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

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Ken Libbrecht, PhD, has been chosen as the cover photographer for *JMCP’s* annual issue featuring an artist with a pharmaceutical, medical, or scientific background. He is a Professor of Physics and Executive Officer for the physics department at the California Institute of Technology (Caltech) in Pasadena, California. Libbrecht is sometimes referred to as “Dr. Snow” because of his research on the properties of 6-sided snow crystals, better known as snowflakes. Many of his spectacular snowflake microphotographs can be seen on his award-winning Web site, SnowCrystals.com. The site has logged over 15 million page views since its inception in 1999, a testament to the timeless appeal of snowflakes.

Libbrecht has an interesting “Snowflake Primer” page on SnowCrystals.com that answers basic questions about snowflake formation, as well as a page devoted to the most popular questions of all: Is it really true that no 2 snowflakes are alike? “The number of possible ways of making a complex snowflake is staggeringly large. When you look at a complex snow crystal, you can often pick out a hundred separate features if you look closely,” Libbrecht explains. “Since all those features could have grown differently, or ended up in slightly different places, it’s extremely unlikely that any 2 complex snow crystals, out of all those made over the entire history of the planet, have ever looked completely alike.”

Growing up in Fargo, North Dakota, may have inspired Libbrecht’s interest in snow crystal research, but for most of his early career, he worked at the other end of the temperature spectrum, investigating the internal structure of the sun. He received his bachelor of science degree in physics from Caltech in 1980 and his doctorate in physics from Princeton University in January 1984. Returning to Southern California after graduation, he joined the physics faculty at Caltech in February 1984.

Libbrecht recalls his early fascination with snowflakes in his first book on the subject, *The Snowflake*: “On snowy afternoons at school, our class sometimes trekked outdoors with magnifying glasses in hand to examine falling snowflakes. The crystals were especially well-formed on colder days, when the starlets would sparkle brightly and linger long enough for a careful inspection of their shape and symmetry.”

Later in life, after his memories of playing in the snow had almost melted away, Libbrecht began to examine the physics of snow crystal formation. He says that crystals grown under various conditions exhibit a broad range of morphologies, growth rates, and other characteristics, reflecting the diverse physical mechanisms that influence crystal growth. Because crystals are at the core of several major industries (such as the computer industry), the research conducted by scientists like Libbrecht is extremely valuable. Discovering advanced techniques for crystal growth can lead to the development of exciting new products. And besides the practical applications of studying and photographing snow crystals, he readily admits that it is a lot of fun! Libbrecht expresses his sentiments about snow in his 2007 book, *The Art of the Snowflake*: “Observing and photographing snowflakes is an unusual pursuit, but I enjoy it immensely. Each new snowfall is another world to explore, and I still often find novel specimens.”

To take the microphotographs of snowflakes such as those found in *Snowflake Trio*, Libbrecht uses a Nikon DLX digital camera attached to a specially designed microscope. He utilizes several different microscope objectives—the Mitutoyo M Plan Apo 2X, 5X, and 10X—mounted on a homemade turret. “The microscope reveals an amazing menagerie of beautiful crystalline forms,” Libbrecht says. Giving new meaning to the term “freeze frame,” he picks up an individual snowflake with a small paintbrush, places it on a glass slide under the microscope, and quickly snaps the picture. Snow crystals are made of ice, which is clear and colorless, so Libbrecht likes to illuminate most of his crystals with colored lights. Each snow crystal then acts like a complex lens that refracts the colors in multiple directions, producing a variety of stunning effects.

In addition to *The Snowflake* and *The Art of the Snowflake*, Libbrecht’s other snowflake books include *The Little Book of Snowflakes*, *Ken Libbrecht’s Field Guide to Snowflakes*, and his latest, *Snowflakes*—a tome filled with more than 500 snowflake photographs. His snowflake images have also graced calendars, prints, posters, cards, and postage stamps. In October 2006, the U.S. Postal Service issued a commemorative set of 4 stamps featuring snowflake microphotographs that he took in Alaska, Michigan, and Ontario, Canada.

Libbrecht is currently involved in advanced detector development for the Laser Interferometer Gravitational-Wave Observatory (LIGO). This facility is being built by Caltech and will be dedicated to the detection of cosmic gravitational waves and the harnessing of these waves for scientific research.

*SOURCES*


EDITORIAL MISSION AND POLICIES

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

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Analysis of Pharmacist-Provided Medication Therapy Management (MTM) Services in Community Pharmacies Over 7 Years

Mitchell J. Barnett, PharmD, MS; Jessica Frank, PharmD; Heidi Wehring, PharmD; Brand Newland, PharmD; Shannon VonMuenster, PharmD; Patty Kumbera, BSPharm; Tom Halterman, BSPharm; and Paul J. Perry, PhD

ABSTRACT

BACKGROUND: Although community pharmacists have historically been paid primarily for drug distribution and dispensing services, medication therapy management (MTM) services evolved in the 1990s as a means for pharmacists and other providers to assist physicians and patients in managing clinical, service, and cost outcomes of drug therapy. The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA 2003) and the subsequent implementation of Medicare Part D in January 2006 for the more than 20 million Medicare beneficiaries enrolled in the Part D benefit formalized MTM services for a subset of high-cost patients. Although Medicare Part D has provided a new opportunity for defining the value of pharmacist-provided MTM services in the health care system, few publications exist which quantify changes in the provision of pharmacist-provided MTM services over time.

OBJECTIVES: To (a) describe the changes over a 7-year period in the primary types of MTM services provided by community pharmacies that have contracted with drug plan sponsors through an MTM administrative services company, and (b) quantify potential MTM-related cost savings based on pharmacists’ self-assessments of the likely effects of their interventions on health care utilization.

METHODS: Medication therapy management claims from a multi-state MTM administrative services company were analyzed over the 7-year period from January 1, 2000, through December 31, 2006. Data extracted from each MTM claim included patient demographics (e.g., age and gender), the drug and type that triggered the intervention (e.g., drug therapeutic class and therapy type as either acute, intermittent, or chronic), and specific information about the service provided (e.g., Reason, Action, Result, and Estimated Cost Avoidance [ECA]). ECA values are derived from average national health care utilization costs, which are applied to pharmacist self-assessment of the “reasonable and foreseeable” outcome of the intervention. ECA values are updated annually for medical care inflation.

RESULTS: From a database of nearly 100,000 MTM claims, a convenience sample of 50 plan sponsors was selected. After exclusion of claims with missing or potentially duplicate data, there were 76,148 claims for 23,798 patients from community pharmacy MTM providers in 47 states. Over the 7-year period from January 1, 2000, through December 31, 2006, the mean (sd) median pharmacy reimbursement was $8.44 ($5.19) $7.00 per MTM service, and the mean (sd) median ECA was $93.78 ($1,022.23) $5.00. During the 7-year period, pharmacist-provided MTM interventions changed from primarily education and monitoring for new or changed prescription therapies to prescriber consultations regarding cost-efficacy management (Pearson chi-square P<0.001). Services also shifted from claims involving acute medications (e.g. penicillin antibiotics, macrolide antibiotics, and narcotic analgesics) to services involving chronic medications (e.g., lipid lowering agents, angiotensin-converting enzyme [ACE] inhibitors, and beta-blockers; P<0.001), resulting in significant changes in the therapeutic classes associated with MTM claims and an increase in the proportion of older patients served (P<0.001). These trends resulted in higher pharmacy reimbursements and greater ECA per claim over time (P<0.001).

CONCLUSION: MTM interventions over a 7-year period evolved from primarily the provision of patient education involving acute medications towards consultation-type services for chronic medications. These changes were associated with increases in reimbursement amounts and pharmacist-estimated cost savings. It is uncertain if this shift in service type is a result of clinical need, documentation requirements, or reimbursement opportunities.


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What is already known about this subject

• Community pharmacists have historically been paid primarily for drug distribution and dispensing services.
• Medication Therapy Management (MTM) was officially recognized in the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA 2003), including the objectives to increase patient adherence, prevent drug complications, and enhance patient understanding of their medication therapy.
• To date, pharmacist-provided MTM services have been shown to reduce patient out-of-pocket costs through interventions such as generic substitution and therapeutic interchange.

