MANAGED CARE INTERFACE

The Official Publication of The Pharmacy & Therapeutics Society

The Pharmacy & Therapeutics Society's 8th Annual Conference Information Inside

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The Peer-Reviewed Journal Read by Decision Makers in Managed Care

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Letter from the Publisher

As we move forward in this autumnal season we enter a new phase in the publication of MANAGED CARE INTERFACE. Today we are inaugurating the first electronic version of MCI. As we transition to this new form of publication, our print publication to all membership will be curtailed, with only certain requesters receiving the printed version. We hope that this does not inconvenience you. Starting with the February edition, all subscribers will have the option of receiving the journal in print or electronic format. We will have a form for you to indicate your preference in the December online edition. As a consequence of this transition into a dual format, print and electronic publication, we will temporarily be publishing MANAGED CARE INTERFACE bimonthly instead of monthly. Once this transition is complete we will return to a monthly publication schedule.

We are happy to announce that our new website is fully operational. We are now equipped to receive manuscripts and other data via the appropriate links. While our print editions of the journal will continue, it is our hope that by expanding our presence on the World Wide Web, we will be able to facilitate a closer interaction with our authors and readership. We are in the process of making the previous editions of this journal available in an online format for our readership so that MCI becomes a quick and easy resource for all people who share an interest in the ongoing management of medical care. Unfortunately, during the transition certain articles were garbled in the electronic transfer and we are attempting to retrieve the articles as time permits. However we believe we will have a full electronic compendium of MCI within the next six months.

Nancy Lee Carlson
President/Publisher

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Are We Getting What We Paid For?

In a recent article, Yin and colleauges[1] reported on their investigation of the effect the Medicare part D prescription drug benefit has on drug utilization and out-of-pocket expenditures. An accompanying editorial summarized the article's methods and findings and called for greater access to the data being collected to assess whether the significant investments being made in prescription drugs are leading to improvements in health and quality of life for part D recipients.[2]

The quest to determine whether investments made in prescription drugs lead to improvements in important health care outcomes, quality of life, and/or reductions in overall health care spending is now a common theme for Pharmacy and Therapeutics (P&T) committees. In this instance, P&T committees can use the experience of government programs to assess the effect of a health care or management intervention in private-sector populations. Many in the private sector serve Medicare beneficiaries, either through prescription drug plans or Medicare Advantage health plans. As a result of the desire to achieve as much consistency as possible in formulary management, the examination of the experience under Medicare part D has important implications.

Yin and colleagues[1] examined prescription utilization and out-of-pocket expenditures for almost 7 million individuals receiving their prescriptions through the Walgreens pharmacy chain. The authors evaluated the utilization and cost data in three periods: (1) the pre-part D period (September 2004 - December 2005), (2) the ramp-up part D period (during which seniors could enroll in these plans without penalty, January 2006 - May 2006), and (3) the stable part D period (after the deadline for penalty-free enrollment, June 2006 - April 2007). They concluded, "The Medicare part D benefit led to modest increases in drug utilization and modest decreases in out-of-pocket expenditures among a random sample of pharmacy customers who were eligible for the benefit."[1] They estimated the drug benefit saved people about $9 a month and gave them an extra 14 days of pills, on average.

Pharmacy and Therapeutics committees frequently triangulate, for lack of a better term, the investments that need to be made in the prescription drug benefit in general and the formulary management of specific drugs. They often confidently estimate the effect of formulary management based on such "hard" measures as plan costs, patient out-of-pocket costs, and "average pill days." A larger issue is involved, as well, as the move occurs toward an era of evidence- or value-based formulary development and implementation. More attention needs to be focused on the challenging calculations of quality-of-life improvements, quality-of-care improvements, and total system cost reductions. First, health plans must do more to understand and quantify these effects. Second, these factors must be assessed relative to the direct cost and utilization data that tend to be easier to collect and process. These broader and integrative assessments should be based on the P&T committee's guiding principles of values, experience, and the best available evidence. They should guide formulary development and implementation based on the overall importance and value within a broader health care context. The assessments need to be made and private- and public-sector policies must account for them going forward.

Marc W. Mora, MD
President, P&T Society;
Medical Director,Consultative Specialty Services; Group Health Cooperative; Seattle.

The federal government, with its significant resources and expertise, seems well positioned to help answer many of these important questions. With accumulating data from the part D benefit, much could be learned about comparative effectiveness, safety, and the ultimate outcomes health plans are striving to achieve for patients and members. When the researchers asked whether the investments in Medicare part D improve quality and affordability, the question should be answered in several different ways, addressing whether plans are able to achieve better (more or less appropriate) drug use, lower (patient, plan, or public) drug cost, lower overall pharmaceutical costs, lower overall health costs, etc. Ultimately health plans need to assess whether the interventions affect patient health care and quality of life.

This article and its accompanying editorial are important for those interested in formulary development and implementation. They help establish a framework for assessing the effect of the Medicare part D benefit and for thinking about how to integrate that assessment into broader formulary management responsibilities. Ultimately they establish the critical question, "Are we getting what we paid for?"

REFERENCE

1. Yin W, Basu A, Zhang JX, et al: The effect of the Medicare part D prescription benefit on drug utilization and expenditure. *Ann Intern Med* 2008;148:169-177.

2. Stuart B: Where are the Medicare part D claims data? *Ann Intern Med* 2008;148:239-240.

REGISTER TODAY!

Program Description

This year's annual conference will educate and inform attendees on new market dynamics impacting formulary policy development. The trend toward comparative effectiveness and the use of evidence for formulary benefit design will be integrated into our discussions on formulary development, management and evaluation. Formulary management techniques, which include the application of evidence-based medicine and the development of an electronic medical record/personal health record, demand increasing attention and will be addressed during interactive panel discussions and workshops. Faculty will describe practical solutions to the challenges of assuring appropriate services across the continuum of patient care. They will also examine pressures, promises and practicalities in health policy for 2009 and beyond. Topics featured in interactive workshops will include oncology, vaccines and electronic medical record/personal health record.

Who Should Attend?

This meeting is designed for medical directors and pharmacy directors, and other health care professionals with an interest in drug formulary policy development from health plans, health systems, hospitals, and physician groups. This program is also designed for academicians, employee benefit managers and benefit consultants who are interested in understanding the impact of the P&T process on drug coverage decisions.

Scientific Agenda

This one-day conference will provide a forum for attendees to interact with health care thought leaders at the forefront of new market dynamics in formulary development, management and evaluation. Attendees will gain insight into the perspectives of academic institutions, employers, government organizations, hospitals and managed care organizations.

At the conclusion of this year's conference, attendees will be able to:

- Analyze the impact of new techniques for formulary policy development, management and evaluation and the implications for patients, providers and payors in both public and private sector programs.
- Evaluate current formulary techniques and incorporate new concepts related to critical areas such as oncology and vaccines as well as medication quality and safety across multiple therapeutic areas.
- Describe anticipated changes to P&T committee policies and incorporate these changes into formulary development and implementation.

Hotel Reservations

The Fairmont Washington, DC
2401 M Street, NW, Washington, DC 20037
Phone: 202.429.2400 Reservations Phone: 800.441.1414
Preferred P&T Society Room Rate: $299/night plus applicable taxes

Please contact the hotel directly to reserve your room. Don't forget to indicate that you are with The P&T Society. Preferred rates for attendees have been secured by The P&T Society. These rates are applicable until Friday, October 10, 2008; however, rooms are limited. All reservations are on a first-come, first-served basis.

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The Pharmacy & Therapeutics (P&T) Society serves professionals concerned with the delivery of high quality, outcomes-oriented pharmaceutical care in all health care environments. Its purpose is to foster interdisciplinary collaboration, information exchange, and the pursuit of continuous quality improvement in the P&T process.

Dear Prospective Attendee:

On behalf of The Pharmacy & Therapeutics Society I extend an invitation to participate in The P&T Society's 8th Annual Conference, November 6-7, 2008, in Washington, DC. This one-day ACCME and ACPE-accredited program will focus on several major areas of interest, each leading to practical recommendations for improving the day-to-day functioning of professionals involved in formulary development and implementation.

The first area will cover the growing trend toward value-based benefit design, evidence-based formulary development and implementation. Our general session presenters will offer insights into current and future efforts to generate the evidence needed for decision making. Our panelists, drawn from the Society's Board of Trustees, will discuss how such evidence will be used in decision making at the employer, health plan, practice and institution level. We will learn how to analyze and apply current and future research, what to expect from health care stakeholders in the future and how we need to prepare ourselves and our organizations for new approaches. These sessions will produce practical recommendations to assist P & T committee membership and leadership evolve their structure.

The second area will focus on current P & T committee issues. Panel presentations will address the management of high cost and injectable medicines in various practice settings by those with responsibility to assure high-quality and cost-effective patient care. Interactive workshops will focus on policy and guidelines and practical application in oncology, vaccines and the future of the electronic medical record/personal health record. Finally, the closing general session will address the practical considerations for health care policy development for 2009 and beyond.

In addition, this conference offers opportunities for colleagues to interact and share information on the challenges and opportunities in their own practice settings. A reception Thursday evening, November 6, 2008, will provide an opportunity for participants, faculty and industry attendees to meet informally and share ideas.

We hope you can join us for this very exciting educational program.

Sincerely,

Marc W. Mora, MD
President
The Pharmacy & Therapeutics Society

The P&T Society's 8th Annual Conference
Access to Pharmaceuticals:Public and Private Solutions

Thursday, November 6, 2008

5:00 pm - 6:00 pm Board of Trustees Meeting
(by invitation only)

6:00 pm - 7:30 pm Opening Reception

Friday, November 7, 2008

7:00 am - 5:00 pm Registration Open

7:00 am - 7:45 am Board of Trustees Meeting & Breakfast
(by invitation only)

7:15 am - 8:00 am Continental Breakfast

8:00 am - 8:15 am Welcome
Joseph Eichenholz
Executive Director
The Pharmacy & Therapeutics Society

8:15 am - 9:30 am Opening General Session:
Clinical Value and Comparative Effectiveness: Generating Evidence

This session will showcase complementary approaches to utilizing evidence to make comparisons on clinical value and cost effectiveness. Faculty will discuss comparative risks and benefits as well as costs of emerging health care technologies and services.

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
Harvard Medical School

Sean Tunis, MD, MSc
Founder and Director
Center for Medical Technology Policy

9:30 am - 9:45 am Break

Don't wait to register! Early-bird registration ends October 10, 2008

9:45 am - 10:45 am Panel Discussion:
Health Care Delivery Systems: Applying Evidence in Clinical Practice

Mary E. Inguanti, RPh, MPH, FASCP
Vice President of Operations and Quality, Chief Quality Officer
St. Francis Hospital and Medical Center

Zachariah Gerger, DO
Medical Director
Southeast Pain Care and Southeast Anesthesiology Consultants

Edmund J. Pezalla, MD, MPH
National Medical Director and Chief Clinical Officer
for Aetna Pharmacy Management
Aetna

Gail Levenson, RPh, CDE, CGP
Director of Health Management Services
National Rural Electric Cooperative Association

Moderator
Marc W. Mora, MD
Medical Director of Specialty Services
Group Health Cooperative of Puget Sound

10:45 am - 11:45 am Panel Presentations:
Coordinating Management of High-cost Oral and Injectable Medications

Physician Office
Managing expensive drugs in a physician's office
Thomas J. McNulty, PharmD (invited)
Chief Clinical Officer
Ancillary Care Management

Specialty Pharmacy
Integration of specialty pharmacy into the P&T process
Atheer A. Kaddis, PharmD
Vice President, Managed Markets
Diplomat Specialty Pharmacy

Community Pharmacy
Role of community pharmacies related to specialty pharmaceuticals
David J. Fong, PharmD (invited)
Corporate Vice President, Pharmacy
Safeway, Inc.

Moderator
Celynda G. Tadlock, PharmD, MBA
Regional Vice President
WellPoint NextRx

The P&T Society's 8th Annual Conference

Access to Pharmaceuticals: *Public and Private Solutions*

12:00 pm - 1:15 pm **Luncheon and President's Address**

Marc W. Mora, MD
President
The Pharmacy & Therapeutics Society

1:30 pm - 2:15 pm **Concurrent Workshops**

Workshop #1: Oncology Treatment Guidelines In the P&T Process

Susan Hoang, PharmD, BCPS
Director, Pathways
US Oncology

Moderator
James A. Jorgenson, RPh, MS
Executive Director of Pharmacy
Clarian Health, Methodist Hospital

Workshop #2: New Challenges In Vaccine Therapy Management

Lee A. Mork, MS, RPh, MBA
Ambulatory Pharmacy Services Manager
Allina Hospitals and Clinics

Moderator
Perry Cohen
President
The Pharmacy Group

Workshop #3: Electronic Medical Record/Personal Health Record

Bruce Wilson, MD
Chairman, Group Health Pharmacy and Therapeutics Committee
Group Health Cooperative

Moderator
John C. Nelson, MD, MPH
Former President,
American Medical Association
HealthInsight, Utah

2:15 pm - 2:30 pm **Break**

2:30 pm - 3:15 pm **Concurrent Workshops**
(Repeat of 1:30 pm workshops)

3:30 pm - 4:15 pm **Final General Session: Pressures, Promises, and Practicalities In Health Policy: 2009 and Beyond**

With the 2008 presidential election held just days before this conference, this session will highlight how Washington activities will affect the playing field for our stakeholders. Attendees will walk away with empowerment to take action, ideas on how to change the way evidence is collected and data is processed, and ways to prepare for the future.

