a standard 4-point assess-

TABLE 2 Oral Triptan Efficacy Trials Comparison: Number of Patients Pain Free Within 2 Hours After Initial Dosing

	Active*†		Placebo		NNT‡	95% CI
	Total	Pain free (%)	Total	Pain free (%)		
Sumatriptan 50 mg						
Cutler et al., 1995[29]	62	10 (16.1)	65	5 (7.7)		
Pfaffenrath et al, 1998[30]	240	72 (30.0)	64	5 (7.8)		
Savani et al., 1999[31]	300	66 (22.0)	145	6 (4.1)		
Combined	**602**	**148 (24.6)**	**274**	**16 (5.8)**	**5.4**	**4.3 – 9.4**
Sumatriptan 100 mg						
Cutler et al., 1995[29]	66	15 (22.7)	65	5 (7.7)		
Geraud et al., 2000[32]	499	150 (30.1)	55	7 (12.7)		
Goadsby et al., 2000[33]	125	29 (23.2)	139	8 (5.8)		
Myllyla et al., 1998[34]	42	21 (50.0)	41	3 (7.9)		
Nappi et al., 1994[35]	158	38 (24.1)	86	10 (11.6)		
Oral Sumatriptan Group, 1991[36]	120	31 (25.8)	75	4 (5.3)		
Pfaffenrath et al., 1998[30]	246	96 (39.0)	64	5 (7.8)		
Tfelt-Hansen et al., 1995[37]	122	36 (29.5)	126	10 (7.9)		
Tfelt-Hansen et al., 1998[38]	387	127 (32.8)	159	15 (9.4)		
Visser et al., 1996[39]	72	16 (22.2)	85	3 (3.5)		
Combined	**1,837**	**559 (30.4)**	**895**	**70 (7.8)**	**4.7**	**4.0 – 5.9**
Rizatriptan 10 mg						
Ahrens et al., 1999[40]	186	78 (42.2)	180	17 (9.5)		
Bomhof et al., 1999[41]	201	90 (44.8)	107	9 (8.4)		
Gijsman et al., 1997[42]	145	40 (27.6)	67	2 (3.0)		
Kramer et al., 1998[43]	320	142 (44.4)	82	6 (7.3)		
Pascual et al., 2000[44]	292	126 (43.2)	146	14 (9.6)		
Teall et al., 1998[45]	455	191 (42.0)	302	30 (9.9)		
Tfelt-Hansen et al., 1998[38]	385	155 (40.3)	159	15 (9.4)		
Visser et al., 1996[39]	89	23 (25.8)	85	3 (3.5)		
Combined	**2,073**	**845 (40.8)**	**1,128**	**96 (8.5)**	**3.2**	**2.9 – 3.5**
Zolmitriptan 2.5 mg						
Pascual et al., 2000[44]	289	103 (35.6)	146	14 (9.6)		
Rapoport et al., 1997[46]	260	70 (26.9)	121	8 (6.6)		
Solomon et al., 1997[47]	178	39 (21.9)	92	9 (9.8)		
Combined	**727**	**212 (29.2)**	**359**	**31 (8.6)**	**5.1**	**3.7 – 8.2**
Zolmitriptan 5 mg						
Dahlof et al., 1998[48]	179	69 (38.5)	88	1 (1.1)		
Geraud et al., 2000[31]	491	144 (29.3)	55	7 (12.7)		
Rapoport et al., 1997[46]	245	81 (33.1)	121	8 (6.6)		
Visser et al., 1996[39]	21	3 (14.3)	20	1 (5.0)		
Combined	**936**	**297 (31.7)**	**284**	**17 (6.0)**	**4.2**	**2.9 – 7.5**
Naratriptan 2.5 mg						
Bomhof et al., 1999[41]	213	44 (20.7)	107	9 (8.4)		
Combined	**213**	**44 (20.7)**	**107**	**9 (8.4)**	**8.2**	**5.0 – 21.4**
Almotriptan 12.5 mg						
Dahlof et al., 2001[49]	164	62 (37.8)	80	9 (11.3)		
Dodick, 2002 (CL14)[50]	183	53 (29.0)	99	15 (15.2)		
Pascual et al., 2000[51]	373	144 (38.6)	176	27 (15.4)		
Combined	**720**	**2,159 (36.0)**	**355**	**51 (14.4)**	**4.7**	**3.5 – 7.0**
Frovatriptan 2.5 mg						
Rapoport et al., 2002[24]	199	27 (13.6)	184	6 (3.3)		
Ryan et al., 2002 (study 1)[23]	204	29 (14.2)	104	2 (1.9)		
Ryan et al., 2002 (study 2)[23]	733	88 (12.0)	378	11 (2.9)		
Ryan et al., 2002 (study 3)[23]	475	43 (9.1)	242	5 (2.1)		
Combined	**1,611**	**187 (11.6)**	**908**	**24 (2.6)**	**11.3**	**9.3 – 14.3**

NNT = number needed to treat; CI = confidence interval.

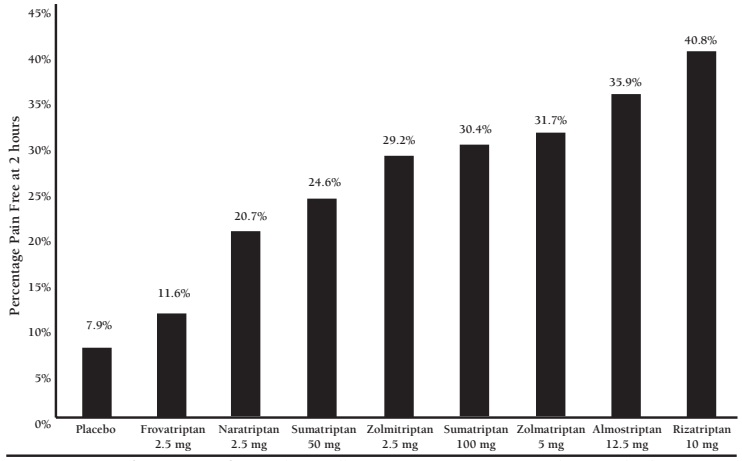
Adapted from Belsey,[22] with additional data from frovatriptan studies included (Ryan et al.[23]; Rapoport et al.[24]).

* *All active treatments are significantly more effective than placebo (P<0.0001 for all comparisons).*

† *When expressed as an NNT, rizatriptan 10 mg is found to be significantly more effective than sumatriptan 100 mg, zolmitriptan 2.5 mg (P<0.05 for both), sumatriptan 50 mg, almotriptan 12.5 mg, (P<0.01 for all), naratriptan 2.5 mg (P<0.001), and frovatriptan 2.5 mg (P<0.0001). There was no significant difference between the NNTs for rizatriptan 10 mg and zolmitriptan 5 mg.*

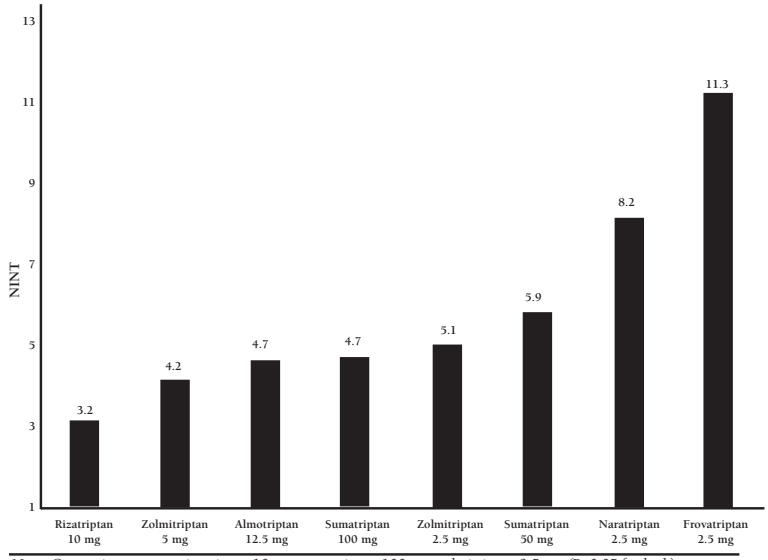
‡ *Combined data for NNT was derived using DerSimonian Laird random effects pooling mode.*

FIGURE 1 Summary of Absolute Triptan Efficacy Data



Note: Percentage of patients pain free at 2 hours. All active treatments were compared against placebo (P<0.0001).

FIGURE 2 Summary of Relative Triptan Efficacy Data: Number Needed to Treat per Patient Pain Free at 2 Hours



Note: Comparisons versus rizatriptan 10 mg: sumatriptan 100 mg, zolmitriptan 2.5 mg (P<0.05 for both), sumatriptan 50 mg, almotriptan 12.5 mg, (P<0. 01 for all), naratriptan 2.5 mg (P<0.001), and frovatriptan 2.5 mg (P<0.0001). There was no significant difference between the NNTs for rizatriptan 10 mg and zolmitriptan 5 mg.

ment scale, for baseline and posttreatment headache severity analysis; and (4) definitive data was available for determining the percentage of patients (in both the treatment arm and the control arm) who were "pain free" at 2 hours postdose.[22] Studies were excluded from the meta-analysis for lack of relevance (not randomized, open label, endpoints solely pharmacologic, or endpoints other than pain free and pain relief used), for use of a drug not approved in the United States or use of a dose or formulation not approved or available in the United States, and for protocol deficiencies.[22] At the time we conducted our analysis, eletriptan had not yet been approved for use in the United States, and therefore data on this drug are not presented. Summary data relating to frovatriptan were published in April 2002[23,24] and have been included in this analysis, although insufficient data were available to carry out a full critical appraisal of these studies.

Data from each study for each triptan were aggregated at commonly used doses. Data relating to dosages below the present recommended starting dose were excluded from the analysis. Thus sumatriptan 25 mg, naratriptan 1mg, rizatriptan 5 mg, and almotriptan 6.25 mg were not included in the meta-analysis. Aggregate efficacy rates were calculated for the percentage of patients who were pain free within 2 hours after initial dosing, from which the number needed to treat (NNT) was calculated (Table 2).[22] The NNT is the number of patients that must be treated to obtain one positive response. It is calculated as the reciprocal of the therapeutic gain, when the therapeutic gain is expressed as a proportion (the therapeutic gain is calculated by subtracting the response to placebo from the response to active drug).[25] Thus if 60% of patients respond to a drug and 25% respond to placebo, the therapeutic gain is 35%, and the NNT is 1 divided by 35% (1/0.35), or 2.86 patients.[25]

The cost-effectiveness ratio (CER), the mean expense to achieve pain-free status in one patient within 2 hours of initial dosing, was then calculated for each triptan by multiplying the NNT by the cost per dose of each triptan. The cost per dose of each triptan was obtained from http://www.drugstore.com and is shown in Table 3. The costs of triptans as listed by this online drug store are generally lower than those at community pharmacies but higher than the discounted prices, before member copayment, enjoyed by many managed care organizations.

Although direct comparative trials are the ideal means of comparing treatments, we found only a few studies that involved direct, head-to-head comparison of triptans.

Nonetheless, nearly all triptan trials use comparable protocols. We therefore assumed, for the sake of analysis, that all placebo-controlled studies not involving direct comparison of triptans were fundamentally comparable.[22] We used the clinical endpoint of pain free at 2 hours as the indicator of efficacy as this is the currently recommended endpoint by the International Headache Society. In addition, this endpoint is the one that patients identify as being the "most important,"[26] and it also correlates well with return to full function. The endpoint of "24-hour sustained pain free" could also have been used in this meta-analysis and would have produced data similar to the "pain-free"[27] data presented here.

We used standard significance testing for paired comparisons of absolute efficacy rates, NNT, and CERs. For each triptan, we combined results for the placebo groups and for the treatment groups to determine clinical efficacy (defined as the percentage of patients who were pain free within 2 hours of initial dosing). The methodology of Cook and Sackett was adopted to calculate the 95% confidence intervals for the NNTs.[28]

Results

Forty-five randomized, controlled trials of acute oral triptan therapy were identified in the primary search. An additional 4 studies were identified in the frovatriptan data summary.[23-24] Twenty-seven of these studies, incorporating 36 active treatment arms, qualified for inclusion in the meta-analysis.[29-51] Reasons for exclusion were as follows:

- 6 studies related to a triptan not licensed in the United States (eletriptan),
- 4 studies related to doses not licensed in the United States,
- 3 studies used methods of ascertaining outcome incompatible with the standard 4-point scale,
- 8 studies did not record the proportion of patients pain free at 2 hours, and
- 1 study presented only aggregated data from multiple attacks.

In addition, data from 8 additional treatment arms from included studies were not incorporated in the meta-analysis because they related to doses below that recommended for most patients (sumatriptan 25 mg, naratriptan 1mg, rizatriptan 5 mg, and almotriptan 6.25 mg). No data for naratriptan 1 mg were included because this is only indicated in a prophylactic role.

Clinical Efficacy

When results from each of the studies meeting our inclusion criteria were combined, the percentage of patients who were pain free within 2 hours after drug administration ranged from 11.6% for frovatriptan 2.5 mg to 40.8% for rizatriptan 10 mg (Table 2 and Figure 1). The absolute percentage of patients who were pain free at 2 hours was significantly higher for all triptan doses than for placebo ($P<0.0001$). Placebo response rates ranged from 2.6% in frovatriptan 2.5 mg studies to 14.4% in almotriptan 12.5 mg studies (Table 2). Although this efficacy comparison is useful in that it gives a general idea as to the relative effectiveness of each of the triptans, it would be more meaningful if the variable placebo rates had been taken into consideration. A more meaningful way to compare clinical effectiveness of the triptans then would be to compute the NNT.

The NNT values ranged from 3.2 for rizatriptan 10 mg to 11.3 for frovatriptan 2.5 mg (Table 2 and Figure 2). Rizatriptan 10 mg was significantly more effective than all the other triptans except zolmitriptan 5 mg. Although the hierarchy of clinical effectiveness of the triptans was maintained as before (Figure 1), broader overlaps in the confidence intervals were obtained with the NNT calculation.

TABLE 3 Cost per Dose of Oral Triptans

Agent	Package Price	Package Size	Cost for Single Dose
Almotriptan 12.5 mg	$61.97	6	$10.33
Zolmitriptan 2.5 mg	$80.64	6	$13.44
Frovatriptan 2.5 mg	$129.69	9	$14.41
Sumatriptan 50 mg	$134.70	9	$14.97
Sumatriptan 100 mg	$134.70	9	$14.97
Rizatriptan 10 mg	$91.45	6	$15.24
Zolmitriptan 5 mg	$47.05	3	$15.68
Naratriptan 2.5 mg	$155.86	9	$17.32

Source: http://www.drugstore.com. Single-pack prices quoted on July 2, 2002, for commonly used doses. Dosages below the present recommended starting dose were excluded from the analyses in this paper.

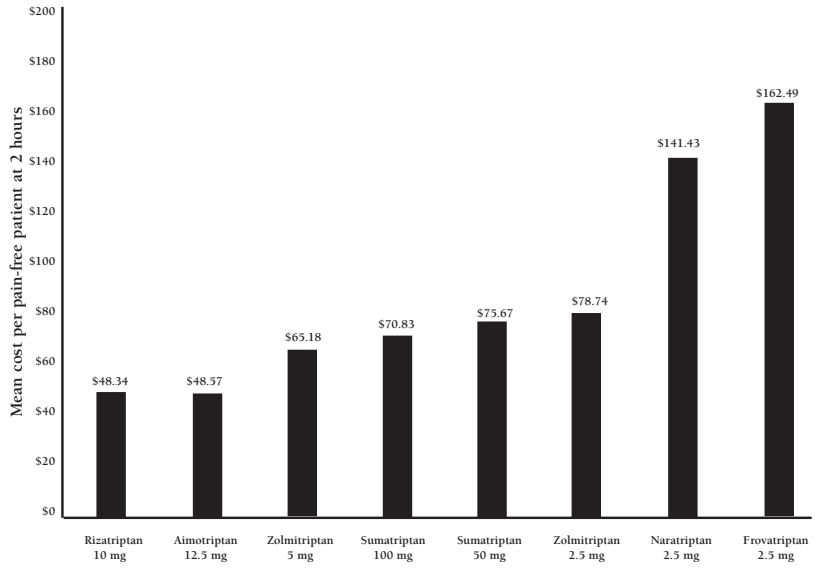
Cost-Effectiveness

The cost per dose of oral triptans varies considerably between $10.33 for almotriptan 12.5 mg to $17.32 for naratriptan 2.5 mg (Table 3). We applied the cost per single dose of each triptan to the NNT to calculate the best "real-world" assessment of the expenditure necessary to yield 1 patient pain free within 2 hours after initial dosing. As shown in Figure 3, the cost to achieve pain-free status in 1 patient within 2 hours postdose ranged from $48.34 for rizatriptan 10 mg to $162.49 for frovatriptan 2.5 mg. Here we report that the most cost-effective triptans in our analysis were rizatriptan 10 mg and almotriptan 12.5 mg.

Discussion

The 2 principal treatment goals for patients with migraine are to (a) decrease the frequency of migraine attacks and (b) decrease the duration and intensity of attacks when they do occur.[52] With acute therapy, the ultimate objective is to eliminate the headache as quickly as possible, with no recurrence of the pain. The results of our meta-analysis indicate that there are differences in the ability of individual oral triptans to completely relieve migraine pain within 2 hours in spite of the fact that triptans are generally considered to be equally effective. Rizatriptan 10 mg and zolmitriptan 5 mg were the most clini-

FIGURE 3 Mean Cost to Achieve Pain-Free Status in One Patient at 2 Hours After Initial Dosing



Note: Comparisons versus rizatriptan 10 mg: sumatriptan 100 mg, sumatriptan 50 mg, (P<0.01 for both), naratriptan 2.5 mg (P<0.001), frovatriptan 2.5 mg (P<0.0001).

cally effective triptans on our measure of clinical effectiveness. When clinical effectiveness was computed with medication costs, rizatriptan 10 mg emerged as the most cost-effective triptan, together with almotriptan 12.5 mg.

A closer analysis of the cost-effectiveness data reveals that though both rizatriptan 10 mg and almotriptan 12.5 mg have a similar CER ($48.34 versus $48.57), this does not necessarily imply that the 2 agents are comparable. In the case of rizatriptan, this CER reflects high levels of clinical efficacy (NNT=3.2), coupled with an average pricing ($15.24 per dose), while for almotriptan, average efficacy (NNT=4.7) is coupled with a low price per dose ($10.33) to achieve the same result. At the other end of the scale, lower efficacy and average or above average pricing results in much higher CERs for naratriptan 2.5 mg ($141.43) and frovatriptan 2.5 mg ($162.49).

The 2 different components of the CER, observed above, may potentially influence the conversion of these theoretical financial benefits into actual budgetary savings. At first sight, the use of both rizatriptan 10 mg and almotriptan 12.5 mg might be expected to yield the most cost-effective outcomes in acute migraine management. The differences in clinical efficacy, however, may be expected to impact on actual drug usage. In a recently published study of triptan consumption,[53] it was shown that significantly more migraine attacks are controlled with a single tablet of rizatriptan 10 mg than with almotriptan 12.5 mg (79.4% versus 56.4; $P<0.005$). This means that average tablet usage per attack was 1.24 for rizatriptan 10 mg compared to 1.55 for almotriptan 12.5 mg ($P<0.005$). The potential cost consequences of this difference are clear.

It should be borne in mind that although drugs are the principal means of treating migraine attacks, drug costs are only a portion of the total costs of migraine management.[52] Indeed, attempting to control costs by limiting the amount of triptan therapy available to a patient each month might not produce the desired results, as demonstrated in a longitudinal retrospective review by Goldfarb et al.[54] These authors studied health maintenance organization direct costs and health care resource use of patients with migraine who were taking sumatriptan and who were subject to a monthly limit on the drug.[54] They found that the limit on sumatriptan access decreased pharmacy costs but did not significantly lower other migraine-related direct medical costs and health care resource use.

Triptans are more effective than older migraine medications for moderate to severe migraine, and their use might decrease the overall direct costs associated with migraine by decreasing the need for physician office visits and emergency department services. Restricting access to these drugs by requiring patients to fill prescriptions with a generic drug, mandating higher copayments for brand-name or off-formulary drugs, or restricting the number of pills a patient can receive each month may decrease the costs of migraine drug therapy but might not decrease the overall costs of treating migraine, of which physician office visits account for the greatest expense.[55] A more rational approach may be to permit access to triptans but encourage prescribing of the more cost-effective drugs within this class.

Study Limitations

Our study is not without limitations. Firstly, we did not include all of the studies of triptans reported in the literature in our meta-analysis. Studies that did not meet our inclusion criteria were excluded.

Secondly, our study is a meta-analysis and, as such, is subject to the limitations of meta-analyses in general. Direct head-to-head comparisons in randomized clinical trials remain the gold standard for comparing the clinical efficacy of drugs. However, in the absence of such trials, meta-analyses provide first approximations of the general efficacy of one drug over the

other. Luckily, most clinical trials of triptans have followed standardized protocols in computing clinical efficacy, which makes comparisons among these trials reliable. However, it should be noted that patient populations may differ between trials, which could contribute to differences in responses.

Our calculations are based on the percentage of patients who achieved pain-free status within 2 hours of dosing using "standard" dosing schemes, in which patients are instructed to take the drug when the headache is moderate to severe. Investigators are now looking at the efficacy of triptans when given early in the headache phase, when the pain is mild. Data available to date indicate that early treatment will yield pain-free response rates higher than those obtained with later dosing.[56] Consequently, cost-effectiveness meta-analyses such as ours will need to be redone taking into account the pain-free response rates achieved with triptan dosing earlier in the headache episode.

Another limitation of our study is the generalizability of our results to a larger population. To provide clinically relevant data, we must differentiate between efficacy studies and effectiveness studies. Efficacy studies, such as those included in our meta-analysis, record the performance of a drug under ideal and controlled circumstances. However, data from efficacy studies might be applicable to the general population only to the extent to which the treatment protocol and patients are comparable to those in the community. Effectiveness studies track the performance of a drug and its treatment outcomes under "usual care conditions."[57] Effectiveness studies typically have less restrictive criteria for entry than do efficacy studies and thus also have larger sample patient populations. Treatment regimens used in effectiveness studies are more likely to reflect usual community practice patterns and usual health care resource use.[57]

Lastly, our study did not include the adverse effects associated with triptans in computing NNT and cost-effectiveness. The true efficacy of a drug is a balance between clinical efficacy and adverse effects. In addition, costs associated with treating adverse effects could contribute to the overall costs of a particular treatment and ideally should be computed in the cost-effective calculations. In general, triptans appear to be well tolerated and have similar adverse-effect profiles. The only exception is naratriptan, which has a lower adverse-effect profile consistent with its lower clinical efficacy.[58]

Conclusion

The NNT method of drug comparison is important for managed care organizations in evaluating the relative value of similar drugs. Using an NNT analysis, the least-costly drugs to achieve migraine cure within 2 hours are rizatriptan 10 mg and almotriptan 12.5 mg. From a population health perspective, the lower acquisition cost of almotriptan 12.5 mg may allow for effective treatment of more patients than rizatriptan 10 mg for no additional medication cost. If, however, lesser treatment efficacy results in increased medication usage, this apparent financial benefit may be partially or totally offset.

DISCLOSURES

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Examining the Value and Quality of Health Economic Analyses: Implications of Utilizing the QHES

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ABSTRACT

OBJECTIVE: To examine the increasing use of health economic studies and practical implications of evaluating their quality utilizing the Quality of Health Economic Studies (QHES) instrument.

METHODS: We first reviewed secondary references to examine ways in which health economic analyses are used in different health care settings, the manner in which these data are appraised and evaluated, and their relevance and value in decision making. The QHES, a new instrument designed to support fast, accurate initial assessments of study quality, was then introduced and validated. A case study was performed using the QHES to score the quality of 30 cost-effectiveness studies in gastroesophageal reflux disease (GERD) published since 1985. Areas where additional research could guide efforts to identify and enhance the use of higher-quality cost-effectiveness studies were suggested.

RESULTS: Results from the published validation study of the QHES demonstrated the validity of this new instrument. The resulting QHES scores in the case study of GERD papers ranged from 43 to 91 with a mean of 63.6 (SD=14.7). Approximately 27% of the studies rated had scores less than 50, and 27% had scores above or equal to 75. All 30 studies made conclusions and recommendations and justified them based on their study results. Most studies used appropriate cost and health outcome measures. Very few studies stated the perspective of their analysis and reasons for its selection. The majority of the studies did not perform incremental analysis.