What this study adds

• MTM services provided by community pharmacists have changed significantly over a relatively short period of time. MTM interventions appear to be evolving from the provision of patient education regarding acute medications toward consultation-type services with prescribers regarding chronic medications.
• This evolution in pharmacist intervention-type was associated with higher pharmacy reimbursements for MTM services.
• Based on pharmacists’ self-assessments of the expected effects of their interventions on health care utilization, estimated cost avoidance attributable to MTM has increased over time and exceeds the pharmacist reimbursement amount for the performance of these services.

Medication Therapy Management (MTM) was officially recognized by Congress in the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA 2003).1 Section 423.153(d) of MMA 2003 established the requirements that Medicare Part D plans must meet regarding quality and cost control, including the requirements for MTM...
Programs “designed” to “optimize therapeutic outcomes through improved medication use” and “reduce the risk of adverse events, including adverse drug reactions.” The Centers for Medicare and Medicaid Services (CMS) require each Medicare Part D plan to establish an MTM program for targeted beneficiaries as part of its benefit. CMS classifies targeted beneficiaries as Part D enrollees who have multiple chronic disease states (number and type determined by the plan sponsor), are taking multiple Part D covered drugs (number determined by the plan sponsor), and are likely to incur annual costs of at least $4,000 for all Part D-covered drugs (2006 predetermined level specified by the Secretary). Part D plans are required to offer an MTM benefit to those enrollees who meet these criteria but may also extend the benefit to all plan enrollees. Plans can choose to offer the MTM benefit as an opt-in or opt-out benefit.

Requirements of an MTM program as outlined by CMS are somewhat ambiguous; however, CMS does require that programs be designed to increase patient adherence to medication regimens, enhance patient understanding of their medication therapy, and prevent drug complications, conflicts, and drug interactions. Although several professional pharmacy associations have attempted to interpret CMS guidance and define specific requirements of MTM for the pharmacy profession, MTM services provided to Medicare beneficiaries continue to vary from sponsor to sponsor. Community pharmacists have historically been paid primarily for drug distribution and dispensing services provided to patients. By year-end 2008, most pharmacists have heard of MTM and many have begun providing MTM services in their practice setting. Some pharmacists have been providing MTM-like professional services for years by participating in programs such as Project Improve Persistence and Compliance with Therapy (ImPACT), the Asheville Project, or other employer- or commercially sponsored programs. However, the advent of Medicare Part D provides pharmacists with a larger opportunity to perform professional services and receive compensation for their medication expertise. Medicare Part D also creates a relatively new opportunity to better define the value of pharmacist-provided MTM services to the health care system, although assessment of the value of such pharmacist-provided MTM services is still in its infancy.

Outcomes Pharmaceutical Health Care is a pharmacist-owned and pharmacist-operated MTM administrative services company that began operation in 1999 to advance the delivery of face-to-face pharmacist-provided MTM services in community pharmacies. Fees are collected by the MTM administrative services company from health plans or other benefit providers, and pharmacies are in turn reimbursed by the administrative services company for MTM services provided to eligible enrollees. Since 1999, this MTM administrative services company has built a comprehensive system enabling pharmacist-provided MTM services, which includes: a national pharmacy network, pharmacist training modules, an Internet-based documentation and billing system, quality assurance procedures, claim payment processing, and data reporting. This MTM administrative services company has administered programs on behalf of self-insured employers, union health plans, a state Medicaid program, pharmaceutical manufacturers (e.g., compliance and persistence programs or community-based research projects), Medicare Part D plan sponsors (including both Prescription Drug Plans and Medicare Advantage Plans) and others.

An early innovation for this MTM administrative services company was the development and implementation of a proprietary Internet-based documentation and billing system in 2000, allowing the capture of claim information submitted by participating pharmacies. The information collected during the provision of MTM services over 7 years through 2006 represents perhaps the most extensive MTM database available. Further, the database is particularly suited to quantify changes in pharmacist-provided MTM services over time because it includes detailed information about each intervention, patient-level demographics, and estimates of cost savings associated with pharmacist interventions.

Analyses of a convenience subsample of MTM plan sponsors in the database of this MTM administrative service company over a 7-year timeframe are presented here for the first time. Specific objectives of this study were to (a) identify trends associated with the provision of MTM services provided by pharmacists, and (b) quantify potential MTM-related cost savings derived from pharmacists’ self-assessments of the likely impact of their interventions on health care utilization. Consent (P#0108) for this study was approved by the Touro University Institutional Review Board.

### Methods

#### Database and Patients

The MTM administrative service company’s database is comprised of MTM services collected from pharmacy-submitted claims for pharmacist-provided interventions. MTM program sponsors identify patients eligible for MTM services and provide the MTM administrative services company with prescription claims data for each eligible member. The prescription claims data are then used to refer patients to primary dispensing pharmacies through the Internet-based documentation and billing system. The pharmacist identifies when a patient needs an MTM service (“pull referral”) in addition to acting on targeted interventions sent by the MTM administrative services company (“push referral”) for specific patients. Payments to pharmacies are processed when claims are submitted through the proprietary Internet-based MTM documentation system. The Internet-based system captures information gathered during the pharmacist documentation process and includes detailed information about each intervention provided. Data are stored by client (plan sponsor) and can be queried through an Internet interface. Pharmacies become MTM providers in the network of this MTM administrative services company for MTM services provided to eligible enrollees.
company by completing a network participation agreement, and each pharmacist that provides MTM services at the participating pharmacy must complete a “Personal Pharmacist” training program. The training program includes the details of billing and documentation for MTM services, such as selection of the most reasonable and foreseeable estimated cost avoidance (ECA) level for each intervention provided (e.g., routine education/monitoring not expected to result in cost savings vs. avoidance of inpatient hospitalization). The 7-year time period of this study was January 1, 2000, through December 31, 2006.

The network of pharmacies for this MTM administrative services company includes a diverse mix of independent, franchise, chain, health-system, and consultant pharmacy providers, located in 47 states during the time period of this study. Eligible patients for MTM services provided by community pharmacists are members of benefit plans that have contracted with the MTM administrative services company. Some MTM sponsors choose to offer the MTM benefit to a subset of enrollees (e.g., high prescription utilizers, targeted disease states), while others choose to offer the benefit to all enrollees. Benefit plans or insurance providers hire the MTM administrative services company to serve as a business partner in the administration of MTM services, including quality control. The MTM administrative services company functions as a stand-alone entity, enabling pharmacists access to a group of enrollees eligible for MTM services as well as providing an efficient mechanism with which to bill and receive payment for these services. Program fees collected by the MTM administrative services company from MTM sponsors are typically capped (i.e., per member per month) and are used to reimburse pharmacies for MTM services provided to benefit enrollees and to cover program administrative costs.

**Outcome Claims**

The documentation of an MTM claim is a 5-step process. In the first 3 steps of claim documentation, the pharmacist selects a Reason, Action, and Result. The Reason can be thought of as the “Indication for Service,” the Action the “Professional Service” provided, and the Result the “Outcome of Service” of the intervention. To facilitate the documentation process, Reason, Action, and Result fields are linked in a sequential manner, whereby the selection of a Reason governs possible choices for Action, and the selection of an Action governs possible choices for Result.

The fourth step in the MTM documentation process involves the pharmacist choosing the most reasonable and foreseeable ECA level, a severity rating of the MTM service provided. ECA is derived from average national health care utilization costs using a previously developed methodology. The pharmacist-derived assessments of “reasonable and foreseeable” outcomes from the intervention are linked to actual ECA dollar values (e.g., $307 per avoided physician visit, $605 per avoided emergency room visit, and $17,706 per avoided hospital admission in 2006). ECA values are updated annually to reflect inflation. In the final step of the documentation process, pharmacists are required to provide detailed notes pertaining to the intervention and substantiate the rationale for the ECA level selected. The required notes are input as free text.

A proprietary MTM claim worksheet, similar to a physician superbill, is made available for pharmacists to use at the point of service (Appendix). Pharmacist worksheet information is used to generate MTM claim information which is submitted via the online documentation and billing system. This Internet-mediated interface is formatted to be similar to the MTM claim worksheet to facilitate real time capture of information. The data fields in the MTM claim documentation are listed in Table 1. Professional service fees for the MTM services provided are tied to the Reason-Action-Result fields selected on the claim worksheet and defined by the fee schedule of the MTM administrative services company. Because the Reason, Action, and Result fields are linked, as described above, the choice of Reason (Indication for Service) in effect determines the MTM fee associated with the intervention. MTM fees are $0 and $2 for claims with a Result (Outcome of Service) of Patient or Prescriber Refusal, respectively.