Mark H. Smith
Senior Government Relations Advisor
King & Spalding LLP

Moderator
Marc W. Mora, MD
Medical Director of Specialty Services
Group Health - Seattle, WA

4:15 pm - 4:30 pm **Closing & Adjournment**

Joseph Eichenholz
Executive Director
The Pharmacy & Therapeutics Society

Physician Accreditation
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Medical Education Resources and The P&T Society. Medical Education Resources is accredited by the ACCME to provide continuing medical education for physicians.

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Provider approved by the California Board of Registered Nursing, Provider #CEP 12299, for 6.5 contact hours.

The P&T Society's 8th Annual Conference
Thursday, November 6 – Friday, November 7, 2008

The Fairmont Washington, DC • 2401 M Street, NW • Washington, DC 20037

Registration Form

Fees:	Early Bird Registration (on/before 10/10/08)	Registration (after 10/10/08)
Member	$375	$450
Non Member* *$100 of the non member fee can be applied towards P&T Society annual dues. Yes, I am interested in joining The P&T Society; please send me a membership application.	$475	$550
Student	$25	$25

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273 Hebron Avenue
Glastonbury, CT 06033

Fax: 860.659.1598

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Degree: _____ Title: _____

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☐ Check (Made payable to The P&T Society) Amount: $ _____

☐ Credit Card (please select one) ☐ VISA ☐ MasterCard Amount: $ _____

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Cardholder Address (if different than above) _____

Signature (required): _____

Cancellation Policy: The P&T Society will accept written cancellations received on or before October 17, 2008. A $100 cancellation fee will be charged. No refunds will be issued after October 17, 2008.

ADA: The P&T Society fully complies with the legal requirements of the Americans with Disabilities Act (ADA) and the rules and regulations thereof. Please notify the Society directly if you have any special needs at 860.657.3207.

Hotel Reservations: The Fairmont Washington, DC, 2401 M Street, NW, Washington, DC 20037
Phone: 202.429.2400 Reservations Phone: 800.441.1414 Preferred P&T Society Room Rate: $299/night plus applicable taxes. Please contact the hotel directly to reserve your room. Don't forget to indicate that you are with The P&T Society. Preferred rates for attendees have been secured by The P&T Society. These rates are applicable until Friday, October 10, 2008; however, rooms are limited. All reservations are on a first-come, first-served basis.

Questions? Please contact The P&T Society directly at 860.657.3207 or dsax@pandtsociety.org.

Neobladder Construct for Neurogenic Bladder:

An Example of Regenerative Medicine

Patrick Shenot, MD, Mary E. Inguanti, RPh, MPH

An innovative treatment for patients with neurogenic bladder dysfunction who fail medical therapy represents an advanced example of the emerging field of regenerative medicine. Patients who typically develop neurogenic bladder are children with spina bifida and both adolescents and adults with spinal cord injury. If not properly managed, patients with neurogenic bladder can develop obstruction and reflux (demonstrated by hydronephrosis), which can lead to renal damage and ultimately, renal failure. Traditionally, physicians had used intermittent catheterization, indwelling catheters, and such medications as anticholinergics and parasympathomimetics to help reduce bladder pressures and control the incontinence that are associated with this condition. Augmentation cystoplasty using gastrointestinal tract segments (gastro-enterocystoplasty), which can improve bladder capacity and compliance, has been performed on patients unable to be managed medically. However, this can lead to complications and may be associated with an increased risk of cancer in the bowel tissue used in the bladder augmentation. A new technology with the potential to significantly increase bladder capacity and assure low-pressure storage of urine without the use of gastrointestinal segments is augmentation cystoplasty with an autologous neobladder construct. This transplant-like procedure does not require immunosuppression therapy. A patient's own bladder cells are seeded onto a biodegradable scaffold, and subsequently surgically augmented onto the existing urinary bladder. The scaffold biodegrades, leaving a neobladder derived from the patient's newly regenerated tissue. Early published studies have demonstrated that it is an effective treatment for some patients with neurogenic bladder dysfunction who require augmentation cystoplasty. It holds the promise to minimize the commonly encountered serious complications and side effects associated with the use of gastrointestinal tissue for bladder augmentation and avoid the long-term risk of cancer with the usage of gastrointestinal tissue in the urinary system.

Regenerative medicine is an emerging field of medicine whose goal is to "replace or regenerate human cells, tissues, or organs to restore or establish normal function."[1] Regenerative medicine is being applied successfully today, leading to new clinical developments that hold the promise to transform the treatment of a broad spectrum of diseases for which treatments are inadequate or unavailable.

According to the National Institutes of Health,[2] research in regenerative medicine can help create living, functional tissues to repair or replace tissue or organ function lost as a result of aging, disease, injury, or congenital abnormalities. This research could significantly transform the way diseases are treated, resulting in more complete recovery, a lower risk of complications, a better quality of life, and lower lifetime health care costs than with current conventional patient management.

Not only does regenerative medicine offer the promise of repairing damaged tissues and organs by regrowth and stimulation to the body to heal itself, the approach also enables scientists to grow tissues and "neo-organs" in the laboratory and implant them into the body. Currently, regenerative tissue-engineered products are commercially available to safely develop skin for replacement in burn victims and patients with diabetic foot ulcers.[2] In another example, knee cartilage cells, removed from a patient's arthritic joint, are grown in vitro, and reimplanted into the patient's knee, allowing improved function.[3] Vascular grafting for cardiac bypass surgery is in preclinical stages of development.[2]

This article details one innovation in regenerative medicine: the ability to create an autologous neobladder, a transplant-like augmentation product derived from a patient's own cells that can be grown outside the body and successfully implanted back into the patient to treat neurogenic bladder dysfunction. The autologous neobladder construct is intended to be attached to the bladder and support its improved functioning.

As in most areas of rapid technologic innovation, progress may be initially expensive. Highly complex, multistep, and novel methods of treating disease and improving function come at a price, which may have implications for insurance coverage and patient access. Although advances in manufacturing methods and product delivery may occur, technology assessment and Pharmacy and Therapeutics committees need to weigh the clinical advances against the short- and long-term costs they engender and the comparative costs as they relate to alternative technologies currently being used to treat the conditions. As effective regenerative medicine technologies are developed, health economic analysis will be developed to consider the comparative benefit of these new technologies to patients, providers, and payers. Health economic and value analysis will need to ensure that the full range of costs and benefits

Dr. Shenot is Assistant Professor, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania Ms. Inguanti is the Vice President of Operations and Quality, Chief Quality Officer at Saint Francis Hospital and Medical Center, Hartford, Connecticut.

are examined over an expected duration for the impact of the regenerative medicine intervention. The initial cost of products and treatments must be viewed in light of any demonstrated overall short- and long-term clinical benefits to patients and possible improvements in quality of life. Regenerative technologies, such as the creation of an autologous bladder construct, may require adaptation in review and payment systems at the institutional level to recognize the longer-term clinical and economic implications of such technology.

The Pharmacy and Therapeutics Society plans to follow the development and progress of the use of autologous neobladder construct in the treatment of neurogenic bladder. As trials are conducted and data published, the Society will review findings and implications for patients, surgeons and institutions, and highlight the technology review and formulary implications of these advances.

BACKGROUND

Etiology of Neurogenic Bladder. The function of the lower urinary tract is to provide urinary storage under low pressure until circumstances exist to permit urination. Bladder function is governed by a complex physiologic process involving the brain, the spinal cord, the smooth muscle of the bladder and bladder neck, and the striated external urethral sphincter. In the absence of neurological disease, the lower urinary tract achieves low-pressure urinary storage and voiding characterized by detrusor contraction coordinated with relaxation of the dual internal and external sphincter mechanism to allow efficient, low-pressure bladder emptying.

Neurogenic bladder dysfunction may be broadly categorized into three main groups, based on their urodynamic findings and clinical symptoms associated with detrusor or sphincter dysfunction: (1) storage problems resulting from involuntary bladder contractions (detrusor hyperreflexia, also known as neurogenic detrusor overactivity) or a poorly functioning sphincter, (2) impaired bladder emptying (detrusor areflexia, or neurogenic detrusor underactivity), and (3) a combination of deficiencies in storage and emptying (detrusor hyperreflexia with detrusor external sphincter dyssynergia [DESD]). Understanding these distinctions is essential to guiding treatment decision making as improper management may result in patients with neurogenic bladder developing obstruction or reflux (demonstrated by hydronephrosis), which can lead to renal parenchymal dysfunction and ultimately renal failure.[4–6]

The two primary conditions that can lead to neurogenic bladder are spina bifida and traumatic spinal cord injury (SCI). Other conditions that affect the nervous system that can lead to neurogenic bladder may include multiple sclerosis, Parkinson's disease, and stroke, but these are rarely reported (anecdotally and not published in the literature).

Spina bifida is a common cause of neurogenic bladder dysfunction. Spina bifida occurs in less than 1 in 1,000 births.[4] Approximately 1,500 new cases of spina bifida are seen in the United States each year.[5] About 50% of patients with spina bifida will develop renal deterioration if not properly managed. This is often related to elevated pressures within the bladder resulting from increased outlet resistance, increased detrusor muscle tone, and a diminished ability of the bladder to passively stretch under low pressure to accommodate urine filling, a condition known as poor bladder compliance. Elevated pressures within the bladder may cause vesicoureteral reflux and hydronephrosis with the potential for significant kidney damage, especially in the presence of urinary tract infections.[6,7] Thirty percent of patients are diagnosed with detrusor sphincter dyssynergia, a urodynamic pattern that, when not managed appropriately, is associated with high rates of upper urinary tract deterioration.[8]

Traumatic SCI can also lead to development of neurogenic bladder.8 The incidence of traumatic SCI is approximately 50 cases per million population (approximately 14,000 patients in the United States each year).[9] The majority of these patients will develop some degree of neurogenic bladder dysfunction. Patients with SCI will require ongoing urologic evaluation and urodynamic testing to accurately define the pattern of bladder dysfunction.

Other, even less frequent causes of nontraumatic injury to the spinal cord can result in neurogenic bladder; these include infections and demyelinating diseases, such as multiple sclerosis.[7,10]

Nonsurgical Treatment. Initial attempts to manage neurogenic bladder have traditionally included use of intermittent catheterization, indwelling catheters, and medications, such as anticholinergics and parasympathomimetics. Treatment must be individualized with the primary emphasis on preserving renal function while achieving urinary continence when possible. To avoid hydronephrosis, vesicoureteral reflux, and ultimately renal deterioration, the bladder must store and empty urine under low pressure. Low-pressure storage can sometimes be achieved through the use of anticholinergic medications in combination with clean intermittent catheterization (CIC). These pharmacotherapies can help increase bladder capacity. Commonly used medications include oxybutynin, tolterodine, hyoscyamine, propantheline, and imipramine. Pharmacotherapy with anticholinergic medications is typically added for patients who have or are at risk for persistent hydronephrosis or high-grade vesicoureteral reflux.[8]

For patients unable to spontaneously void, clean intermittent catheterization allows the bladder to be completely emptied at low pressures at regular intervals. Also, evidence shows that patients with high detrusor leak point pressures or with evidence of DESD who are treated early with a combination of clean intermittent catheterization and anticholinergic medications may have better long-term function of both the upper and lower urinary tract.[8]

The use of botulinum toxin (type A) has been investigated in the management of both DESD and neurogenic detrusor overactivity. Studies have shown that when injected into the external sphincter of the bladder, the toxin can improve urodynamic measurements for at least three months by preventing peripheral neurotransmitter release at presynaptic cholinergic nerve terminals and blocking neuromuscular activity in sphincter skeletal muscle.[11] When injected directly into the detrusor muscle, botulinum toxin may inhibit detrusor contraction by blocking the release of acetylcholine and other neurotransmitters in the afferent and efferent pathways of the bladder wall, urothelium, or lamina propria.

A study of botulinum toxin used to treat neurogenic detrusor overactivity showed decreases in incontinence episodes from baseline and improvements in bladder function in patients receiving the treatment. Botulinum toxin has been most extensively studied in the treatment of patients with SCI who have neurogenic detrusor overactivity (nearly 900 patients across multiple trials, and it has shown to improve continence in 70% or more of patients,[12] but there are little data regarding lowered bladder pressures). Although botulinum toxin A has been associated with continence improvement in some patients, few of those with spina bifida have undergone treatment with this agent; it is unclear whether they benefit from it.[12] Furthermore, the long-term benefits or risks of botulinum toxin usage in the bladder are unknown.