CONCLUSION: An examination of the QHES validation study and the case study in GERD suggests that there is a rationale and potential utility to use a quality scoring system for cost-effectiveness studies. The QHES may play an important role in discriminating higher-quality cost-effectiveness information to enhance decision making. The QHES can also serve as a guideline for conducting and reporting future cost-effectiveness studies, as an aid in the editorial process, and for stratification in systematic reviews. Complex decisions regarding resource allocation rarely rely solely on economic considerations but do increasingly use health economic analyses. To the extent that such analyses are used, the QHES may help ensure that higher-quality analyses receive more analytic attention and greater weight in the decision-making process.

KEYWORDS: Cost-effectiveness analysis, Quality, Checklist, Guideline

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Health economic analyses are increasingly common in the published literature.[1] They are also increasingly important. Decision makers face growing pressure to optimize value as well as quality of care. To identify technologies and therapies that provide the greatest value, payers, managed care organizations, and regulatory bodies are all beginning to use health economic analyses, typically in the framework of evidence-based decision making.

This trend is especially important in the pharmaceutical and biotechnology sectors worldwide. Manufacturers are increasingly required to demonstrate the economic as well as clinical value of their products. Both published and unpublished economic analyses now inform decisions on purchasing, subsidization, and formulary acceptance of new pharmaceuticals. The demand for these economic analyses comes from public and private organizations and is seen both in the United States and abroad.[2,3]

With this broader use has come greater concern about the validity, methodological quality, and utility of health economic analyses as well as the potential for bias and misuse.[4-7] This is a particular concern because the professionals who must rely on these analyses to guide decisions may not be expert at evaluating them. One possible solution is to devise a mechanism to more easily select the highest-quality data for such decision makers to use. The objective of this article is to assess the potential of such a mechanism. To do so, 3 issues are reviewed first: the growing importance of health economic analyses in decision making, how they are used in specific health care settings, and the challenges involved in evaluating their quality. Next, we introduce a newly developed tool for evaluating the quality of health economic analyses. Finally, we examine the value of this new tool in a particular case study as well as the limitations to the approach and areas where additional research is needed.

Why Health Economic Analyses Are Becoming More Common and Increasingly Important

One major objective of health economic analyses is relating the clinical attributes and health outcomes of treatment strategies to their net costs. Such analyses help compare the relative value of competing strategies for medical/surgical care, therapeutic drugs, devices, or diagnostic tests. Thus, they have an obvious role in purchasing, pricing, and formulary decision making.

With drug and device manufacturers funding large numbers of such studies,[8] the supply of health economic analyses is growing. On the demand side, the 1997 U.S. Food and Drug Administration (FDA) Modernization Act I implemented Section 114, which regulates the use of information submitted by pharmaceutical and device manufacturers to drug formulary committees in managed care or similar entities. This code change, too, has spawned

renewed interest in health economic analyses. Moreover, major managed care organizations in the United States are requesting more formal economic dossiers to be supplied by manufacturers to support their products' applications for formulary or reimbursement programs. Outside the United States, national and provincial policies are placing greater emphasis on economic evaluations as well. Australia, the United Kingdom, Denmark, Finland, Norway, Portugal, Belgium, the Netherlands, and some Canadian provinces use the value-for-money equation explicitly in purchasing and pricing decisions.[9] As mechanisms for assessing value improve and as decision processes emphasize value, this proliferation of economic analyses is likely to continue.

How Health Economic Evaluations Are Used in the Real World

Published data are scarce, but from our literature review and experience, health economic analyses seem to be used primarily in purchasing and formulary decisions, less often in developing clinical guidelines.[10] Their use in clinical decision making remains unclear and not rigorously explored.

Benefits Coverage (Formulary) Decisions

Managed care, the advent of capitation, and managed formularies to control rising drug spending have all prompted renewed United States interest in assessing the value of pharmaceuticals and other technologies. Government efforts have been limited; the Medicare Coverage Advisory Committee evaluates the coverage of technology by Medicare but does not have a formal statement for the use of health economic evaluation.[11] The private sector has pursued more expansive initiatives. The Academy of Managed Care Pharmacy (AMCP) has adopted guidelines for submitting economic dossiers to help health plans and managed care organizations objectively evaluate therapeutic agents. So have at least 14 health plans. (These guidelines were first issued by Regence BlueShield, Seattle, Washington, in an effort to set an industry standard for including economic data in formulary decisions.)

A recent evaluation suggests the guidelines have had measurable impact; over the last 3 years, the percentage of submissions containing an economic model increased from 55% to 78%.[12]

Outside the United States, economic analyses are widely used by government payers. In Australia, decisions to place drugs in the Pharmaceutical Benefits Scheme (a publicly funded insurance program) are made by the federal health minister on the advice of the Pharmaceutical Benefits Advisory Committee, which has a technical economics subcommittee.[13] In the United Kingdom, the National Institute for Clinical Excellence was established within the National Health System in 1999 to provide guidance related to the use of new and existing technology.[2] In North America, the Canadian Coordinating Office for Health Technology Assessment and other organizations have issued formal criteria for the conduct and reporting of health economic analyses. In 5 of the 11 Canadian provinces, submission of economic evaluations is a requirement for inclusion in the provincial formulary, while, in others, it is encouraged.[14] In analyzing these examples, the influence of health economic evaluations was generally less than expected.

Clinical Practice Guidelines

It seems logical that health economic evaluations would inform the development of clinical practice guidelines (CPGs). Since these evaluations address the effectiveness and efficiency of care,[15] it is apparent that they could inform the practice of evidence-based medicine.[16] Several sources, including the Consensus Statement on the Role of Cost-Effectiveness Analysis in Health and Medicine, recommend that cost-effectiveness analyses be used as an aid to decision makers[17] and that economic data be incorporated into guidelines where possible.[18] One example of how this can be done comes from the third U.S. Preventive Services Task Forces, which in the year 2000 initiated a process for systematically reviewing cost-effectiveness analyses in formulating its recommendations about clinical preventive services.[19] The group also suggested that this framework should be used in evaluating health care services more broadly.

Despite these promising recommendations, research suggests that the actual integration of economic data into CPGs has not yet been achieved at a meaningful level. A recent review of the development process and quality of CPGs noted that one deficiency was the omission of economic data.[20,21] Another recent report determined that economic analyses were infrequently incorporated into CPGs even when high quality, compelling economic data existed before the guideline was developed.[10] It appears that more research is needed on 2 issues: how relevant economic evaluations are to practicing clinicians and what mechanisms work for integrating issues of efficiency into clinical decision making.

Is It Possible to Identify High-Quality Economic Analyses to Inform Decision Making?

Despite the growing use of health economic information, the quality of published analyses remains less than optimal.[4,6,22,23] This is especially problematic because many of those who need to use these analyses are not equipped to critically evaluate their quality. The recent European Network on Methodology and Application of Economic Evaluation Techniques (EUROMET) survey, for instance, suggests that European decision makers often find health economic analyses to be a "black box," even though they are considered increasingly important in decision making.[14]

Increasing the "usability" of economic analyses involves several steps. A number of guidelines and tools are being developed to improve the science behind such analyses. The underlying assumption is that if higher-quality studies are used, then better decisions will be made. While this assumption remains unproven, a quantitative approach has been adopted in the appraisal of randomized clinical trials in systematic reviews.[24] A parallel approach in health economic analysis seems worth investigating.

The goal of many such efforts is to improve methodological performance by "producers" of health economic analyses. But there are also several instruments intended for critical appraisal

TABLE 1 The QHES Instrument

	Questions	Points	Yes	No
1.	Was the study objective presented in a clear, specific, and measurable manner?	7		
2.	Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4		
3.	Were variable estimates used in the analysis from the best available source (i.e., randomized control trial - best, expert opinion - worst)?	8		
4.	If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	1		
5.	Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9		
6.	Was incremental analysis performed between alternatives for resources and costs?	6		
7.	Was the methodology for data abstraction (including the value of health states and other benefits) stated?	5		
8.	Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	7		
9.	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8		
10.	Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term was justification given for the measures/scales used?	6		
11.	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	7		
12.	Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	8		
13.	Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7		
14.	Did the author(s) explicitly discuss direction and magnitude of potential biases?	6		
15.	Were the conclusions/recommendations of the study justified and based on the study results?	8		
16.	Was there a statement disclosing the source of funding for the study?	3		
	TOTAL POINTS	100		

by "consumers." Among these instruments, the *British Medical Journal* checklist,[25-27] the Canadian Guidelines,[28] and the *Journal of the American Medical Association* user's guide[26,27] are most commonly used. With all, the goal is to enable more effective interpretation and use of such analyses.

Although such tools have substantial value, they also face barriers to both widespread adoption and to achieving their ultimate value. First, the construct validity (e.g., convergent and discriminant validity) of these tools has not been formally tested. Second, all existing instruments are qualitative, most contain subjective and open-ended items, and none provide a score to enable simple comparison among studies; thus, they require a relatively sophisticated user. Finally, the existing checklists and appraisal criteria assume that each criterion is of equal weight. Overall, then, it is not clear that tools and guidelines can accurately identify high-quality health economic analyses, nor that users without specific expertise can use them to derive the information they need.

One potentially promising solution is to give the clinical staff who support the decision-making process a mechanism to more easily select the highest-quality health economic analyses for consideration (to the extent quality can be measured). Toward that end, we have developed and validated a weighted scoring instrument that simplifies assessment of the quality of health economic evaluations.[29]

The Quality of Health Economic Studies (QHES) Instrument

The QHES instrument was designed to evaluate all 3 common types of health economic analyses: *cost-minimization, cost-effectiveness,* and *cost-utility.* The instrument emphasizes appropriate methods, valid and transparent results, and comprehensive reporting of results in each study (Table 1). Its 16 criteria were selected by a panel of 8 health economics experts with experience conducting these analyses. Their selection was made from criteria included in 19 existing guidelines and checklists for cost-effectiveness evaluations (Table 2). Each criterion has a weighted point value (Table 1) that was generated using

TABLE 2 Summary of Existing Guidelines, Checklists, and Recommendations for Health Economic Studies*

Criterion/Source	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	SUM
Objective			•	•					•	•	•	•				•				7
Perspective			•	•	•	•		•	•	•	•	•	•	•	•	•			•	14
Study design			•	•	•	•	•		•	•	•	•	•	•		•				12
Analysis		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	18
Data collection	•		•	•				•		•	•				•	•			•	9
Time horizon								•		•			•			•				4
Cost/resources		•		•	•	•	•	•		•	•	•	•	•	•	•		•	•	15
Outcome measures		•	•	•		•		•	•	•	•		•	•	•	•	•	•	•	15
Discounting			•	•	•			•			•	•		•	•	•	•	•	•	12
Transparency				•				•	•				•						•	5
Cost-effectiveness ratio	•		•						•					•		•				5
Discussion		•	•								•		•	•		•		•		7
Conclusions	•		•							•	•		•	•		•	•	•		9
Sponsorship			•	•				•	•											4
Nonspecified		•	•					•	•			•						•		6
TOTAL	3	5	12	10	5	5	3	10	9	9	10	7	9	9	6	12	4	7	7	
Number of criteria†	9	15	36	16	8	16	8	24	18	21	40	13	23	28	15	35	10	8	14	

** I, N, P, and R are commonly referred to as the "Canadian guidelines," "Drummond's guidelines," "BMJ guidelines," and "U.S. Panel recommendations," respectively.*

† Criteria were presented in the format of "yes/no" questions, statements, or recommendations.

***A:** Problems with the interpretation of pharmacoeconomic analyses: a review of submissions to the Australian Pharmaceutical Benefits Scheme. Hill et al., 2000.*[65]

***B**: The revised Canadian Guidelines for the Economic Evaluation of Pharmaceuticals. Glennie et al., 1999.*[66]

***C:** Evaluating the quality of published pharmacoeconomic evaluations. Sanchez et al., 1995.*[67]

***D:** Emerging standardization in pharmacoeconomics. Mullins et al., 1998.*[68]

***E:** Use of economic evaluation guidelines: 2 years' experience in Canada. Baladi et al., 1998.*[69]

***F:** Common errors and controversies in pharmacoeconomic analyses. Byford et al., 1998.*[70]

***G:** The Danish approach to standards for economic evaluation methodologies. Alban et al., 1997.*[71]

***H:** Canada's new guidelines for the economic evaluation of pharmaceuticals. Menon et al., 1996.*[72]

***I:** Canadian guidelines for economic evaluation of pharmaceuticals. Torrance et al., 1996.*[73]

***J:** Methodological and conduct principles for pharmacoeconomic research. Pharmaceutical Research and Manufacturers of America. Clemens et al., 1995.*[74]

***K:** Evaluation of pharmacoeconomic studies: utilization of a checklist. Sacristan et al., 1993.*[75]

***L:** Guidelines for the clinical and economic evaluation of health care technologies. Guyatt, G. et al., 1986.*[76]

***M:** Economic analysis of health care technology. A report on principles. Task Force on Principles for Economic Analysis of Health Care Technology, 1995.*[77]

***N:** Critical assessment of economic evaluation. Drummond et al., 1997.*[78]

***O:** The U.K. NHS economic evaluation database. Economic issues in evaluations of health technology. Nixon, et al., 2000.*[79]

***P:** Guidelines for authors and peer reviewers of economic submissions to the BMJ. Drummond et al., 1996.*[80]

***Q:** Users' guides to the medical literature. XIII. How to use an article on economic analysis of clinical practice. A. Are the results of the study valid? Evidence-based Medicine Working Group. Drummond et al., 1997.*[26]

***R:** Recommendations of the Panel on Cost-effectiveness in Health and Medicine. Weinstein et al., 1996.* [81]

***S:** Pharmacoeconomic models in disease management. A guide for the novice or the perplexed. Milne, 1998.*[82]

random-effects general least-squares regression based on a conjoint analysis of survey results from 120 international health economists.[29] The perfect quality score for a study is 100. The quality score can be calculated by adding up all of the points for questions answered "yes."

The QHES was subsequently validated in a survey including 60 experts (30 clinicians and 30 health economists) in 6 disease categories. We asked the experts to rate 3 health economic evaluation articles in their disease category, first using a global assessment (judgment) and then using the new instrument. Assuming the global assessment of experts is the "gold standard," results of Spearman's rho test (coefficient=0.78, $P<0.0001$) and the Wilcoxon test ($P=0.53$) indicated that the QHES has good convergent validity. The result of analysis of covariance (ANCOVA, F3, 146=5.97, $P=0.001$) implied that the instrument has good discriminant validity[29] as well. These results indicated that the QHES has good overall construct validity.

Perceived Value of the QHES

The perceived value of the QHES, as discerned from the rela-

tively small sample of experts in the validation study, seems to vary with the user's professional background. Experts in health economics (the 180 experts used to develop and validate the QHES) perceived, on average, moderate value in the instrument. This was measured by questions about the potential value of a tool that could provide a quantitative quality score for a published report so that relative quality among reports could be appraised in a more reliable fashion. Of the 180 experts, 156 returned the survey (i.e., a response rate of 87%). Among those, 117 rated the value of such a tool as greater or equal to 3 on a scale of 1 to 5 (1 = "not valuable at all" and 5 = "extremely valuable") with a mean of 3.6 (±1.0) (Table 3). A total of 84 experts indicated that they would use the tool or recommend it to others versus 39 who said "no" (Table 4).

Among users who are not generally expert in evaluating health economic analyses, interest was stronger. A symposium was convened to introduce the QHES at AMCP's 14th Annual Meeting (Salt Lake City, Utah, 2002). When asked whether they would use the QHES, 67 of the 88 participants (76%) who responded to the question answered "yes." Among the 129 symposium participants, 40% were employed by pharmaceutical manufacturers, 26% by pharmacy benefits management companies, 15% by provider groups or managed care organizations, and the rest by other institutions.

There is another reason that tools or guidelines like the QHES inspire mixed reactions: health economics evidence is only one factor among many shaping policy and formulary decisions. Noneconomic factors such as institutional culture, the influence of the decision makers' medical specialty and education, and political considerations may all play a role.[30] If such factors are seen as prominent in the decision process, economic information—and methods to improve its quality—may seem less vital.

Applying the QHES: A Case Study

To better understand the potential application of the QHES, we undertook a small case study, examining 30 cost-effectiveness analyses that compared care strategies in gastroesophageal reflux disease.[31-60] (The studies, published after 1985, were identified through a search of PubMed.) Rating the studies with the QHES produced scores ranging from 43 to 91 with a mean of 63.6 (SD=14.7). Approximately 27% of the studies rated had scores less than 50 (n= 8), while another 27% had scores above or equal to 75 (n= 8) (Table 5). The studies having scores below 50 were conducted outside the United States, mainly before 1996 by researchers without academic affiliations, and did not disclose their source of funding. Those scored at 75 or above were generally conducted in the United States after 1996, and all were performed by researchers with academic affiliations. Table 6 presents information regarding how frequently each QHES criterion was met by the 30 studies. All studies did a reasonable job in drawing and justifying conclusions and recommendations based on the study results. Most of them (97%) chose valid and reliable outcome measures or provided justifications for use of previously unvalidated measures. When conducting subgroup analysis, the groups were usually prespecified (93%). Most studies (90%) measured costs appropriately and clearly described the quantities used and unit costs. Surprisingly, only a few studies (13%) performed incremental analysis. The perspective of the analysis and reasons for its selection were stated in

TABLE 3 Value of a Tool That Can Provide a Quality Score for a Published Health Economic Analysis, as Rated by 156 Experts

Value	Frequency	%
1.0	6	4
2.0	24	15
2.5	2	1
3.0	46	30
3.5	3	2
4.0	45	29
4.5	3	2
5.0	20	13
Missing	7	4
Total	156	100

TABLE 4 Opinions of 156 Experts Regarding the Use of a Tool That Can Provide a Quality Score for a Published Health Economic Analysis or Recommending It to Others

Will Use or Recommend Others to Use the Grading System?	Frequency	%
Yes	84	54
No	39	25
Not sure	27	17
Missing	6	4
Total	156	100

TABLE 5 QHES Score of Cost-effectiveness Analysis Studies in Gastroesophageal Reflux Disease (N= 30)[31-60]

Score*	Number of Studies	%
0-24	0	0
25-49	8	27
50-74	14	47
75-100	8	27
Total	30	100

**Average score: 63.6; standard deviation: 14.7.*

TABLE 6 *Frequency of Each QHES Criterion Met by Cost-effectiveness Analysis Studies in Gastroesophageal Reflux Disease (N= 30)*[31-60]

	Questions	Frequency	%
1.	Was the study objective presented in a clear, specific, and measurable manner?	23	77
2.	Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	8	27
3.	Were variable estimates used in the analysis from the best available source (i.e., randomized control trial - best, expert opinion - worst)?	21	70
4.	If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	28	93
5.	Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	14	47
6.	Was incremental analysis performed between alternatives for resources and costs?	4	13
7.	Was the methodology for data abstraction (including the value of health states and other benefits) stated?	11	37
8.	Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	15	50
9.	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	27	90
10.	Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term, and negative outcomes?	22	73
11.	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	29	97
12.	Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	23	77
13.	Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	18	60
14.	Did the author(s) explicitly discuss direction and magnitude of potential biases?	12	40
15.	Were the conclusions/recommendations of the study justified and based on the study results?	30	100
16.	Was there a statement disclosing the source of funding for the study?	12	40

only 27% of these studies. The method of data abstraction was stated in 37% of these studies; direction and magnitude of potential biases were explicitly discussed in 40%. More than half of the studies (60%) did not disclose the source of funding.

Possible Applications for the QHES

We believe that the quantitative score available with the QHES may enable a variety of users to better judge the relative quality of different studies and to facilitate the decision-making process. It might, for example, streamline the production of the systematic reviews that have become the standard "evidence-based" approach to topic review (supplanting the previous "narrative" reviews from experts). A research team performing such a review might use QHES scores to quickly and accurately stratify studies by quality level (e.g., scores <75 versus >75), as is frequently done in meta-analyses of randomized clinical trials. Similarly, a journal editor confronted by several economic analyses on similar topics might choose to review only those with scores above 50.

The QHES may be especially beneficial to the clinical staff that supports decision makers on Pharmacy and Therapeutics committees. If the P&T committee was reviewing a therapeutic class, the clinical staff could use this tool, at a minimum, to categorize studies as either low or high quality. Even this "blunt" categorization may increase the efficiency of the evaluation process, allowing first-line evaluators to optimize the number of economic analyses actually used to inform the formulary or coverage decisions; it could also help ensure that higher-quality studies play a larger role in the decision-making process. In each of these potential real-world scenarios, the value of the QHES or similar tool would be enabling the end-user to concentrate efforts on a more thorough evaluation and interpretation of the highest-quality data.

Limitations of the QHES Approach and the Case Study

Clearly, widespread adoption of the QHES would require pilot testing the applicability of the tool in several different settings. In addition to the lessons that remain to be learned from such tests, it is important to acknowledge the recognized limitations of any critical appraisal method or scoring instrument as well as limitations specific to the QHES.

First, while few studies have evaluated the use of checklists compared to scoring systems for economic analyses, this topic has generated considerable debate related to the critical appraisal of randomized clinical trials. The debate is largely focused around the reliability and validity of the checklists to truly

measure study quality, the ability to capture elements of study quality as opposed to study reporting, and the utility of a score compared to a more comprehensive checklist.[61-64]

We recognize that simplified checklists or scoring tools cannot replace a detailed review of the study methods by those with requisite economics and clinical expertise. This was evident in our case study in which we rated 30 cost-effectiveness analyses in gastroesophageal reflux disease and reported the results (e.g., their scores and frequency in meeting each criterion). However, one application of the QHES is to facilitate a more detailed review by providing an efficient screening mechanism to identify the highest-quality studies so that expert reviewers can concentrate their attention on these. Since another possible use would be to help nonexpert users identify higher-quality studies, it is important to assess the inter-rater reliability among nonexperts and to compare the QHES score to a detailed review among nonexperts.

Second, further research is needed to determine the impact of these tools on the results of clinical and policy decisions. In order for quality assessment to become part of the use of economic evaluations, it must be demonstrated that consumers can use the tools to discriminate high-quality analyses from others and, more importantly, that the "use" of higher-quality economic analyses will result in optimal decisions.

Third, there is currently a temporal problem in applying such tools to formulary decisions. These tools require that the health economic evaluation be published, or at least be available in relatively final manuscript form, to permit scoring. In our experience, very few cost-effectiveness analyses for formulary applications have been accompanied by a published paper or a final manuscript. The typical case for new drugs (including new chemicals/biologics and new forms of existing chemicals/biologics) is that there is a detailed description of the economic evaluation within the submitted dossier, accompanied by a spreadsheet model.

Two limitations are specific to the QHES. One is that this instrument employs yes/no responses rather than a continuous scale for each criterion. In practice, studies often fail to perfectly meet those criteria, but awarding them zero points on that measure seems unlikely to accurately convey the quality associated with each criterion. The other limitation is that some users might not have the knowledge or experience to determine whether studies are properly characterized on the dimensions evaluated by the QHES. For example, we have seen studies stating that models were constructed from the societal perspective but that did not include the impact of productivity loss in either the costs or effectiveness measures. Some users might erroneously give such studies credit in using the QHES since the perspective was stated clearly, although inaccurately.

Discussion

In a wide range of settings worldwide, economic analyses are viewed as valuable tools for incorporating cost considerations into evidence-based clinical decisions. Tools like the QHES may play an important role in enhancing the value of such analyses. On the most basic level, cost-effectiveness evaluations and other economic analyses should be methodologically sound, clinically oriented, and policy relevant. With ever more such studies being submitted, journal editors and reviewers need tools to more efficiently and reliably identify high-quality studies. The QHES could enable them to make faster, less-subjective decisions regarding the peer-review process and thus enhance the quality of studies published.

In managed care, the QHES could improve the efficiency of P&T review, the objectivity of the process, and the resulting decisions. Although the tool may be of limited use for decisions about new therapies (since published data may be scarce until several months after the therapy's introduction to the market), it could play an important role in routine formulary evaluations. For example, most formulary review processes include an annual review of the top 15 to 20 therapeutic classes. In this case, the instrument might be used to score the host of economic data on the impact of established therapies; this could provide important insights for keeping formularies current as research accumulates over time.