To ensure a high level of quality and provide a feedback mechanism, an outside company verifies the integrity of each claim. The quality assurance team comprises clinical pharmacists, and each claim is reviewed before reimbursement to the pharmacy is processed. The quality assurance process includes verification that MTM claim documentation is in accordance with the MTM administrative services company’s policies and procedures and that the ECA level selected is reasonable and foreseeable. Claims lacking sufficient documentation of the MTM service provided, as well as those with an inappropriate ECA level (e.g., ECA Level 6 [avoidance of a hospital admission] is inappropriately selected for a cost efficacy management [therapeutic substitution] intervention) are returned to the pharmacist for further review and resubmission or rejection. Claims rejected for insufficient documentation or inappropriate or unverifiable ECA level represent a small percentage (<3.0%) of total claims and were not included in this analysis.

**Data Elements**

Data extracted from each claim included patient demographic information (e.g., age and gender), specific information about the medication triggering the intervention (e.g., date of service, therapeutic class, and therapy type specified as acute, chronic or intermediate/other), and specific information about the service provided (e.g., Reason, Action, Result, ECA and associated ECA dollar amount). Acute therapy included medications used for a limited time period (e.g., antibiotic and one-time analgesic prescriptions), chronic therapy included medications prescribed for chronic conditions (e.g., lipid-lowering and antihypertensive medications), and intermediate/other medications included primarily seasonal allergy treatments. In addition, pharmacy payment information was extracted.
TABLE 1  Documentation of Interventions and Description of Levels of Estimated Cost Avoidance (ECA)*

<table>
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<tr>
<th>1. Indication for MTM Service (REASON)</th>
<th>Description/Examples</th>
</tr>
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<tbody>
<tr>
<td>1.1 Complex drug therapy</td>
<td>Typically applies to the presentation of a patient taking multiple medications (e.g., a patient taking 4 or more chronic medications). A few plan sponsors have slightly different thresholds (e.g., 6 or more chronic medications).</td>
</tr>
<tr>
<td>1.2 Cost-efficacy management</td>
<td>An order for a drug product where a more cost-effective therapeutic alternative is available (e.g., a patient is prescribed a tier-3 medication when a tier-1 medication is available and appropriate for the indication).</td>
</tr>
<tr>
<td>1.3 New or changed therapy</td>
<td>An order to initiate new prescription therapy or change an existing prescription therapy (e.g., patient presents with a new prescription for an antibiotic).</td>
</tr>
<tr>
<td>1.4 OTC therapy</td>
<td>Patient with an untreated indication for OTC therapy (e.g., male patient with an enlarged prostate seeks pharmacist’s advice on avoiding cold medication containing an antihistamine).</td>
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Drug Therapy Problems Detected

<table>
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<tr>
<th>1.8 Drug Therapy Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.8a. Overuse</td>
</tr>
<tr>
<td>1.8b. Underuse</td>
</tr>
<tr>
<td>1.8c. Administration technique</td>
</tr>
<tr>
<td>1.9 Other</td>
</tr>
</tbody>
</table>

2. Professional Service (ACTION)

| 2.1 CMR                                | Comprehensive review of a patient’s drug profile to identify any cost-efficacy issues or drug therapy problems. |
| 2.2 Prescriber consultation             | Consulting a prescriber to recommend a drug order change due to either a cost-efficacy issue or drug therapy problem. |
| 2.3 Patient consultation                | Consulting a patient to address a cost-efficacy issue or compliance-related drug therapy problem. |
| 2.4 Patient education and monitoring    | Patient education and monitoring of a drug therapy. Minimum patient education includes information related to the name of the drug, therapeutic class, directions for use, side effects, warnings, storage requirements, missed dose actions, and appropriate written material. Minimum patient monitoring includes collecting information about change in patient-reportable symptoms, side effects, compliance, and additional patient questions. |
| 2.5 Patient compliance consultation     | Consulting a patient to address medication overuse, underuse, or inappropriate administration technique. Pharmacist should provide follow-up monitoring to assess if compliance has been altered. |
| 2.6 Other                              | Professional service provided not covered in above (e.g., patient-specific special project). |

3. Outcome of Service (RESULT)

| 3.1 CMR with drug therapy problem(s)   | Completion of a CMR that results in an additional intervention being conducted due to the identification of a cost-efficacy issue or a drug therapy problem. |
| 3.2 CMR without drug therapy problem(s)| Completion of a CMR that does not result in an additional intervention. |
| 3.3 Initiation of a cost-effective drug | Prescriber approval of a more cost-effective drug following a pharmacist recommendation to change a drug order due to a cost-efficacy issue. |
| 3.4 Therapeutic success                 | A monitoring situation in which the pharmacist has determined that a patient’s condition(s) are resolved or stabilized as a result of drug therapy. |
TABLE 1 Documentation of Interventions and Description of Levels of Estimated Cost Avoidance (ECA)* (continued from previous page)

3.5 Therapeutic failure Monitoring situation in which the pharmacist has determined that a patient’s condition(s) are unresolved, unstable, or worsened as a result of drug therapy.

**Drug Therapy Problems Resolved**

3.6 Drug Therapy Indication

3.6a Initiated new therapy Prescriber approval of a pharmacist recommendation to initiate a drug order for an untreated indication.

3.6b Discontinued therapy Prescriber approval of a pharmacist recommendation to discontinue a drug order that is not indicated.

3.7 Drug Therapy Efficacy

3.7a Increased dose/duration Prescriber approval of a pharmacist recommendation to change a drug order that has a dose or duration insufficient to be effective.

3.8 Drug Therapy Safety

3.8a Altered regimen/changed drug Prescriber approval of a pharmacist recommendation to change a drug order with an adverse reaction or drug interaction risk significant enough to render the therapy unsafe.

3.8b Decreased dose/duration Prescriber approval of a pharmacist recommendation to change a drug order that has a dose or duration too excessive to be safe.

3.9 Drug Therapy Compliance

3.9a Altered compliance Altering a patient’s behavior to become compliant with a drug therapy that he or she has previously been overusing or underusing (e.g., patient’s receipt of refill is within an appropriate interval, such as ±20% of the days supply dispensed).

3.9b Altered administration/technique Altering a patient’s behavior to become compliant with a drug therapy that had previously been administered with inappropriate technique.

3.10 Patient refusal Patient refusal to (a) participate in a CMR, (b) receive Patient Education/Monitoring, (c) permit a physician consultation on cost-efficacy issues, or (d) alter compliance-related behavior.

3.11 Prescriber refusal Prescriber refusal of a pharmacist recommendation to change a drug order associated with a cost-efficacy issue or a drug therapy problem.

3.12 Other Patient or physician intervention that results in significant health care cost or quality improvement that does not correspond with other available billing codes.

**4. ECA Levels**

For each MTM claim, the pharmacist must select the most reasonable and foreseeable ECA from 1 of the 8 available levels below:

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1</td>
<td>Completed patient education/monitoring whether therapeutic success or failure, all CMRs, and all other interventions that do not result in any reasonable and foreseeable cost avoidance.</td>
</tr>
<tr>
<td>4.2</td>
<td>Cost-efﬁciency management in combination with prescriber consultations that result in changes in prescribed therapy.</td>
</tr>
<tr>
<td>4.3</td>
<td>Drug therapy problem identiﬁed and resolved by the pharmacist for which it is reasonable and foreseeable that the patient would have visited a physician if not addressed by the pharmacist.</td>
</tr>
<tr>
<td>4.4</td>
<td>Drug therapy problem identiﬁed and resolved by the pharmacist for which it is reasonable and foreseeable that the patient would have obtained a new prescription order if not addressed by the pharmacist.</td>
</tr>
<tr>
<td>4.5</td>
<td>Drug therapy problem identiﬁed and resolved by the pharmacist for which it is reasonable and foreseeable that the patient would have needed to visit the ER if not addressed by the pharmacist.</td>
</tr>
<tr>
<td>4.6</td>
<td>Drug therapy problem identiﬁed and resolved by the pharmacist for which it is reasonable and foreseeable that the patient would have been admitted to the hospital if not addressed by the pharmacist.</td>
</tr>
<tr>
<td>4.7</td>
<td>Drug therapy problem identiﬁed and resolved by the pharmacist for which it is reasonable and foreseeable that the patient would have faced a life-threatening situation if not addressed by the pharmacist.</td>
</tr>
<tr>
<td>4.8</td>
<td>Prescriber refuses drug therapy problem recommendation or patient refuses comprehensive medication review, education/monitoring, medication change, or compliance recommendation.</td>
</tr>
</tbody>
</table>

* For each MTM claim, the pharmacist must document an ECA level, a severity rating assigned to the MTM service among 8 ECA levels. "Reasonable and foreseeable" is the self-reported test for avoidance of an outcome associated with a problem identiﬁed and resolved by the pharmacist.