Despite the availability of pharmacotherapies and CIC, up to 30% of patients with spina bifida are still unable to achieve urinary continence without surgical intervention.[8]

Surgical Options. Different options are available for surgical reconstruction of the bladder to improve urinary function. The conventional approach consists of augmentation of the bladder using a segment of reconfigured intestine (enterocystoplasty) or stomach (gastrocystoplasty). A new method of bladder augmentation uses autologous bladder cells to regrow tissue around a biodegradable scaffold, which is then implanted within the patient's bladder (referred to as bladder augmentation with a neobladder construct).

Augmentation Cystoplasty. Augmentation cystoplasty should be considered for patients with elevated bladder pressures and associated signs of renal deterioration (absolute indication) and for those with socially unacceptable incontinence (relative indication).[14]

The goal of augmentation cystoplasty is to convert a dysfunctional neurogenic bladder to a low-pressure, higher-capacity reservoir. This helps prevent or resolve hydronephrosis and vesicoureteral reflux, thereby protecting the kidneys from further insult. Secondary benefits include improved urinary continence and a need for less-frequent catheterization.[14]

Reconstruction of urinary bladder is coded as ICD-9-CM 57.87. Bladder augmentation is included in this coding (orthotopic neobladder reconstruction in adult patients with cancer is also coded as 57.87, but the precise portion is unknown). According to the Agency for Healthcare Research and Quality's Health Care Utilization and Procedure (HCUP) Kid's Inpatient Database (KID) database, 722 discharges were reported nationwide in 2003 for bladder augmentation in patients up to 17 years of age (ICD-9-CM 57.87).[15] The 2003 HCUP NIS database estimated 1,168 bladder reconstruction procedures were performed in adults 18 to 84 years of age.[16]

Many of these pediatric procedures are performed in children's hospitals.[15] Lendvay and associates[17] estimated that a mean of four augmentation cystoplasties in patients with spina bifida were performed annually at each of 35 children's hospitals surveyed. In their study, which retrospectively evaluated nearly 13,000 hospital encounters for patients with spina bifida over a five-year period, they found that no single medical center performed more than 121 enterocystoplasties in these patients over this period.[17] Lendvay's group[17] also noted that the use of augmentation cystoplasty rates varied from fewer than 1% to more than 5% of patients with spina bifida. This wide variation in practice may reflect different parent, patient, or physician concerns regarding the high complication rate of the procedure when using gastrointestinal tissue.

In enterocystoplasty, a segment of the bowel is used to augment bladder capacity (Figures 1-3). The procedure is usually reserved for patients for whom conservative options, such as anticholinergic medications in combination with CIC, have been exhausted. The interposition of gastrointestinal tissue into the urinary tract can lead to mucous production, infections, electrolyte imbalances (including metabolic acidosis), stone formation, spontaneous rupture of the bladder, and development of malignancy.[4,18] In addition to overt metabolic acidosis, there is some concern that augmentation enterocystoplasty may lead to subclinical acidosis, resulting in leaching of mineral from bone and decreased bone mineral density.[19,20] Although augmentation enterocystoplasty can greatly improve a patient's quality of life, the procedure has the potential for significant morbidity (Table).

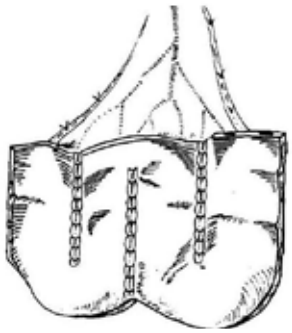

Figure 1:
Intestine is opened & fashioned into a patch.

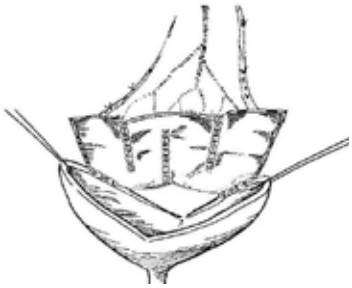

Figure 2:
Intestinal patch is sewn onto open bladder to complete conventional augmentation cystoplasty. The bladder is now a composite of native bladder and intestinal tissues.

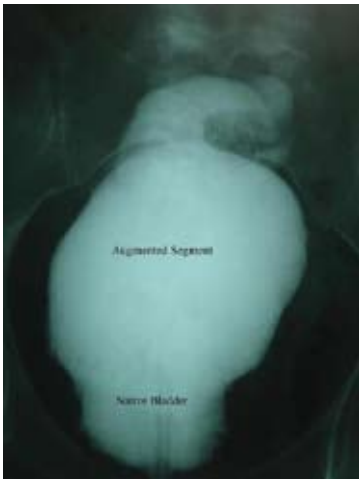

Figure 3:
Cystogram showing native bladder and augmentation created using ileum.

Table: Morbidity and Complications Associated with Augmentation	
Metabolic acidosis	50% to 80%
Osteomalacia	N/A
Adenocarcinoma	1.2% to 19.0%
Hyperammonemia	< 1%
Steatorrhea	N/A
Vitamin B12 deficiency	3% to 20%
Bacteriuria	8% to 23%
Renal caculi	18% to 30%
Bladder perforation	5% to 10%
Small bowel obstruction	~ 5%
Renal deteriotation	3%

*Varies with type of intestine used.
N/A = Not available
Adapted from Gilbert and Hensel[23] and Shekarriz B et al[24]

Metcalfe and colleagues[21] examined the need for additional bladder surgery after enterocystoplasty in childhood. The authors reviewed the charts of 500 enterocystoplasty procedures performed between 1978 and 2003 and found complications at the level of the bladder that resulted in additional surgery in 169 (34%) of patients, for a total of 254 surgeries. Four patients died as a result of malignancy and bladder perforation.[21]

The Neobladder Construct. A new technology to potentially improve neurogenic bladder treatment is referred to as augmentation cystoplasty with a "neobladder construct."

In order to perform augmentation cystoplasty with a neobladder construct, a surgeon begins by obtaining a small full-thickness biopsy of the patient's bladder. Urothelial and smooth-muscle cells from the patient's biopsy are then cultured separately for several weeks before being seeded onto a bladder-shaped biodegradable polyglycolic acid (PGA) scaffold to create the neobladder construct, a process that takes between five to eight weeks.[22] The porous cell scaffolding seeded with cells allows for regeneration of bladder tissue as well as vessels and nerve growth into the regenerating tissue. As the bladder regenerates, the scaffolding biodegrades.

A study completed by Atala and colleagues[22] suggested this new technology has the potential to improve outcomes with fewer complications than currently available options using gastrointestinal tissue for urologic reconstruction. In their study, they biopsied bladders to harvest cells from seven patients who were candidates for augmentation cystoplasty. All seven had myelomeningocele and ranged in age from four to 19 years old. Urothelial and smooth muscle cells were then grown in culture and seeded onto a biodegradable bladder-shaped scaffold, made of either collagen or a collagen and PGA composite. Seven to eight weeks later, the bladder constructs were implanted either with or without an omental wrap, which is endogenous tissue thought to improve successful implantation of engineered bladders.22 Twelve months postoperatively, all test subjects on whom data were available demonstrated decreased mean leak point pressures at capacity and increased bladder compliance. Those with the composite scaffolds and omental wrap exhibited improvements of leak point pressures at capacity of 56% compared with preoperative values. Mean maximum bladder capacity was increased in all groups except the collagen engineered bladders without an omental wrap. In those with the composite scaffolds and omental wrap, maximum bladder capacity increased by a mean 58% over preoperative measurements. The postoperative maximum average daytime dry intervals ranged from 1.5 to 3.5 hours for the collagen bladders, 2.5 to 4.0 hours for collagen bladders with an omental wrap, and 3.0 to 7.0 hours for composite engineered bladders with an omental wrap.[22] Renal function remained stable, and serum electrolyte levels were normal, and there was no evidence of renal or bladder calculi. Mucous production, a common complication of enterocystoplasty, was not observed.

The authors of the study concluded that bladders reconstructed with engineered tissues made with composite collagen and PGA scaffolds and wrapped in omentum resulted in improved function.[22]

The Atala study demonstrated a proof of concept for the use of the autologous neobladder construct in patients with spina bifida. Although the use of the new technology was successful, the study authors concluded that additional studies would be needed before it could be widely accepted.

Although the initial effort by Atala and associates[22] demonstrated encouraging results, the study results must also be interpreted with caution because of the limited number of patients provided an autologous neobladder construct wrapped with omentum and the need for a longer follow-up period. More research and evaluation are necessary through the performance of rigorously structured randomized clinical trials.

Three Phase 2 clinical trials of augmentation cystoplasty with the autologous neobladder construct in patients have been initiated (www.clinicaltrials.gov). Current patient populations under study include children with neurogenic bladder resulting from spina bifida, adults with neurogenic bladder owing to SCI, and adults with overactive bladder and urge incontinence who are unable to be managed with conventional therapy.

COST AND PAYMENT ISSUES

As is commonly the case, clinical advances often come at increased cost. In order to understand the overall impact of new technologies, these costs are weighed against the benefits provided and the efficacy and safety of the technologies they may replace.

Augmentation cystoplasty with a neobladder construct may represent an important clinical advance in technology that uses autologous tissue (and thus does not require immunosuppression).

Differences in complication rates and adverse outcomes will need to be factored into technology assessment and coverage/payment decisions once this technology advances into clinical practice. For example, if further study bears out that this technology results in equal efficacy but with lower complication rates compared with conventional cystoplasty, this could positively influence the coverage decision. As with organ transplants, benefit and cost must be defined and evaluated more broadly than for the use of procedures that would be expected to have only immediate results.

The cost of autologous neobladder constructs may be expected to be driven by the process for generating the new organ construct. Each autologous neobladder construct represents a custom produced product for each patient. The neobladder construct with bladder augmentation will be more expensive than the currently utilized enterocystoplasty procedure. However, in comparison with enterocystoplasty, it has the potential to reduce operating time cost, intensive care requirements, and the risk of serious and expensive complications associated with the use of bowel tissue in other locations.

Increasingly, various technology assessment organizations are being asked to invest resources in procedures and services with more immediate costs and longer-term benefits. Technology assessment groups will no doubt consider the use of this innovative technology against the backdrop of conventional treatment. Many questions remain unanswered. For example:

- When is this technology appropriate for patients who require augmentation cystoplasty, including those with spina bifida and spinal cord injury? Are there other patient groups who potentially might benefit?
- Should patients be required to undergo other nonsurgical interventions first?
- Would patients be considered candidates for this procedure only if they would currently be considered for gastro-enterocystoplasty?
- What is the benefit of the autologous neobladder construct in patients who have already undergone gastro-enterocystoplasty and is this practical?
- What are the mechanisms by which this treatment will be paid for by third parties?
- How do hospitals offering this technology balance financial, operational, and quality considerations?

According to Atala and colleagues,[22] the longest follow-up had been 61 months as of 2006. Many patients with spina bifida live actively through adulthood. The potential impact of this new technology and whether it will become the new standard of treatment or lead to development of other types of interventions for these patients remains to be seen. In the meantime, researchers await the clinical trial data necessary to appropriately evaluate the technology from the perspective of all stakeholders in the process.

CONCLUSION

Regenerative medical technology has progressed a long way since the introduction of bone marrow transplantation a few decades ago. These new technologies challenge not only the way patients are treated but how the health system categorizes them (with consequences for coding and payment) and how it manages their utilization.

The example of bladder augmentation with the autologous neobladder construct demonstrates an innovative approach to treating a relatively small patient population that offers a promising alternative to current pharmacologic and reconstructive surgical interventions, which are associated with significant comorbidity, resource use, and potential for longer-term complications. Current and future studies of this technology will better inform payers and institutions, and their decision-making committees as to its value. The Pharmacy & Therapeutics Society intends to follow the evolution of this technology and to report on its implications as an example of regenerative medicine and new issues in technology assessment and formulary management processes.

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Population-Wide Medication Possession ratio Measurements May Mask Poor Adherence to Medication Therapies in Patients New To Therapy

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The objective of this study was to compare adherence rates, as defined by medication possession ratio (MPR), across several highly utilized therapeutic categories of medications, for the subset populations of 'new to therapy' and 'continuers' and determine if the practice of providing a population aggregated MPR analysis misrepresents adherence rates in these two patient sub-groups. Retrospective pharmacy claims analysis was used in the therapy classes of statins, beta-blockers, ACE inhibitors, SSRIs, and oral anti-diabetic agents to generate and compare MPR and persistence calculations in patients identified as 'new to therapy' and 'continuers' over 9 months. The study found MPRs at 9 months for 'new to therapy' patients were less than MPRs for 'continuers' in all therapy classes studied. MPRs in 'new to therapy' patients were significantly less than the calculated MPRs for the aggregated study populations in the therapy classes of ACE inhibitors, beta-blockers, and SSRIs. In all therapeutic classes, persistence at 9 months was lower in the 'new to therapy' groups than in the 'continuer' groups. Current practices of measuring medication adherence by using a single population aggregated MPR within a therapy class can mask significantly lower medication adherence in patients who are new to therapy. This can lead to a conclusion that efforts to improve medication adherence have met success goals while significant deficiencies in adherence continue to exist in 'new to therapy' patients.