A practical weighted scoring instrument such as the QHES may also make the economics literature truly accessible to a wider and more diverse audience, allowing users of the literature at all levels to be more informed "consumers." Finally, we hope that with the advent of such a tool, authors of cost-effectiveness studies will pay more attention to many threats to the internal and external validity of their studies early in the design phase.

Further Research Opportunities

The issues reviewed in this paper, and our experience with the QHES, suggest several steps to advance the field and enhance the use of such tools. First, with growing use of economic studies by a broad audience often including nonspecialists, it is important to increase awareness of both the quality variation in published studies and the potential a weighted instrument has to help consumers identify valid, high-quality economic data to support decision making. This awareness could be created by collaborating with national organizations such as AMCP to emphasize methodological quality and to encourage managed care organizations and payers to use tools that help them identify high-quality evaluations. Web-based or other tools could be developed to facilitate the use of the tool and to collect and share the scores assigned to different papers. If this practice were adopted, it might inspire manufacturers to submit more formal presentations or to draft write-ups of their economic analyses that accompany the dossiers submitted to health plans.

Second, input is needed from a wide range of potential users to enhance the scoring tool, increasing both its overall validity and ease of use. While the QHES was validated using experts, it requires further testing and refinement in the "field": among formulary P&T committees, peer reviewers and editors, and those performing systematic reviews. Only this type of scrutiny will reveal whether the tool is improving the use of information,

or even improving decisions based on economic analyses. For example, a case study of the actual decision process used by pharmacy directors in a specific therapeutic area would be very helpful, as would an evaluation of how the decision process varies for pharmaceuticals versus medical devices.

Conclusion

The allocation of limited health care resources will never depend only on economic considerations, and the professional judgment of experts will always be required in reviewing the economic analyses that *do* shape these decisions. But in an environment where health economic analyses are being produced in greater numbers, by a wide range of sources, and evaluated by an even broader group, it seems vital to devise tools that focus attention on objective, high-quality analyses.

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CONTEMPORARY SUBJECT

The Role of Managed Care Pharmacy in Reducing Medication Errors

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ABSTRACT

OBJECTIVE: To outline some of the causes of medication errors and recommend ways that managed care pharmacy organizations and managed care pharmacists can prevent some of these errors through practitioner and patient education.

BACKGROUND: Patient safety has become a major concern since the November 1999 release of the Institute of Medicine (IOM) report, *To Err Is Human*. Errors involving prescription medications are responsible for up to 7,000 American deaths per year and the financial costs of drug-related morbidity and mortality may cost nearly $77 billion a year. The Institute for Safe Medication Practices (ISMP) collects and analyzes voluntary confidential medication error reports and makes recommendations on the prevention of these errors. This article uses the expertise of ISMP in medication error prevention to make recommendations on educational programs for patients and managed care and community pharmacists to reduce medication errors in the outpatient (community) setting. These educational areas focus on patient education, compliance, and health care literacy.

CONCLUSION: Managed care pharmacy is well positioned to affect change in the health care system. Through information dissemination and education, managed care pharmacists should play a more active role in medication error-reduction activities by improving the patient education process and in assisting the pharmacy community in its goal of improving patient safety.

KEYWORDS: Medication error, Patient education, Patient compliance, Health care literacy, Patient safety

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Patient safety has become a major concern since the November 1999 release of the Institute of Medicine (IOM) report, *To Err Is Human*. Health care practitioners may have been surprised to learn from this report that errors involving prescription medications are responsible for up to 7,000 American deaths per year and that the financial costs of drug-related morbidity and mortality may cost nearly $77 billion a year.[1] A retrospective analysis of medication errors reported to the U.S. Food and Drug Administration Adverse Event Reporting System from 1993 to 1998 showed that fatal medication errors accounted for approximately 10% of medication errors reported.[2]

Research demonstrates that injuries resulting from medication errors are not the fault of any individual health care professional but, rather, represent the failure of a complex health care system. Medication error prevention starts with recognizing that errors are multifactorial and are faults of the system as a whole rather than results of the acts or omissions of the people in the system.[3] Even when an error can be directly traced to a specific individual (e.g., the pharmacist dispensing and the nurse administering the wrong medication to the patient), further investigation will determine that a variety of factors such as poor order communication between the physician and pharmacist, dangerous storage practices in pharmacies, and look-alike labeling may have played a role in the error.

The key elements that make up the medication-use system include patient information; drug information; communication of drug information; drug packaging, labeling, and nomenclature; drug device acquisition and use; drug storage, stock, and distribution; environmental factors; staff competency and education; patient education; quality processes; and risk management.[4] Patient education is one of the areas in which a managed care pharmacist can have the greatest impact in reducing medication errors.

The patient usually is the last individual in the medication-use process, and the pharmacist-patient interface can play a significant role in capturing medication errors before they occur. Unfortunately, many health care organizations do not take advantage of this key interaction opportunity. There are 3 important factors that play a role in any patient interface, which often determines the outcome of error prevention efforts. These include patient education, patient and health care literacy, and patient compliance.

Patient Education

In 2001, the number of retail prescriptions was 3.3 billion, which is an increase from 2.7 billion in 2000. By 2004, this figure is estimated to exceed 4 billion.[5] This increase in prescrip-

tion volume, when combined with the shortage of pharmacists, often results in a decrease in the amount of time available for direct pharmacist involvement in patient education. Studies have shown that pharmacy staff is not routinely involved in direct patient education. A 1999 study involving community pharmacies in 8 states revealed that 87% of all patients received written information with their prescriptions. However, only 35% of pharmacists made any reference to the written leaflet, and only 8% actually reviewed it with the patient.[6] Sometimes health care practitioners take for granted that patients fully understand the instructions given during the patient education process. Unfortunately, patients often misunderstand the instructions. The Institute for Safe Medication Practices (ISMP) received a report about an asthmatic patient who was not responding to therapy. During follow-up, the patient described how he was using his inhaler. He would get into his car, roll up the windows, release 2 puffs of medication into the air, and breathe deeply for 15 minutes! At first, he did this in his house. Later he thought it might be more effective to use the inhaler in a confined space. He said he'd been instructed to do this by his doctor, who had picked up an inhaler, held it in the air, and released 2 puffs to demonstrate its use. The doctor gave no additional instructions. Additional examples of errors that have occurred due to inadequate education on medications include parents placing *oral* antibiotic suspensions *into* a child's ear for an ear infection, patient's taking the desiccant that comes packaged with oral medications, wrong medications being dispensed that are undetected by a patient due to the lack of counseling while in the pharmacy, and errors related to patient use of devices because of inadequate education (data from the U.S. Pharmacopeia (USP/ISMP) Medical Error Reporting Program). This gap in patient education is exacerbated by the failure of health care practitioners to provide patients with understandable written instructions.

Patient and Health Care Literacy

The second factor in error prevention is patient literacy, which includes general literacy levels and health care literacy. Many people have difficulty understanding their illness or disease, the proper management of it, and their role in maintaining their health. Whether limited by knowledge, socioeconomic factors, emotional or clinical state, or cultural background, their level of health literacy—the ability to read, understand, and act on health care information—is often much lower than many health care providers may appreciate.

Examples of patients who have had difficulty reading and understanding medication directions are plentiful: an elderly patient who could not tell the difference between his bottle of Coumadin (warfarin) or Celebrex (celecoxib); a mother who, after reading the label on a bottle of acetaminophen, could not accurately state her child's dose; and a teenager who misunderstood directions for contraceptive jelly and ate it on toast every morning to prevent pregnancy. These occurrences are adapted from medication error reports submitted to the USP/ISMP Medication Error Reporting Program. The ISMP provides an independent review of confidentially reported medication errors that have been voluntarily submitted by practitioners to a national Medication Errors Reporting Program operated by the USP. Poor health literacy is not an isolated problem with the elderly, uneducated, or certain socioeconomic classes.[7]

According to a report published by the American Medical Association Ad Hoc Committee on Health Literacy, more than 40% of patients with chronic illnesses are functionally illiterate, and almost a quarter of all adult Americans read at or below a 5th-grade level. Unfortunately, medical information leaflets typically are written at a 10th-grade reading level or above. It is estimated that low health-literacy skills have increased our annual health care expenditures by $73 billion. Further contributing to the dilemma is the fact that an estimated three quarters of patients throw out the medication leaflet stapled to the prescription bag without reading it, and only one half of all patients take their medications as directed.[8]

One reason for this lack of understanding may be that people who have difficulty reading or understanding health information are too embarrassed or ashamed to acknowledge their deficits. Instead, they refuse to ask questions and often pretend to understand instructions. In addition, low literacy is not obvious. Researchers have reported poor reading skills in some of the most poised and articulate patients.[5]

Patient Compliance

Compliance is the third patient-related factor contributing to medication errors. One study found a 76% difference between medications patients actually are taking as compared to those recorded in their charts as being prescribed. Confusion that may accompany advancing age combined with an increase in the number of medicines prescribed for patients are the 2 factors most likely to contribute to this high rate of discrepancy.[9] Another study demonstrated that patient noncompliance played a role in 33% of hospital admissions.[10] Noncompliance may be exhibited by patients in many ways, such as not having a prescription initially filled or refilled, dose omission, taking the wrong dose, stopping a medication without the physician's advice, taking a medication incorrectly or at the wrong time, taking someone else's medication, and the financial inability to purchase their medications. Patients at risk for being noncompliant include patients taking more than one drug, patients with a chronic condition who are on complex drug regimens that may result in bothersome side effects, patients who take a drug more than once daily, and patients who have a condition that produces no overt symptoms or physical impairment, such as hypertension or diabetes.[11] In addition, the elderly patient is more at risk for drug-related problems such as noncompliance due to factors such as decrease in mental acuity and increased confusion, lack of family or caregiver support, decreased coordination and dexterity, and impaired vision.[12] The managed care

pharmacist must consider these factors in the development of patient education tools, strategies, and methods.

Recommendations

Managed care pharmacy organizations can play a significant role in preventing medication errors through patient education. Success may require employing new techniques for providing patients with the information they need and ensuring that it is understood. First, pharmacists should assume that every person has low-level health care literacy even if they do not have a general literacy problem. Secondly, regardless of their level of understanding, most people prefer simple, straightforward instructions and written materials. Managed care pharmacy needs to address patient education issues at the organizational level and promote these activities among the provider pharmacies. Important organizational factors to keep in mind are recommendations that have been compiled from many years of medication error reporting and analysis at ISMP as well as longstanding relationships with many patient safety organizations. These recommendations include the following:

- Develop and implement programs to increase patient compliance (e.g., educational interventions, monitoring activities, and compliance packaging aids). Keep health care providers informed about these programs so they can refer appropriate patients as part of an individualized compliance regimen.
- Develop and implement innovative programs that promote the patients' responsibility for and involvement in their health care.
- Review drug-use policies, such as formulary policy guidelines, from a patient compliance perspective. Revise policies accordingly to facilitate compliance.
- Individualize patient care, including medication management, considering factors such as age, culture, gender, attitudes, and personal situation.
- Use existing databases (e.g., pharmacy claims data) to profile the extent of medicine noncompliance among your health plan members. Devise a mechanism to bring these patients to the attention of all relevant health care providers.
- Provide written materials at a 5th-grade reading level or lower. Use clear captions, ample white space, and pictures, diagrams, or videotapes to help explain concepts. Most people, even those who read well, depend on visual clues to reinforce learning and spark memory.
- Involve patients when producing patient education material. Use focus groups of patients to help write personally relevant and culturally sensitive education materials. After they understand the information, ask patients how you should explain it to others. Use a different focus group of patients to review the final materials and highlight any word or concept they do not fully understand.

Managed care organizations should encourage patients to become engaged participants in treatment decisions and solving problems that could inhibit proper medication use. Patient education materials should be developed to engage patients in their own care to

- ask their health professionals about the purpose of and proper use of their medications and to make sure they understand the response they receive;
- read the label every time they take their medication;
- know what their medication should look like;
- keep medications in original containers;
- never take someone else's medication;
- check their medications every 6 months for their expiration date and don't save old medications;
- ask their doctor or pharmacist if the medication comes in a liquid if swallowing medications is problematic;
- ask for assistance when purchasing over-the-counter medications; and
- keep a current list of their medications. (This medication profile should include the name, strength, dose, and frequency of dosage of all prescription medications; name of all over-the-counter medicines, vitamins and herbal products, and dietary supplements; known medication and food allergies; and medications that the patient used to take and the reason why the medication was discontinued.)

Managed care organizations must reach out and partner with the community/ambulatory pharmacies in preventing medication errors through patient education efforts. An example of this collaboration may be for the managed care organization to provide continuing education programs to community pharmacists since they may not be fully aware of ways to reduce adverse events or to provide preferred methods of managing errors when they occur. Training programs should incorporate patient communication skills and new teaching methods as well as encourage pharmacies to become proactive about gathering and providing medication information. Pharmacists should concentrate on learning to

- provide written materials to the patient to reinforce oral counseling, not as a substitute for it;
- engage in a dialogue with patients and involve them as partners in the medication use process;
- offer small amounts of information at a time, first telling patients what they truly need to know to follow directions, emphasizing desired behavior, not the medical facts, and leaving background information for later encounters;
- verify that the patient understands the drug information provided (avoid asking yes/no questions; instead ask patients to show and tell you how they would take their medicine so that you can spot problems); and
- provide compliance monitoring and documentation for at least one at-risk patient per month. Share your findings with the patient and with his or her other health care providers, including the managed care pharmacy.

Conclusion

Managed care pharmacy is well positioned to affect change in

the health care system. Through information dissemination and education, managed care pharmacists should play a more active role in medication error-reduction activities by improving the patient education process and in assisting the pharmacy community in its goal of improving patient safety.

DISCLOSURES

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CONTEMPORARY SUBJECT

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the Pharmacy Benefit: Implications for Health Plans, PBMs, and Providers

DANIEL C. WALDEN, JD, and ROBERT P. CRAIG, PharmD

ABSTRACT

OBJECTIVE: To summarize and analyze the key provisions of the Health Insurance Portability and Accountability Act (HIPAA) and the impact on pharmacies, health plans, pharmacy benefit managers, and others involved in the delivery of pharmacy services and managed pharmacy benefits.

BACKGROUND: HIPAA was enacted by Congress in 1996 with the goals of administrative simplification in the health care system as well as protecting the privacy of individuals. HIPAA imposes new standards for health care transactions and patient privacy and defines new patient rights regarding their health care information. Transaction standards took effect October 16, 2002, while the privacy standards have a compliance date of April 14, 2003. Regulations, or "standards," will apply to health plans, pharmacies, and other health care providers and other businesses involved in the delivery of health care services. Failure to comply will be punishable under the law. The U.S. Department of Health and Human Services estimated the 10-year cost of compliance to be $17.6 billion.

CONCLUSION: HIPAA's new requirements will demand significant effort and expense for systems and business process development. Businesses from the smallest independent pharmacy to the largest health plans must be compliant by the deadlines imposed by HIPAA.

KEYWORDS: HIPAA, PBM, Regulation, Transaction, Patient privacy, Business associate, Covered entity

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With the passage of the Administrative Simplification provisions of the Health Insurance Portability and Accountability Act of 1996 (HIPAA),[1] lawmakers sought to improve the efficiency and effectiveness of the health care system by encouraging the development of national standards and requirements for electronic transmissions of health information among health care providers, insurance companies, and other health care payers.[2] The hope was that standardization would reduce the expense and inefficiencies that existed then because of multiple systems. Congress also required national standards to protect the privacy of patient information and give people greater control of and access to their health records.[3]

HIPAA required the U.S. Department of Health and Human Services (HHS) to adopt a series of standards that, overall, impose significant requirements and responsibilities on health care payers and providers. The regulations apply directly to "covered entities," including entities defined as "health plans," such as insurers, HMOs, and employer-sponsored benefit plans, and entities defined as health care "providers," such as community, mail service, or other pharmacies. Covered entities may contract with "business associates," including pharmacy benefit managers (PBMs) and other administrative service providers, to perform functions for them. These business associates are indirectly subject to HIPAA requirements since their services must be compliant with HIPAA to meet their contractual and service commitments to their health plan clients.

It would be difficult to overstate HIPAA's impact on health care organizations. For "covered entities," among them health plans (including employee welfare benefit plans such as those sponsored by employers) and most health care providers, compliance, particularly with the standards for transactions, privacy, and security, requires extensive technical, administrative, and cultural changes within health care organizations. Compliance also requires covered entities, including the payers for health care benefits, to take a close look at each of their business partners to ensure that they, too, have adequate safeguards in place.

This article provides a summary of HIPAA's requirements and deadlines and a brief analysis of the impact of HIPAA on pharmacies, payers, and PBMs, the principal parties involved in providing patients access to pharmacy services and the pharmacy benefit.

Understanding HIPAA's Requirements and Deadlines

HIPAA required HHS to adopt standards in 8 specific areas. A summary of the standards required by HIPAA and the status of the rule-making process with respect to each is presented in Table 1.

TABLE 1 Summary of HIPAA Standards

HIPAA Standard	Requirements	Compliance Date/Status
Electronic transactions (formats and code sets)	Defines 10 common information exchanges (each a transaction) between parties in health care (e.g., claims information, payment advice, eligibility). Specifies standard formats (e.g., NCPDP Version 5.1) to be used when those exchanges are communicated electronically and the code sets (e.g., National Drug Code) to be used to encode data elements.	For large covered entities: October 16, 2002[4] (a one-year extension is available to October 16, 2003, by submitting a plan to HHS for achieving compliance by the new deadline.)[5] For small covered entities (fewer than 50 participants): October 16, 2003
Privacy	Limits use and disclosures of individual health information, primarily to activities related to treatment, payment, and health care operations, and includes safeguards and restrictions regarding disclosure of records for public health, research, and law-enforcement purposes. Establishes additional patient rights, including giving patients access to their medical records. Restricts use or disclosure of health information to the minimum needed for the intended purpose. Adds significant administrative requirements.	For large covered entities: April 14, 2003[6] or small covered entities: April 14, 2004
Security	Specifies the administrative procedures and physical means to ensure the confidentiality, integrity, and availability of protected health information.	Proposed standards first issued in 1998 have not been finalized.[7] The compliance deadline will be 24 months after date of final adoption.
National employer identifier	Standardizes identifying numbers assigned to employers by health plans, using existing employer identification number (EIN) used by the IRS.	July 1, 2004[8]
National provider identifier	Creates a single ID system to identify hospitals, doctors, nursing homes, and health care providers when filing electronic claims.	Proposed standards have not been finalized.[9] The compliance deadline will be 24 months after date of final adoption.
National health plan identifier	Creates a standard system for identifying health plans to make it easier for health care providers to conduct transactions with different health plans.	HHS has not yet proposed standards. The compliance deadline will be 24 months after date of final adoption.[10]
National individual identifier	Would have created a standard unique identifier for individuals for use in health care transactions.	HHS has not proposed a standard and indications are that it will not.[11]
Electronic signature standards	Creates standards for an acceptable signature in an electronic transaction that is the subject of the transaction standards.	Originally included as part of the 1998 security standards proposal.[12] The prospect for a final standard is uncertain. The compliance deadline will be 24 months after date of final adoption.

Note: This table was prepared from data available in December 2002.

Changes Required for Compliance

The various standards adopted by HHS under HIPAA will have a significant and lasting impact on all organizations participating in the delivery of health care. This is not simply a matter of a few new regulations; rather, the HIPAA standards include a broad range of new obligations and requirements that will require extensive changes in systems, administrative procedures, and contracting practices. In many instances, compliance with the HIPAA standards will require organizations to develop capabilities they would otherwise not even have considered, and those developments will come at a great expense.

Transaction Standards

The most immediate change for the health care industry has been the need to develop systems able to use the formats and code sets specified in the transaction standards. Prior to the transaction standards, which took effect in October 2002, communications among doctors, hospitals, HMOs, insurance com-

panies, PBMs, and other participants in the care of patients were conducted in a series of privately determined formats, each requiring different information and often using different words or codes to describe the same condition or treatment protocol. The goal of the transaction standards is to require all parties to use specific required formats for certain classes of electronic transmissions, such as eligibility verifications, claims submissions to health plans by providers serving their members, and remittance advice back to providers.

In choosing those formats and code sets that would become the standards, HHS relies on existing organizations that have been engaged for many years in setting standards for various aspects of the health care delivery system based on industry consensus. In the area of pharmacy benefits, HHS designated the National Council for Prescription Drug Programs (NCPDP) as the Designated Standards Maintenance Organization and adopted the NCPDP telecommunication standard version 5.1 and batch standard version 1.0 (modified version 1.1) formats as the standard for pharmacy claims.[13] In December 2001, Congress made available a one-year extension for providers and health plans.[14] For pharmacies, this extension has provided only a limited respite, since a critical mass of payers, including a number of Medicaid plans, have converted or are intending to convert to the 5.1 standard and likely will stop accepting claims submissions in the earlier versions well before the extended deadline of October 2003.

Privacy Standards

HIPAA's privacy standards affect not only an organization's systems but also the entire way that an organization operates. Covered entities must undertake a number of administrative or procedural changes, including appointment of a chief privacy officer responsible for developing and implementing confidentiality policies and procedures; developing procedures to safeguard protected health information; training all members of its workforce to follow those procedures; and implementing processes to handle grievances, whistle-blower complaints, and sanctions for noncompliance by members of its workforce.[15]

In addition, health care organizations must comply with a set of newly created patients' rights established under the privacy standards. To address these, an organization must make arrangements to

1. provide a Notice of Privacy Practices clearly explaining how organizations might use and disclose protected health information[16];
2. enable patients to request privacy protections[17];
3. allow patients to inspect and copy portions of their protected health information, known as the Designated Record Set (DRS)[18];
4. develop a process for patients to request amendments to their DRS[19]; and
5. provide, on request, an accounting of any disclosures of the individual's protected health information (PHI) made other than in the course of treatment, payment, or health care operations.[20]

The privacy standards provide detailed descriptions of these rights, including mandatory language, time frames for responding, and record-keeping requirements. Since these are rights that did not previously exist, most involve the development of new capabilities and mechanisms.

Originally, a provider engaged in direct patient care, although not a health plan, was obligated to obtain written consent from an individual prior to using or disclosing information even to perform requested treatment, such as to dispense a prescription. In August 2002, HHS modified the privacy rule. The final rule requires the provider to use reasonable efforts to obtain acknowledgment that the individual received the provider's Notice of Privacy Practices but no longer prohibits services from being rendered in the absence of formal written consent from the patient.

The central feature of the privacy standards is the provision that PHI, essentially identifiable health information held by a covered entity, may be used or disclosed by a covered entity only for purposes specifically approved in the standards.[21] These limitations apply not just to the disclosure of information to third parties (the concern we have traditionally considered confidentiality) but also to uses or disclosures of information within an organization.

HHS clearly contemplated, however, the legitimate uses of health care information to effectively deliver health care services and protect the public.[22] The standards therefore provide that PHI may be used for purposes of treatment, payment, or health care operations[23] as well as to meet a number of public policy purposes such as responding to requests for information from law enforcement or the Secretary of HHS.[24] In using information for payment or health care operations, a covered entity must make reasonable efforts to use the minimum amount necessary to achieve the intended purpose.[25]

Finally, under the privacy standards, it is the responsibility of the covered entity, including a health care payer, to ensure that its business associates, such as PBMs, perform services in a manner consistent with the applicable HIPAA standards.[26]

It is important to note that the HIPAA privacy standards establish minimum standards for compliance nationwide. States may have more stringent privacy rules than those established under HIPAA. In those instances, a health care organization is required to follow the state rules.[27] HIPAA privacy standards represent the floor for compliance, not the ceiling.

Other Standards

The standards that address transactions and privacy no doubt require the most sweeping changes of all the standards mandated by HIPAA. Covered entities must anticipate, however, the potential impact of the security and other standards.

First proposed in 1998, HHS has not yet issued final security standards, and covered entities will have 24 months after the effective date in which to assure compliance. On the other

hand, certain capabilities required under the security standards are building blocks for compliance with the privacy standards. For instance, to effectively meet the requirement to make reasonable efforts to only use or disclose the minimum amount of information needed for a HIPAA-approved purpose, a company must have an effective way to control access by individuals to PHI within their organizations, an issue HHS has addressed in the proposed security standards. A covered entity taking guidance from the proposed security standards in developing its systems and processes for the utilization of data will be well ahead when the standards are finally adopted.