**Study Sample**

A convenience sample of 50 MTM programs covering a 7-year time period from January 1, 2000, through December 31, 2006 was selected for analysis. The 50 programs represented approximately 90% of the drug plan sponsors of the MTM administration service company. Some data were not available for analysis because of conﬁdentiality agreements with some drug plan sponsors and a few drug plan sponsors that did not use the Internet-based system. In addition, several individualized disease management programs using the Internet-based system during
Analysis of Pharmacist-Provided Medication Therapy Management (MTM) Services in Community Pharmacies Over 7 Years

Results

Data analyses for a selected subsample of MTM claims from 2000 through 2006 showed 76,148 sampled pharmacist interventions. The average age of a patient receiving MTM services over the 7-year study period was 44 years, and 39% were male (Table 2). The mean ([SD] median) MTM interventions over the 7 years were 3.2 ([3.5] 2.0) per patient. Half of the MTM interventions (49.9%) were related to medication therapy classified as acute, while 37.9% were related to therapy classified as chronic, and 12.2% of the interventions involved “intermediate” or “other” medications. The most common drug categories were antimicrobial (e.g., penicillins, macrolides), cardiovascular (e.g., statin or other lipid-lowering), and central nervous system (e.g., narcotic analgesic) agents. The most common Reason for MTM intervention was new/changed therapy (85.6%); the most common Action was patient education/monitoring (86.7%); and the most common Result was therapeutic success (70.2%; self-determined by the pharmacist). The most common ECA level selected was Level 1—Improved Quality of Care (78.8%). Interventions resulted in a mean ([SD] median) $8.44 ($5.19) [$7.00] in reimbursement per intervention to the pharmacy, with an ECA of $93.78 ($1,022) $5.00 per claim.

The characteristics of the patients who received MTM services changed from 2000 to 2006, including an increase in the average age from 30.4 years to 57.6 years (P < 0.001) and a decrease in the percentage of males, from 39.6% to 35.4% (P < 0.001; Table 3). However, no significant differences in the mean number of MTM interventions received per patient per year from 2000 to 2006 (from 2.0 to 1.8, P = 0.104) were observed. The classification of medication therapy associated with the MTM services changed from 2000 to 2006, with a decrease in interventions for acute medications from 86.0% to 35.6% (P < 0.001) and a corresponding increase in interventions for chronic medications from 10.2% to 43.7% (P < 0.001; Figure 1). Changes were also observed in drug categories over time, with decreases in antimicrobials (from 35.5% to 8.7%, P < 0.001) and increases in cardiovascular and central nervous system agents (from 8.2% to 21.6%, P < 0.001 and 5.7% to 22.7%, P < 0.001, respectively; Table 3). The most common agents associated with MTM services in 2000 were penicillins (11.1%) versus statins and other lipid lowering agents (12.5%) in 2006.

Corresponding shifts in the Reasons, Actions, and Results for MTM services over time also were observed. Notable changes in the Reason for pharmacist intervention included a decrease in new/changed drug therapy (from 87.1% to 40.0%, P < 0.001) and an increase in cost-efficacy management (from 9.6% to 18.2%, P < 0.001) from 2000 to 2006. The observed increase in cost-efficacy management claims was driven by pharmacist-initiated therapeutic substitution from a brand to a similarly effective, within-class generic product (e.g., escitalopram [Lexapro] to citalopram).

The study timeframe were excluded from this analysis.

Over 82,000 claims for 25,143 unique beneficiaries from the 50 drug plan sponsors were originally eligible for analysis. Before analysis, 1,874 claims with missing drug or incomplete patient (age and gender) information were excluded. In addition, claims from the same pharmacy with the same drug and date of service for the same beneficiary (n = 3,303) also were excluded because it was thought that these most likely represented duplicate claims. These exclusions left a final analytical cohort of 76,148 claims from 50 groups administered by the MTM administrative services company. These claims represent MTM interventions performed by 1,158 unique pharmacists at 1,054 unique pharmacies for 23,798 patients.

Analytic Strategy

Analyses were performed on the sample of 76,148 MTM claims. Distributions of the Reasons, Actions, Results, and ECA for pharmacist-generated MTM interventions were calculated, along with measures of central tendency and dispersion (mean, median, and SD) for pharmacy reimbursement per claim and ECA dollar amount. Descriptors of the unique patients comprising the study cohort also were generated. Trends occurring in MTM interventions over time were explored by comparing claims in years 2000, 2002, 2004, and 2006. These years represent time periods at the beginning, end, and 2 midpoints in the study time frame. Differences were tested for significance using Pearson chi-square tests for categorical variables and Analysis of Variance (ANOVA) for continuous variables. All analyses were conducted using SAS for Windows, Version 9.1 (SAS Institute, Cary, NC).

FIGURE 1  MTM Claims Over 7 Years by Drug Therapy Type

Acute is defined as one-time use medications such as penicillin antibiotics, macrolide antibiotics, and one-time narcotic analgesics. Chronic is defined as medications prescribed for chronic conditions such as lipid-lowering agents, angiotensin converting enzyme (ACE) inhibitors, and beta-blockers. Examples of intermediate/other category include medications for seasonal allergy. MTM = medication therapy management.
Specific subcategories related to drug therapy problems detected over the 7 years were also explored. Specific examples of pharmacist-identified drug therapy problems included patients with systolic heart failure receiving a prescription for propranolol or other beta-blocker not shown to decrease mortality (Suboptimal Drug Selection); patients skipping maintenance antipsychotic or  