INTRODUCTION

Approximately 125,000 deaths occur annually in the United States directly as a result of nonadherence to cardiovascular medications.[1] To provide a relative reference for the magnitude of the problem, a comparison of this number to annual CDC death statistics from accidents shows that three times as many people will die from nonadherence than from motor vehicle accidents (~42,000 per year), the leading cause of accidental death in the United States.[2]

Medication nonadherence also creates a significant, but largely avoidable cost burden on the U.S. healthcare system. A 2007 study by the National Council on Patient Information and Education (NCPIE) found that nonadherence to medication therapy in the United States adds $177 billion in annual healthcare costs from avoidable disease progression, disease complications, drug-related hospitalizations, reduced functional abilities, decreased quality of life, and death.[3] The study also found that 40% of nursing home admissions are attributable to failure to take medications as prescribed and that per patient physician office visit costs increase by $2,000 per year in nonadherent patients.[3] Although improved medication adherence can lead to increased costs for medications, net savings through decreased avoidable medical costs have been demonstrated.[4,5]

The problem of medication nonadherence is not an issue that is isolated to only a small portion of those who are prescribed medication therapies. Less than half of patients receiving prescription medications have been found to take their medication over time without missing a significant number of doses and approximately 25% of people who are prescribed a medication either do not get the prescription filled or do not initiate therapy after obtaining the medication.[6,7] Factors causing non-adherence are varied and complicated. The patient's personality, culture, values, mental capacity, health literacy, social support network, physician empathy and communication skills, characteristics of the therapeutic regimen, and financial considerations are among the many interwoven factors that influence adherence to therapy.[8]

Recognizing the important role that medication adherence plays in reducing the overall cost burden of healthcare, managed healthcare organizations and employers are increasingly engaged in the delivery of a variety of medication adherence improvement strategies and services to their patients. These activities often occur in conjunction with co-pay reduction programs and clinical intervention programs designed to foster adherence in disease states typically associated with high cost burdens.[9-13]

Additionally, the Centers for Medicare and Medicaid Services (CMS), the body responsible for administration of the federal government's Medicare and Medicaid programs, has adopted medication adherence as a core strategy in the delivery of quality care to Medicare and Medicaid recipients. Reimbursements are provided for counseling that includes medication adherence improvement activities.[14]

A common method employed by managed care organizations to identify patients who are possibly not adhering to their medication regimes is utilization of prescription claims records to generate adherence measures.[15] Typically, managed care organizations will measure adherence based on several different types of measures.[16]

Medication Possession Ratio (MPR). MPR is a measure that looks at medication refill history over a given period of time, usually 180 or 365 days, and calculates how many doses of medication a patient obtained during the study period to how many doses should have been obtained. An MPR of 1.0 indicates that the patient obtained enough supply of medication to be treated without missing doses, while an MPR of 0.5 indicates that a patient is likely missing half of prescribed doses. Typically, a patient is considered 'adherent' if an MPR is above 0.7-0.8 in any time period studied.

Length of Therapy (LOT). LOT is useful for certain medications that should be administered for a minimal period of time and to determine how long a patient, or patient population is typically staying on a medication after initiation of therapy. This measure is commonly used in assessing performance against HEDIS standards regarding length of therapy for antidepressants.[17]

Persistence. On a per-patient basis, persistence is the same as length of therapy. Some measures have attempted to define persistence on a monthly basis that is dependent on reaching a consumption threshold in any given month. In a population of individuals taking a medication, persistence is used to determine what portion of the original group continues to take their medication at specific time intervals after the initiation of therapy.

Gap Days and Median Gap Days. Gap Days is a measure that is derived from measuring how many days an individual goes beyond the anticipated date of their next refill of a medication. As an example, if a person receives a 30 day prescription on June 1, ideally the next refill should occur on July 1. If the person does not refill their medication until July 15, a total of 15 gap days are accrued. By repeatedly measuring gap days from refill to refill, it is possible to look at the median of gap days measured. This compared to average days supply of the prescription over multiple fills becomes a good short and long-term indicator of overall medication adherence.

Although Gap Days and Median Gap Days provide an excellent measure of both individual and population performance,[15] it is a process intensive measure to generate for groups of patients over multiple months. Because the MPR is an easier measure to generate and is easily understood by most clinicians, many managed care organizations utilize MPR in assessing adherence.

Even though it is an easy measure to use, MPR is not without potential drawbacks when applied as a sole measure of adherence to a population of persons receiving any given therapy. It is well known that patient drop-out rates are higher for persons who are new to therapy than those who have been taking any given medication for a number of months.[17,18] As many as 60% of patients new to statin therapy have been shown to discontinue their medication within 12 months of their first prescriptions with over half of the discontinuations occurring within three months of therapy initiation and about one-quarter occurring sometime during the first prescription.[18] Coupled with the knowledge that approximately 25% of patients prescribed medications never even attempt to initiate therapy,[6,7] the discontinuation rate for persons who are new candidates for therapy may be as high as 60% within the first three months of prescription activity (25% non-fill rate + 50% discontinuation in the remaining ¾ of new to therapy individuals ceasing therapy by month 3 of initiation).

Many possible reasons exist for early discontinuation of therapy and include financial barriers, side effects, access to care, poor patient-provider communication, attitudes and cultural beliefs, family support, and health literacy barriers to understanding the importance of pharmaceutical healthcare. The bottom line though is that persons who have continued therapy for a length of time that includes multiple medication refills (continuers) will have developed good medication-taking behaviors relative to persons who are entirely new to therapy.[19] Consequently, lower discontinuation rates over time should be expected with continuers vs. new-to-therapy individuals.

Since population-wide MPR analyses do not routinely differentiate between individuals who are new to therapy and patients who have been on therapy for a long period of time, it is possible that a population-wide MPR measure may not accurately identify adherence deficiencies that exist in underlying segments of the population. This issue could be critical to understanding how well a managed care organization's members are responding to adherence improvement activities as well as managing customer expectations for outcomes derived from adherence improvement activities.

Consider a situation where a new chronic disease state is discovered and one drug is used to treat that disease. In the beginning of therapy across the patient population, persistence curves would show rapid declines in therapy continuation because all persons receiving the drug would be 'new to therapy.' But over time as more and more persons become 'continuers' relative to new therapy starts, persistence levels in future adherence measures will appear to rise due to the relatively low dropout rate of the ever-growing 'continuer' sub-group. This would have the same effect on MPR and over time the MPR would be expected to naturally increase.

On the opposite end of the spectrum where the majority of persons with a chronic disease are already being treated, utilization of a population-wide MPR measure could easily mask a less than desirable MPR for the relatively smaller population of new to therapy starts in any given measurement period. Consequently, application of a global MPR measurement to an entire population could lead to the erroneous conclusion that medication adherence for the whole population is at an acceptable level. In spite of measures of good overall medication adherence, the additional investment in medications that adherence improvement requires could fail to result in reduced total medical expense if the new to therapy sub-group continues to experience a high rate of avoidable medical events because of non-adherent behaviors.

OBJECTIVE

The objective of this study was to examine adherence rates, as defined by MPR, across several highly utilized therapeutic categories of medications, and by comparing MPR rates for entire populations to MPRs for the subsets of 'new to therapy' and 'continuers,' to determine if existing practices for MPR calculations are misrepresenting medication adherence rates.

METHODS

Historical pharmacy claims for statins, beta-blockers, ACE inhibitors, selective serotonin uptake inhibitors, and selected oral anti-diabetic agents were extracted from the Aetna data warehouse for the period of January 2006 through December 2007. From this data extract, patients who were continuously eligible for pharmacy benefits through December 2007 and were receiving any of the above classes of medications in the period of January 2007 through March 2007 without claims for similar medications in 2006 were defined as 'new to therapy.' This process of patient identification allowed creation of a group of patients, defined as 'continuers' who had a minimum of 6-12 months of medication

exposure prior to the MPR analysis, and a comparison group of 'new to therapy' patients who had no prior experience with medications in the therapeutic classes being studied.

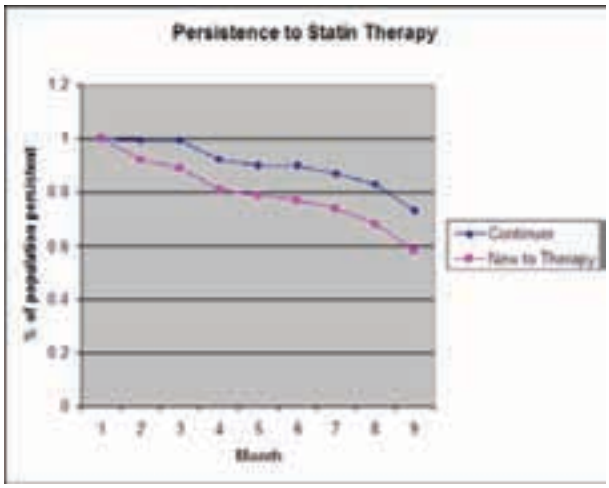
After identification of 'continuers' and 'new to therapy' patients, a 9 month MPR analysis was conducted for the aggregated group and each sub-group of patients to compare MPRs. The MPR calculation was based on accumulated days supply from prescription claims during the period of January through September 2007 for the 'continuers,' and January through December 2007 for the 'new to therapy' patients. Prescription claims for each 'new to therapy' patient were monitored for a total of nine months forward from the date of first fill to account for the fact that the 'new to therapy' patients received their first prescription at different times within the three month therapy initiation window (January 2007 – March 2007).

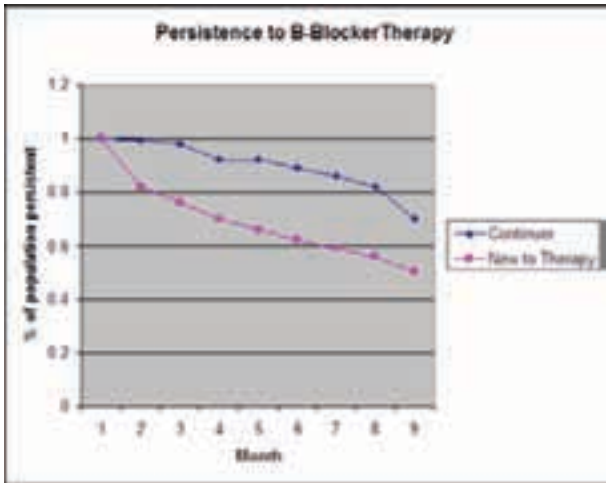
The study was conducted in an 'intent to treat' manner which allowed for patients to switch between different agents within the same general therapeutic class during the time frame of the study without disruption of therapy that would decrease MPR in persons experiencing therapy switches during the study period. As an example, if a patient started therapy with atorvastatin in month 1 and switched to simvastatin in month 3, all atorvastatin and simvastatin claims and accumulated days supply would be calculated as a single MPR for atorvastatin. In the SSRI analysis, SNRIs were included as were ARBs in the ACE inhibitor analysis as agents that patients could potentially switch to so that intent-to-treat MPR calculation accuracy would be maintained over time when such switching occurred.

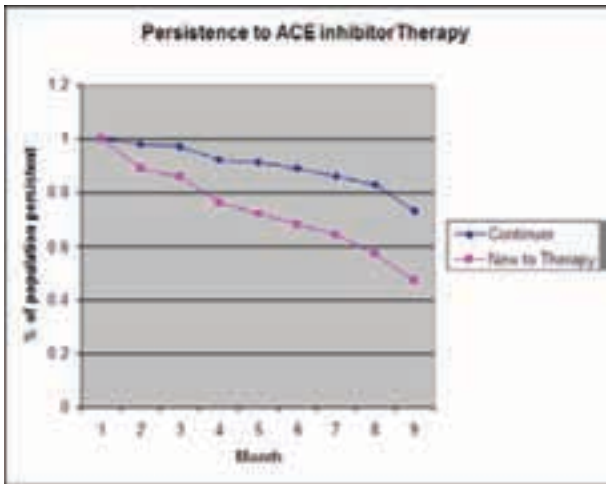
After identification of patients and construction of therapy groups to allow an intent to treat analysis, persistence curves were constructed to observe for differences in therapy drop-out rates for 'continuers' and 'new to therapy' patients. MPR calculations for each patient were then determined by dividing accumulated days supply by 270 days (9 months). In situation where patients obtained > 270 days supply during the study period because of issues such as timing of first and last refills with respect to the start and stop dates of the analysis and excess supplies due to therapy switches between agents in the same class, the MPR was rounded down to 1.0. Finally, MPRs were averaged for the "new to therapy," "continuer," and aggregated sub-groups and compared. A Chi Square analysis was performed between the continuers and new to therapy patients utilizing the aggregated MPRs for both groups as the expected MPR to determine statistical significance of observed MPR differences.