In May 2002, HHS adopted the standard for health plan identifier, essentially selecting the federal employer tax ID number already assigned by the Internal Revenue Service to be the identifier used when submitting an electronic transmission subject to one of the transaction standards. HHS is expected to adopt single identifiers for health plans and providers. HIPAA originally required HHS to adopt an identifier for individuals, but this is a highly controversial proposition opposed by many privacy advocates, and it has been set aside.

Consequences of Noncompliance With HIPAA

Health plans, pharmacies, and others directly subject to HIPAA are required to comply with the regulations by the specified deadlines, except where extensions have been granted. HHS has named its Office for Civil Rights to enforce the privacy standards and the Centers for Medicare and Medicaid Services (CMS) to enforce the transaction and code set standards. Penalties for violations of the HIPAA standards are $100 per violation, with an annual limit of $25,000 for violations of an identical requirement.[28] Certain offenses relating to misuse or disclosure of individually identifiable health information carry penalties of up to $50,000 and imprisonment for not more than 1 year, with offenses "committed with intent to sell, transfer, or use individually identifiable health information for commercial advantage, personal gain, or malicious harm" carrying penalties of up to $250,000 and imprisonment for not more than 10 years.[29]

Although business associates are not directly subject to HIPAA or its penalty provisions, HIPAA requires that the covered entity cause its business associate to comply with the standards and, in fact, the privacy rule requires a business associate contract containing provisions that assure the business associate is compliant with the privacy rule and other aspects of HIPAA. Failure by business associates to comply, therefore, would expose them to the risk of contract termination with the covered entity (health plan sponsor) or loss of business at the very least. Companies such as PBMs, which serve in different business lines as business associates of covered entities, directly subject to HIPAA, may face greater risk of enforcement than companies that only act as business associates.

Implications for Pharmacy and the Pharmacy Benefit

While all health care organizations will be affected by the sweeping changes required by HIPAA, the various industries within health care, such as hospitals, physicians, and dental providers, will have to develop different approaches to meet the challenges, depending on their existing practices. The following describes how HIPAA applies to pharmacy and the pharmacy benefit, listing some of the issues and interpretations of specific note.

Pharmacies

Pharmacies are health care providers that are directly regulated as a "covered entity" subject to HIPAA. The pharmacy, whether a community, mail, or specialty pharmacy, is obligated to meet all of the HIPAA standards summarized above.

Under the transaction standards, the pharmacy must be prepared to submit claims in the NCPDP version 5.1 or batch 1.0 format and receive payment advice in Accredited Standards Committee X12 837. The requirement took effect on October 16, 2002, although Congress provided that covered entities that filed for an extension could continue to use older formats for up to an additional year and still be in compliance with the law. Even among those pharmacies that filed for extensions, most have already expended substantial time and resources preparing to migrate to the new standards and will likely want to convert as soon as they are able, well before the one-year maximum extension.

Under the privacy standards, pharmacies must meet all of the new administrative requirements, including appointing their chief privacy officer, developing policies and procedures, and training their workforce in privacy procedures. They must also accommodate the 5 new patient rights. As noted above, under the final privacy rule, providers, including pharmacies, are no longer required to obtain written consent from an individual prior to using or disclosing information but must use reasonable efforts to obtain acknowledgment that the individual received the pharmacy's Notice of Privacy Practices.[30]

Pharmacies may use and disclose PHI to the extent specifically permitted under the privacy rule, and, of course, much of the activity undertaken by a dispensing pharmacy fits clearly within HIPAA's definition of treatment. Other functions undertaken by a pharmacy may fit within the definitions of payment or health care operations.

For activities permitted under the privacy rule (other than those fitting the definition of treatment that are exempt from this requirement), pharmacies are required to use reasonable efforts to insure that any use or disclosure of or request for PHI involves the minimum amount necessary. This clearly requires a pharmacy to look at its internal operations, packaging, and customer service policies to determine that information not needed to complete a transaction is not used or disclosed. For example, the information included on the outside of a prescription package a patient might take to a cashier in a retail pharmacy should be limited to avoid unnecessary disclosures. However, the prescription label, itself, involves pharmacy practice, a treatment activity not subject to the minimum-necessary requirement, and the drug name may be included.

The minimum-necessary requirement applicable to providers in the context of claims submission has been a source of considerable discussion within the industry. Health plans that are asked to approve and pay claims are entitled to ask for information they believe is needed to conduct their functions. Such plans are covered entities that have a specific obligation to apply the minimum-necessary standard before making a request for information,[31] and HHS specifically allows a provider to rely on the request of another covered entity. A pharmacy may, therefore, provide information required by health plans or their PBMs acting as business associates, without liability under the HIPAA privacy rule.[32] Ultimately, the health plan determines what information is needed from providers to authorize payment and to conduct other aspects of their health care operations.

Health Plans

A second type of covered entity directly regulated under the HIPAA standards is the "health plan." A health plan is defined as "an individual or group plan that provides or pays the cost of medical care."[33] The rule provides a nonexclusive list of the types of payers for health services covered by the rule, specifically including insurers, BlueCross BlueShield plans, health maintenance organizations, Medicare and Medicaid, and a number of other government programs. Employee welfare benefit plans are also health plans that are covered entities directly subject to HIPAA (the employer who sponsors an ERISA plan is not a health plan subject to HIPAA, but its health plan is and must meet specific requirements prior to allowing the plan sponsor access to PHI). Since more than 90% of drug spend in America today is covered at least in part by a third party, there will generally be a health plan with HIPAA obligations involved in most pharmacy activities.

As with providers, health plans, including insurers, health maintenance organizations, and ERISA plans, have direct responsibility to meet the HIPAA privacy requirements, providing to individuals the protections and rights under the HIPAA standards and having in place a privacy officer and other administrative requirements.

Some requirements will be virtually impossible for many health plans to meet without assistance. For instance, the transaction standards require that the health plan accept claims from pharmacy providers in the "standard" format (NCPDP 5.1), but a plan typically does not contract directly with pharmacies or communicate with them directly. Rather, most health plans retain a PBM or other administrator to manage the network. The administrator would be a business associate of the health plan and may accept claims or submit payment advice in standard formats on the health plan's behalf.

Health plans may use, disclose, or request PHI for treatment, payment, or health care operations, and may retain business associates to perform these functions. The activities involved in the administration of the drug benefit fall within these definitions. Health plans may use or disclose data for financial, actuarial, and clinical purposes. These functions may include analyses of utilization behavior, financial metrics related to plan performance, or performance of actuarial modeling. Other health care operations may include member and provider fraud and abuse surveillance, retrospective drug utilization review activities, disease and case management, and formulary administration.

Pharmacy Benefit Managers

A health plan may retain a "business associate" to perform functions the health plan would be permitted to perform under HIPAA. For instance, a health plan that offers a retail pharmacy benefit may retain a PBM to manage the pharmacy network and adjudicate claims. In this context, the PBM acts as a business associate of the health plan; it is not a business associate of the pharmacies in its networks.

Acting as a business associate, PBMs offer a broad array of services to health plans. It is useful to think of health plans in 2 groups. One group consists of plan sponsors that are primarily the final payers for the benefit, such as the ERISA plans sponsored by self-insuring employers. These clients tend to be engaged in their core businesses, such as auto manufacturing or financial services, unrelated to health care, and are unlikely to have the capabilities needed to meet HIPAA requirements. They are likely to require from PBMs a broader range of services to meet their HIPAA obligations. For instance, an employer-sponsored health plan may not have customer-service capabilities to accommodate a patient's request for health care information and, therefore, may turn this request back to its PBM.

The second type of health plan consists of clients that are part of the health care delivery system, including HMOs and insurers. These and other participants in health care delivery will likely develop the internal capabilities needed to comply with HIPAA's new requirements. In fact, they will, in turn, often serve as business associates of other payers, such as employers. For these, PBMs need to offer more robust capabilities to support the health plans' systems. For instance, the PBM may provide regular data transmissions for use by the client's customer-service staff. For either type of health plan client, PBMs must be fully prepared to meet the HIPAA standards by the respective deadlines.

First, a PBM must have made substantial investments of money and resources preparing to migrate from older NCPDP versions such as 3.2 and 4.1 to the new NCPDP version 5.1 standard by October 16, 2002. The legal responsibility to conduct transactions in compliance with the standards rests with the health plans, not the PBMs. The health plans look to their business associates—the PBMs—to meet the requirements on their behalf. If a PBM was not ready, therefore, all of the health plan clients would be out of compliance with the transaction standards. Because the extension was not available to a business associate, all of a PBM's clients would have been required to file for an extension. The one-year extension legally available to retail pharmacies was of no practical use to the PBMs or their health plan clients.

Second, a PBM must have made the extensive changes in systems and organization required to establish the new admin-

istrative controls. They must have appointed a privacy officer, conducted gap assessments, developed new policies and procedures, and trained their workforce. They must have entered into appropriate agreements with their vendors to meet the business associate requirement.

Third, a PBM must have the capability to assist the client in making available the 5 patient rights.

Fourth, the PBM must assure that the programs it operates as a business associate of its health plan clients are permitted under HIPAA. As noted in discussing the impact of the privacy rule on health plans, the activities of PBMs in managing the prescription benefit generally fit within the definitions of treatment, payment, or health care operations. The PBM must review its programs and services to assure that the specifics of each are consistent with the privacy rule and are operated consistent with the transactions and other standards where applicable.

Of course, some PBMs have mail and specialty pharmacy subsidiaries that are providers and are "covered entities" under HIPAA and must comply with all of the applicable requirements.

Conclusion

Everyone impacted by HIPAA faces significant effort to achieve compliance. Each of the key participants in the delivery of a funded drug benefit, including pharmacies, the health plans that pay for the benefit, and the PBMs they may retain, has specific obligations under HIPAA. In addition to the direct penalties under the statute, they risk breaching the terms of their business associate agreements and face client or customer loss.

Health plans that retain a PBM must, of course, exercise care and perform a level of due diligence, but, in the end, it is the PBMs themselves that can develop and implement the needed policies and practices. Similarly, managed care organizations and PBMs engaged in managing pharmacy networks must ensure that pharmacies will meet their responsibilities.

Health plans, their business associates, and pharmacies will be working diligently to complete the development work necessary to comply with all of the privacy standards by the April 14, 2003, deadline. At the same time, stakeholders should also be monitoring the finalization of remaining standards and any changes in the newly adopted privacy standards.

Notwithstanding the hundreds of pages of regulations, the HHS preamble to its proposed and final rules, official guidelines, and FAQs issued by HHS, not to mention the thousands of pages of legal analysis, there remains a good deal of ambiguity in what would be appropriate compliance with the various HIPAA standards. The roles of different participants and the specifics of compliance continue to be defined. What is certain, however, is that HIPAA is the law, it is not going away, and compliance is not optional.

DISCLOSURES

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11. Ibid., at page 4. HHS and Congress have put development on hold, and since 1999, Congress has adopted budget language to assure no standard is developed without congressional approval.

12. Although the original proposed electronic signature standard was included together with the proposed security standard (see note 7, above), the subject matter is quite distinct. When the final security rule is published, it may not address electronic signatures.

13. Health Insurance Reform: Announcement of Designated Standard Maintenance Organizations; Notice, 65 FR, No. 160:50373 (2000).

14. See note 5 above.

15. 45 Code of Federal Regulations (C.F.R.) 164.530.

16. 45 C.F.R. 164.520.

17. 45 C.F.R. 164.522.

18. 45 C.F.R. 164.524.

19. 45 C.F.R. 164.526.

20. 45 C.F.R. 164.528.

21. 45 C.F.R. 164.502.

22. E.g., 65 FR at 82471-82472.

23. 45 C.F.R. 164.502 (a)(1)(ii) and 45 C.F.R. 164.506.

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25. 45 C.F.R. 164.502(b).

26. 45 C.F.R. 164.504(e).

27. 45 C.F.R. 160.203.

28. Public Law 104-191 Sec. 1176.

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30. 45 C.F.R. 164.520(c)(2)(ii).

31. 45 C.F.R. 514(d)(4).

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ADDITIONAL RESOURCES

Further information can be found at the official federal HIPAA Web site at http://aspe.hhs.gov/admnsimp.

CONTEMPORARY SUBJECT

2002 White Paper on Pharmacy Technicians

Needed Changes Can No Longer Wait

The counting and pouring now often alleged to be the pharmacist's chief occupation will in time be done by technicians and eventually by automation. The pharmacist of tomorrow will function by reason of what he knows, increasing the efficiency and safety of drug therapy and working as a specialist in his own right. It is in this direction that pharmaceutical education must evolve without delay.

Linwood F. Tice, D. Sc., Dean, Philadelphia College of Pharmacy and Science (1966)[1]

Editor's Note

The "2002 White Paper on Pharmacy Technicians: Needed Changes Can No Longer Wait," endorsed by the Council on Credentialing in Pharmacy, is being printed in its entirety (with an abridged appendix), without alteration. It is being printed simultaneously in a number of journals.

Introduction

Health care and the profession of pharmacy have changed enormously since Dr. Tice articulated this vision more than 35 years ago. The role of the pharmacy technician has likewise undergone substantial change. Technicians have increased in number. They may access a wide array of training opportunities, some of which are formal academic programs that have earned national accreditation. Technicians may now seek voluntary national certification as a means to demonstrate their knowledge and skills. State boards are increasingly recognizing technicians in their pharmacy practice acts.

Nonetheless, Dr. Tice's vision remains unrealized. Although pharmacy technicians are employed widely in all pharmacy practice settings, their qualifications, knowledge, and responsibilities are markedly diverse. Their scope of practice has not been sufficiently examined. Basic competencies have not been articulated. Standards for technician training programs are not widely adopted. Board regulations governing technicians vary substantially from state to state.

Is there a way to bring greater uniformity in technician competencies, education, training, and regulation while ensuring that the technician workforce remains sufficiently diverse to meet the needs and expectations of a broad range of practice settings? This is the question that continues to face the profession of pharmacy today as it seeks to fulfill its mission to help people make the best use of medications.

The purpose of this paper is to set forth in context the issues that must be resolved in order to promote the development of a strong and competent pharmacy technician workforce. Helping pharmacists to fulfill their potential, as providers of pharmaceutical care, would be one of many positive outcomes of such a development. The paper begins with a description of the evolution of the role of pharmacy technicians and of their status in the workforce today. The next section sets forth a rationale for building a strong pharmacy technician workforce. The paper then turns to three issues that are key to realizing the pharmacy technician's potential: (1) education and training; (2) accreditation of training institutions and programs; and (3) certification. Issues relating to state regulation of pharmacy technicians are then discussed. The paper concludes with a call to action and summary of major issues to be resolved.

Many of the issues discussed in this report were originally laid out in a white paper developed by the American Pharmaceutical Association (APhA) and the American Society of Health-System Pharmacists (ASHP) and published in 1996.[2] For this reason, this paper focuses primarily on events that have occurred since that time. Other sources used in the preparation of this paper include Institute of Medicine (IOM) reports,[3,4] a report to the U.S. Congress on the pharmacy workforce,[5] and input from professional associations representing pharmacists and technicians as well as from educators, regulators, and consumers.

The Pharmacy Technician: Past to Present

A pharmacy technician is "an individual working in a pharmacy [setting] who, under the supervision of a licensed pharmacist, assists in pharmacy activities that do not require the professional judgment of a pharmacist."[6] The technician is part of a larger category of "supportive personnel," a term used to describe all non-pharmacist pharmacy personnel.[7]

There have been a number of positive developments affecting pharmacy technicians in the past decade, including national certification, the development of a model curriculum for pharmacy technician training and greater recognition of pharmacy technicians in state pharmacy practice acts. The role of the pharmacy technician has become increasingly well defined in both hospital and community settings. Technicians have gained greater acceptance from pharmacists, and their numbers and responsibilities are expanding.[8-11] They are starting to play a role in the governance of state pharmacy associations and state boards of pharmacy. Yet more needs to be done. There is still marked diversity in requirements for entry into the pharmacy technician workforce, in the way in which technicians are educated and trained, in the knowledge and skills they bring to the workplace, and in the titles they hold and the functions they perform.[12,13] The absence of uniform national training standards further complicates the picture. Because of factors such as these, pharmacists and other health professionals, as well as the public at large, have varying degrees of understanding and acceptance of pharmacy technicians and of their role in health care delivery.

An awareness of developments relevant to pharmacy technical personnel over the last several decades is an essential starting point for any discussion of issues related to pharmacy technicians today and in the future. That information is available in detail elsewhere.[14,15] A summary of key events of the past half-century appears in the following paragraphs.

1950s–1990s

Beginning in the late 1950s, hospital pharmacy and the American Society of Hospital Pharmacists (ASHP) took the lead in advocating utilization of pharmacy technicians (although the term itself had not come into use at the time), in developing technician training programs, and in calling for changes needed to ensure that the role of technicians was appropriately articulated in state law and regulations.[16] Among the initial objectives was to make a distinction between tasks to be performed by professional and by nonprofessional staff in hospital and community settings. This was largely accomplished by 1969.[17,18]

In the community pharmacy sector, chain pharmacies supported the use of pharmacy technicians and favored on-the-job training. By contrast, the National Association of Retail Druggists (NARD, now the National Community Pharmacist Association [NCPA]), in 1974, stated its opposition to the use of technicians and other "subprofessionals of limited training," out of concern for public safety.[14]

Largely because of its origins, technician practice was initially better defined and standardized in hospitals than in community pharmacies. As the need for technicians in both settings became increasingly apparent, however, many pharmacists and pharmacy educators began to call for collaborative discussions and greater standardization on a number of issues related to pharmacy technicians, and in recent years, progress has been made toward this goal.

The Pharmacy Technician Workforce Today

Based on Pharmacy Technician Certification Board (PTCB) and Bureau of Labor Statistics (BLS) estimates, there are as many as 250,000 pharmacy technicians in the United States.[8,19] This is a significant increase over the 1996 estimate of 150,000.[2] The BLS predicts that pharmacy technician employment will grow by 36 percent or more between 2000 and 2010.[8] This percentage growth is "much faster than the average for all occupations", but in line with that of a majority of other supportive personnel in the health sector.

Pharmacy technicians work in a wide variety of settings, including community pharmacies (approximately 70% of the total workforce), hospitals and health systems (approximately 20%), long-term care facilities, home health care agencies, clinic pharmacies, mail-order pharmacies, pharmaceutical wholesalers, managed care organizations, health insurance companies, and medical computer software companies.[8] The 2001 Schering Report showed that nine out of ten community pharmacies employ pharmacy technicians.[10] Recent studies in acute care settings indicate that this figure would be nearly 100% for the hospital sector.[20]

What functions do technicians perform? Their primary function today, as in decades past, is to assist with the dispensing of prescriptions. A 1999 National Association of Chain Drug Stores (NACDS)/Arthur Andersen study showed that, in a chain pharmacy setting, pharmacy technicians' time was taken up with dispensing (76%), pharmacy administration (3%), inventory management (11%), disease management (< 1%), and miscellaneous activities, including insurance-related inquiries (10%).[21] Surveys by the PTCB have yielded similar results.[19,22] The nature of dispensing activities may be different in a hospital than in a community pharmacy; in hospitals, technicians may perform additional specialized tasks, such as preparing total parenteral nutrition solutions and intravenous admixtures, preparing medications used in clinical investigations, and participating in nursing unit inspections.[22]

In the past, pharmacists traditionally have been reluctant to delegate even their more routine work to technicians.[14] The 2001 Schering Report concluded that, in the past five years, pharmacists have become more receptive to pharmacy technicians. And indeed, much has changed in the scope of potential practice activities for pharmacy technicians, as well as pharmacy's perception of the significant role technicians might play.[10,23] New roles for pharmacy technicians continue to emerge as a result of practice innovation and new technologies.[9,11] Regardless of their expanded responsibilities, however, many technicians feel they can do more. For example, one study reported that 85% of technicians employed in chain pharmacies, compared with 58% of those working in independent pharmacies, felt that their knowledge and skills were being used to the maximum extent.[10]

Pharmacy Technicians: The Rationale

Several developments in health care as a whole, and in pharmacy in particular, combine to create an increasing demand for pharmacy technicians; three of significant importance are: (1) the pharmacist workforce shortage, (2) the momentum for pharmaceutical care, and (3) increased concern about safe medication use.

Pharmacist Workforce Shortage

In 1995, a report by the Pew Health Professions Commission predicted that automation and centralization of services would reduce the need for pharmacists, and that the supply of these professionals would soon exceed demand.[24] The predicted oversupply has failed to materialize; in fact, there is now a national shortage of pharmacists. A 2000 report of the federal Health Resources and Services Administration (HRSA) states: "While the overall supply of pharmacists has increased in the past decade, there has been an unprecedented demand for pharmacists and pharmaceutical care services, which has not been met by the currently available supply."[5] The workforce shortage is

affecting all pharmacy sectors. Ongoing studies (by the Pharmacy Manpower Project and other researchers) indicate that the pharmacy manpower shortages will not be solved in the short-term.[25]

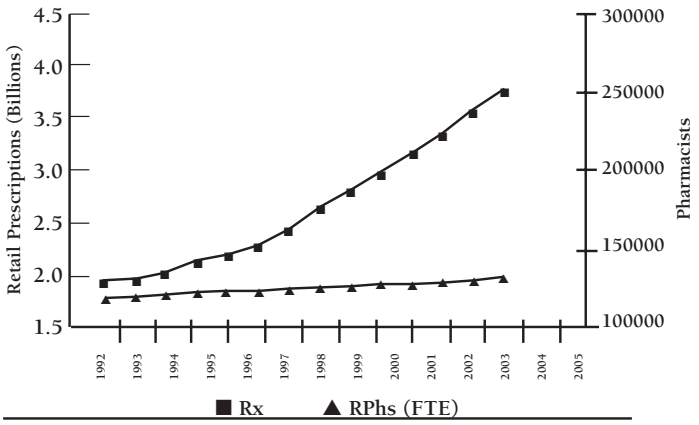
For pharmacy practitioners, the results of the workforce shortage are clear: more work must be done with fewer pharmacist staff. Between 1990 and 1999, the number of prescriptions dispensed in ambulatory-care settings increased by 44%, while the number of active pharmacists per 100,000 population increased by only about 5%.[5] Chain pharmacists now fill an average of 86 prescriptions during a normal shift – a 54% increase since 1993.[26] NACDS/IMS HEALTH estimate that between 1999 and 2004, the number of prescriptions will increase by 36% while the number of pharmacists will increase by only 4.5%.[27] (Refer Figure 1.)

Faced with greater numbers of prescriptions to dispense, pharmacists have less time to counsel patients. Working conditions and schedules have deteriorated, and job-related stress has risen.[10] Professional satisfaction has diminished. Perhaps most ominous, fatigue and overwork increase the potential for medication error.[5,28]

Increased use of technicians is one obvious way of reducing workload pressures and freeing pharmacists to spend more time with patients. A white paper issued in 1999 by APhA, NACDS, and NCPA emphasized the need for augmenting the pharmacist's resources through the appropriate use of pharmacy technicians and the enhanced use of technology.[29]

The situation in pharmacy is not unique. A report from the Institute of Medicine concludes that the health care system, as currently structured, does not make the best use of its resources.[4] Broader use of pharmacy technicians, in itself, will not solve the pharmacist workforce crisis. It would ensure, however, that the profession makes better use of existing resources.

FIGURE 1 *Community Prescriptions and Pharmacists 1992–2005*



Source: IMS Health and NACDS Economics Department

Momentum for Pharmaceutical Care

More than a decade ago, Hepler and Strand expressed the societal need for "pharmaceutical care."[30] Since that time, the concept has been refined and its impact on the health care system and on patient care has been documented. Studies have shown that pharmaceutical care can improve patient outcomes, reduce the incidence of negative therapeutic outcomes, and avoid the economic costs resulting from such negative outcomes.[31-34] Nonetheless, other studies indicate that pharmacists continue to spend much of their time performing routine product-handling functions.[20,21] Widespread implementation of pharmaceutical care, a goal for the entire profession, has been difficult to achieve thus far.