"TABLE 2  Seven-Year Summary of MTM Encounter Data

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Results</th>
<th>Characteristics of MTM Claims</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 23,798</td>
<td></td>
<td>n = 76,148</td>
<td></td>
</tr>
<tr>
<td>Mean [SD] age in years 44.2 [26.5]</td>
<td></td>
<td>2.2 Prescriber consultation 8.7% (6,617)</td>
<td></td>
</tr>
<tr>
<td>% male 38.9%</td>
<td></td>
<td>2.3 Patient consultation 2.6% (1,964)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD) median) claims per patient over 7-year study time period 3.2 (13.5) 2.0</td>
<td></td>
<td>2.4 Patient education and monitoring 86.7% (66,048)</td>
<td></td>
</tr>
<tr>
<td>Characteristics of MTM Claims n = 76,148</td>
<td></td>
<td>2.5 Patient compliance consultation 0.1% (114)</td>
<td></td>
</tr>
<tr>
<td>Therapy Type: Intervention* - % (n)</td>
<td></td>
<td>2.6 Other 0.1% (89)</td>
<td></td>
</tr>
<tr>
<td>Acute 49.9% (38,029)</td>
<td></td>
<td>3.1 CMR with drug therapy problem(s) 0.9% (661)</td>
<td></td>
</tr>
<tr>
<td>Chronic 37.9% (28,829)</td>
<td></td>
<td>3.2 CMR without drug therapy problem(s) 0.9% (655)</td>
<td></td>
</tr>
<tr>
<td>Intermediate/Other 12.2% (9,290)</td>
<td></td>
<td>3.3 Initiation of a cost-effective drug 4.2% (3,180)</td>
<td></td>
</tr>
<tr>
<td>Most Common Drug Categories - % (n)</td>
<td></td>
<td>3.4 Therapeutic success 70.2% (53,474)</td>
<td></td>
</tr>
<tr>
<td>Antimicrobial 24.1% (18,383)</td>
<td></td>
<td>3.5 Therapeutic failure 5.3% (4,024)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular system 14.4% (10,994)</td>
<td></td>
<td>3.6 Drug Therapy Indication</td>
<td></td>
</tr>
<tr>
<td>Central nervous system 10.6% (8,083)</td>
<td></td>
<td>3.6a Initiated new therapy 0.6% (430)</td>
<td></td>
</tr>
<tr>
<td>Most Common Drug Sub-Categories - % (n)</td>
<td></td>
<td>3.6b Discontinued therapy 0.6% (466)</td>
<td></td>
</tr>
<tr>
<td>Penicillin antibiotics 7.3% (5,543)</td>
<td></td>
<td>3.7 Drug Therapy Efficacy</td>
<td></td>
</tr>
<tr>
<td>Narcotic analgesics 6.4% (4,858)</td>
<td></td>
<td>3.7a Changed drug 0.6% (462)</td>
<td></td>
</tr>
<tr>
<td>Macrolide antibiotics 5.1% (3,849)</td>
<td></td>
<td>3.7b Increased dose/duration 0.4% (303)</td>
<td></td>
</tr>
<tr>
<td>Statins and other lipid lowering agents 3.7% (2,808)</td>
<td></td>
<td>3.8 Drug Therapy Safety</td>
<td></td>
</tr>
<tr>
<td>Reasons for MTM Intervention - % (n)</td>
<td></td>
<td>3.8a Altered regimen/changed drug 0.9% (651)</td>
<td></td>
</tr>
<tr>
<td>1.1 Complex drug therapy 1.9% (1,430)</td>
<td></td>
<td>3.8b Decreased dose/duration 0.4% (323)</td>
<td></td>
</tr>
<tr>
<td>1.2 Cost-efficacy management 4.8% (3,656)</td>
<td></td>
<td>3.9 Drug Therapy Compliance</td>
<td></td>
</tr>
<tr>
<td>1.3 New or changed drug therapy 85.6% (65,199)</td>
<td></td>
<td>3.9a Altered compliance 1.6% (1,233)</td>
<td></td>
</tr>
<tr>
<td>1.4 OTC therapy 1.1% (849)</td>
<td></td>
<td>3.9b Altered administration/technique 0.4% (282)</td>
<td></td>
</tr>
<tr>
<td>1.5 Drug Therapy Indication</td>
<td></td>
<td>3.10 Patient refusal 11.7% (8,906)</td>
<td></td>
</tr>
<tr>
<td>1.5a Needs therapy 0.6% (468)</td>
<td></td>
<td>3.11 Prescriber refusal 1.0% (778)</td>
<td></td>
</tr>
<tr>
<td>1.5b Unnecessary therapy 0.8% (625)</td>
<td></td>
<td>3.12 Other 0.4% (320)</td>
<td></td>
</tr>
<tr>
<td>1.6 Drug Therapy Efficacy</td>
<td></td>
<td>Estimated Cost Avoidance Level* - % (n)</td>
<td></td>
</tr>
<tr>
<td>1.6a Suboptimal drug selection 0.7% (530)</td>
<td></td>
<td>4.1 Improved quality of care 78.8% (60,032)</td>
<td></td>
</tr>
<tr>
<td>1.6b Insufficient dose or duration 0.4% (331)</td>
<td></td>
<td>4.2 Reduced drug product cost 4.7% (3,602)</td>
<td></td>
</tr>
<tr>
<td>1.7 Drug Therapy Safety</td>
<td></td>
<td>4.3 Avoided physician visit 2.4% (1,830)</td>
<td></td>
</tr>
<tr>
<td>1.7a Adverse drug reaction 0.7% (511)</td>
<td></td>
<td>4.4 Avoided new prescription order 0.6% (485)</td>
<td></td>
</tr>
<tr>
<td>1.7b Drug interaction 0.5% (365)</td>
<td></td>
<td>4.5 Avoided emergency room visit 0.4% (285)</td>
<td></td>
</tr>
<tr>
<td>1.7c Excessive dose or duration 0.5% (353)</td>
<td></td>
<td>4.6 Avoided hospital admission 0.3% (195)</td>
<td></td>
</tr>
<tr>
<td>1.8 Drug therapy compliance</td>
<td></td>
<td>4.7 Avoided life-threatening event 0.1% (92)</td>
<td></td>
</tr>
<tr>
<td>1.8a Overuse 0.2% (124)</td>
<td></td>
<td>4.8 Prescriber or patient refusal of recommendation 12.6% (9,627)</td>
<td></td>
</tr>
<tr>
<td>1.8b Underuse 1.6% (1,185)</td>
<td></td>
<td>Mean [SD] MTM Claim Reimbursement and Estimated Cost</td>
<td></td>
</tr>
<tr>
<td>1.8c Administration technique 0.4% (293)</td>
<td></td>
<td>$8.44 [5.19] $7.00</td>
<td></td>
</tr>
<tr>
<td>1.9 Other 0.3% (229)</td>
<td></td>
<td>Mean [SD] median pharmacy reimbursement $93.78 [51,022.23] $50.0</td>
<td></td>
</tr>
<tr>
<td>Action or MTM Intervention - % (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.1 CMR 1.7% (1,316)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Acute is defined as one-time use medications; examples include penicillin antibiotics, macrolide antibiotics, and one-time narcotic analgesics. Chronic is defined as medications prescribed for chronic conditions; examples include lipid lowering agents, ACE inhibitors, and beta-blockers. Examples of intermediate/other include medications such as seasonal allergy treatments.

Self-assessed by the pharmacist when recording the intervention.

ACE = angiotensin-converting enzyme; CMR = comprehensive medication review; DTP = drug therapy problems (e.g., drug interactions, adverse drug reactions, insufficient dose/duration); MTM = medication therapy management; OTC = over-the-counter; Rx = prescription.

Analysis of Pharmacist-Provided Medication Therapy Management (MTM) Services in Community Pharmacies Over 7 Years
### TABLE 3 Changes in Characteristics of Patients and MTM Claims Over 7 Years