FINDINGS

107,754 continuously eligible patients across seven similarly designed pharmacy benefit plans were included in the analysis. In terms of persistence, each analysis showed fewer patients in the 'new to therapy' group to be continuing therapy at any of the monthly time intervals (Figures 1-5). The analysis also revealed differences in MPR between the aggregate, continuer, and new to therapy groups across all therapy classes studied (Table 1). In terms of both persistence and MPR measures, similar patterns were observed across all therapy classes with the 'continuer' patients exhibiting greater adherence than the 'new to therapy' patients in each of the therapeutic classes of medications included in the study.



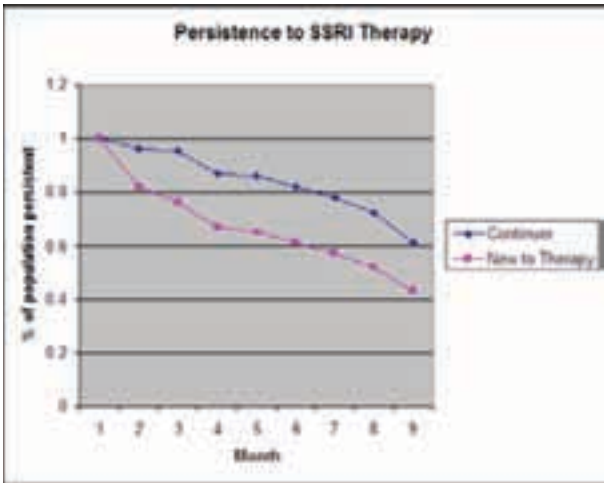


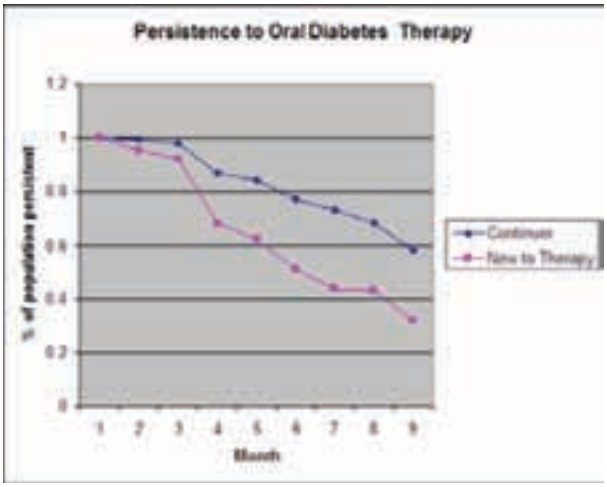


The difference in persistence at 9 months of observation ranged from a 15% - 26% decline in continuation of therapy among 'new to therapy' patients vs. 'continuers.' ACE inhibitors and oral anti-diabetic agents exhibited the greatest difference in 9 month persistence (26%), while patients receiving statins showed the least difference in persistence between groups (15%).

'New to therapy' patients exhibited a lower MPR-270 in all classes of agents in both comparison to aggregate MPR-270 and continuer-only MPR-270 scores (11 - 20% vs. aggregate and 15 - 26% vs. continuers). Differences were the greatest in the b-blocker therapy class (20% vs. aggregate and 26% vs. continuers) and least in the statin therapy class (12% vs. aggregate and 15% vs. continuers).

Using the aggregate MPR-270 value in each therapy class as an expected value for the MPR-270 in the 'continuer' and 'new to therapy' groups and applying a Chi Square analysis to the difference in observed vs. expected MPR-270 values, the practice of aggregating groups to generate MPR calculations was determined to significantly over-estimate medication adherence in the 'new to therapy' groups for b-blockers, ACE inhibitors, and SSRIs ($p < .05$). In the 'continuer' groups, the practice of aggregation did not cause the continuer groups in any therapy class to significantly differ for the aggregate MPR-270 calculation.





DISCUSSION

This study demonstrates a potential problem with the practice of reporting one aggregate MPR when measuring medication adherence. If an MPR of > 0.80 is considered as an 'adequate' population goal, and medication adherence program success is based upon achieving an MPR measure of > 0.80, it would mask sub-optimal adherence rates for 'new to therapy' patients in 3 of the 5 therapeutic classes studied. Therefore, a more complete picture of performance success for adherence interventions can be achieved by producing MPR calculations for both the 'continuer' and 'new to therapy' sub-groups in any given population of chronic medication users.

If one believes that the medication adherence improvement programs are conducted to improve quality of life and decrease avoidable medical events in the future, then this study also highlights the need to develop strategies that focus intervention resources on those persons who will most likely derive benefit from improved medication adherence.

	Aggregate		Continuer			New to Therapy				
	n	MPR	n	MPR	Difference from aggregate	n	MPR	% of aggregate population	Difference from aggregate MPR	Difference from continuer
Statin	2461	.940	1884	.976	.036	577	.823	23.4%	-.117	-.153
B-blocker	1412	.916	1078	.978	.062	334	.717*	23.7%	-.199*	-.261
ACE inhibitor	1522	.941	1159	.998	.057	363	.753*	23.8%	-.188*	-.247
SSRI	2032	.899	1441	.972	.073	541	.723*	26.6%	-.176*	-.249
Oral anti-diabetic	350	.873	207	.911	.038	63	.696	18.0%	-.177	-.215

* significantly below expected value from aggregate score ($p < .05$)

Table: MPR-270 calculations for selected therapy classes of agents for continuous and new to therapy patients.

Although this study was not conduced to measure downstream medical outcomes related to level of medication adherence, from a population perspective, it suggests that the opportunity for adherence improvement lies more in the 'new to therapy' sub-group than in the 'continuer' sub-group. This study also suggests that the 'continuer' group has a higher adherence than the aggregated group and as a consequence there may be little opportunity for further adherence improvement in the major sub-population that makes up the aggregated group.

Additionally, because 'new to therapy' patients discontinue therapy at a faster rate than continuers, providing persistence measures for each sub-group of patients in addition to MPR reporting yields important information that is not available in programs that report on MPR alone. Over time, patients who discontinue therapy will cease to be included in MPR calculations because they will eventually have no prescription claims appearing in the data subsets used to perform MPR calculations. Ongoing identification of non-persistent individuals provides opportunities to re-initiate therapy in an important group that would presumably benefit from resuming medication therapy. It may also help managed care organizations explain why medication adherence improvement activities that show success through high population-wide MPR measures are resulting in a smaller than expected downstream reduction in avoidable medical events.

Another question that this study raises is the need to examine which sub-groups of individuals generate the greatest relative number of downstream events that can be avoided through improved medication adherence. Such studies may be helpful in further refining strategies to improve medication adherence in a manner that maximizes program investment value. For example, if it is ultimately found that the greatest number of events and avoidable cost is being generated from 'new to therapy' discontinuers in the ACE inhibitor therapy class, an MPR-based adherence improvement programs' resources could be shifted to include routine persistence reporting in 'new to therapy' patients placed on ACE inhibitors.

This study shows that 'new to therapy' users have a higher nonadherence rate from the 'continuer' population and this implies that the barriers for adherence may be higher in the 'new to therapy' group than in the 'continuer' group. This seems to be consistent with the many generally accepted reasons for nonadherence.[7,19] Barriers to adherence are likely to be more influential in the 'new to therapy' group vs. the 'continuer' group as continuers have most likely overcome many of these barriers as evidenced by their higher long-term persistence and MPR measures.

CONCLUSIONS

At present, many managed care organizations are relying primarily on aggregate MPR measures to demonstrate adherence improvement program success. However, this study demonstrates that such measures can mask significant adherence problems with patients who are 'new to therapy' and lead to the erroneous conclusions that population adherence rates are at an acceptable level for both 'continuer' and 'new to therapy' patients. Additionally, this study shows that 'new to therapy' patients are less persistent than 'continuers' across multiple therapeutic classes. These finding suggests that managed care organizations should provide their customers with more detailed sub-group MPR reports along with ongoing persistence analyses that will help their customers to gain a better picture of medication adherence and an improved appreciation for the need to target adherence improvement activities where they can produce the greatest value.

RECOMMENDATIONS

Managed care organizations engaged in medication adherence improvement programs should consider expanding their adherence reporting capabilities to include sub-group persistence analyses as well as therapy class-specific MPR reports that are designed to better demonstrate performance of these programs in patient groups that may differ in their medication taking experience. Studies are also needed to quantify the downstream medical event and cost consequences associated with both 'new to therapy' and 'continuer' sub-groups within specific classes of medications. Studies of this sort could provide value in targeting adherence intervention programs at specific groups of patients who present the greatest downstream risk for avoidable medical events and cost.

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Impact of Drug Copayment on Adherence and Subsequent Clinical and Economic Outcomes Among Privately-Insured Type 2 Diabetes Patients Converting to Insulin Pen Therapy

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A retrospective pre-post integrated managed care claims database analysis was performed to assess the correlation between prescription drug copayment and medication adherence, and economic impact upon initiating insulin aspart pen (IAP) therapy from previous vial/syringe (VS) use among type 2 diabetes patients. End-points included prescription copayment, medication possession ratio [MPR], association between post-index medication adherence [MPR $\geq$ 80%] and copayment, hypoglycemic events, association between adherence and hypoglycemic events, and all-cause (AC), hypoglycemia-attributable (HA), and other diabetes-attributable (DA) costs. Among the 670 study subjects, post-conversion, adherence was significantly improved (MPR: 65% to 70%; P = 0.01). Odds of post-index adherence being $\geq$ 80% decreased by 17% among individuals with copayments $\geq$ $21 and by 10% among individuals with post-index copayments ranging from $11-$20, compared to individuals with copayments $\leq$ $10. Post-conversion, significant reductions in total mean AC annual treatment costs, HA costs, and DA costs were observed; P < 0.01.

INTRODUCTION

In recent years, many health plans have adjusted their formularies to include three- and four-tier cost-sharing systems such that 74% of covered workers in the United States in 2006 were enrolled in plans with these tiered arrangements.[1] Tiered formularies were created to be an incentive for patients to use preferred brand name or generic drugs and therefore lessen their prescription drug costs.[2] A large majority of covered workers face copayments rather than coinsurance. Average copayments in 2006 were $11, $24, and $38 for generic, preferred, and nonpreferred drugs, respectively, and have been steadily increasing over the past few years.[1] This growing system has worked reasonably well at reducing the amounts paid for prescription drugs, as illustrated in a study conducted by Huskamp and colleagues,[2] that found 35.1% to 49.4% of beneficiaries whose health plan moved from a one-tier to a three-tier formulary with higher copayments switched their medication to a lower tier, as compared to 1.5% to 17.3% of beneficiaries who were not affected by the change. However, enrollees affected by this policy change resulting in higher copayments were also significantly more likely than those in the comparison group to stop using a drug in the class altogether, with those taking ACE inhibitors and statins being twice as likely to discontinue the use of drugs in these classes.[2]

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Type 2 diabetes is a chronic illness where medication adherence is strongly associated with cost.[3-6] In 2005, there were 14.6 million people with diagnosed diabetes mellitus in the United States, of which 90% – 95% have type 2 diabetes. Among adults with diagnosed diabetes 16% are treated solely with insulin while an additional 12% take oral antidiabetic medication in addition to insulin.[7] However, adherence to insulin treatment has been shown to be significantly lower than oral medications.8 A study by Rajagopalan and associates[8] found a mean adherence of 62% among patients taking insulin, compared to 81% taking metformin and 85% taking pioglitazone. Adherence to diabetes therapy is extremely important in that it helps reach and maintain glycemic control and therefore avoid major complications among those most susceptible.

The decrease in adherence to prescribed medication in response to higher copayments leads to two issues in chronically ill patients. First, a lower medication adherence means that a patient is not receiving the full benefits of pharmacotherapy treatment, which can cause their illness to be prolonged or worsened. Second, a decrease in adherence often leads to adverse events, necessitating higher resource utilization and costs in the future.[9] However, to date no studies among diabetes patients have specifically evaluated the association between insulin copayment disparities and adherence to treatment.

To this end and to the best of our knowledge, the present study is a first comprehensive analysis to evaluate the changes in medication adherence and subsequent effects on clinical and economic outcomes and evaluate impact of post-conversion

prescription copayment on post-conversion medication adherence in type 2 diabetes patients converting to insulin pen therapy from preexisting insulin preparations administered with vial/syringe. The present study is intended to be a follow-up sub-group analysis to data previously reported by Lee et al,[10] which examined adherence, hypoglycemic events, associations between adherence and hypoglycemic events, and healthcare costs among type 2 diabetes patients converting to new insulin pen delivery devices. The present analysis focuses primarily on the effect of insulin pen prescription copayment on medication adherence across a variety of health plans, in addition to the above parameters, specifically evaluating a sub-set of patients converting to the insulin aspart pen device from a stratified set of pre-conversion insulin formulations.