Technicians are instrumental in the advancement of pharmaceutical care. As Strand suggests, prerequisites to successful implementation of pharmaceutical care include: enthusiastic pharmacists, pharmacy supportive personnel willing to work in a pharmacy where dispensing is done by technicians rather than pharmacists, and a different mindset—i.e., the pharmacist will no longer be expected to "count and pour" but to "care for patients."[35,36]

Implementation of pharmaceutical care, in other words, requires a fundamental change in the way pharmacies operate. Pharmacists must turn over routine product-handling functions to competent technicians and technology. This is a difficult shift for many pharmacists to make and pharmacists may need guidance on how to make it. For example, they may need training in how to best use and work with technicians. In recognition of this need, some practice sites have developed successful practice models of pharmacy technicians working with pharmacists to improve patient care. Several of these have been recognized through the PTCB "Innovations in Pharmaceutical Care Award."[37]

Safe Medication Use

Used inappropriately, medications may cause unnecessary suffering, increased health expenditure, patient harm, or even death.[34] Ernst and Grizzle estimated the total cost of drug-related morbidity and mortality in the ambulatory care setting in 2000 at more than $177 billion – more than the cost of the medications themselves.[38] They stressed the urgent need for strategies to prevent drug-related morbidity and mortality.

The problems associated with inappropriate medication use have received broad publicity in recent years. For example, To Err Is Human: Building a Safer Health System, published by the Institute of Medicine in 2000, drew attention to medical errors.[3] It criticized the silence that too often surrounds the issue. Many members of the public were shocked to realize that the system, in which they place so much trust, was far from perfect.

Sometimes pharmacists have been implicated in medication errors. Technicians, too, have not escaped culpability.[39-44] Several studies, most of which were performed in hospitals, have, however, demonstrated that appropriately trained and supervised pharmacy technicians can have a positive effect on equalizing

the distributive workload, reducing medication errors, allowing more time for clinical pharmacy practice, and checking other technical personnel.[45,46] One study showed that pharmacy technicians, when specially trained for the purpose, were as accurate as pharmacists in checking for dispensing errors.[47] The United States Pharmacopoeia Medication Errors Reporting Program (USP MERP) has noted the contribution that pharmacy technicians can make to medication error prevention in the course of their involvement in inventory management (e.g., identifying problems relating to "look-alike" labeling and packaging).[48] USP MERP also believes that a "team approach" and "proactive attitudes" by pharmacists and technicians are important elements in reducing medication errors.[48] The National Coordinating Council for Medication Error Reporting and Prevention advocates that a series of checks be established to assess the accuracy of the dispensing process and that, whenever possible, an independent check by a second individual (not necessarily a pharmacist) should be used.[49]

Reports such as these call for an expanded role for pharmacy technicians in a much-needed, systematic approach to medication error prevention.

Preparing Pharmacy Technicians for Practice

Historical Overview

Originally, all pharmacy technicians received informal, on-the-job training. The majority of pharmacy technicians are probably still trained in this way.[8,19,50,51] Nevertheless, formal training programs, some of which are provided at the work site, are becoming more widespread. As state regulations, procedures, medications, record-keeping, and insurance requirements have become more complex, there has been a move toward more formal programs.[19,52] Some employers have found that formal training improves staff retention and job satisfaction.[19,53] Another advantage of a formal training program is that it can confer a sense of vocational identity.[50]

Formal training programs for pharmacy technicians are not new; they were introduced in the armed forces in the early 1940s, and more structured programs were developed by the military in 1958. In the late 1960s, the Department of Health, Education and Welfare recommended the development of "pharmacist aide" curricula in junior colleges and other educational institutions.[54] The first formal hospital-based technician training program was initiated around this time.[14] Training programs proliferated in the 1970s as the profession sought to meet the need for a differentiated pharmacy workforce.[55] Many of these programs were established in response to requests from hospital pharmacy administrators; there was at that time little interest informally trained technicians in community pharmacies, which continued to train technicians on the job.[56]

In the 1980s, ASHP issued training guidelines that were intended to help hospital pharmacists develop their own training programs.[7] ASHP recommended minimum entry requirements for trainees and a competency evaluation that included written, oral, and practical components. The guidelines were used not only by hospitals but also by vocational schools and community colleges that wanted to develop certificate and associate degree programs.[50]

Acknowledging the importance of a common body of core knowledge and skills for all pharmacy technicians that would complement site-specific training, the NACDS and NCPA developed a training manual that is arranged into nine instructional sections and a reference section.[57] Each section has learning objectives, self-assessment questions, and competency assessment for the supervising pharmacist to complete. The manual focuses on the practical, legal, and procedural aspects of dispensing of prescriptions, sterile product compounding, patient interaction, and reimbursement systems. APhA and ASHP also produce technician-training manuals and resource materials for pharmacy technicians.[58]

To date, most programs have referred to the "training", rather than the "education" of pharmacy technicians. Following a review of these "training" programs, further discussion of the need for clarification of the "education" and "training" needs of pharmacy technicians is provided below.

Academic Pharmacy Technician Training Programs

In 2001, approximately 247 schools or training institutions in 42 states offered a range of credentials, including associate degrees, diplomas, and certificates, to pharmacy technicians. The military also continues to provide formal training programs for pharmacy technicians.

Formal technician training programs differ in many respects, one of which is length. The *Accrediting Commission of Career Schools and Colleges of Technology Directory* lists 36 "pharmacy" programs.[12] These programs vary in length from 540 to 2145 contact hours (24 to 87 weeks), with a median of 970 hours. ASHP, which accredits technician training programs, requires that programs have a minimum of 600 contact hours and a minimum duration of 15 weeks.[59] The Pharmacy Technicians Educators Council (PTEC), an association representing pharmacy technician educators, supports the ASHP minimum.[60]

The minimum acceptable length of the program is a matter of debate. Some pharmacy technician educators deplore a move within the education system to get people into the workforce quickly. They feel that the pharmacy profession should make it clear that, while workforce shortages and the needs of the marketplace are an important consideration, rapid-training strategies do not seem appropriate for health care personnel whose activities impact directly on the safe and effective use of medications.[52] There should be a clear relationship between the nature and intensity of education and/or training, and the scope of practice.Entrance requirements for training programs also vary. Some have expressed concern that a substantial number of trainees may lack the necessary basic skills and aptitude to perform the functions expected of technicians.[52] The fact that about

30% of a certified pharmacy technician's time is spent performing tasks that require mathematical calculations reinforces the importance of suitably qualified training applicants.[22] ASHP acknowledged the need for minimum qualifications for training program applicants more than 20 years ago, but the issue continues to be a matter of discussion.[7]

Progress Toward Standardization: The Model Curriculum

The absence of national training standards and the resultant variations in program content, length, and quality are barriers to the development of a strong technician workforce. The problem is not unique to pharmacy technician training; other occupations in the health care sector also lack national standards. Nonetheless, it would seem ironic that persons in certain other occupations whose services have far less impact on public safety than do those of pharmacy technicians (for example, barbers and cosmetologists) have training programs that, on average, are longer and less diverse than are pharmacy technician programs.[61] Reflecting a common sentiment on this issue, a 1999 PTEC survey concluded that, "Expansion of the role of pharmacy technicians must be in tandem with standardizing training and establishment of competencies. Increased responsibilities should be commensurate with increased education…"[62] Likewise, there was a consensus at the Third PTCB Stakeholders' Forum, held in June 2001, that national standards for pharmacy technician training are needed.[63]

Progress toward standardization has been facilitated by the *Model Curriculum for Pharmacy Technician Training*.[64] Having taken the initiative and the leadership role, ASHP collaborated with several other pharmacy associations (APhA, the American Association of Pharmacy Technicians, PTEC, the American Association of Colleges of Pharmacy [first edition only] and NACDS [second edition only]) to develop the model curriculum. The first edition, released in 1996, was based on the findings of the 1992–1994 *Scope of Pharmacy Practice Project*.[65] Many of the revisions in the second edition, released in 2001, were based on a 1999 PTCB task analysis, and took into account changes in the scope of activities of today's pharmacy technicians, as well as changes expected to occur over the next five years.[22,23] Significant changes were made, for example, in sections dealing with the technician's role in enhancing safe medication use and in assisting with immunizations, and with "tech-check-tech", (a system where pharmacy technicians are responsible for checking the work of other technicians, with minimal pharmacist oversight).

The organizations that developed the model curriculum do not expect that every training program will cover every goal and objective of the curriculum; rather, the curriculum should be seen as a "menu" of possible learning outcomes. The model curriculum provides a starting point for identifying core competencies for pharmacy technicians.[23] It acknowledges the need for a level of understanding of basic therapeutics, anatomy, physiology, and pharmacology. The curriculum does not include recommendations regarding the relative amount of time that should be allotted to each module, but such guidelines are under consideration.[66]

The Future Preparation of Pharmacy Technicians: Education versus Training

Virtually all the consensus-development meetings and studies that have investigated training requirements for pharmacy technicians have called for the development of standardized training in some form.[52,67] APhA and ASHP concur with this position.[2,68,69]

Such a recommendation would best be accompanied by two important caveats. The first is that any national standards for education and training of pharmacy technicians will not eliminate the need for additional, site-specific training that focuses on local policies and procedures.[52,63] Second, a standards-based education or training can, conceivably, be delivered successfully in a variety of different settings.

However, is it clear what exactly is meant when the terms "education" and "training" are applied to pharmacy technicians? They have tended in the past to be used somewhat interchangeably. There is, however, a distinction that needs to be made, and a balance between the two that needs to be reached, to ensure that pharmacy technicians are adequately and appropriately prepared to perform, in a safe and efficient manner, the functions and responsibilities that are assigned to them — both now and in the future. As has already been noted in this paper, the roles and responsibilities of pharmacy technicians have evolved and expanded in recent years. While, in the main, pharmacy technicians perform routine tasks that do not require the professional judgment of a pharmacist, state pharmacy practice acts now recognize that pharmacy technicians are being assigned new and different functions in the practice setting, some of which may require a level of judgment and/or product knowledge and understanding.

Training involves learning through specialized instruction, repetition and practice of a task, or series of tasks, until proficiency is achieved. Education, on the other hand, involves a deeper understanding of a subject, based on explanation and reasoning, through systematic instruction and teaching. Conceivably a person may be proficient in performing a task, without knowing why they are doing it, what its importance is, or the logic behind the steps being performed. While education (as described above) may involve a training component, both are vital to the learning (or preparation) of the technician. Barrow and Milburn give a useful treatise on this subject.[70] The education and training of pharmacy technicians (and other supportive personnel) must be commensurate with the roles they are performing. To ensure quality, both the education and training components should be standards-based.

Accreditation of Pharmacy Technician Education and Training

The Council on Credentialing in Pharmacy (CCP) defines

accreditation as "the process by which a private association, organization, or government agency, after initial and periodic evaluations, grants recognition to an organization that has met certain established criteria." [71] Accreditation is an integral aspect of ensuring a quality educational experience.

For pharmacy technician education and training, there are two types of accreditation — programmatic (also referred to as "specialized") and institutional. Programmatic accreditation focuses specifically on an individual program, whereas institutional accreditation evaluates theeducational institution as a whole, with less specific attention being paid to the standards of individual programs offered by the institution. Institutional accreditors operate either on a regional or national basis; the latter usually having a more focused area of interest. A system of dual accreditation, where institutional accreditation is carried out by regional accrediting bodies and programmatic accreditation is carried out by the American Council on Pharmaceutical Education (ACPE), has worked well for schools and colleges of pharmacy since the 1930s.

Based on information obtained from published directories, it is estimated that only 43% of the 247 schools and training institutions referred to earlier are accredited by bodies specializing in technical, allied health and para-professional education, 36% have their programs accredited by ASHP and 12% are accredited by both ASHP and one, or more, of the institutional accrediting bodies specializing in technical, allied health and para-professional education.

Institutional Accreditation

For institutions offering pharmacy technician training, national institutional accreditation is carried out by at least four agencies — the Accrediting Commission of Career Schools and Colleges of Technology (ACCSCT), the Accrediting Bureau of Health Education Schools (ABHES), the Council on Occupational Education (COE) and the Accrediting Council for Independent Colleges and Schools (ACICS). All of these agencies are recognized by the U.S. Department of Education. None have a formal national affiliation with the profession of pharmacy.

Because there are no nationally adopted standards for pharmacy technician training, it is difficult for institutional accrediting bodies to set detailed program requirements. ACCSCT standards require programs to have an Advisory Committee, the majority of whose members represent employers in the field of training.[72] ABHES has a suggested curriculum outline for pharmacy technician programs. In an effort to improve the quality of their programs, COE and ABHES plan to switch from institutional to program accreditation.[73] Of some concern is the fact that such accreditation systems (for pharmacy technician training programs) would be outside the pharmacy profession, and would not be based on standards recognized nationally by the profession.

Program Accreditation

Program accreditation for technician training is offered by the American Society of Health-System Pharmacists. ASHP accreditation of technician training programs began in 1982 at the request of hospital pharmacists. Many hospital-based technician training programs were already using ASHP guidelines and standards, but they expressed a need for a more formal method of oversight to ensure the quality of training. ASHP already accredited pharmacy residency programs, and moving into technician accreditation seemed a logical step.

Initially, nearly all ASHP-accredited programs were hospital based. This is no longer the case; of the nearly 90 technician-training programs currently accredited by ASHP, only three are hospital based. Over 90% of programs are located at vocational, technical, or community colleges.[74]

The objectives, standards, and regulations of the accreditation program, as well as a directory of accredited programs, are available on the ASHP Web site.[59,74-76] The accreditation standards are geared toward preparing technicians for all practice settings and, therefore, require that pharmacy technicians be trained in a wide variety of practice environments, and that they complete laboratory exercises before beginning their experiential training.

While accreditation is voluntary for both pharmacy degree programs and technician-training programs, an important distinction exists. State boards of pharmacy and NAPLEX[77] have recognized ACPE accreditation as an eligibility for the pharmacist licensing examination. Completion of an accredited program is not usually a prerequisite for employment, registration, or certification as a pharmacy technician. However, accreditation does bring a number of benefits. For the program, the benefits include enhanced recruitment potential for trainees, improved marketing, and the opportunity for peer review and quality improvement. For employers, completion of an accredited program may be an indication of the level of competence of a technician. Most importantly, accreditation provides all stakeholders with an objective, external, and independent evaluation of the quality of the education or training experience. Employers have a strong interest in the quality of training of their employees, not least of which is in terms of potential liability issues were they also to be the provider of the training. It would, therefore, also appear to be in the best interests of employers for the onus of quality assurance to rest with an independent party.

A New Role for ACPE?

ASHP recognizes that the education, training and utilization of pharmacy technicians now has broader professional implications than it did when it introduced its accreditation program nearly 20 years ago. For this reason, ASHP has asked the American Council on Pharmaceutical Education (ACPE) to explore assuming responsibility for this function. Many people now believe that accreditation is best carried out by an independent agency that has no direct or indirect interest in the provision of training or in the activities of the graduates of the training program.[78]

Involving ACPE might have an additional advantage, should a decision be made to develop national training standards. ACPE, which has broad experience spearheading collaborative efforts to develop educational standards for pharmaceutical education, could be an appropriate organization to lead the process of developing uniform national standards for technician education and training. Responses to a 2000 ACPE survey indicate strong support for an ACPE role in this area.[79]

Certification of Pharmacy Technicians

Certification is the process by which a non-governmental agency or association grants recognition to an individual who has met certain predetermined qualifications specified by that agency or association.[2] For pharmacy, the Pharmacy Technician Certification Board, created in 1995, has been one of the most positive developments of the past half-decade."Certified Pharmacy Technician," or CPhT, is the only national credential available to pharmacy technicians. A credential is documented evidence of an individual's or program's qualifications or characteristics. Credentials may include diplomas, licenses, certificates, and certifications.[71] The Council on Credentialing in Pharmacy (CCP) was established in 1999. The development and application of credentialing standards for the pharmacy profession are integral components of CCP's vision and mission statements. PTCB was one of CCP's founding organizations. For a pharmacy technician, certification is an indication of the mastery of a specific core of knowledge.[2] Certification is mainly voluntary, although some state boards of pharmacy have moved to requiring certification (see section entitled "Regulation of Pharmacy Technicians").

The PTCB examination is based on a task analysis that defined the work of pharmacy technicians nationwide: 64% of the exam is based on knowledge required to assist the pharmacist in serving patients; 25% on medication distribution and inventory control systems; and 11% on the administration and management of pharmacy practice.[22] By the end of 2001, more than 100,000 technicians had been certified under this program.[37] CPhTs must renew certification every two years and complete at least 20 hours of pharmacy-related continuing education (including an hour of pharmacy law) over that period.

For many technicians, achieving PTCB certification is an important part of their professional development.[19] Many pharmacy chains have recognized the value of certification, and provide assistance and incentives to staff to achieve certification, including reimbursement of costs, advancement to a higher grade, and a salary increase.[19] Studies have revealed that certified technicians remain in practice longer than non-certified technicians do. Staff turnover of both pharmacists and technicians has gone down in pharmacies employing certified technicians. Improved staff morale, higher productivity, reduced errors, and higher levels of customer satisfaction have also been noted.[80,81] Additional benefits for employers include improved risk management, reduced technician training times and lower training costs.[82] Some pharmacists feel more confident delegating dispensing activities to certified technicians than to technicians who are not certified.[10,22]

PTCB recognizes the need to reassess and modify its policies and procedures, as well as the examination, in response to the changing needs of practice and of the profession, as well as trends in the marketplace. To make such assessments, PTCB engages in research and seeks input from its stakeholders. PTCB also reviews its eligibility criteria for candidates who wish to sit for the certification examination. Under consideration are specialty certification assessments in areas such as preparation of intravenous admixtures and third party payment systems.

Regulation of Pharmacy Technicians

Introduction

For many years, most state boards of pharmacy, often reflecting the attitudes of pharmacists, opposed recognizing technicians and expanding the scope of their activities.[52,83] As pharmacists' roles changed and use of supportive personnel expanded, these attitudes began to shift. Over thepast five years, a majority of states have revised their pharmacy practice acts in areas related to technicians. Today, Ohio is the only state that does not formally address pharmacy technicians in state statutes or regulations.

The National Association of Boards of Pharmacy (NABP) regularly surveys state pharmacy practice acts. The results of these surveys are bellwethers of change at the state level; collectively, they reveal trends. The most recent survey was done in 2001.[13] To highlight changes that have taken place since the publication of the 1996 White Paper, the results of NABP's 1996/1997[84] and 2001/2002 surveys are compared. The NABP also appoints task forces to study and make recommendations on major issues. The deliberations of these task forces have resulted in, among other things, a call for formal recognition of pharmacy technicians, simplified state registration procedures, site-specific training, a national technician competency exam, and a disciplinary clearinghouse. Key developments in regulation, as evidenced in the NABP surveys, and in recent NABP task force recommendations and actions, are summarized in the following paragraphs.

Changes in State Regulations: 1996–2001

Terminology. In the 1996/1997 NABP survey, at least 11 terms were used to describe pharmacy supportive personnel. At that time, 24 states used the term "pharmacy technician." By 2001, 38 states had adopted this designation.

Technician Registration. In its "model act", designed to provide boards of pharmacy with model language that may be used when developing state laws or board rules, NAPB advocates that pharmacists be licensed and that pharmacy technicians be registered.[85] "Registration" is defined as the process of making a list or being included on a list. It carries no indication or guarantee of the registrant's knowledge or skills. "Licensure" is the process by which an agency of government grants permission to

an individual to engage in a given occupation upon finding that the applicant has attained the minimal degree of competency necessary to ensure that the public health, safety and welfare will be reasonably well protected.[2] Like NABP, ASHP and APhA support registration and oppose licensure of pharmacy technicians. APhA and ASHP believe that licensed pharmacists must retain responsibility and accountability for the quality of service in a pharmacy.[68,69,86]

By 2001, 24 states required registration and 5 required "licensure" of pharmacy technicians, in line with the NABP recommendations. Although the term "license" is used in these regulations, in some cases the process would appear to more closely resemble "registration", in terms of the definitions used in this paper. The increase in the number of states (up from 14 in 1996) that now require either registration or licensure of pharmacy technicians, is noteworthy.

Pharmacist: Technician Ratios. Since 1996, at least 25 states have liberalized their pharmacist: technician ratios (from a norm of 1:1 or 1:2, to a norm of 1:2 or 1:3). Some states further relaxed ratios in sites where certified pharmacy technicians are employed. In their 1996 white paper, APhA and ASHP called for a reassessment of mandated arbitrary pharmacist: technician ratios.[2] This stance reflects the organizations' conviction that the pharmacist should be responsible andaccountable for pharmacy technicians under their charge.[68,69] NACDS believes that each practice setting should be allowed to determine its own optimal ratio.[87] Following the recommendation of a 1999 Task Force on Standardization of Technicians' Roles and Competencies,[88] NABP encouraged states to modify or eliminate ratios in pharmacy settings with quality assurance programs in place.

Standard Training Requirements. Between 1996 and 2001, the number of states that had incorporated training requirements into their regulations rose by 34% (from 19 to 26). Training requirements had been recommended in 1996 by an NABP task force.

The training requirements that state boards have put in place are in some cases minimal. Many states require nothing more than a training manual; there are no detailed minimum requirements. Some states, on the other hand, have enacted competency-based regulations, or well-defined standards for training program assessment.[89] Some states require continuing education for renewal of registration or licensure; others are considering such a requirement.

Technician Certification. A small number of states have made certification a requirement for registration or licensure.[90] Texas was the first to introduce the requirement in 1996. The law was implemented in January 2001; a provision exists, however, for certain technicians to be exempted.[91] In Utah, the licensing authority has defined compliance with minimum training standards, as well as certification and the passing of a law examination, as requirements for licensure.[92] Some states have altered pharmacist:technician ratios, responsibilities, supervision, or other requirements on the basis of a technician's certification status.[93]

Levels of Personnel and Scope of Practice. Based on findings of its 1999 task force (referred to above), NABP has recognized two levels of supportive personnel — "pharmacy technician" and "certified pharmacy technician", and specified the scope of practice that would be allowed for technicians working under the supervision of a pharmacist.[94-96] The task force had recommended a third, and higher, level of supportive personnel - the "pharmacist assistant" — but the NABP did not adopt this recommendation. APhA and ASHP likewise oppose the creation of this category of supportive personnel.[68,69]

Many of the changes in state regulations are reflected in the functions that technicians perform. For example, the number of states allowing a pharmacy technician to "Call physician for refill authorization" increased by 41% (from 25 to 36) in a hospital/institutional setting and by 47% (from 24 to 36) in a community setting between 1996 and 2001. Few states have traditionally allowed pharmacy technicians in any work setting to accept called-in [new] prescriptions from a physician's office, and there was little change in this area in the last five years. There was likewise little change in the dispensing-related activities that pharmacy technicians perform; however, the percentage of states allowing these activities was already high (generally > 85% in 1996). The only dispensing-related activity to show a more than 15% increase (in the number of states that allow it) in the past five years is "Reconstitution of oral liquids," which increased by 22% (from 41 to 51) in hospitals and by 23% (from 40 to 50) in community settings. In the hospital/institutional setting, the number of states allowing technicians to "Compoundmedications for dispensing" increased by 33% (from 34 to 46); the number increased by 24% (from 34 to 43) in the community setting.

Competency Assessment. In May 2000, NABP resolved that it would: (1) develop a national program to assess the competencies necessary for technicians to safely assist in the practice of pharmacy, (2) review existing technician certification programs to determine whether the development of its competence assessment program should be a cooperative effort with other groups, and (3) urge state boards to use this program as one criterion in determining the eligibility of technicians to assist in the practice of pharmacy.[97] NABP has now joined PTCB on the national certification program for pharmacy technicians, and will work with state boards of pharmacy to encourage acceptance of the PTCB certification program as a recognized assessment tool for pharmacy technicians.[98] The use of the PTCB certification program will also be incorporated into *NABP's Model State Pharmacy Act and Model Rules.*

The Need for Regulation

The difficulties stemming from lack of regulatory oversight over pharmacy technicians go further than one might initially foresee. For example, if state regulations do not recognize a class of personnel (through registration or licensure), it is difficult to

discipline such personnel in the event of misconduct. Several state boards have reported that the absence of such regulation is creating problems.[99] For example, in the absence of adequate controls, pharmacy technicians, who have committed an act of misconduct, such as drug diversion, can move from site to site, or state to state, without being traced or being held accountable. NABP, and many state executives and pharmacists have called for better systems of control and measures to track disciplinary actions. By 2000, at least 25 states had incorporated disciplinary procedures for technicians in their regulations.[97]

Among the regulatory issues that remain in flux, none is more important than defining the roles and responsibilities of supportive personnel and the titles they are assigned. Pharmacy supportive personnel perform a wide array of services. Some state regulations recognize this and have differentiated levels of supportive personnel; some states have specific requirements for technicians-in-training. Multiple levels of pharmacy supportive personnel may continue to be required in the future, and the levels may vary among and within practice settings. The profession needs to determine what these levels should be and to define the role and function, competencies, education, training, and level of supervision appropriate for each.