<table>
<thead>
<tr>
<th>Characteristics of Patients (n)</th>
<th>Year 2000</th>
<th>Year 2002</th>
<th>Year 2004</th>
<th>Year 2006</th>
<th>P Value (Overall Differences)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>(2,070)</td>
<td>(5,427)</td>
<td>(4,216)</td>
<td>(1,995)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>SD</td>
<td>[19.0]</td>
<td>[19.6]</td>
<td>[26.1]</td>
<td>[24.8]</td>
<td></td>
</tr>
<tr>
<td>% male</td>
<td>39.6%</td>
<td>41.5%</td>
<td>40.4%</td>
<td>35.4%</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Average # [SD] claims per patient</td>
<td>2.0 [1.8]</td>
<td>2.3 [2.1]</td>
<td>2.8 [3.2]</td>
<td>1.8 [2.0]</td>
<td>0.104*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics of MTM claims (n = 4,065) (n = 12,338) (n = 11,452) (n = 3,525)</th>
<th>Therapy Type Initiating Interventionb - % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>86.0% (3,495)</td>
</tr>
<tr>
<td>Chronic</td>
<td>10.2% (414)</td>
</tr>
<tr>
<td>Intermediate/other</td>
<td>3.8% (156)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Most Common Drug Categories - % (n)</th>
<th>Antimicrobial</th>
<th>35.5% (1,444)</th>
<th>33.9% (4,186)</th>
<th>15.8% (1,815)</th>
<th>8.7% (305)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular system</td>
<td>8.2% (332)</td>
<td>6.3% (773)</td>
<td>16.7% (1,907)</td>
<td>21.6% (760)</td>
<td></td>
</tr>
<tr>
<td>Central nervous system</td>
<td>5.7% (233)</td>
<td>7.7% (945)</td>
<td>14.5% (1,663)</td>
<td>22.7% (802)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Most Common Drug Sub-Categories - % (n)</th>
<th>Penicillin antibiotics</th>
<th>11.1% (452)</th>
<th>11.1% (1,375)</th>
<th>4.8% (544)</th>
<th>2.0% (70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins and other lipid-lowering agents</td>
<td>3.6% (408)</td>
<td>12.5% (441)</td>
<td>&lt;0.001*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary Reason for MTM Intervention - % (n)</th>
<th>1.1 Complex drug therapyc</th>
<th>0.0% (0)</th>
<th>0.0% (0)</th>
<th>1.2% (139)</th>
<th>6.6% (231)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2 Cost-efﬁcacy management</td>
<td>9.6% (390)</td>
<td>3.6% (446)</td>
<td>1.2% (134)</td>
<td>18.2% (640)</td>
<td></td>
</tr>
<tr>
<td>1.3 New or changed drug therapy</td>
<td>87.1% (3,541)</td>
<td>94.0% (11,022)</td>
<td>88.1% (10,089)</td>
<td>40.0% (1,409)</td>
<td></td>
</tr>
<tr>
<td>1.4 OTC therapy</td>
<td>0.0% (0)</td>
<td>0.3% (32)</td>
<td>0.6% (72)</td>
<td>9.2% (323)</td>
<td></td>
</tr>
<tr>
<td>1.5 Drug therapy indication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5a. Needs therapy</td>
<td>0.5% (21)</td>
<td>0.2% (30)</td>
<td>0.9% (101)</td>
<td>2.4% (79)</td>
<td></td>
</tr>
<tr>
<td>1.5b. Unnecessary therapy</td>
<td>0.1% (4)</td>
<td>0.0% (5)</td>
<td>1.6% (177)</td>
<td>2.6% (92)</td>
<td></td>
</tr>
<tr>
<td>1.6 Drug therapy efﬁcacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.6a. Suboptimal drug selection</td>
<td>0.2% (9)</td>
<td>0.1% (16)</td>
<td>0.6% (65)</td>
<td>4.3% (142)</td>
<td></td>
</tr>
<tr>
<td>1.6b. Insufﬁcient dose or duration</td>
<td>0.4% (18)</td>
<td>0.2% (22)</td>
<td>0.6% (69)</td>
<td>0.7% (23)</td>
<td></td>
</tr>
<tr>
<td>1.7 Drug therapy safety</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.7a. Adverse drug reaction</td>
<td>0.5% (22)</td>
<td>0.4% (48)</td>
<td>0.9% (98)</td>
<td>0.9% (31)</td>
<td></td>
</tr>
<tr>
<td>1.7b. Drug interaction</td>
<td>0.3% (12)</td>
<td>0.2% (18)</td>
<td>0.6% (70)</td>
<td>0.5% (17)</td>
<td></td>
</tr>
<tr>
<td>1.7c. Excessive dose or duration</td>
<td>0.3% (12)</td>
<td>0.2% (23)</td>
<td>0.9% (100)</td>
<td>0.5% (18)</td>
<td></td>
</tr>
<tr>
<td>1.8 Drug therapy compliance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.8a. Overuse</td>
<td>0.1% (2)</td>
<td>0.1% (12)</td>
<td>0.2% (19)</td>
<td>0.1% (5)</td>
<td></td>
</tr>
<tr>
<td>1.8b. Underuse</td>
<td>0.5% (19)</td>
<td>0.5% (57)</td>
<td>1.6% (182)</td>
<td>11.8% (416)</td>
<td></td>
</tr>
<tr>
<td>1.8c. Administration technique</td>
<td>0.2% (7)</td>
<td>0.1% (16)</td>
<td>0.4% (42)</td>
<td>0.9% (30)</td>
<td></td>
</tr>
<tr>
<td>1.9 Other</td>
<td>0.2% (8)</td>
<td>0.1% (11)</td>
<td>0.8% (95)</td>
<td>2.0% (69)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Action or MTM Intervention - % (n)</th>
<th>2.1 CMRc</th>
<th>0.0% (0)</th>
<th>0.0% (0)</th>
<th>1.2% (139)</th>
<th>3.3% (117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2 Prescriber consultation</td>
<td>12.1% (491)</td>
<td>4.4% (33)</td>
<td>7.0% (801)</td>
<td>27.8% (980)</td>
<td></td>
</tr>
<tr>
<td>2.3 Patient consultation</td>
<td>0.8% (33)</td>
<td>1.3% (165)</td>
<td>2.3% (262)</td>
<td>16.5% (582)</td>
<td></td>
</tr>
<tr>
<td>2.4 Patient education or monitoring</td>
<td>87.1% (3,541)</td>
<td>94.3% (11,063)</td>
<td>88.7% (10,161)</td>
<td>49.1% (1,732)</td>
<td></td>
</tr>
<tr>
<td>2.5 Patient compliance consultationc</td>
<td>0.0% (0)</td>
<td>0.0% (0)</td>
<td>0.0% (0)</td>
<td>3.2% (114)</td>
<td></td>
</tr>
<tr>
<td>2.6 Otherc</td>
<td>0.0% (0)</td>
<td>0.0% (0)</td>
<td>0.8% (89)</td>
<td>0.0% (0)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Result of MTM Intervention - % (n)</th>
<th>3.1 CMR with DTF(s)c</th>
<th>0.0% (0)</th>
<th>0.0% (0)</th>
<th>0.7% (75)</th>
<th>0.8% (30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2 CMR without DTF(s)c</td>
<td>0.0% (0)</td>
<td>0.0% (0)</td>
<td>0.6% (64)</td>
<td>2.4% (87)</td>
<td></td>
</tr>
<tr>
<td>3.3 Initiation of cost-effective drug</td>
<td>9.4% (382)</td>
<td>2.8% (350)</td>
<td>1.0% (114)</td>
<td>13.2% (467)</td>
<td></td>
</tr>
</tbody>
</table>

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TABLE 3
Changes in Characteristics of Patients and MTM Claims Over 7 Years

(continued from previous page)

<table>
<thead>
<tr>
<th>Year 2000</th>
<th>Year 2002</th>
<th>Year 2004</th>
<th>Year 2006</th>
<th>P Value (Overall Differences)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.4 Therapeutic success</td>
<td>75.2% (3,055)</td>
<td>70.3% (8,677)</td>
<td>77.6% (8,892)</td>
<td>46.4% (1,634)</td>
</tr>
<tr>
<td>3.5 Therapeutic failure</td>
<td>8.1% (331)</td>
<td>5.5% (673)</td>
<td>5.5% (626)</td>
<td>1.8% (63)</td>
</tr>
<tr>
<td>3.6 Drug therapy indication</td>
<td>0.5% (21)</td>
<td>0.3% (31)</td>
<td>0.8% (88)</td>
<td>2.0% (69)</td>
</tr>
<tr>
<td>3.8 Drug therapy safety</td>
<td>0.2% (9)</td>
<td>0.1% (14)</td>
<td>0.5% (54)</td>
<td>3.1% (110)</td>
</tr>
<tr>
<td>3.9 Drug therapy compliance</td>
<td>0.3% (10)</td>
<td>0.2% (19)</td>
<td>0.7% (83)</td>
<td>0.6% (21)</td>
</tr>
<tr>
<td>3.10 Patient refusal</td>
<td>0.2% (12)</td>
<td>0.1% (11)</td>
<td>0.3% (39)</td>
<td>0.6% (23)</td>
</tr>
<tr>
<td>3.11 Prescriber refusal</td>
<td>0.3% (11)</td>
<td>0.3% (11)</td>
<td>0.3% (39)</td>
<td>0.6% (23)</td>
</tr>
<tr>
<td>3.12 Other</td>
<td>0.1% (6)</td>
<td>0.1% (9)</td>
<td>0.8% (93)</td>
<td>4.3% (152)</td>
</tr>
</tbody>
</table>

ECA Level - % (n)

<table>
<thead>
<tr>
<th>Year 2000</th>
<th>Year 2002</th>
<th>Year 2004</th>
<th>Year 2006</th>
<th>P Value (Overall Differences)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1 Improved quality of care</td>
<td>85.1% (3,461)</td>
<td>76.0% (9,375)</td>
<td>86.2% (9,871)</td>
<td>66.1% (2,331)</td>
</tr>
<tr>
<td>4.2 Reduced drug product cost</td>
<td>9.6% (391)</td>
<td>2.9% (361)</td>
<td>2.1% (245)</td>
<td>15.0% (528)</td>
</tr>
<tr>
<td>4.3 Avoided physician visit</td>
<td>2.0% (80)</td>
<td>0.9% (113)</td>
<td>2.6% (299)</td>
<td>7.6% (267)</td>
</tr>
<tr>
<td>4.4 Avoided new Rx order</td>
<td>0.7% (27)</td>
<td>0.4% (48)</td>
<td>1.0% (113)</td>
<td>0.4% (15)</td>
</tr>
<tr>
<td>4.5 Avoided ER visit</td>
<td>0.2% (7)</td>
<td>0.1% (18)</td>
<td>0.5% (52)</td>
<td>0.7% (24)</td>
</tr>
<tr>
<td>4.6 Avoided hospital admission</td>
<td>0.0% (1)</td>
<td>0.1% (13)</td>
<td>0.4% (43)</td>
<td>1.7% (61)</td>
</tr>
<tr>
<td>4.7 Avoided life-threatening event</td>
<td>0.0% (0)</td>
<td>0.1% (9)</td>
<td>0.2% (19)</td>
<td>0.1% (4)</td>
</tr>
<tr>
<td>4.8 Prescriber or patient refusal</td>
<td>2.4% (98)</td>
<td>19.5% (2,401)</td>
<td>7.1% (810)</td>
<td>8.4% (295)</td>
</tr>
</tbody>
</table>

MTM claim reimbursement and cost avoidance

| Mean [SD] ECA | $24.18 [139.33] | $37.47 [566.98] | $114.39 [1,197.65] | $429.39 [2,420.77] | <0.001<sup>a</sup> |

\textsuperscript{a} All P values derived from Pearson chi-square except ANOVA where marked by this superscript.