METHODS

Data Source. This study used the PharMetrics database, containing a fully integrated and adjudicated set of medical and pharmaceutical claims for all covered services for > 40 million lives from 57 commercial health plans across the United States (at the time of data acquisition). It is comprised of a broad, representative sample of national, commercially-insured healthcare beneficiaries on a variety of measures, including geographic dispersion, age, sex, and health plan structure. As the database includes a continuously enrolled managed care population, longitudinal retrospective assessment of medical practice patterns and healthcare resource utilization is permissible.

Descriptive information on patients' dates of coverage, sex, geographic region, and age is included in the enrollment file, while the medical file contains details on claims for physician office visits, outpatient services, and hospital stays. Specifically, the information available includes dates of service, medical diagnoses, and procedures performed, coded using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and Current Procedural Terminology version 4 (CPT-4) codes. Documentation of each prescription filled, including records of the dispensing date, National Drug Code (NDC), quantity of drug, and number of days supplied is contained in the outpatient pharmacy file. Each of these files is linked through a unique patient identification number, allowing integration of individual patient records across the entire analytic file to create episodes of care over time. The database is fully compliant with the Health Insurance Portability and Accountability Act of 1996.[11]

Study Design and Cohort Selection. The study design was a retrospective, longitudinal, intra-patient (pre–post) analysis similar to that employed in recently published database research aimed at assessing the clinical and health outcomes, as well as costs, of various therapy conversions from a third-party payer perspective.[10,12,13] A cohort of patients with a confirmed diagnosis of type 2 diabetes who converted to insulin aspart pen (IAP) therapy for the first time (i.e. index event) and who had previously been treated with either human or analog insulin administered by vial and syringe were identified as the study group. Various characteristics of the cohort in the 6 month period before the index event (pre-index period) were compared with those in the ≥ 2 year period after the index event (post-index period).

The primary study endpoints included changes in prescription copayment and medication adherence after conversion to the IAP device. Association between post-index drug copayment and adherence, and association between adherence, hypoglycemic events, and related healthcare costs, were also analyzed. The overall study cohort was entirely comprised of and divided into 4 sub-cohorts by type of pre-index medication for further analysis: NPH insulin users, human premix insulin users, insulin glargine users, and premixed analog insulin users.

Data were collected for the period from January 1, 2001 to April 30, 2005. Patient inclusion criteria consisted of: age ≥ 18 years, multiple diagnostic claims for type 2 diabetes (i.e. ICD-9-CM code 250.xx, excluding type 1 sub-codes), and first use of IAP therapy initiated between July 1, 2001 and December 31, 2002. These patients were identified by NDC and assigned an index date (i.e. the date of the first prescription for the device).

All patients included in the study were required to have longitudinal data characterized by at least 6 months of continuous enrollment prior to the index date and at least a 2 year length of follow-up after the index date. First use of IAP therapy was determined by the absence of its prescription during the pre-index period. Data were collected longitudinally from the index date to first occurrence of either discontinuation of the index medication or to the end of the study period (April 30, 2005).

Statistical Analysis. Descriptive statistics were calculated, with categorical variables reported as percentages. Patient demographic and clinical characteristics between groups were analyzed using the Pearson x^2 test. For continuous variables means (SDs) and medians (ranges) were generated. The Student t test was used to analyze mean differences between sub-cohorts. An a priori level of significance of 0.05 was set for all of the analyses.

Clinical characteristics (i.e. patient comorbidities, complications related to diabetes) were assessed over the pre-index period. Comorbid conditions and complications associated with diabetes were comprehensively chosen for consideration upon having been identified from the literature. Those conditions included: cardiovascular disease, diabetes-related infections, other metabolic diseases, nephropathy, neuropathy, retinopathy, obesity, lower-extremity amputation, depression, and hypoglycemic events. Specifically metabolic complications such as hypoglycemic coma (ICD-9-CM code 251.0), other specified hypoglycemia (251.1), unspecified hypoglycemia (251.2), postsurgical hypoinsulinemia (251.3), and disturbances of branched-chain amino acid metabolism (270.3) were included. These conditions were tracked using primary and secondary ICD-9-CM diagnosis codes. Binary indicator variables (1 = yes, 0 = no) were used to signify the presence or absence of these medical conditions during the pre-index period.

Since the database lacked a separate copayment variable, we identified each patient's copayment through an imputed methodology. Two variables of interest in computing copayment values for each patient were considered: the allowed amount and the paid amount for the health services. Creation of a copayment variable for each record was done by subtracting the paid amount from the allowed amount. Exclusion of any record where both paid amount and allowed amount ≤ zero and where allowed amount was smaller in value as compared to paid amount was also performed

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prior to copayment estimation. Copayments were created for each record for a patient based on a 30-day prescription supply. The mean copayment/prescription across repeated drug prescriptions dispensed was calculated. Since administrative claims were collected over several years, all imputed copayments, as well as patient healthcare costs, were adjusted for inflation to 2005 dollars using the medical care Consumer Price Index.[14]

Adherence to diabetes treatment before and after the index event was evaluated using the medication possession ratio (MPR). The MPR, a value used commonly in database-related outcomes research to assess levels of optimal or suboptimal adherence,[15-17] is defined as the sum of the day's supply of medication divided by the number of days between the first fill and the last refill plus the day's supply of the last refill. This measure has been validated in previous studies on insulin and allows for a representation of the proportion of time during the follow-up period that a patient was in possession of a supply of their index medication.[18-23] This designation of MPR usually results in a ratio of ≤ 1 due to time gaps in refilling the medication; MPR values > 1 were adjusted to 1. An MPR value of $< 80\%$ was defined as poor adherence (conversely $\geq 80\%$ was defined as optimal adherence). The statistical significance of differences in MPR between cohorts was assessed using a t test.

Annualized odds ratios (OR), quantities used to compare whether the probability or likelihood of a certain event differs between 2 groups, were estimated using person-time and event-time analyses with adjustment for varying length of follow-up. The annualized odds ratio used in our study pertains to the probability or likelihood of a certain event (hypoglycemia) differing between 2 groups or analytic periods (pre-index vial/syringe insulin vs. post-index insulin pen) for one given year. Hypoglycemic events before and after the index event were estimated using the OR, including associated data on healthcare resource utilization (e.g. physician visits, hospitalization, emergency department [ED] visits).

A logistic regression was employed as an appropriate multivariate regression model for analyzing association between level of prescription copayment and medication adherence in the post-index period. The outcome variable of the regression model was medication adherence in the post-index period. Adherence values $\geq 80\%$ were coded as 1, while adherence values $< 80\%$ were coded 0. A stepwise and systematic approach to building the statistical models was taken. Variable advancement in the logistic regression models was driven solely on theoretical background as follows: in model 1, associations between post-index adherence, baseline demographic and clinical variables, and post-index copayment were analyzed (to account for the impact of age, gender, comorbidities or complications of diabetes, geographic region, and study sub-cohort); model 2 involved addition of pre-index MPR (to account or adjust for level of adherence prior to conversion, i.e. patients' past history of self-management is important to consider when evaluating 'future' adherence). In addition to observing the association between post-index copayment and adherence, this model also facilitated analyzing the impact of adding pre-index MPR variable on the coefficients of baseline demographic and clinical variables, and post-index copayment variable. Lastly, model 3 included the categorical variable, pre-index copayment, which prior research demonstrates may be closely related to medication adherence and self-management behavior. Addition of this variable facilitated analyzing the impact this variable has on the adherence coefficient. Odds ratios with 95% CI levels were derived from the model and presented. Methodology used for estimation of total healthcare cost, HA, and DA costs, along with testing association between adherence and hypoglycemic events was the same as published in previous reports.10 All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Patient Characteristics. The overall study population consisted of 670 patients newly initiating treatment with the insulin aspart pen device. Subjects previously treated with an insulin analog vial and syringe (328 patients [49.0%]) and subjects previously treated with human insulin vial and syringe (342 patients [51.0%]) constituted two general subcohorts within this study group. Among those treated with human insulin during the pre-index period, 158 (46.2%) had been prescribed NPH insulin and 184 (53.8%) were prescribed premixed biphasic human insulin. Among patients using an insulin analog vial and syringe during the pre-index period, 171 (52.1%) and 157 (47.9%) were prescribed insulin glargine and a premixed biphasic insulin analog respectively.

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	Analog insulin users* (N=328)	Human insulin users † (N=342)	All patients (N=670)	p-value
Age (years)				
Mean (SD) Median	43.1 (14.1) 45.0	48.1 (13.4) 49.0	45.7 (13.8) 47.0	0.03
18-30 (%)	21.3	11.6	16.1	< 0.01
31-45 (%)	29	28.1	28.5	
46+ (%)	49.6	60.5	55.3	
Region				
East (%)	25.5	25.6	25.6	0.72
Midwest (%)	46.5	45.5	46	
South (%)	18.8	20.5	19.6	
West (%)	9.2	8.3	8.8	
Gender				
Male (%)	48.7	53.3	50.8	0.03
Female (%)	51.3	46.7	49.2	
Comorbid conditions or complications prior to index event				
Cardiovascular disease δ, n (%)	16 (4.9)	23 (6.7)	39 (5.8)	0.18
Infections related to diabetes; n (%)	2 (0.6)	0 (0.0)	2 (0.3)	0.13
Metabolic diseases; n (%)	26 (7.9)	21 (6.1)	47 (7.0)	0.16
Nephropathy; n (%)	19 (5.8)	21 (6.1)	40 (6.0)	0.76
Neuropathy; n (%)	24 (7.3)	25 (7.3)	49 (7.3)	0.84
Retinopathy; n (%)	24 (7.3)	18 (5.3)	42 (6.3)	0.19
Depression; n (%)	1 (0.3)	1 (0.3)	2 (0.3)	0.88
Leg amputation; n (%)	0 (0.0)	1 (0.3)	1 (0.1)	0.28

* Patients using analog insulin only before index event;
† Patients using human insulin only before index event
δ Does not include hypertension

The mean (SD) age of the study population was 45.7 (13.8) years; 50.8% of subjects were male (Table 1). Generally patients had an elevated prevalence of diagnosed comorbid conditions: metabolic disease (47 [7.0%]), nephropathy (40 [6.0%]), neuropathy (49 [7.3%]), retinopathy (42 [6.3%]), and cardiovascular disease (39 [5.8%]). Previous insulin analog users were significantly younger than previous human insulin users (mean [SD] age, 43.1 [14.1] vs. 48.1 [13.4] years, respectively; $P = 0.03$), with the proportion of subjects aged > 45 years also significantly lower compared with previous human insulin users (49.6% vs. 60.5%; $P < 0.01$). Males comprised a higher proportion of the previous human insulin vial and syringe subcohort than previous analog insulin users (53.3% vs. 48.7%; $P = 0.03$). However no significant baseline differences were observed with respect to level of individual comorbid conditions or diabetes-related complications.

Table 2: Copayment Per Prescription* for Individual Cohorts

	Analog Insulin Users (N=328)				Human Insulin Users (N=342)			
	Prior Glargine Users (N=171)		Prior Analog Pre-mix Users (N=157)		Prior NPH Users (N=158)		Prior Human Pre-mix Users (N=184)	
Copayment/Rx	Before Index Event	After Index Event	Before Index Event	After Index Event	Before Index Event	After Index Event	Before Index Event	After Index Event
Mean ($)	11	13	12	14	11	13	10	13
Median ($)	7	8	8	9	7	9	7	8
Minimum ($)	0	0	0	0	0	0	0	0
Maximum ($)	25	30	27	28	26	30	27	30

* For a 30-day supply

Copayment. Drug copayments in the pre-index and post-index periods for each sub-cohort are shown in Table 2. The mean copayment in the pre-index period for the entire study cohort (n = 670) was approximately $11, while the post-index mean copayment increased to approximately $13. The highest increase in post-index copayment was found in individuals who were prescribed premixed human insulin during the pre-index period ($10 to $13). Individuals who were prescribed glargine insulin in the pre-index period showed an increase of $2 post conversion to IAP therapy ($11 to $13). Similarly individuals who were prescribed premixed analog insulin and NPH in the pre-index period also showed a $2 increase in copayment post conversion ($12 to $14 and $11 to $13 respectively).

Medication Adherence. Adherence (measured by MPR) increased significantly after conversion to the pen device (Mean [SD]: 70% [32%] vs. 65% [29%], respectively; P = 0.01). Furthermore the percent of individuals exhibiting an adherence rate ≥80% was significantly higher in the post-index period compared with the pre-index period (55.4% vs. 37.9%; P < 0.01). These improvements in MPR were also observed across the two general pre-index subcohorts (previous insulin analog users, MPR: 65% [27%] vs. 61% [29%]; P = 0.01 and previous human insulin users, MPR: 76% [30%] vs. 71% [29%]; P = 0.01). Among individuals who were prescribed an insulin analog in the pre-index period, premixed biphasic analog users (MPR: 63% [29%] vs. 59% [27%]; P = 0.03) and insulin glargine users (MPR: 67% [30%] vs. 63% [26%]; P = 0.03) showed a similar increase in medication adherence percentage points upon conversion. Among individuals who were prescribed human insulin in the pre-index period, premixed human insulin users showed a 6% increase in adherence (MPR: 82% [38%] vs. 76% [35%]; P = 0.01), while NPH insulin users showed an 4% point increase in adherence (MPR: 70% [33%] vs. 66% [29%]; P = 0.02).