Time for Action

Pharmacy faces a serious workforce shortage at a time when the public and health care providers alike are looking to pharmacists to assume expanded responsibility for better medication use. Better use of human resources is essential. When pharmacists limit their direct involvement in the technical aspects of dispensing, delegate this responsibility to pharmacy technicians working under their supervision, and increase the use of automated dispensing technology, they can fully concentrate on the services for which they are uniquely educated and trained. Only then will Dr. Tice's vision of the future become reality.

The utilization, education, training, and regulation of pharmacy technicians have changed dramatically in the past five years. National certification has played a particularly important role in these changes. Nonetheless, many challenges remain. Because these challenges are interrelated, resolving them requires a coordinated approach. The profession needs a shared vision for pharmacy technicians and other supportive personnel. This vision will provide the framework within which further necessary change can take place. Beginning with that much-needed vision, the major issues to be discussed and resolved might be expressed as follows:

Vision

- Define a vision for pharmacy technicians as an integral part of the vision and mission of the profession of pharmacy.
- Develop goals, objectives, and strategies to realize this vision, including determining who will lead the process and the specific roles, present and future, of all parties;
- Communicate the vision and goals to all stakeholders, including policy makers and the public.

Roles, Responsibilities, and Competencies

- Define the different levels of pharmacy supportive personnel and the responsibilities or functions appropriate for individuals at each level.
- Determine the competencies required for high-level performance at each level.

Education and Training

- Establish standards (including eligibility criteria) for the education and training of each level of pharmacy supportive personnel.
- Establish requirements for maintenance of competence, where applicable, and create the systems to achieve this.
- Consider the cost implications of any new training model, and devise appropriate strategies to address cost concerns.

Credentialing and Accreditation

- Develop or enhance appropriate credentials, in collaboration with PTCB and the Council on Credentialing in Pharmacy (CCP), to reflect what is happening and required in practice.
- Determine what the most appropriate systems of accreditation for education and training programs for pharmacy technicians are, and who should lead this process on behalf of the profession.

Regulation

- Determine the appropriate regulatory framework under which pharmacy technicians can optimally contribute to the achievement of pharmacy's mission.
- Work to bring about further changes in state pharmacy practice acts and regulations in order to achieve the desired regulatory framework.
- Work to bring about the development and adoption of standardized definitions and terminology for pharmacy supportive personnel.

Conclusion

Change does not come easily, and it is seldom embraced by everyone. As Kenneth Shine, M.D., put it, when discussing the need for change in the health system: "The issue…will be whether these needed changes occur only begrudgingly as a reaction to external forces, or whether they occur proactively as a result of professional leadership."[100] The profession of pharmacy is changing in response to internal as well as external influences. Both pharmacists and pharmacy technicians are, therefore, part of an evolving partnership. Pharmacy must respond to the changes that are already taking place and be sufficiently creative and flexible to anticipate and accommodate future developments. The need to address the issues surrounding pharmacy technicians in a timely manner cannot be overemphasized. Proper preparation of pharmacy technicians

to work with pharmacists is important in the promotion of public health and better use of medication. The Council on Credentialing in Pharmacy, on behalf of its member organizations, offers this paper to provide a stimulus for profession-wide action that can no longer wait.

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APPENDIX: POLICY STATEMENTS OF NATIONAL ASSOCIATIONS

The following are published with the permission of the respective organizations and are accurate as of March 2002, with the exception of (d), which is accurate as of June 2002.

a) The American Association of Colleges of Pharmacy: http://www.aacp.org/Docs/AACPFunctions/AboutAACP/4308_CumulativePolicies,1980-2001.pdf Accessed April 2, 2002.

b) The American Association of Pharmacy Technicians: http://www.pharmacytechnician.com/

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See also http://www.ashp.org/public/hq/ Accessed 2002 April 4.
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f) The National Community Pharmacists Association: www.ncpanet.org

g) The National Pharmacy Technician Association: http://www.pharmacytechnician.org/

h) The Pharmacy Technicians Educators Council: http://www.rxptec.org/

A Closer Look at Pharmacy Technicians

An important component of discussions around the pharmacy workforce shortage issue is the appropriate use of technicians in various practice settings, the extent to which technicians are licensed and regulated, and the level of training necessary for technicians. Simultaneously, the growth of the number of pharmacy technicians presents a boon to the profession and a substantive challenge.

On one hand, the use of technicians helps to address the dramatic shortage of pharmacists that exists in today's marketplace.[1] That shortage is expected to increase. Technicians are being used in a variety of ways in many different venues. As referenced in the "2002 White Paper on Pharmacy Technicians: Needed Changes Can No Longer Wait," it is noted that there are as many as 250,000 technicians operating in the United States. Functioning under the management of licensed pharmacists, technicians can perform repetitive, rote tasks that free pharmacists to deal with issues that necessitate their extensive training and expertise. In this manner, they provide a definite boon to the profession.

On the other hand, the lack of standardization in the preparation requirements for technicians is an Achilles' heel for the profession. While the profession vests technicians with the provision of direct service to the public, training and education requirements vary dramatically from state to state. In some jurisdictions, technicians must have successfully completed comprehensive education programs. Others mandate that technicians become certified through the Pharmacy Technician Certification Board. Employers often mandate in-service training to introduce the new technician to their roles, but this is at the discretion of the employer, creating great variations. Alarmingly, in some states, all that is required is a modest registration fee, without attestation to training of any sort.

The 2002 white paper is an update of a white paper on pharmacy technicians that was originally published by the American Pharmaceutical Association and the American Society of Health-System Pharmacists in 1996. The Council on Credentialing in Pharmacy authorized an update to the piece to reflect the dynamic changes that have occurred in the intervening years.

The Council on Credentialing in Pharmacy is dedicated to credentialing programs in pharmacy that meet established standards of quality that will contribute to significant improvement in the pharmaceutical care of patients and the overall public health. The council strives to introduce standardization into postlicensure training for pharmacists and training for technicians. Its members include:

- Academy of Managed Care Pharmacy
- American College of Apothecaries
- American Council on Pharmaceutical Education
- American Society of Consultant Pharmacists
- Board of Pharmaceutical Specialties
- Pharmacy Technician Certification Board
- American Association of Colleges of Pharmacy
- American College of Clinical Pharmacy
- American Pharmaceutical Association
- American Society of Health-System Pharmacists
- Commission for Certification in Geriatric Pharmacy

Similar to the individual pharmacist-supervisor bearing the responsibility for the technician's work product, the profession has a responsibility to assure that technicians are properly educated and trained to undertake the work assigned to them. Without standardization of professional training requirements for technicians, the profession is deficient in meeting its responsibility to society. The 2002 white paper is mandatory reading for anyone concerned with this issue. It clearly lays out the challenge to the profession.

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

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1. Bureau of Health Professions, Report to Congress: the pharmacist workforce: a study of the supply and demand for pharmacists. Washington, D.C.: U.S. Department of Health and Human Services, 2000.

Editor's note: The "2002 White Paper on Pharmacy Technicians; Needed Changes Can No Longer Wait," published in this issue of the *Journal (72-83),* is also being published in identical substance in a number of journals.

Impact of the ALLHAT Study Results on Managed Care

The results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) were released on December 17, 2002. Up to that time, many clinicians and managed care Pharmacy & Therapeutics (P&T) committees relied on the JNC VI (Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure) guidelines that were published in 1997.[1] Based on evidence-based studies, these guidelines strongly encouraged the use of low-cost diuretics and beta adrenergic blockers as the preferred initial therapy for most patients diagnosed with hypertension.

Though hundreds of clinical studies have been published since 1997, most had fewer patient numbers, lower-risk patients with milder forms of hypertension, and limited comparisons with other classes of pharmacological agents. The JNC has patiently waited for the results of ALLHAT before updating their national guidelines. How will the angiotensin converting enzyme inhibitors (ACEIs) and calcium channel blockers (CCBs) compare to the diuretics in patient outcomes? Are the increased costs of these agents balanced by improved clinical outcomes, including lower mortality and fewer hospitalizations? Many health care dollars have awaited the decision from ALLHAT and JNC VII on which drug is preferred for hypertension.

The ALLHAT study was a practice-based, randomized clinical trial of antihypertensive pharmacologic treatment (also cholesterol treatment in a subset) in more than 40,000 high-risk patients over the age of 55 years, with a large minority representation. To be included, patients had to have stage 1 or stage 2 hypertension with at least one additional cardiovascular risk factor: history of myocardial infarction (MI) or stroke, any revascularization procedure, documented atherosclerotic heart disease, type 2 diabetes

mellitus, high-density lipoprotein (HDL) < 35 mg/dL, left ventricular hypertrophy (LVH), or cigarette smoking. Notable exclusions included patients with recent MI, stroke, congestive heart failure or angina, those with ejection fractions less than 35%, and those with renal insufficiency.

The primary objective of the ALLHAT study was to determine whether the combined incidence of fatal coronary heart disease (CHD) and nonfatal MI differs between a diuretic (chlorthalidone) versus an angiotensin converting enzyme inhibitor (lisinopril), a calcium channel blocker (amlodipine), or an alpha adrenergic blocker (doxazosin). These agents were selected as representative of their therapeutic class. Open-label drugs (atenolol, clonidine, reserpine, hydralazine) were allowed in combination therapy in order to reach the therapeutic goal of blood pressure <140/90 mm Hg. Secondary objectives included all-cause mortality, stroke, combined CHD, combined cardiovascular disease (CVD), and others.

The objective of the lipid-lowering arm was to determine if an HMG-CoA reductase agent (pravastatin) would decrease the risk of all-cause mortality in patients with and without CHD over the age of 55 years with moderate cholesterol elevations (and hypertension) compared to "usual care" (lifestyle change). For entry into this arm of the study, patients with documented CHD had to have a baseline fasting low-density lipoprotein (LDL) in the range of 100 mg/dL to 129 mg/dL, be without coronary heart disease, and have a baseline fasting LDL in the range of 120 mg/dL to 189 mg/dL. Patients were excluded if they were prescribed a cholesterol-lowering drug.

The scope of the ALLHAT trial is unprecedented in clinical research. The study started in 1994 and included 623 clinical sites that enrolled 42,418 patients in the hypertension arm and 10,355 patients in the cholesterol arm, with an average follow-up of 5 years. More than 500,000 visits were conducted, with more than 2 million bottles of prescription medication dispensed. Subset analysis included age, gender, ethnicity, and diabetes. The study was sufficiently powered to detect very small differences in clinical outcomes.

In January 2000, the doxazosin arm of the ALLHAT study was prematurely discontinued. When compared to chlorthalidone, patients assigned to doxazosin had no difference in the risk of fatal CHD, nonfatal MI, or total mortality.[2] However, the doxazosin arm did have a higher risk of stroke and combined CVD. In particular, the CHF risk was doubled (the 4-year rates were 8.13% versus 4.45%; relative risk was 2.04; 95% confidence interval 1.79-2.32; *P*<.001).

The initial results of the hypertension and cholesterol arms of the ALLHAT study have now been published.[3-4] In the cholesterol arm, the baseline characteristics for the statin and usual-care group were comparable. At year 4, the statins had a greater decrease in total cholesterol (17% versus 8%) and LDL (28% versus 11%) compared to the usual-care group. The average decrease in total cholesterol for all patients (statins and usual care) in this arm of the study was 9.6% compared to 20.2% in the 8 other major lipid trials. There were no statistical differences in all-cause mortality, CHD, or incidence of cancer between the groups. At year 4, 17% of the usual-care patients were placed on a statin, which may have impacted the final results. It is also possible that improved blood pressure control may have favorably impacted the clinical outcomes. The conclusion was that both lifestyle changes and statin therapy can lower cholesterol; these results are in agreement with the current National Cholesterol Education Program's Adult Treatment Panel III guidelines.[5]

The baseline characteristics of all 3 treatment groups in the hypertension arm of the study were comparable. At 5-year follow-up, the average blood pressure in the diuretic (chlorthalidone) group was 133.9/75.4 mm Hg versus amlodipine 134.7/74.6 mm Hg versus lisinopril 135.9/75.4 mm Hg. The difference in the systolic blood pressure between chlorthalidone and lisinopril was statistically significant (*P*<.001) as was the difference in diastolic blood pressure between chlorthalidone and amlodipine (*P*<.001); the differences may not be clinically significant, however. Nearly 60% of all treatment groups required additional therapy to reach the blood pressure goal; the impact of open-label drugs on the results is unknown at this time. In the diuretic group, 68.2% of the patients were at their blood pressure goal at year 5 of the study compared to 61.2% on lisinopril (*P*<.001) and 66.3% on amlodipine (*P*=.09). Chlorthalidone and amlodipine were better tolerated than the lisinopril. In the diuretic group, there was a slight, but statistically significant, difference in biochemical abnormalities such as total cholesterol, potassium, and incidence of new diabetes.

There were no differences in the primary outcome (fatal CHD and/or nonfatal MI) among the treatment groups. However, there was an increase in the risk of stroke in the African American patient subset in the lisinopril group compared to the diuretic group (relative risk 1.40; 95% confidence interval 1.17-1.68; *P* value not stated in subset analysis). There was no increase in risk of stroke in the non-African American patient subset. The diuretic group had a significantly lower incidence of heart failure compared to amlodipine (relative risk 1.38, 95% confidence interval 1.25-1.52; *P*<.001) and lisinopril (relative risk 1.19, 95% confidence interval 1.07-1.31; *P*<.001). The higher incidence of biochemical abnormalities in the diuretic group did not adversely impact any clinical outcome.

One of the practical effects of these new ALLHAT study findings is that managed care pharmacists have additional support to recommend diuretics as first-line agents for hypertension. In the past, most of us have encouraged the use of diuretics based on the results of older studies and their lower cost. Their use has been validated with additional evidence from the ALLHAT study findings that demonstrated equal or superior clinical outcomes with the diuretics compared to the highly marketed, widely prescribed, and more expensive ACEIs and CCBs. The ALLHAT study results will no doubt be challenged vigorously by the pharmaceutical industry, and further analyses of the data will be forthcoming over the next one to two years.

There is certainly a place for ACEIs, CCBs, and beta adrenergic blockers in the management of hypertension, especially in

select patients (diabetes mellitus, chronic renal failure, post-MI) and in combination therapy. The beta-blockers were not compared with the diuretic for study design reasons. Some may argue that these agents may be more cost effective than the diuretics that often require laboratory testing and potassium supplementation. However, for a majority of patients with mild to moderate hypertension, a diuretic should be the initial, or perhaps second, agent chosen to control blood pressure and reduce adverse clinical outcomes. Managed care pharmacists should be familiar with the ALLHAT study findings and help educate clinicians and members of P & T committees regarding these findings.

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Co-Principal Investigator, ALLHAT site 022A

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4. The ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs. usual care. *JAMA.* 2002;288:2998-3007.

5. Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA.* 2001;285:2486-97.

Assessing the Value of the Quality of Health Economic Studies (QHES)

Ofman and colleagues address an important challenge, that of increasing the use of economic evaluations among decision makers.[1] Specifically, the study examines whether a scoring algorithm for checklists, referred to as the Quality of Health Economic Studies (QHES), facilitates the identification of high-quality economic evaluations. The use of checklists and summary scores is not new to health care, and the limitations of quality checklists have been previously identified.[2]

Checklists typically cannot separate the quality of reporting from the validity of the design and conduct of a trial. Many checklists contain items that are not directly related to validity but to the precision of results (e.g., power calculations) or generalizability (e.g., inclusion and exclusion criteria).[3] When checklist items are weighted and aggregated into a summary score, such limitations can be compounded. Despite the appeal of a summary score to measure quality, research has found that the use of summary scores provides unreliable assessments of validity.[4,5]

It is against this backdrop that the QHES should be considered. While the objective of QHES is to discriminate the quality of studies, its theoretical basis is unclear. Many checklist items are more closely related to reporting quality or interpretation of results than internal validity (i.e., the strength of the cause-effect relationship). For example, the checklist places significant weight on issues such as transparency, whether the study objective was clearly stated, and to a lesser extent, the funding source.

Important issues related to internal validity were not included in the checklist, such as the nature of randomization and blinding. For example, a cost-effectiveness study that had adequately concealed randomization and was double-blinded could receive the same score as a study that inadequately concealed randomization and had no blinding. This is problematic since both poor allocation concealment and blinding have been associated with bias.[6] Similarly, the checklist lacks questions to address the internal validity of observational economic evaluations.

The authors did attempt to validate the QHES among health economists, decision makers, and through their own work. For the health economists who were surveyed, the summary score generally correlated with a more qualitative evaluation. However, no such assessment was conducted for decision makers, who were identified as the key audience for the QHES.

Furthermore, while there was evidence of convergent validity among health economists, there was a mixed reaction to the usefulness of the instrument. The authors indicated that they found a greater acceptance for the QHES among decision makers than among health economists. However, the forum in which the data was collected, a group discussion at an annual meeting of a professional society, set the stage for possible selection bias (as evidenced by the large representation from the pharmaceutical industry), social desirability bias, and, hence, overestimation of the utility of the instrument.

The authors cite further evidence of the utility of the instrument based on its use in the review of 30 economic evaluations of GERD treatments. Yet, no evidence of validity or utility was presented since QHES results were not compared to a separate assessment and no mention was made of the time or difficulty in completing the QHES in this application, relative to other approaches. That said, higher scores on the QHES were associated with GERD studies that were published after 1996, had researchers with academic affiliations, and had been conducted in the United States. Perhaps these characteristics are proxies for higher-quality studies, but the authors never addressed this issue.

The authors propose that the QHES may be simpler for decision makers to use and that it may have equal or perhaps greater ability to discriminate study quality than other checklists. To adequately answer these questions will require rigorous research among decision makers in real-world situations. However, it should be made clear that the need for validation is not unique to the QHES checklist. Many checklists have been designed to facilitate the review of economic evaluations by decision makers, yet the ability of any of these checklists to

measure what they are supposed to measure remains unclear.

Research is needed to examine which criteria for assessing the validity of cost-effectiveness studies are important determinants of study results and in what situations. For example, what is the relationship between quality scores (QHES, as an example) and treatment effect (i.e., cost-effectiveness measure)? Do lower-scoring studies tend to produce more variable estimates of cost-effectiveness? Do certain components of the checklist (e.g., sufficient time horizon) relate to the size of the treatment effect? Do quality scores vary across study type (i.e., randomized controlled trial, model, and observational study)? This type of methodological work is virtually extant in the pharmacoeconomic discipline, but with the plethora of quality checklists and the substantial resources devoted to the conduct of pharmacoeconomic studies, such a strategic approach seems viable.

Meanwhile, readers of economic evaluations should be cautious not to assume a false sense of precision in the use of summary quality scores since they generally have not been supported by empirical evidence, may actually be misleading, and are potentially more time consuming.

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Summary Quality Scores for Pharmacoeconomic Studies: Balancing Validity With Need

Once a product has received marketing approval from the U.S. Food and Drug Administration, decisions regarding insured access to these agents are immediately raised. The existence and amount of the insured benefit for specific agents requires weighing the evidence for clinical gains and their associated costs against similar measures for competing products and therapies.

Pharmacoeconomics provides a systematic, explicit, and objective basis for making and defending such drug benefit decisions. However, lack of standardization in the field[1] and the differences in perspectives, knowledge, and interests across and within the producers and consumers of pharmacoeconomics has limited its impact on drug coverage decisions. As the methodology advances, consumers of pharmacoeconomic studies require an efficient tool to identify superior studies. In this issue of the *Journal*, Offman et al. propose such a scoring instrument, the Quality of Health Economic Studies (QHES).[2]

Beginning in 1973, clinical epidemiology has consistently identified large variations in the rates of performance of medical procedures and use of specific products.[3] As health care costs have increased, drug costs and effectiveness analyses have become common; however, the explosion of pharmacoeconomic studies has also included some of uncertain quality, rigor, or validity. Pharmacoeconomic studies have nevertheless been subject to increasing standardization. Some are still viewed with skepticism by health plans and insurers who perceive the potential latitude in permissible assumptions as resulting in less than objective evidence. However, purchasers face constant pressure to determine the relative value of marketed pharmaceuticals and to make decisions with imperfect and disparate information. Analyses to assist these determinations come from multiple sources, with attendant variations in quality, reliability, validity, and timeliness of content. Consequently, the assessment of quality and validity of specific pharmacoeconomic results is at the center of the decision process, and uncertainty here will continue to influence the impact of pharmacoeconomic studies.

The proposed QHES instrument will be a substantial contribution if it assists end-users of pharmacoeconomic studies to discriminate among the exploding body of literature[4] and efficiently identify the studies with superior merit. For producers of pharmacoeconomic studies, an accepted rating instrument could establish a clearer target—potentially encouraging higher quality and greater rigor. To achieve this level of acceptance and use, however, the QHES must demonstrate key validity characteristics.

A precondition for a valid rating instrument is that it be reliable. It must yield the same results on repeated trials. On this dimension, the qualitative nature of some of the QHES questions could mean lower reliability if the raters are not trained and their assessments not standardized. Otherwise, different observers may weigh the validity and reliability of health outcomes measures or scales differently. Without reliability, no instrument or measure can be valid.

Beyond being reliable, the QHES must rate studies on how well they actually answer the question posed by the research. Criterion validity, the closest aspect to what is commonly meant by validity, assesses the extent to which the measure being developed correlates with another, "gold standard" measure at the same time.[5]

Questions of external validity, or generalizability, are at the forefront of issues confronting decision makers as users of such information. Whether the original study has a societal, patient, provider, or health plan perspective will determine the relevance of results to a specific setting or decision maker. One of the biggest challenges in evaluating pharmacoeconomic studies may be the

interpretation and extension of the results to a different health care settin0g. Given the relative shortage of trained pharmacoeconomic analysts among management, clinicians, and other decision makers, such judgments often may be required of professionals who lack expertise in pharmacoeconomics.[6,7]

The QHES was assessed for concurrent validity by comparison against the *British Medical Journal* checklist, the Canadian guidelines, and the *Journal of the American Medical Association* user's guide. Further, it was assessed against the global opinion of experts ("criterion validity") and validated among economists, some decision makers, and through the authors' own work. However, the method for selecting these experts, the use of convenience sampling, may present a selection bias and limit confidence in the extent of generalizability of the results.

Acceptance of an instrument as scientifically sound requires that it represent the full content of each of the attributes being measured ("content validity"). While content validity may be relatively easy to assess in established disciplines and with established tests, content validity has proven to be exceedingly difficult to establish with evolving concepts or disciplines, such as pharmacoeconomics. The QHES addresses many of the essential domains by which the soundness of an economic analysis is assessed; however, to the extent that it omits items pertinent to observational qualitative studies, its content validity might be compromised. Such studies may involve domains that are not captured by the questions in the QHES.

The value of an applied instrument is largely determined by its construct validity, a concept more appropriate to a dynamic field such as pharmacoeconomics. Construct validity is established over time by the consistency of findings across different QHES users. Such consistency was found among the experts consulted for this study, and, to that extent, the instrument was determined to have adequate construct validity. However, results from its application have yet to be demonstrated (a) across the spectrum of decision makers from health plans, managed care providers, pharmacy benefit managers, hospital Pharmacy and Therapeutics committees, or researchers, and (b) for the range of the decisions that must be made.

In general, however, it is important to note that the concept of validity is broader than just the validity of individual aspects or measurement approaches. The QHES attempts to synthesize health economic evaluations so that they are useful in decision making and, ultimately, insurance coverage determinations as well as the development of practice guidelines. Summary scores should constitute just one component of an economic evaluation. Until a gold standard for pharmacoeconomic studies is developed, more research is needed to strengthen the link between theory and practice.

Survey research supports decision makers' ability to discern differences and to balance the overall influence of socioeconomic assessments that vary in quality, availability, timeliness, comprehensiveness, and validity.[7] Ultimately, executives and managers must make timely decisions—often with incomplete information or with information from sources from which potential conflicts of interest cannot be ruled out and must be balanced with their results.[8] Consequently, the QHES may initially be more useful as the first of a 2-stage screening process for decision makers under time pressure and with limited resources and less experienced analysts. Not surprisingly, the authors noted that the QHES had greater acceptance among decision makers than among health economists. For the former, the QHES might efficiently help identify those studies not to be included in a dossier or subjected to more rigorous assessment. A subsequent, in-depth second stage might then focus time and resources on critical examination of the remaining studies—possibly not being bound or influenced by the initial QHES score used to sort the studies initially.