In addition, it should be noted that, although 11.7% of claims and Compliance-Underuse (from 0.5% to 11.8%, P<0.001).

Notable changes in the “Action” of MTM interventions provided from 2000 to 2006 included a shift from patient education/monitoring (87.1% to 49.1%, P<0.001) to more prescriber consultations (12.1% to 27.8%, P<0.001). Changes in the “Result” associated with the MTM intervention included a shift from the outcome of therapeutic success (75.2% to 46.4%, P<0.001) to an alteration in medication compliance (0.5% to 12.3%, P<0.001).
increases in the percentage of total claims that were assigned ECA Level 4.6, avoidance of a hospital admission, occurred in both 2004 and 2006 relative to previous years.

Discussion

This MTM administrative services company has one of the largest databases of MTM service claims and includes a nationwide sample of claims submitted over more than 7 years. The present study represents the first analysis of the MTM claims in this database. The MTM administrative services company has adopted a cost avoidance model as a means to demonstrate the value that pharmacists add to the U.S. health care system, and this study includes the first report of pharmacist self-assessment of the ECA associated with MTM interventions. Examination of claims from 50 MTM programs over a 7-year period found that the types of pharmacist-provided MTM services have changed over time, associated with increases in mean MTM reimbursement to pharmacies and ECA.

Over the past several years, MTM interventions have evolved from the provision of patient education involving acute medications toward consultation-type services for chronic medications. These shifts suggest that the provision of MTM services will become increasingly vital as the population ages. Specific trends related to drug therapy problems included an increase in services related to suboptimal drug selection, unnecessary therapy,
and compliance-underuse. In addition, the MTM services evaluated in this study show an increase over time in the MTM-related ECA derived from pharmacists’ self-assessments. This change suggests that pharmacists are well-suited and positioned to identify, resolve and prevent medication-related complications that result in substantial health care costs. However, it should be noted that since this study lacked a comparison group, other explanations for observed changes in MTM services cannot be fully dismissed. Other plausible explanations include changes in the number and demographics of the populations served, as well as possible changes in pharmacist documentation patterns related to MTM interventions.

In a landmark 1995 study, Johnson and Bootman projected the costs associated with drug therapy problems to be $76.6 billion. In an update 6 years later, the projected costs associated with drug therapy problems had increased to $177.4 billion. The authors also expressed that the high costs of drug-related morbidity and mortality should play a factor in health policy decisions and that pharmaceutical care, now termed Medication Therapy Management, could be a strategy to prevent drug therapy problems and reduce associated costs. A 2005 study by Stebbsins et al. of pharmacist provided MTM type services found that pharmacists could significantly decrease patients’ out-of-pocket expenses by enrolling patients in manufacturer-sponsored patient assistance programs, switching patients to appropriate generic or therapeutic alternatives, and employing other cost-saving measures such as tablet splitting. Pharmacists at the clinic were able to save the average patient over $90 during the first year of the study and over $60 during the second year of the study. Although the findings of the study by Stebbsins et al. are encouraging, it should be noted that they were limited to elderly lower-income patients who used a single medical clinic, and that the cost-saving estimates were limited to savings in out-of-pocket prescription drug expenses.

The current study suggests that MTM services provided by community pharmacists may have favorable effects beyond educational benefits and out-of-pocket medication costs for patients and MTM program sponsors. Specifically, MTM services provided by community pharmacists may have a favorable effect on medical costs associated with avoidance of physician visits, emergency room visits, hospital admissions, etc. The proportion of MTM claims in which pharmacists self-rated their services as avoiding higher dollar medical cost events increased from 2000 to 2006. While the exact reason for these sharp increases is unknown, this trend is expected to continue as pharmacists are given more opportunities to provide MTM services and receive reimbursement for the identification and resolution of increasingly complex drug therapy problems. Further, this observation may reflect the expanding role of pharmacists in the avoidance of significant morbidity and mortality as MTM programs mature. Activities undertaken to avoid high-cost medical events included ensuring that patients were on appropriate guideline-recommended therapy, such as aspirin and beta-blocker use in patients following a myocardial infarction and use of ACE inhibitors in diabetic patients without a contraindication. Other specific examples of pharmacist interventions that were considered as preventing a hospitalization included patients taking multiple beta-blockers, patients prescribed multiple potassium products, patients reporting severe cramps or leg pains while on statin therapy, and mental health patients grossly noncompliant on chronic antipsychotic therapy.

Limitations

Foremost among the study limitations are the self-reported estimates of cost avoidance without follow-up assessment of the actual avoidance of health care utilization events, such as office visits and hospitalizations. In addition, a recent (2008) study of pharmacist interventions, conducted by Kroner et al., found that projected medication cost savings overstated actual cost savings by 14%. However the Kroner et al. study was limited to medication conversion savings and did not include cost-saving analyses of other resources, such as physician visits and hospitalizations, which were included in the present study. Second, the absence of a comparison group makes this a descriptive report without the ability to attribute outcomes to the pharmacist interventions; there is no way to determine if the billed MTM intervention would have been performed without the MTM administrative services company’s network, either by another health care provider or by a patient representative.

Third, the study employed a sample of MTM claims from some but not all MTM programs in the database of the MTM administrative services company. For example, the company administers a number of comprehensive disease state management programs, and the claims for these programs were not included in this analysis because they use a different documentation and billing system. In addition, not all MTM programs were active throughout the entire study timeframe. While most original plans renewed their contract for services, some plans left and other plans were added; thus some observed trends may be attributable to changes in the eligibility cohort. In addition, data were presented for even calendar years, but many programs were administered in accordance with insurer fiscal year dates. Thus, the apparent relative decrease in the number of patients and claims in 2006 is misleading. Follow-up analyses from calendar year 2005 and early calendar year 2007 show an upward trend in the number of patients provided MTM services by this MTM administration company. In addition, it should be noted that the claims represent real-world pharmacist MTM interventions across a 7-year time period, from 2000-2006, and encompass 50 MTM programs which were administered nationally to a wide variety of patients.
Conclusions

MTM services appear to be evolving from patient education involving acute medications to more complex prescriber consultation-type services for older patients receiving chronic medications. Further, these changes are associated with greater reimbursement amounts and greater estimated cost savings. While the causal factors underlying these changes remain to be fully explained, the changes appear to be directly linked to requirements outlined in Medicare Part D legislation. Opportunities beyond Medicare Part D are likely to expand as well, particularly for employers and other government-sponsored programs.

DISCLOSURES

There was no external funding for this research. Four of the authors are employees of the MTM administrative services company described in this article. The authors acknowledge Danielle M. Richardson, BS, PharmD Candidate, for her assistance in the preparation of this manuscript.