Association Between Post-Index Copayment Level and Adherence: Logistic Regression Model. Adjusted odds ratios and 95% confidence intervals for medication adherence by copayment level after controlling for differences in studied variables are summarized in Table 3. Full analysis (Model 3) using the logistic regression revealed that individuals with higher drug copayments had a significantly lower medication adherence (MPR < 80%) as compared to individuals with lower copayments. Odds of adherence being ≥ 80% decreased by 17% among individuals with a $21 and above drug copayment [Odds Ratio (OR): 0.83 (0.71 - 0.94); p < 0.05], while the odds among individuals with copayments ranging from $11-$20 decreased by 10% [OR: 0.90 (0.80 - 0.99); P < 0.05], when compared to individuals with drug copayments ≤ $10. As expected, several comorbid conditions and complications emerged as significant characteristics of subjects experiencing lower adherence in the post-index period: cardiovascular events (OR = 0.78; CI, 0.68 – 0.92; P < 0.05), neuropathy (OR = 0.81; CI, 0.71 – 0.95; P < 0.05), nephropathy (OR = 0.79; CI, 0.68 – 0.98; P < 0.05), and depression (OR = 0.69; CI, 0.55 – 0.87; P < 0.05).

Hypoglycemic Events. Nineteen individuals were found to have 33 hypoglycemic events during the pre-index period and 36 individuals had 75 hypoglycemic events during the post-index period (Table 4). The percent of individuals experiencing a hypoglycemic event while on IAP therapy, after controlling for differences in length of follow-up, was reduced by 47% (OR = 0.53; CI, 0.30 – 0.94; P < 0.05).

Table 3: Association between Copayment and Adherence: A Logistic Regression Model*

Variables	Model 1[1]		Model 2[2]		Model 3[3]	
	Estimate	OR (95% CI)**	Estimate	OR (95% CI)**	Estimate	OR (95% CI)**
Previous Glargine users	- 0.15*	0.86 (0.74-0.98)	- 0.16*	0.85 (0.75-0.96)	- 0.17*	0.84 (0.72-0.97)
Previous Analog Pre-mix users	- 0.14*	0.87 (0.75-0.98)	- 0.16*	0.85 (0.74-0.97)	- 0.18*	0.84 (0.73-0.98)
Previous NPH users	- 0.13*	0.88 (0.78-0.98)	- 0.16*	0.85 (0.72-0.98)	-0.19	0.83 (0.60-1.05)
Age 18-30 years	- 0.19*	0.83 (0.72-0.94)	- 0.22*	0.80 (0.72-0.99)	- 0.25*	0.78 (0.65-0.99)
Age 31-45 years	-0.15	0.86 (0.57-1.16)	-0.17	0.84 (0.55-1.19)	-0.17	0.84 (0.53-1.22)
Male	0.07	1.07 (0.79-1.36)	0.05	1.05 (0.81-1.32)	0.04	1.04 (0.80-1.29)
West region	0.04	1.04 (0.66-1.41)	0.03	1.03 (0.69-1.41)	0.02	1.02 (0.66-1.39)
Midwest region	0.06	1.06 (0.71-1.43)	0.05	1.05 (0.70-1.39)	0.04	1.04 (0.69-1.31)
South region	-0.06	0.94 (0.77-1.17)	-0.08	0.92 (0.75-1.20)	-0.09	0.91 (0.75-1.19)
Post-index copayment						
$11 - $20	- 0.13*	0.88 (0.79-0.98)	- 0.12*	0.89 (0.78-0.99)	- 0.11*	0.90 (0.80-0.99)
Post-index copayment						
$21 and above	- 0.21*	0.81 (0.71-0.94)	- 0.20*	0.82 (0.72-0.93)	- 0.19*	0.83 (0.71-0.94)
Cardiovascular Events	- 0.21*	0.81 (0.70-0.93)	- 0.23*	0.79 (0.70-0.90)	- 0.25*	0.78 (0.68-0.92)
Infections Related to Diabetes	-0.02	0.98 (0.80-1.14)	-0.03	0.97 (0.79-1.14)	-0.03	0.97 (0.78-1.12)
Retinopathy	-0.09	0.91 (0.64-1.27)	-0.11	0.90 (0.57-1.36)	-0.12	0.89 (0.55-1.32)
Neuropathy	- 0.18*	0.84 (0.72-0.98)	- 0.20*	0.82 (0.70-0.96)	- 0.21*	0.81 (0.71-0.95)
Leg Amputation	-0.01	0.99 (0.55-1.56)	-0.01	0.99 (0.54-1.55)	-0.01	0.99 (0.52-1.54)
Nephropathy	- 0.21*	0.81 (0.70-0.94)	- 0.22*	0.80 (0.70-0.96)	- 0.23*	0.79 (0.68-0.98)
Depression	- 0.35*	0.70 (0.58-0.81)	- 0.36*	0.70 (0.60-0.82)	- 0.37*	0.69 (0.55-0.87)
Other Metabolic Diseases	-0.11	0.90 (0.74-1.08)	-0.14	0.87 (0.72-1.07)	-0.14	0.87 (0.71-1.06)
Pre-index MPR ≥ 80 %	-	-	0.51*	1.67 (1.15-2.14)	0.47*	1.60 (1.11-2.12)
Pre-index copayment						
$11 - $20	-	-	-	-	0.27*	1.31 (1.11-1.52)
Pre-index copayment						
$21 and above					- 0.17*	0.84 (0.71-0.97)

* Adherence during the follow-up period was used as the dependent variable. MPR ≥ 80% was coded 1, while MPR < 80% was coded 0. Reference categories were female, previous human pre-mix insulin users, age 46 years and above, east region, pre-index MPR category < 80%, post-index copayment of $0 - $10, and pre-index copayment of $0 - $10. Pearson Chi-square/DF: 0.73 for Model 1, 0.67 for Model 2, and 0.65 for Model 3.

[1] Model 1 includes age, gender, region, insulin cohort, post-index copayment, and clinical comorbidities and complications.

[2] Model 2 extends model 1 by adding MPR categories and post-index treatment duration.

[3] Model 3 extends model 2 by adding baseline total cost.

Similarly, the likelihood of experiencing a hypoglycemic event was reduced by 36% (OR = 0.64; CI, 0.41 – 0.98; P < 0.05). Similar to previous studies,[10] the incidence of hypoglycemic events in subjects with an MPR ≥ 80% decreased by nearly two-thirds (IRR = 0.35; CI, 0.09 – 0.64; P < 0.05).

Hypoglycemic events requiring resource utilization (i.e. 3rd party medical intervention) are summarized in Table 4. Significant decreases in hypoglycemic event–related emergency department (ED) visits (OR = 0.40; CI, 0.17 – 0.96; P < 0.05) and physician visits (OR = 0.40; CI, 0.17 – 0.96; P < 0.05) were observed, though hypoglycemic event–related hospitalizations (OR = 0.88; CI, 0.35 – 2.24) and outpatient services (OR = 0.93; CI, 0.25 – 3.41) were non-significantly reduced.

Table 4: Hypoglycemic events ["Total person-years" mean annualized sum of treatment duration for all the study patients]

Hypoglycemic events		Before Index Event (N=670)	After Index Event (N = 670)
Total number of hypoglycemic events		33	75
ER visits	Number of events (%)	9 (27.3%)	13 (17.3%)
	Total person years	212.7	761.2
	Odds	0.04	0.02
	Odds ratio (95% CI)	0.40 (0.17 to 0.96); p< 0.05	
Hospitalizations	Number of events (%)	6 (18.2%)	19 (25.3%)
	Total person years	212.7	761.2
	Odds	0.03	0.02
	Odds ratio (95% CI)	0.88 (0.35 to 2.24); p> 0.05	
Physician Visits	Number of events (%)	9 (27.3%)	13 (17.3%)
	Total person years	212.7	761.2
	Odds	0.04	0.02
	Odds ratio (95% CI)	0.40 (0.17 to 0.96); p< 0.05	
Outpatient Services	Number of events (%)	3 (9.1%)	10 (13.3%)
	Total person years	212.7	761.2
	Odds	0.01	0.01
	Odds ratio (95% CI)	0.93 (0.25 to 3.41); p> 0.05	
Others	Number of events (%)	6 (18.2%)	20 (26.7%)
	Total person years	212.7	761.2
	Odds	0.03	0.03
	Odds ratio (95% CI)	0.93 (0.37 to 2.35); p> 0.05	

Comorbid conditions and diabetes-related complications including neuropathy (IRR = 1.68; CI, 1.18 – 2.81; $P < 0.05$), nephropathy (IRR = 3.25; CI, 2.14 – 4.88; $P < 0.05$), cardiovascular events (IRR = 1.39; CI, 1.03 – 2.09; $P < 0.05$), and other metabolic diseases (IRR = 4.44; CI, 2.71 – 6.59; $P < 0.05$) were also found to significantly affect the likelihood of experiencing hypoglycemia in the post-index period.

Healthcare Costs. Annually adjusted mean all-cause healthcare costs per patient decreased significantly after conversion to the IAP device ($16,714 vs. $15,282, respectively; $P < 0.01$). HA costs decreased by $668 from the pre-index period to the post-index period ($1,302 vs. $634; $P < 0.01$), mainly reflected in significant annualized mean savings in associated ED costs of $63 ($89 vs. $26; $P < 0.01$), hospitalization costs of $553 ($819 vs. $266; $P < 0.01$), and physician-visit costs of $88 ($144 vs. $56; $P < 0.01$). Reductions in hospitalization and ED costs were mainly due to decreases in the mean annual number of associated ED visits (7.1 vs. 5.4 visits; $P < 0.01$) and hospital length of stay during those visits (9.3 vs. 6.8 days; $P < 0.01$).

Other DA costs decreased by $557 in the post-index period compared with the pre-index period ($8,955 vs. $8,398, respectively; $P < 0.01$), reflected mainly in mean per-patient reductions of $116 in associated ED visits ($322 vs. $206; $P < 0.01$), $1,723 in physician visits ($2,116 vs. $393; $P < 0.01$), and $825 in pharmacy costs ($3,312 vs. $2,487; $P < 0.01$). Similar to the HA ED cost reductions, decreases in the cost of DA ED resource utilization were driven by a significant annual mean decrease in ED visits upon conversion (11.3 vs. 8.0 visits; $P < 0.01$).

DISCUSSION

This study aimed to provide a detailed and comprehensive first-time evaluation of prescription copayment, medication adherence, and association between copayment and adherence by examining the impact of conversion to the pen device of a specified class of insulin from a refined, stratified variety of pre-existing vial/syringe preparations. In addition, this study also provides an analytical extension from previous reports[10] by assessing clinical and economic consequences of improved adherence with primary focus on the impact of disparities in copayment level as discrete variables to a specific insulin pen.

The present analysis reveals increases in mean drug copayments by approximately $2 from pre-index to post-index periods. This result is not surprising given that modern insulin analog preparations and pen devices are, in general, more expensive compared to traditional vial/syringe insulins. Upon conversion to the insulin aspart pen device, optimal medication adherence, one of the primary endpoints defined by an MPR $\geq$ 80%, was significantly improved compared with the pre-index period (70% vs. 65%, respectively; $P < 0.01$) This positive impact on MPR for conversion to IAP therapy was less pronounced than was found for the more general, inclusive insulin pen cohort previously reported,[10] however, this result reinforces the potential benefit of conversion to pen therapy, and reveals the unique effects of treatment with insulin aspart. Given the evidence that less favorable tier assignment may induce suboptimal adherence,[24] and the fact that insulin analogs and pen devices are typically placed on less favorable managed care formulary tiers compared to human insulin and insulin vials, the finding of improved MPR despite a marginal increase in cost-sharing after conversion to IAP therapy may be particularly noteworthy from a managed care organization's perspective.[4] The improvement in adherence despite the increase in copayment could be attributed to several potential factors, including reported improvements in dosing accuracy, and greater mealtime flexibility and convenience of insulin delivery when using pen devices.[25,26] Increased patient preference and treatment satisfaction has also been reported for pen devices, including modern insulin analog pens.[27-31] Additional advantages of insulin pens that could have outweighed the slight increase in copayment include improved user confidence, ease of training, patient acceptance of therapy, and greater stability during injection (handling).[25,26,32-34]

Furthermore, a significant negative association between higher levels of drug copayments by patients and medication adherence after conversion to pen therapy was observed in this study, with odds of optimal adherence decreasing by 17% among individuals with a $21 and greater drug copayment [Odds Ratio (OR): 0.83 (0.71 - 0.94); $P < 0.05$]. For individuals with copayments ranging from $11-$20, the odds decreased by 10% [OR: 0.90 (0.80 - 0.99); $P < 0.05$] in comparison to individuals with the lowest copayments ($\leq$ $10). This result may highlight the incrementally negative impact that escalating copayments may have among insulin-prescribed type 2 diabetes patients.