To remain relevant for pharmacoeconomic studies, the QHES instrument must evolve and continue to improve in reliability and validity for a broad spectrum of decision makers. Performing pharmacoeconomic assessments is time-consuming and expensive; if the QHES can validly expedite these reviews, it may lower their initial cost and encourage more timely updates.

Just as the QHES will require refinement as experience with it accumulates, users will also need to address the minimal competencies required of those who use it and who make decisions based upon it. Even if the QHES validly predicts the quality of the studies being used by formulary decision makers, it does not, and probably should not, predict the extent to which these studies influence the decision-making process. A screening instrument such as the QHES should probably not be a replacement for expertise in pharmacoeconomics, only a supplement to it.

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Out of Illness, Into Life: Pain Management and the Need for Triptans

In some ways, my favorite patients are those with no insurance. The reason? They choose reasonably. They choose the way America says it wants us to choose, in a cost-reasonable way that insured patients often feel little inclination to choose.

Would one of my uninsured patients choose to take triptans several times a week? Not a chance. The costs would clearly be too high. My uninsured patient would be more likely happy with amitriptyline—preventing the headaches, for pennies a day. Of course, we would discuss the possibility of weight gain. But we'd handle that, possibly by a healthier hypoglycemic diet.

My uninsured patient might not see me for months. The headaches that break through would be handled with over-the-counter drugs, occasional pain pills, or maybe that rare triptan if the "miseries" had really set in. The rest of the time the illness would be handled by prevention—combined with a healthy dose of reasonable expectations.

Now, my headache colleagues might be saying "but these aren't my patients, the ones with the really miserable migraines, the ones who feel miserable every day." Actually, they are. They have the same biology. They just don't have the same way of behaving with that biology.

My uninsured patients don't have easy lives. Many of them have fallen on quite hard times. They have the miseries. A lot of them just don't discuss their anguish via their headaches. They have pain, but they don't discuss it via "the pain." And, part of the reason they don't do this is because they can't afford to manage the pain by taking all of this expensive medication to chase after it. They have migraine. They fulfill all the International Headache Society criteria. They just don't find it practical to translate the pain of their life anguish into the pain called migraine. And so the migraine disease doesn't become the way of being.

Consider, in this regard, and for comparison, one of my favorite insured patients. She is a very nice young woman I've treated for years. She has migraine, and she has had "bad migraine" (whatever we may conceive of this to be in biological terms). In the last couple of years, she has had a very difficult time. Her headaches were very frequent and very difficult to treat in spite of all the best management strategies. She had her therapeutic layer of preventative mediations, her therapeutic layer of healthy lifestyle (diet, exercise, sleep, etc.), her therapeutic layer of trigger-factor controls (hormones, stress, foods, etc.), her therapeutic layer of ancillary techniques (biofeedback, acupuncture, chiropractic, etc.), her therapeutic layer of limited (nonrebound) analgesics, and, of course, her therapeutic layer of limited (nonrebound) abortives, including the triptans. Yet, she was doing poorly. Headaches were frequent. She was unhappy.

Actually, I should turn that around: she was unhappy, headaches were frequent. She and her husband had been struggling for a long time. And, finally, she decided that in spite of her "being alone" fears, her 3 children, financial worries, and the rest, it was time for the two of them to go in different directions. She pursued divorce.

It was difficult. But, there is a point to our story. She saw me recently—about 8 months into the divorce—and, beaming, she told me that she has not had a bad headache since her husband moved out. She still has the migraine illness. But, the illness is now vastly easier to control. Mostly, we are treating her anxiety at this point.

Here is another experience to ponder. While recently at some neurological meetings, I took the opportunity, as I often do, to inquire of colleagues about how common illnesses are managed in other countries. I think this helps me to determine what is "necessary" and what is cultural. One of my colleagues at this meeting was from India. And, it so happens his mother had migraines. She lives in rural India. And, she has no insurance. So I asked, "What does your mother do to treat her headaches?" His answer: "When she gets them, she lays down for about half an hour." Apparently this is her major form of treatment. Of course, this is "N=1." This is anecdotal. And, in a rural setting, it might be more practical to lie down for half an hour. Yet, this is a worthwhile piece of information. This is inexpensive treatment, and she feels it is acceptable.

And, here is one more story. I was recently reading the report of another neurologist in which he described one of his patients who was on a great deal of medication for migraines. She was in his office complaining of severe migraine. He was evaluating what to do next. He reported that on her analog pain scale, she reported pain being 9 out of 10 (10 being the score of "the worst pain imaginable"). So, by her appraisal, she was very close to the most extreme end of the scale. Yet, interestingly, on his exam, he observed her to be "a woman in no apparent distress," and he didn't seem bothered by the disparity.

It is actually rather common to see patients who report having severe headaches—including at the moment of evaluation—while physical examination reveals the patient appearing normal, or even cheerful. This disparity is so common that it often no longer even generates recognition. Yet, isn't it revealing? Intriguingly, in my patients with no insurance, this is rather rare. If they have a bad migraine, they look ill.

The notion of "bad migraine" is complex. For a few patients, it is the presentation of visible misery. During a bad migraine, the patient may appear pale, diaphoretic, obviously nauseated, and withdrawn into wincing pain. Yet, it is quite routine to see patients who report having "bad migraine" illness where this is never really observed. Instead, the patient presents to the office with major report of pain but, often, remarkably little evidence of pain (although perhaps the haggard appearance of chronic stress). When the literature talks about "bad migraine," it does not talk about patients who are measured to have bad physiology (analogous to a patient with bad cancer who has metastases everywhere, or a cardiac patient with bad heart disease who has ankles the size of calves). Rather, literature discussions of "bad migraine" tend to proceed based on patient claims of pain, often "measured" via instruments such as a visual analog scale, that really only succeed in documenting a claim. Therefore, discussions of "bad migraine" need to be recognized as not the scientific equivalent of many of

our other discussions of severe disease.

So, with these 3 stories, we may then return to the perception of "need" for triptans. As in other realms of life, perception is a critical aspect of perceived need. My uninsured patients do not perceive that they need great quantities of these expensive medications. On the other hand, my insured patients may feel that they do. So, what part of this "need" is biology, and what part is sociology?

Even in my own patients that I have revealed above, the issues are not simple. I knew my young female patient with refractory headaches was suffering anguish as much as migraine. But, I also knew that she was not willing to "go there." So, I managed the illness as well as I could under biological approaches while still discussing with her that high-grade stress was actually the cause of her refractory state (later confirmed). When she was ready, she could obtain more effective solutions.

The management of pain, whether under the auspices of migraine or some other mechanism, is complex. Unlike congestive heart failure, renal failure, or a host of other clearly structural problems, the management of pain is a management of mixed issues: partly biology, partly psychology, and partly sociology. Physicians may choose to ignore the latter 2 factors because of the convenience of doing so. However, high cost and excessive service will be the result. And, in the final analysis, the patient's quality of life will deteriorate.

In this issue of the *Journal*, Adelman and Belsey examine the relative cost-effectiveness of triptans. The erudite work by the authors adds to our perspective of choices within the class. But, possibly, it makes a subtle yet critical transition that is problematical. The initial portions of the article address quite well the cost considerations between drugs. However, the latter portion of the article presumes that freer use of triptans may reduce costs overall by reducing emergency room visits. However, as a headache specialist, it is my opinion that the best way to reduce ER visits is to prevent the headaches. And, triptans are not effective in that regard. If patients excessively chase after the headaches, they tend to beget more of the same—chasing after the headaches. This is not ultimately the route to reducing costs. So, the class of drugs is certainly excellent. And, the authors help us choose among the class for appropriate use. However, in my opinion, freer use of abortives may only abort, and not control.

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EDITORIAL

Medicare PPOs and Managed Care

It appears to be a good time to review some of the fundamental principles of managed care. A recent caption read "PPOs will halt the slide in Medicare managed care."[1] More than 15 years ago, managed care was defined by core principles that included negotiated, provider reimbursement rates through preferred provider organizations (PPOs)[2,3] risk-contracting between health plans and providers,[4] and increased accountability from determination of medical necessity and appropriateness through operation of utilization management programs.[5] By the end of the 1980s, managed care was defined by at least one of 10 fundamental components that included prospective pricing, usual, customary and reasonable price determinations, service bundling, peer review, mandatory use review, benefit redesign, capitation payments, channeling, quality criteria, or health promotion.[6]

The Medicare PPO demonstration program that began January 1, 2003, modified, but did not change, the managed care features of the Medicare+Choice program. In fact, the Medicare+Choice PPO option in 2003 is not new at all. PPOs have been eligible to participate in Medicare+Choice since its inception, but only 2 PPOs had participated in Medicare+Choice prior to the program change in 2003 that pays participating PPOs the greater of the county-specific premium amount or 99% of the national per-patient average annual payment amount in fee-for-service Medicare. The media attention to the Medicare+Choice PPO option may overstate the potential since, ironically, anti-trust enforcement from the federal government makes it difficult for physicians and other providers to form collective units to contract with Medicare PPO sponsors. Nevertheless, Medicare+Choice was not abandoning managed care in 2003 but, in fact, retained all of the former features of Medicare+Choice and all of the features that were first used to describe managed care 15 years ago. For Medicare members, the "new" feature in Medicare+Choice in 2003 allowed the use of providers outside the designated network, but at a higher out-of-pocket cost. In this way, Medicare+Choice resembles most employer-sponsored health plans that had years earlier adopted tiered, point-of-care, cost-share features to permit beneficiaries more choices in providers and services.

Burden of Prescription Drug Costs in the United States

What is the true "burden" of prescription drug costs in the United States? Talk to a cab driver without insurance, and prescription drug costs are expensive and even unaffordable. Talk to the person who builds the cab, and prescription costs in the United States are not a problem. One person pays $3 or more per day to lower serum cholesterol, and the other pays less than 10 cents per day for the same drug.

The cab driver pays for the entire cost of the prescription drug at the point of service. The union worker who builds the taxi cab pays a fraction of the cost of the prescription drug at point of service, often less than 10 percent of a negotiated, contract price of the drug. This copayment arrangement for the insured, union worker reduces the personal burden of prescription drug costs and can "insulate" the worker from true prescription drug costs.

The burden of prescription drug costs can be more acute for the elderly, who on average use 3 times the number of prescriptions per month compared to persons younger than 65 years.[7] Yet, a remarkable 17% of Medicare beneficiaries had no ($0) spending on prescription drugs in CY 2001.[8] Spending of $1,000 or more was found among 28% of Medicare beneficiaries and accounted for 76% of total expenditures for prescription drugs for this population.

Survey data from 10,927 nonstitutionalized seniors in 8 geographically diverse states in 2001 showed that 35% of seniors had drug coverage under a Medigap policy, 25% of seniors were enrolled in state pharmacy assistance programs, and 19% of seniors in Medicare health maintenance organizations (HMOs) spent at least $100 per month ($1,200 per year) on prescriptions in 2001.[9] Medicare HMOs were important sources of drug coverage for seniors in California (30%) and Colorado (24%) but were less important in other states, ranging from a low of 7% in Illinois to 14% in Pennsylvania. Unfortunately, Medicare+Choice plans became unavailable to about one third of all Medicare+Choice members, about 2.5 million people, between 1998 and 2002,[10] and access to zero-dollar premium Medicare+Choice plans fell from 61% in 1999 to 53% in 2000 to 39% in 2001 and to 32% in 2002.[11] Access to any Medicare+Choice plan with drug coverage fell from 65% of the entire U.S. Medicare population in 1999 to 50% in 2002. This report from the Centers for Medicare and Medicaid Services (CMS) also found that the average monthly value of cost sharing for Medicare-covered services increased by 79% from $14.88 per enrollee per month in 2001 to $26.60 in 2002.

In a previous issue of the *Journal*, Cox and Henderson found that Medicare+Choice members with an annual drug benefit maximum (dollar limit) relied on prescription drug samples to mitigate the financial burden of prescription drug needs.[12] This finding highlighted the controversy surrounding this potentially self-defeating behavior since drug samples in physician offices are generally higher-cost drugs without generic equivalents. The use of drug samples might contribute to complacency among some physicians rather than encouraging them to select lower-cost therapeutic alternatives for these patients that would truly reduce the financial burden of prescription drugs for the elderly. In this issue of the *Journal,* McKercher, Taylor, Lee, Chao, and Kumar found that prescription drugs in elderly families accounted for approximately twice the proportion of total out-of-pocket medical care burden compared to nonelderly families, 45.6% versus 23.7%, respectively. The higher proportion of total medical care burden and total economic burden attributable to prescription drugs in the elderly was traced to larger prescription quantities, price, and utilization but not more expensive drugs.[13] This finding may be explained, in part, by the higher proportion of total prescription drug spending

attributable to generic drugs, 20.5% for the elderly families versus 18.7% for nonelderly families. Access to data on days of therapy, in addition to prescription (Rx) counts and dosage units, would have helped to further clarify this finding.[14]

The economic burden of prescription drugs for nonelderly and elderly families will increase, at least in the short term. Prescription drug spending is projected to grow by at least 13% and as much as 20% in 2003.[15-17] An upward spiral of economic burden is created by rising prescription drug prices and prescription drug utilization coincident with stagnant personal income. The perceived burden of prescription drug expenditures also will increase with declining household wealth in the United States, which fell in the third quarter of 2002 to its lowest level since 1995.[18] The burden for elderly families is not distributed evenly, and prescription drug coverage is associated with higher utilization for elderly persons with ostensibly the same health status. For elderly persons with no chronic disease conditions, drug utilization is more than 2 times (112%) higher for persons with prescription drug coverage than for persons without prescription coverage. The difference in drug utilization for the elderly with and without prescription drug coverage declines steadily with declining health status. For the elderly with 5 or more chronic disease conditions, the difference in prescription drug utilization is just 15%, 3.7 prescriptions per person per month for the elderly with prescription drug coverage versus 3.2 prescriptions per person per month for the elderly without prescription drug coverage.[19] About 76% of Medicare beneficiaries had prescription drug coverage at some point in 1999.[20]

Preventing Medication Errors and Adverse Drug Events

The House Energy and Commerce Committee on September 25, 2002, approved a bill to create a confidential, voluntary database that health care providers could use to report medical errors.[21] The legislation would have to be reconciled with a similar bill approved the previous week by the House Ways and Means Committee and a Senate bill, the Patient Safety and Quality Improvement Act.[22] The House Energy and Commerce Committee bill would allow patient-safety organizations to monitor the database and use the information to develop recommendations on ways to prevent future mistakes.[23] The legislative proposal received fuel from a government research report that estimated medical errors cause thousands of deaths and injuries and cost $29 billion a year.

Yet, there is disagreement about the scope and severity of the threat to patient safety posed by the U.S. health care system. The first Institute of Medicine report on the matter, *To Err Is Human,* was released in late 1999 and set off a firestorm of debate about the estimated versus true magnitude of the threat to patient safety in the current U.S. health care system.[24] This IOM report was criticized for overestimating the incidence of preventable deaths due to medical errors and for adding to the miscommunication on the subject by fostering the interchangeable use of "medical error" and "adverse event."[25-27] A recent study of physicians and nonphysicians of their first-hand experiences with medical errors helped to provide additional perspective on the perceived severity of the threat to patient safety. Parallel surveys of 831 physicians and 1,207 nonphysicians (adults age 18 or older) conducted between April 11 and June 11, 2002, found that 35% of physicians and 42% of the public reported personal experience with medical errors in their own or a family member's care. However, neither group viewed medical errors as one of the most important problems in health care in 2002.[28] These findings may call into question the sense of urgency to stamp out medical errors expressed by many observers, consultants, and national organizations. The findings of these surveys also appear to add support to those who disagree with the reports of widespread medical errors in the U.S. health care system[29] and to those critical of patchwork methods to improve health system quality.[30] Reliable measures are necessary to benchmark and assess the value and return on investment from allocation of finite resources to eliminate errors of commission in health care. Some argue that finite resources might be better spent to reduce errors of omission, such as the failure to control hypertension.[31]

While the debate continues regarding the true magnitude of the threat to patient safety posed by the U.S. health care system, evidence is accumulating regarding the disparity between estimates of medical errors and the actual incidence of medical errors and harm. Fundamental to our understanding is the recognition that a medical error (ME) may or may not be associated with an adverse event (AE).[32] Similarly, a medication error may result in no harm and no adverse drug event (ADE).[33] The U.S. Pharmacopeia Center for the Advancement of Patient Safety reported in December 2002 that data reported by 368 health care facilities in 2001 showed 2.4% of hospital medication errors to have resulted in patient injury or death; the incidence of death from medication error was 14, or 1.3 per 10,000 medication errors.[34] A study published in September 2002 based upon direct observation, a method more reliable than other methods, found a 19% error rate in medications (drug MEs) and a 7% rate of potentially harmful drug errors (ADEs).[35]

Certainly, the first priority is to prevent the ADEs and adverse medical events (AMEs) with the worst outcomes, death or disability. Categorization and differentiation of medical errors and medication errors from ADEs and AMEs and stratification of the events by level of severity of harm[36] will permit the focus necessary to allocate the resources to prevent them. It is now well accepted that the preferred method to improve identification and prevention of errors and adverse outcomes from errors involves self-investigation of system causes rather than external review and punishment of organizations and individuals.[37-38] The method of error reporting is also critical to the identification of true-positive incidences of medical errors, including medication errors. Self-reporting of medication errors may under-report the true incidence by as much as 95%,[39] and current methods of collecting information on ADEs may under-

report the true incidence by as much as 99%.[40]

In this issue of the *Journal,* Grissinger, Globus, and Fricker, from the Institute of Safe Medication Practices (ISMP), focus on the patient-practitioner interaction as a primary opportunity to reduce medication errors.[41] This is also the principal focus of a campaign launched by the U.S. Food and Drug Administration (FDA) in August 2002 that had the theme: "Think through the risks and benefits of medicines."[42] This consumer-oriented education campaign urged patients to ask questions of their physicians and pharmacists and to become more active in the process of assessing the benefits and risk of prescription drugs: "before using any medicine—as with many things that you do every day—you should think through the benefits and the risks in order to make the best choice for you." Managed care pharmacy can effectively use the same metaphor: when driving a car, you wear your seat belt; when taking medications, you talk to your pharmacist and physician.

Managed care pharmacy can also have a measurable effect on the medication errors and ADEs through reliance on the principles of continuous quality improvement, a fundamental, core area of the Academy of Managed Care Pharmacy's "Pharmacy's Framework for Drug Therapy Management in the 21st Century." The framework's self-assessment tool contains specific tasks and components within key functional areas that permit individual, organization, and system analysis of opportunities for quality improvement in drug therapy management. Key functional areas in patient safety and reduction of medication errors and ADEs are interspersed throughout the framework, with emphasis on patient-practitioner interaction in interpersonal communication (area 1.1), patient education (1.3, 4.4, 5.3, and 6.3), patient and worker safety (1.4), drug selection (3.2), coordination of care (3.5), etc.[43] Many of the solutions necessary to prevent and reduce medical errors and medication errors will involve changes in processes and systems that "make it easy to do it right."[44]

Quality of Health Economic Studies (QHES)—Tool or Mask?

Managed care pharmacists face a mountain of data when making decisions about the relative value of alternate drug therapies in individual patients and in the selection of preferred agents in prescription drug formularies. The objective is to apply rules of evidence-based medicine to derive the information that will be important to develop and refine clinical practice guidelines (CPGs) and clinical practice models (CPMs) that will make it possible to achieve effective disease management. This paradigm might be made more clear by thinking of this continuum in terms of structure, process, and outcome in which the "structure" derives from evidence-based medicine, the "process" from application of CPGs and CPMs, and the outcome as successful attainment of disease management.

The U.S. National Library of Medicine reported an average 10,000 new lines (articles) referenced in MEDLINE each week at year-end 2001.[45] The amount of data and information in the medical literature is growing further and is now quite easily overwhelming, setting aside the additional data and information disseminated in the lay press and on the Internet. It is now more important than ever to find tools to help filter and interpret enormous amounts of data and thousands of medical literature references. The Quality of Health Economics (QHES) instrument may be such a tool. On the other hand, this tool, as any tool, can be misapplied. In addition to possible inherent flaws in the instrument, some of which will only be discovered upon repeated use and scrutiny of the results, users of the QHES have the potential to distort the findings of the studies that they are measuring.

Ofman, Sullivan, Neumann, et al. in this issue of the *Journal,* take the bold step of introducing a new instrument, the QHES.[46] The true value of this instrument and method will not be determined immediately, and readers have reason to be critical. Shaya and Lyles in an accompanying editorial suggest that managed care pharmacy should evaluate critically this new instrument and method.[47] Motheral argues for caution and even rejection of the instrument and method.[48] Science advances through scholarly debate. By articulating and applying the QHES, Ofman et al. permit others to critique the instrument and method and to propose changes that will enhance value by increasing its validity, reliability, and usefulness. We are certainly in need of better tools to evaluate published data.

The QHES has value, perhaps not so much for its final numeric "score," but in its qualitative analysis of the results of assessment of individual items in the 16-item instrument. Some researchers will no doubt want to change the weight of individual items to improve the utility of the QHES in application to particular uses. The architects of the QHES will need to explain for other researchers that the 3 compound items (numbers 5, 8 and 11) in the QHES require affirmation of both questions. Item number 5, "Was uncertainty handled by: 1) statistical analysis to address random events; 2) sensitivity analysis to cover a range of assumptions?" could have one "yes" and one "no" answer, yet the weight for the item is "9." Item number 8 asks 2 questions and has a weight of "7": "Did the analytic horizon allow time for all relevant and important outcomes?" "Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?" Item no. 11 also has 2 questions, with one score of "7": "Were the health outcome measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?" At the least, the QHES instrument and method present us with a useful platform for scholarly debate on attempts to bring more science to pharmacoeconomics, a relatively young discipline still in search of credibility in the scientific community.

Antihypertensive Drug Effects on Renal Function and Myocardial Infarction and Implications of the ALLHAT Study Results

In managed care we must study the effects of drugs outside the

realm of randomized clinical trials (RCTs) to ascertain their real value in uncontrolled, real-world settings. This is particularly true in the ubiquitous treatment of hypertension. One area of particular interest is in the growing body of evidence that some drugs have renal protective effects in excess of their hemodynamic effects in blood pressure reduction. A randomized trial involving 1,094 African Americans aged 18 to 70 years followed for a minimum period of 3 years and up to 6.4 years found that ramipril, an angiotensin converting enzyme inhibitor (ACEI), in a dose range of 2.5 mg up to 10 mg per day, appeared to be more effective than beta-blockers (metoprolol dosed between 50 mg and 200 mg per day) or dihydropyridine calcium channel blockers (amlodipine dosed between 5 mg and 10 mg per day) in slowing the decline in glomerular filtration rate (GFR), an important indicator of kidney function.[49] The ACEI was associated with risk reduction of 22% in the composite outcome (reduction in GFR by 50% or more [or greater than or equal to 5 mL/min per 1.73 m^2]) from baseline, end-stage renal disease or death), compared to metoprolol or amlodipine; there was no significant difference in the clinical composite outcome between the amlodipine and metoprolol groups; and there was no apparent additional benefit in slowing progression of hypertensive nephrosclerosis associated with a lower blood pressure goal of 92 mm Hg or less, compared to the usual blood pressure goal of 102 mm Hg to 107 mm Hg.

Nephropathy, defined as proteinuria greater than 300 mg in 24 hours, will develop in 35% of patients with type 1 diabetes, usually manifested first as persistent microalbuminuria that appears 5 to 10 years after the onset of diabetes. Nephropathy will progress to end-stage renal failure. Drug therapy that lowers blood pressure and protects diabetics from development of nephropathy is obviously important in reducing morbidity and mortality. Ten years ago, captopril 25 mg 3 times a day was found to reduce by 50% the risk of the combined endpoint of death, dialysis, and transplantation compared to placebo in patients with type 1 diabetes.[50] Since then, lisinopril dosed at 10 mg to 20 mg per day was found to significantly reduce albumin excretion and microalbuminuria in normotensive type 1 diabetics,[51] thereby demonstrating the utility of ACEIs in the prevention of diabetic nephropathy as well as in its treatment. Meta-regression analysis has shown that ACEIs can decrease proteinuria and preserve GFR in patients with diabetes mellitus.[52] The MICRO-HOPE trial of more than 3,500 diabetic patients from the HOPE trial (97% of whom had type 2 diabetes) showed a 24% reduction in risk of nephropathy in an average 4.5 years of follow-up in patients who received the ACEI, ramipril.[53] There was a significantly lower albumin-creatinine ratio in the ramipril group, and these effects were greater than could be attributed to reduction in blood pressure alone.

The dihydropyridine (DHP) calcium channel blockers (CCBs) have not been shown to have comparable effects in protection from nephropathy in either diabetic or non-diabetic patients. In the Irbesartan Diabetes Nephropathy Trial, the DHP CCB, amlodipine, at 10 mg per day appeared to fare worse than placebo in the composite endpoint of time to doubling of baseline serum creatinine, development of ESRD or death from any cause, in type 2 diabetics with hypertension.[54] The effects of CCBs on risk of MI in patients with or without diabetes warrant further study. While short-acting and intermediate-acting DHPs may be associated with an increased risk of myocardial infarction (MI)[55-56] this relationship has not been found with the long-acting DHPs,[57] but experts have requested caution in the use of CCBs in treating hypertension,[58] particularly in diabetics.[59] The researchers at Wake Forest University School of Medicine who found in 1995 that short-acting calcium channel blockers may cause more harm than benefit, presented at the European Society of Cardiology in Amsterdam in August 2000 the results of a meta-analysis of 9 RCTs that compared outcomes of the use of calcium channel blockers versus diuretics, ACE inhibitors or beta-blockers for hypertension.[60] The pooled data showed a 27% higher risk of heart attack and a 26% higher risk of heart failure in patients on calcium channel blockers versus alternative therapies for hypertension: diuretics, ACEIs, or beta-blockers.[61] Overall survival was not significantly different among the alternative therapies.

Anderson, Alabi, Kelly, Diseker, and Roblin, in this issue of the *Journal,* failed to find a higher risk of MI in high-risk diabetic patients prescribed a combination antihypertensive drug regimen that included a DHP CCB or a nondihydropyridine CCB.[62] The well-conceived study design was undermined by a small sample size and missing data for variables such as ethnicity, smoking status, vital signs, and laboratory tests. Nevertheless, this research is useful in articulating a study design that may be used by others in managed care pharmacy to examine retrospective databases to ferret out the relationships of combination drug therapies in the development of adverse myocardial and renal outcomes in high-risk patients. Future research should also address the important question regarding dose-related effects of CCBs in combination with ACEIs or diuretics.

The impetus to perform more clinical studies of the relative value of ACEIs and CCBs in the treatment of hypertension increased in light of the results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), released in December 2002. It is hard to overstate the importance and potential impact of the results of the ALLHAT study. These results suggest that most of the more than 40 million Americans with hypertension[63] could be treated more effectively and more safely with low-cost diuretics such as chlorthalidone and hydrochlorothiazide, at a fraction of the cost of ACEIs such as ramipril or quinapril and CCBs such as amlodipine, felodipine and long-acting nifedipine and diltiazem.[64] The 8-year study, with a mean follow-up of 4.9 years, produced unequivocal evidence that amlodipine and lisinopril were associated with the same incidence of the primary outcome of combined fatal coronary heart disease or nonfatal MI as chlorthalidone; all-cause mortality was also the same among

the three treatment groups. However, chlorthalidone was superior to amlodipine in the 6-year rate of heart failure (HF), 7.7% vs. 10.2%, relative risk 1.38, and chlorthalidone was superior to lisinopril in the 6-year rates of combined cardiovascular disease, 30.9% versus 33.3%, RR 1.10, stroke (5.6% versus 6.3%, RR 1.15) and HF (8.7% versus 7.7%, RR 1.19). Robert Anderson, one of the ALLHAT investigators, has additional observations regarding the ALLHAT study findings in this issue of the *Journal*.[65]

Prior Authorization to Manage Drug Utilization and Costs

In 1998, state Medicaid programs were responding in various ways to double-digit increases in prescription drug benefit costs. In some states such as Massachusetts, the cost increases threatened to push drug benefit costs ahead of the costs of hospital acute care services by the year 2003. Massachusetts Medicaid planned to implement "more aggressive utilization practices," Kentucky required prescribers to use lower-cost first-generation antihistamines and Florida used prescriber profiling, focusing on the use of "fourth-generation" antibiotics for upper respiratory infection in adults.[66] Florida also planned "provider education forums" to focus on drug prices. Drug formularies were not an option since state Medicaid programs have essentially open formularies because nearly all drug manufacturers pay rebates to obtain formulary status, leaving only prior authorization (PA) programs to discourage use of certain high-cost drugs. Medicaid rebates for single source and innovator multiple-source brand drugs in 1998 was the greater of 15.1% of average manufacturer price or AMP less best price. For noninnovator drugs, the rebate was 11%.

By 1999 and 2000, state Medicaid officials began to complain more openly about requirement of state programs to operate open drug formularies as part of the OBRA 1990 statute on mandatory drug manufacturer rebates. Oklahoma Health Care Authority CEO, Michael Fogarty, testified at a 29 March 2000 Senate Finance Committee hearing that two factors in the Medicaid "best price" approach contributed to the "evaporation" of savings: (a) open formularies, and (b) price adjustments by manufacturers to compensate for the mandatory rebates.[67] Fogarty recommended that state Medicaid programs be permitted to institute closed formularies to make drug manufacturers compete with lower prices.

OBRA 1993 amended the OBRA 1990 language and no longer required state Medicaid programs to reimburse for new drugs approved by the FDA, for the first 6 months after introduction. However, federal law and regulations prohibit states from denying access to drugs by Medicaid recipients, and 43 states and the District of Columbia had PA programs in place in 1996 to limit the use of nonformulary and nonpreferred drugs.[68] States have reported limited success with PA programs, and New York adopted a mandatory generic drug substitution program in November 2002 in which brand-name drugs with a generic equivalent would require a PA to be covered by the Medicaid program. The PA program could be utilized by physicians using voice recognition or a keypad and required the physicians to answer a "brief set of questions about why the patient required the brand product." For a multiple-source brand product to be dispensed, the prescription must include the PA number obtained by the physician, and must indicate "DAW" (dispense as written) and "brand (medically) necessary."[69] New York hoped to push its generic substitution rate to 95% from 88% of multiple-source brand drug prescriptions with the mandatory generic/PA program, a modest goal for managed care organizations working in the private employer sector.

The absence of reliable data on the cost-effectiveness of prescription drug benefit prior PA programs was highlighted in a previous issue of the *Journal*.[70] Any reasonable assessment of the cost-effectiveness of PA programs in prescription drug benefits would include consideration of the potential, and predictable, adverse service outcomes, including physician, pharmacy, and beneficiary, satisfaction as well as wait time and additional service costs. Such considerations in the public arena appear to be outweighed by budget concerns. Beginning with the Florida PA program for nonpreferred drugs that was launched in July 2001, several other states implemented similar programs by mid-2002.[71] The principal feature of all of these state Medicaid PA programs, including Michigan, Illinois, Louisiana, and North Carolina, was to extract additional rebates from pharmaceutical manufacturers to bring their drugs down to the "reference price" within therapeutic classes. Failure to match the reference price through supplemental rebates subjects the drug to PA. Cox-2 drugs were the first of 2 drug classes implemented in the Louisiana Medicaid preferred drug program in June 2002.

In this issue of the *Journal*, LaPensee describes the experience of a drug PA program in a Medicaid managed care organization (MCO) in the northeast in early 2002.[72] While Medicaid HMOs operate under a different set of rules than private MCOs and have fewer tools to manage drug benefit costs, particularly the absence of tier-copay benefit designs, the description of this Medicaid PA program has some useful information for all managed care observers. Nearly 4 out of 5 PA requests were for formulary drugs. Second, the PA rejection rate was low: only 4.4% of the more than 22,000 PA requests received each month were denied. Clearly, this is a large administrative burden, nearly 1,000 PA requests per day, of which an average of 44 were denied. The 93% acceptance rate for PAs for nonformulary drugs compares with an acceptance rate of about 75% for drug benefit PAs for commercial health plans in 1999 and 2000.[73-74]

HIPAA Effects on Health Research and PBM Functions in Drug Utilization Review

The Health Insurance Portability and Accountability Act (HIPAA) of 1996 was crafted originally with the intent to better protect health insurance coverage for employees and their families when employees changed employers; i.e., to ensure portability of health insurance.[75] By the time the legislative process was complete, HIPAA had 2 primary impacts beyond portabil-

ity of health insurance benefits: the standardization of medical claim information and patient privacy. For patient privacy, the original Clinton administration rules released in late 2000 were so onerous as to threaten the quality of patient care by making important patient information unavailable to the health care provider at the point of care. The proposed policy was ironic since the lack of sufficient patient information at the point of care is a major and under-recognized source of medical errors.

HIPAA implementation rules for privacy of health information released in December 2000 ultimately culminated in the "final rule" on August 14, 2002, that specified 9 elements for the disclosure authorization form for all research.[76] The December 2000 proposed rule required time-limited authorization forms for "research involving treatment" or access to existing medical records. The August 2002 version required a single form for all research, required no expiration date but specified 9 elements, including (a) proposed use and (b) amount of disclosure. The 2002 rule also permits providers to share a "limited data set" for research. As with the earlier proposed rules, the final rule on medical privacy exempts only information that has been "de-identified." Despite the relaxation of most aspects of the proposed rules, the August 2002 rules did not go far enough to relax the imminent stranglehold on communication of information necessary for optimum medical care and for adequate health care research.[77]

For pharmacy benefit managers (PBMs), the effects of HIPAA are mostly additional administrative costs in policy, procedures and training. There is much to complain about in the HIPAA regulations for health plans and employers (covered entities) and for contractors to health plans and employers ("business associates") such as PBMs. There are additional administrative costs, which ultimately have to be passed along to customers, i.e., employers including public (taxpayers) as well as private employers. Yet, there is some "good" in the effects of HIPAA.

Part of the favorable aspects of HIPAA and the attention to privacy of protected health information (PHI) is more careful use of private information. Many people who previously had, and some who still have, access to certain PHI should not have had access to this personal information and will not have access in the future. It was common for the human resources manager or staff person in the HR department or finance office to receive, routinely, drug claim detail including patient name, drug name, and date of service.

Today, most PBMs have taken 2 courses of action to protect PHI while permitting officers of employers and health plans to fulfill their fiduciary responsibilities. First, drug claim detail is shared with third-party administrators, employers, and other agents with fiduciary responsibility, with the patient ID and name stripped from this claim detail; i.e., the drug claim detail is de-identified. Drug claim databases shared with the clients of PBMs typically employ scrambled patient ID numbers (de-identified). These scrambled patient ID numbers are unique and can be traced by the PBM back to the patient in cases where patient safety may be threatened, such as in a market recall of a drug. (This ability to unscramble the beneficiary identifier is not an insignificant matter since many physicians and medical practices, even today, are not able to identify active patients who have been prescribed a particular drug without searching individual medical records, one at a time.) Second, most PBMs now produce aggregate financial information, with identification of the beneficiaries, such as the list of high-cost claimants with the summary financial fields, but without identification of drugs by name. These and other business practices of PBMs protect PHI while allowing health plan sponsors and their agents to fulfill their fiduciary responsibilities.

Prior to these changes in PBM privacy policies, the human resources manager at a physician medical group, for example, would have received the drug claim detail that showed that one of its internal medicine physicians was prescribing narcotics routinely, allegedly for his spouse. Today, the PBM would investigate the matter and perhaps caution the physician about routine prescribing for immediate family members.[78] The situation was more than it appeared since the physician was suspected by the dispensing pharmacist of prescribing the narcotics for his own use. The medical director for the medical group-employer and the PBM worked together, with the medical director blinded to the identity of the beneficiary-physician, to monitor the narcotic prescriptions from this physician for his family use. Prior to these revised PBM privacy policies, the physician could have had a reasonable charge of discrimination if any employment action had been taken against the physician-employee. In other words, the privacy policy of the PBM protected the PHI from disclosure to the medical director or other officer of the employer (medical group).

The unfavorable aspects of proposed HIPAA regulations and some state patient privacy rules include conflicts with efforts by health care professionals to and improve the quality of care. Some physicians and patients wave "privacy" flags in order to protect profitable conspiracies in drug diversion or drug misuse by shielding themselves from scrutiny in utilization review (UR) performed by health plans and by business associates on behalf of plan sponsors. Think this happens infrequently? Ask any utilization management coordinator who deals daily with exceptional prescription drug use. The list is long. For example, patients who pay physicians to prescribe tens of thousands of dollars of sustained-release oxycodone, with street-value of hundreds of thousands of dollars. Any drug that has high value in everyday commerce, monetary or otherwise, may be associated with "theft" from a drug plan through prescriptions that are not medically necessary. HIPAA and the public attention to privacy of medical records sometimes makes more difficult the job of attaining coordination of care through utilization management (UM) interventions.

Also in the unfavorable portion of the spectrum of HIPAA privacy rules is the plethora of lawyers and consultants who talk jargon that borders on gibberish, selling compliance advice and

assessment tools. HIPAA appears to be creating some new arcane rules on record-keeping, contracting, and other ministerial functions that may add to cost without necessarily adding anything to patient privacy or its protection. One health law attorney coined this phrase, "HIPAA, the death of common sense."[79]

As a technical matter, the HIPAA (1996) standards for electronic transmission of health care information were delayed for one year, until October 16, 2003, by the Administrative Simplification Compliance Act (P.L. 107-105). However, covered entities (e.g., group health plans and health insurers, health care clearinghouses) and their business associates (e.g., PBMs) were required to submit a compliance extension plan to the Department of Health and Human Services (HHS) by October 16, 2002, to receive an extension. Ironically, the form for this purpose was available at the Centers for Medicare and Medicaid Services Web site[80] but could not be submitted electronically to CMS. The form had to be printed, completed, and mailed to CMS.

The final regulations for protection of PHI were effective April 14, 2001, but compliance was not required until 14 April 2003 (except for small group plans, which have until April 14, 2004, to be compliant). Proposed changes released by HHS since the December 2000 publication of the "final rules" have eased some of the onerous restrictions but do not yet make the job of UM coordinators any easier. Specifically, the patient's *advance* written permission is *not* required for most treatment, payment, or other health care transactions. However, covered entities do not escape the requirement to (a) notify patients of their medical privacy rights, (b) notify patients of the policy and procedures employed by the covered entity to protect PHI, and (c) obtain the signatures of patients acknowledging receipt of this notification. Second, among the changes particularly relevant to prescription drug benefit management, disease management programs have a limited exception to permit covered entities to discuss treatment options and share PHI for the purpose of conducting disease management interventions. Third, individually identifiable health information included in the employer's personnel records is not considered protected PHI.[81] Fourth, covered entities may disclose protected PHI to a business associate (e.g., PBM) and allow the associate to use the information on behalf of the covered entity pursuant to a written contract. Walden and Craig, in this issue of the *Journal*, provide a more comprehensive overview of the HIPAA legislation and regulations, particularly as they apply to health plans and PBMs.[82]

Policy makers should weigh the experiences of prescription drug benefit managers in the evolving domain of patient privacy as rules are modified to meet patient needs for safety while preserving the privacy of personal health information. It is not as easy as saying that all PHI should be shared only on a need-to-know basis. Yet, there is some relevance to this general dictum. The "rules of the road" for managed care pharmacists can be referenced by the acronym "TPO" to guide the use and disclosure of PHI. TPO refers to "treatment," "payment," or "operations," the permitted "uses" (internal) and "disclosures" (external) of PHI. Disclosure of PHI outside of TPO requires patient- and purpose-specific authorization for this disclosure. Ultimately, the covered entity is responsible for compliance, but practically, this responsibility is transferred to the business associate (e.g., PBM) by written agreement between the covered entity and the business associate.

"Payment" includes the drug UR and UM activities performed by health plans or PBMs. Disclosure of PHI to providers by UR case managers and staff does not require patient authorization. Likewise, requests of providers for patient-specific medical record information for determinations of medical necessity do not require patient authorization. However, UR and UM personnel and operations will be held to a "minimum necessary" disclosure standard in which the requested PHI is the amount minimally necessary to fulfill obligations related to determination of medical necessity and similar language and criteria in description of benefits and summary plan documents (SPDs) of health plans.[83] The definition of minimum necessary will likely give rise to jurisprudence quicksand for health plans and in-earnest PBMs as trial lawyers strive to make cases around unnecessary privacy breaches. UR and UM personnel must navigate more perilous passage as a result of current, but still evolving, HIPAA privacy regulations.

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Editor's note: *"Validation of a Single-Patient Drug Trial Methodology for Personalized Management of Gastroesophageal Reflux Disease," which was published in the November/December 2002 issue of this* Journal, *is similar to the article, "Single-Patient Drug Trial Methodology for Allergic Rhinitis" by several of the same authors, which was published in the September 2002 issue of the* Annals of Pharmacotherapy. *However, the single-patient drug trial methodology was different in its application (e.g., number of crossovers, length of study legs, endpoints measured, outcomes measured) in the 2 articles. The data, results, and clinical/economic implications from each study are independent.*

Oral Isotretinoin and the Use of "Conventional Therapy"

Dear Editor,

We wish to take issue with several points in the recent article that appeared in the *Journal of Managed Care Pharmacy* (July/August 2002), "Oral Isotretinoin: An Analysis of Its Utilization in a Managed Care Organization."

Of particular concern are the claims of the authors that up to 70% of patients had not received a trial of a topical retinoid before oral isotretinoin therapy, even though the product labeling advises that oral isotretinoin (Accutane) should be used only in patients unresponsive to "conventional therapy." The authors failed to note that "conventional therapy" as defined in the Accutane U.S. package insert includes systemic antibiotics. Therefore, the failure to note the percentage of patients who had received oral antibiotics (i.e., tetracycline, minocycline, doxycycline, and erythromycin) as a precursor therapy to Accutane is misleading. In fact, data from the Accutane Survey, which was previously conducted by the Slone Epidemiology Center, Boston University School of Public Health, a long-term epidemiologic study, revealed that 93% of all female respondents indicated that they had been on an oral antibiotic previously for their acne (N=36,481), 74% on a topical tretinoin (N=29,078), and 73% on a benzoyl peroxide (N=28,913) (Data on file, covering the time period of January 1, 1995, to June 30, 2002).

Further, the authors stated that more than one quarter of patients continued a course of treatment for longer than the 15 to 20 weeks advised in the product labeling. A recent study conducted using national drug c ode health data indicated that the average length of therapy for an Accutane patient is approximately 98.7 days or 14.1 weeks (Roche, data on file, 2002). It should also be noted that Accutane packaging comes in blister packs containing a 10-day supply (10 mg, 20 mg, and 40 mg), so each patient would receive 3 to 6 packs per month. Depending on how the packages were counted, it could lead to a perception on the part of the authors that therapy was "prolonged" when, in fact, the prescriber may be within the recommended dosage of 0.5 mg/kg to 2.0 mg/kg body mass or 120 mg/kg total dose over a course of treatment.

The authors report that only 52% of oral isotretinoin prescriptions were written by dermatologists. As the authors presented a limited description of the HMO and its policy and procedures, it is unclear if there is a policy that would limit the number of specialist referrals a nondermatologist could make for dermatologic conditions such as acne. According to the authors, this particular HMO has in place "a prior-authorization policy for topical tazarotene and adapalene, and in patients aged 25 or older (aged 35 in some cases) for topical tretinoin." This policy appears to be in place to limit prescriptions for topical retinoids used in photo-aging. Nondermatologists unfamiliar with other acne therapies thus may have prescribed isotretinoin inappropriately in the context of an HMO trying to limit use of topical retinoids for photo-aging. The extent of this type of prescribing after denial of topical retinoids could not be determined from the database, as the authors state. A study conducted by IMS indicated that in the years 1995 through 1997, more than 97% of the Accutane prescriptions written for an acne indication were done so by a dermatologist (Roche, data on file).

Conclusions of the authors regarding the use of oral isotretinoin without first receiving "conventional therapy" and that oral isotretinoin is being used for a longer period of time than recommended are both inaccurate and misleading.

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The Authors Respond

We would like to respond to a letter that contends that some of the findings from our study published in the *Journal of Managed Care Pharmacy* (July/August 2002), entitled "Oral Isotretinoin: An Analysis of Its Utilization in a Managed Care Organization," are inaccurate and misleading.

The letter states that our findings regarding the absence of a previous topical retinoid prescription in up to 70% of patients who were prescribed oral isotretinoin does not strongly support the conclusion that the medication is not being used strictly in patients unresponsive to conventional therapy (topical retinoids and/or oral antibiotics), as the product labeling advises. It claims that conventional therapy also includes oral antibiotics, and therefore utilization of this type of therapy prior to the initiation of oral isotretinoin should have been examined. However, although the number (percent) of patients using oral antibiotics for treatment of acne in this study was not delineated separately, this subset was included in the 31% who had prescription medications other than a topical retinoid during the preindex period. The oral antibiotic utilization was purposely not specified separately because of the uncertainty in the actual indications of its use from the database. Also, at least 39% of patients were found to have not received any acne pharmacotherapy, including oral antibiotics, during the 6 months prior to their Accutane prescription. In addition, the designs of the epidemiological studies referenced by the authors of the letter were not explained and, therefore, it could not be determined whether the various cohorts were comparable. For instance, there is the question of how much time elapsed between the end of conventional acne treatment and Accutane initiation in the referenced studies.

The letter also claims that "depending on how the packages (of oral isotretinoin) were counted, it could lead to a perception on the part of the authors that the therapy was prolonged, when, in fact, the prescriber may be within the recommended (guidelines)." The duration of therapy was analyzed using the days supply information submitted by the dispensing pharmacists. Based upon the prescribing physician's instructions as to dosage and duration of therapy, the correct days supply of

Accutane should have been provided to the patient by the pharmacist. As a result, the perception of prolonged therapy is not likely. Furthermore, since the maximum recommended total duration for a course of treatment is 150 days (5 x 30 days) and oral isotretinoin is supplied in 30-day increments, there should not be "extra" dosage dispensed to cover the maximum treatment course. For these reasons, we feel that the days-supply information entered by the pharmacists are accurate and that the issue of "how the packages were counted" does not account for the results presented in the manuscript.

The authors of the letter compared the finding that the average duration of Accutane use was 14.1 weeks to the manuscript's finding that 27% of patients had received the medication for longer than the recommended duration of therapy. The result of the referenced study, however, does not negate the original finding in the article due to the fact that average duration of therapy may be within the drug's guidelines while a significant portion of patients still may receive the medication for longer than 20 weeks.

Furthermore, the study investigators mentioned in the manuscript the limitation that prior authorization guidelines in place at this particular managed care organization may confound the finding that only 52% of oral isotretinoin prescriptions were written by dermatologists. It is unlikely, however, that this, in addition to the other limitations mentioned, account for all of the remaining prescriptions written by nondermatologists. Also, it would be reasonable to conclude that had a larger percentage of dermatologists prescribed oral isotretinoin, results would have indicated greater use of conventional therapy prior to Accutane use. This would reflect the specialists' increased experience with and knowledge of this medication and its prescribing guidelines.

The study investigators remain confident in their claims that conventional therapy is not consistently being initiated prior to oral isotretinoin use and also that a significant percentage of patients (27%) who receive Accutane are prescribed a course of therapy that extends beyond the recommended guidelines. The results presented in the article represent utilization patterns from a naturalistic setting and are therefore likely to represent "real world" oral isotretinoin usage.

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

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Corrigan PW, Luchins DJ, Malan RD, Harris J. User-friendly CQI for the mental health team. *Med Interface.* December 1994:7:89-92, 95.

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Chernow B, ed. *Critical Care Pharmacotherapy*. Baltimore, MD: Williams & Wilkins; 1995.

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7. Government agency publication

Akutsu T. *Total Heart Replacement Device*. Bethesda, MD: National Institutes of Health, National Heart and Lung Institute; 1974 Apr. Report no.: NIH-NHLI-69-2185-84.

8. Dissertation or thesis

Youssef NM. School Adjustment of Children With Congenital Heart Disease [dissertation]. Pittsburgh, PA: University of Pittsburgh; 1988.

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1. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *N Engl J Med* 1991;324:424-48.