In addition, similar reductions in all-cause, HA, and DA costs upon conversion to IAP therapy were observed when compared to analyses within a larger pen group ($1,432 vs. $1590, $668 vs. $788 and $557 vs. $600 respectively).10 The number of hypoglycemic events during the post-index period also decreased significantly (OR = 0.64; CI, 0.41 – 0.98; $P < 0.05$); this reduction, in parallel to the results for MPR and health care costs, was found to be lower than the previously reported odds ratio of 0.50.10 Utilization of specific health care resources associated with hypoglycemic events also paralleled those published previously,10 thereby supporting the notion that patients experiencing hypoglycemia

events during the post-index period also decreased significantly (OR = 0.64; CI, 0.41 – 0.98; $P < 0.05$); this reduction, in parallel to the results for MPR and health care costs, was found to be lower than the previously reported odds ratio of 0.50.[10] Utilization of specific health care resources associated with hypoglycemic events also paralleled those published previously,[10] thereby supporting the notion that patients experiencing hypoglycemia severe enough to warrant third-party intervention may be more prone to receiving care in an ED setting or through a physician visit as opposed to treatment provided within other hospital units or settings of outpatient care.

In response to higher drug prices, patients may exhibit behavioral changes that may have a bearing on disease management. These behaviors may include reduction in the amount of medications consumed including skipping doses and stretching out refills.[35] Studies examining various diseases have illustrated an inverse relationship between prescription drug costs and medication adherence.[36-39] In particular, higher copayments have been associated with lower adherence rates.[40-46] A retrospective database analysis of patients taking statins to lower cholesterol found almost half of those who had a copay of less than $10 to be non-adherent (cumulative multiple refill-interval gap >10%), while over 75% of patients with a copay over $20 were non-adherent.[40] Another study examining statin adherence found that an immediate increase in copayment, such as those seen from formulary adjustment, had a much larger negative affect on adherence than a copayment increase of the same amount over time.[41] Similarly, level of copayment has also been found to be strongly associated with adherence to antihypertensive medications.[45] This retrospective claims data study found that in comparison to patients having a $5 copayment, the odds ratio for adherence with drugs having a $20 copayment was 0.76 (95% CI: 075 - 0.78), whereas the odds ratio for drugs with a copayment in the range of $20-$165 was 0.48 (95% CI: 0.47 - 0.49). Similar results were obtained among chronic heart failure patients who were prescribed beta blockers or angiotensin-converting enzyme inhibitors.[46] In general, adherence rates for medications taken for chronic illnesses were fairly sensitive to cost, ranging from an 8% to 23% reduction in days supplied when copayments were doubled.[42]

Very few studies have directly evaluated the association between drug copayments and adherence among individuals with type 2 diabetes. One health plan that reduced costs by moving all diabetes drugs from tiers two and three to tier one showed that adherence improved as costs were lowered. In addition, they found a 26% decrease in emergency department visits, leading to an overall decline in direct healthcare costs.[43] Similar results have been reported when employing an economic model to examine the cost-effectiveness among diabetes patients taking ACE inhibitors, where first-dollar (no cost-sharing) Medicare coverage resulted in both an increase in quality-adjusted life years and cost savings.[47] A retrospective database analysis found that adherence levels above a threshold (20% to 39% category) were associated with fewer emergency department and inpatient admissions, as well as decreased medical care costs.[38] Furthermore, a survey examining the underuse of medication among a chronically ill population found that 18% of respondents cut back on their medication utilization in the past year and 14% used less medication at least monthly,[36] while 11% and 7% of adults with diabetes had reduced their adherence to antidiabetic medication in the last month and year, respectively.[37]

Our study results demonstrate significant implications in reducing overall healthcare costs irrespective of a minor increase in mean drug copayment through improved medication adherence, thus signifying the potential clinical and economic benefits of early initiation of insulin pen therapy. However, after conversion to pen therapy, the association between higher copayment levels and sub-optimal adherence suggests that patients transitioning to pen therapy under less burdensome cost-sharing features may benefit most.

Symptoms and levels of severity of hypoglycemia can vary considerably from patient to patient, potentially leading to unreported or unidentified occurrences of the condition.[48-50] The coded hypoglycemic events in the claims data used to estimate resource utilization in the present analysis were likely to be of a more severe nature, as some patients may either not detect or have a higher tolerance for the effects of minor events, which may therefore not require a third-party and go unreported. An MPR value $\geq$ 80% was associated with fewer hypoglycemic events (IRR = 0.35; CI, 0.09 – 0.64; $P < 0.05$). This result is very similar to that previously observed,[10] thereby augmenting the potential association between improved adherence and reduced hypoglycemia over an annually-adjusted time period.

LIMITATIONS OF MPR AND CLAIMS DATABASE ANALYSES

It is noteworthy to mention limitations inherent to this and other claims data analyses. First, the calculation of copayment values was based on imputation. Estimation of copayments through this method may have led to inaccurate reflection of actual copayments made by the study patients. This method of calculation should provide the copayment actually paid by the insured. The copayment paid can be different, but is not necessarily different, from the expected copayment as shown in the benefits design information because of how deductibles, out-of-pocket maximums, lifetime maximums and other benefit features are applied. However, the limitation of its use is that if the paid copayment amount is different from the actual copayment amount, the patient would not have observed the actual price prior to the purchase transaction. If the actual price (copayment) was available prior to purchase, the choice to buy or not might have been different. Second, although MPR is well-established in the literature as an appropriate measure of medication adherence, there is a limited ability to analyze the continuity of medication usage with this value. Particularly, when calculating MPR, important aspects in assessing medication intake such as medication sharing or wastage are not able to be included. Although MPR provides insight as to whether a patient was adequately or inadequately in possession of the correct amount of medication, it is not possible to confirm with claims data that patients are correctly or accurately administering their medication. In addition, although efforts were made to reduce potential skewing effects in our calculation of MPR, the drugs in the present analysis are dispensed in separate volumes (i.e. 10-ml vials and 15-ml box of pens [3 x 5 ml] per prescription), potential affecting refill gaps. Third, although efforts were made to employ

appropriate multivariate analyses to adjust for differences in demographic and clinical characteristics, data on race or income were absent, which may have revealed notable impacts on clinical and economic outcomes and resource use. Fourth, although the data source used in the present analysis contained a study population that was well-dispersed geographically and covered by a variety of private managed care structures, prudence should be taken in generalizing these results across populations receiving health benefits in other countries or within public health insurance systems, as potentially confounding factors regarding treatment paradigms and access to therapy may be unobserved or missed. Fifth, data were not available regarding over the counter medications, which may have included testing supplies related to diabetes care. However, it is unknown whether the requirement for or actual adherence to such resource use would differ between the pre-index and post-index medications. Additionally, we could not always distinguish the cost of the pen needles, which in most cases, is a separate prescription. However, these costs would still have been captured and reflected in patients' overall pharmacy costs. Finally, these study findings are those from a retrospective, observational approach evaluating data from a community practice rather than within a randomized controlled setting. Thus, the data allow examination of associations between patient/treatment variables and outcomes, but limit the ability to draw conclusions regarding causality.

CONCLUSIONS

Type 2 diabetes patients receiving private healthcare insurance coverage may exhibit an improvement in medication adherence despite a marginal increase in average patient copayment and be associated with reductions in the resource use and related costs of treating hypoglycemia upon insulin therapy conversion from vial/syringe to a pen device. Increased levels of copayments were found to have an incrementally negative impact on achieving optimal adherence after conversion to pen therapy. Given the effectiveness of long-term insulin therapy on outcomes, future research is warranted and should address the potential effects that other attributes of health plan benefit designs may have among these patients. Research determining whether reducing copayments to improve medication adherence has a beneficial effect on clinical lab values is also required to further demonstrate this as a cost-effective option for managed care organizations.

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ERRATA. In the article by Jiang et al., titled "Changes in Hospital Readmissions for Diabetes-Related Conditions: Differences by Payer," published in the July 2008 issue of Managed Care Interface, three tables contain errors.

In Table I, the percentage of Medicare patients aged 65-79 in 2003 should be 67.0%, the percentage of Private patients from low median family income zip codes in 1999 should be 17.7%, and the percentage of Private patients from rural areas in 2003 should be 13.4%.

The corrected version of Table II is shown as below. In 2003, the observed 180-day readmission rate should be 19.67% for Private HMO patients and 26.81% for Medicare HMO patients. The odds ratios for 1999 should all be 1.00.

	Observed 180-day readmission rate (%)		Risk-adjusted odds ratio[a] of readmission (95% CI)	
	1999	2003	1999	2003
Private, age 18-64[b]				
Overall	20.28	19.37 **	1	0.943 (0.904, 0.984) **
HMO	21.03	19.67 **	1	0.904 (0.847, 0.964) **
FFS	20.19	18.93 *	1	0.932 (0.869, 0.999) *
Medicare, age 65+[b]				
Overall	28.34	28.33	1	0.980 (0.956, 1.004)
HMO	27.18	26.81	1	0.942 (0.889, 0.998) *
FFS	28.81	28.8	1	0.985 (0.956, 1.015)
Medicaid, age 18-64				
Overall	31.75	31.27	1	0.969 (0.929, 1.011)

[a]Logistic regression models were fitted by payer, and by type of health plan. Data of both years were combined in each model. The odds ratios for year 2003 were adjusted for patient demographic, socioeconomic, and clinical characteristics at the index admission, and state effects, with standard errors corrected for clustering by hospital at the index admission. Full results of the models are available from the authors.
[b]Results for each payer were based on all 6 states (AZ, CA, MO, NY, TN, VA) whereas results specific to type of health plan were based on only 3 states (AZ, CA, NY) that provided data indicating HMO vs. FFS plans.
**$P < 0.01$, *$P < 0.05$

In Table III, the risk-adjusted odds ratios of readmission for congestive heart failure among Private patients and for diabetes acute complications among Medicare patients were both significant at the $P < .01$ level.

Article Submission Guidelines: Managed Care Interface

A. Article Submission Categories

1. Editorials and Commentaries
2. Reviews on issues of importance to health care (including but not limited to primary, specialty, and long-term care) and quality management
3. Case reports on specific managed care systems
4. Reviews on topics of interest to the operation of managed care organizations (including but not limited to administration, claims processing, and information systems)
5. Original research conducted in and involving managed care environments
6. Original reports and reviews of pharmacoeconomics
7. Reviews on clinical topics of interest to primary care
8. Original reports and reviews in disease management
9. Original reports and reviews in areas of importance to pharmacy practice
10. Letters to the editor regarding recently published articles

B. Manuscript Submission Instructions

In the cover letter, which is sent to the publisher (nancyleecarlson@msn.com), the corresponding author must verify that the manuscript is an original submission and is not under consideration by any other journal, and validate that each of the authors has read and approved the manuscript. The cover letter should provide full contact information for the corresponding author, including his or her name, address, e-mail address, and telephone number. The manuscript should be in Microsoft Word (any version is acceptable, but preferably saved in .doc format). Authors should also include color headshots with their manuscript submissions.

In the case of Manage Care Interface, the corresponding author may suggest the names of possible peer reviews, as appropriate for the subject.

C. Preparing your Manuscript

Manuscripts should consist of a title page, 100-word abstract, author affiliations, text references (cited consecutively in text), tables, and figure legends.

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The article abstract should be a brief summary of its content. It should not be used as an introduction to the paper. It is suggested that the author provide up to five key words for indexing purposes.
The text should make liberal use of section headings and references. References should be supplied in a numeric listing following the article. Do not use the word processor's endnote, footnote, or comment functions to input reference citations. Please list them as they would appear in the publication: a consecutive, superscript numeral in the text, with the full number listed at the article's conclusion. It is the author(s)' responsibility to verify the accuracy of the reference list.

D. Article Length Considerations

Both regular and feature articles should not exceed 2,500 words in length (approximately 10 double-spaced manuscript pages of text, not including references or ancillary information).

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Managed Care Interface has a unique editorial house style that has evolved over their many years of publication. Although manuscripts are not accepted or rejected on the basis of adherence to house style, authors can follow certain basic rules.

- Use generic names whenever drugs are identified in the text; do not mention brand names unless necessary to distinguish among multi-source products. Drug manufacturers should be identified only when necessary.
- Do not write in the first or second person (unless the article is a commentary or letter to the editor, in which case this is permissible).
- When citing other authors' works, avoid the use of "et al" within the text (use "and colleagues, associates, or co-workers," instead), and place the reference citation after the name (i.e. Smith and colleagues[22]), not at the end of the sentence.
- Be sure to appropriately reference any statistics provided. Weblogs are not acceptable references.

F. Tables and Figures

The Editor requests that the author provide visual graphics such as tables or figures. If the author cannot provide these, suggestions of graphic ideas would be appreciated.

- **Tables** should be typed double-spaced on a separate sheet. Each column should have a separate heading. The table title should be concise and footnotes should be cited in the table body. The author should define abbreviations and acronyms used in a footnote.
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