Concept and design, data collection, data interpretation, and revision of the manuscript were primarily the work of Barnett. Newland and Perry assisted with concept and design and with data interpretation, Frank and Newland assisted with data collection, and Frank and VonMuenster assisted with revision of the manuscript. The work of writing the manuscript was shared equally by Barnett, Wehring, Kumbera, and Halterman.
REFERENCES


## APPENDIX
### MTM Encounter Worksheet

### PRESCRIPTION INFORMATION
- **Patient Info/Rx Info**
  - [Details]

### MONITORING
- **Attempts**
  - 1. Date: __/__/__ Time: __:__ a.m./p.m.
  - 2. Date: __/__/__ Time: __:__ a.m./p.m.
  - 3. Date: __/__/__ Time: __:__ a.m./p.m.
- **Appointment**
  - [Details]

### ENCLOSED DOCUMENTATION
- **Date of Encounter**: __/__/__
- **Claim Number**: __

<table>
<thead>
<tr>
<th>I. Indication For Service (Reason)</th>
<th>II. Professional Service (Action)</th>
<th>III. Outcome Of Service (Result)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex Drug Therapy 100</td>
<td>Comprehensive Med Review (CMR) 200</td>
<td>CMR with Encounter 300</td>
</tr>
<tr>
<td>Cost Efficacy Management 105</td>
<td>Prescriber Consultation 205</td>
<td>CMR without Encounter 301</td>
</tr>
<tr>
<td>Cost Efficacy Management 105</td>
<td>Patient Consultation 215</td>
<td>Initiation of Cost Effective Drug 305</td>
</tr>
<tr>
<td>New/Changed Prescription Therapy 110</td>
<td>[Details]</td>
<td>Prescriber Refusal 375</td>
</tr>
<tr>
<td>OTC Therapy 117</td>
<td></td>
<td>Patient Refusal 380</td>
</tr>
</tbody>
</table>

### Drug Therapy Problem Detected:
- **Indications**
  - Needs Therapy 120
  - Unnecessary Therapy 125
- **Efficacy**
  - Suboptimal Drug Selection 130
  - Insufficient Dose/Duration 135
- **Safety**
  - Adverse Drug Reaction 140
  - Drug Interaction 145
  - Excessive Dose/Duration 150
- **Compliance**
  - Overuse 155
  - Underuse 160
  - Administration/Technique 165
  - Other 170

### Special Project 190
- **Special Project 290**

### IV. Estimated Cost Avoidance
- [Details]

### V. Encounter Notes And Estimated Cost Avoidance Rationale

**Monitoring Questions**
- Have any new health problems developed?
- How have symptoms changed?
- Have you run out of any medications?
- What other questions or concerns do you have?

**RDH ID Number**

**SOID/WHO**

**EMT Region**

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Encounter Form (Rev 0803)
Evaluation of the First Year of a Pilot Program in Community Pharmacy: HIV/AIDS Medication Therapy Management for Medi-Cal Beneficiaries

Jan D. Hirsch, RPh, PhD; Ashley Rosenquist, PharmD; Brookie M. Best, PharmD, MAS; Teresa Ann Miller, PharmD, FCSHP; and Todd P. Gilmer, PhD

ABSTRACT
BACKGROUND: The advent of combined antiretroviral therapy (ART) has increased treatment effectiveness but created new challenges for patients infected with human immunodeficiency virus (HIV) and for community pharmacists managing patients’ drug therapy. The ability of pharmacist-provided medication therapy management (MTM) services to increase medication adherence, improve health outcomes, and reduce overall medical costs has been demonstrated in community pharmacies for chronic diseases such as diabetes and hypertension. However, the effectiveness of pharmacist-provided MTM services in HIV/acquired immune deficiency syndrome (AIDS) has not been well studied. In January 2005, a pilot program to evaluate MTM services for patients with HIV/AIDS began in California, allowing 10 HIV/AIDS specialty pharmacies to receive compensation for the MTM services that they provided to HIV/AIDS patients.

OBJECTIVES: To examine the first year of the HIV/AIDS pharmacy MTM compensation pilot program, which described and compared pilot and nonpilot pharmacies with respect to (a) patient characteristics; (b) intermediate outcomes including type and number of ART medication regimens used, rates of adherence and excess medication fills for ART, use of contraindicated ART regimens, and occurrence of opportunistic infections; and (c) pharmacy and medical costs.

METHODS: This was a cohort study examining 2005 Medi-Cal pharmacy and medical claims data for patients with HIV/AIDS who were served by pilot pharmacies versus other pharmacies. The HIV/AIDS patients were Medi-Cal beneficiaries aged 18 years or older as of January 1, 2005, who were continuously enrolled from January 1, 2004, through December 31, 2005, and diagnosed with HIV/AIDS, identified by receipt of at least 1 ART prescription and at least 1 medical claim with a diagnosis (primary or secondary) of HIV/AIDS (ICD-9-CM code 042.0) during both the index period (the year before pilot program implementation, 2004) and the intervention period (the study year, 2005). The only difference in the inclusion criteria for the 2 cohorts was that the pilot pharmacy patients were required to have filled 50% or more of their antiretroviral prescriptions in 2005 at 1 of the 10 pilot pharmacies. Adherence was defined as a medication possession ratio (MPR) of 80%-120% and excess medication fills as MPR greater than 120%. Comparisons were made between groups using bivariate statistics (Pearson chi-square for categorical variables and t-tests for continuous variables). For comparisons of costs, generalized linear models assuming a gamma distribution and log link function were used; predictor variables for the models included age, gender, race/ethnicity, and dual coverage under Medicare.

RESULTS: A total of 7,018 HIV/AIDS patients in the Medi-Cal population were identified as meeting the study criteria. Of these, 19.3% (n = 1,353) were pilot pharmacy patients. The demographic profile of pilot pharmacy patients was similar, but not identical, to that of patients receiving medications at other pharmacies. A larger percentage of pilot pharmacy patients were on protease inhibitor-based ART medication regimens (83.8% vs. 54.8%, P < 0.001), remained on a single type of ART therapy throughout the study year (56.8% vs. 34.2%, P < 0.001), and were classified as adherent (56.3% vs. 38.1%, P < 0.001), compared with other pharmacy patients. Fewer pilot pharmacy patients used contraindicated regimens (11.6% vs. 16.6%, P < 0.001) or had excess medication fills (19.7% vs. 44.8%, P < 0.001). The rate of opportunistic infections did not differ significantly between groups (28.2% vs. 26.1%, P = 0.121). The total mean (standard error) annual health care cost per patient was 10% higher in pilot pharmacies than in other pharmacies ($40,596 [$889] vs. $36,937 [$479], P = 0.001); driven by use of (a) medications (primarily non-ART medications) and (b) mental health services. Payment from the California Department of Health Care Services for MTM services averaged $1,014 per pilot pharmacy study patient.

CONCLUSION: Study findings for the first year of the MTM program suggest that the pilot pharmacy patients received more appropriate HIV treatment. The degree to which these differences are affected by self-selection of patients into the pilot pharmacies is unknown. Longer-term outcomes and costs of the pilot program will be examined when data for subsequent years are available.

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What is already known about this subject
- The only 2 published studies related to pharmacist-provided MTM services in HIV/AIDS patients both concluded that pharmacist-led interventions had a positive effect on clinical outcomes. However, these studies were small and based in specialized HIV clinics, not community pharmacies.
- A chart review study demonstrated improved medication adherence (refilling prescriptions on average every 31 vs. 50 days) and a significantly greater reduction in viral load at 6 and 12 months after initiating therapy (both comparisons P < 0.05) for patients with HIV/AIDS who attended a pharmacist-led medication adherence clinic (n = 80) than for patients not attending.
- A prospective study of patients (n = 34) attending a pharmacist-managed drug optimization clinic reported significant improvement from baseline in CD4+ T-lymphocyte counts (mean [SD] improvement 54 [78] cells per cubic millimeter [mm3], P < 0.001) and viral loads (mean reduction 1.02 log10 copies per milliliter [mL], P = 0.004). However, that study lacked a comparison group.
- Larger studies using pharmacy records have demonstrated that improved adherence was correlated with reduced viral load; for example, for each 10% increase in adherence rate, viral load decreased by 0.12 log10 copies per mL (95% confidence interval [CI] = 0.01-0.23 log10 copies per mL), and when adherence fell below 95%, the percentage of patients with viral load below 400 copies per mL fell below 60%.
Evaluation of the First Year of a Pilot Program in Community Pharmacy: HIV/AIDS Medication Therapy Management for Medi-Cal Beneficiaries

What this study adds

- To our knowledge, this is the first large-scale evaluation of an MTM program in HIV/AIDS patients.
- Among Medi-Cal patients diagnosed with HIV/AIDS and using ART, patients of pilot MTM pharmacies (those filling 30% or more of their ART prescriptions at pharmacies that were reimbursed for MTM services) were more likely to use protease inhibitor-based ART medication regimens (63.8% vs. 54.8%, P<0.001) and to remain on a single type of ART regimen throughout the study year (56.8% vs. 34.2%, P<0.001), compared with patients using other pharmacies.
- More pilot pharmacy patients were classified as adherent (56.3% vs. 38.1%, P<0.001) and fewer pilot pharmacy patients were on contraindicated regimens (11.6% vs. 16.6%, P<0.001), compared with other pharmacy patients. However, the rate of opportunistic infections did not differ significantly between groups (28.2% vs. 26.1%, P=0.121) during the study year.
- The total mean [SD] annual health care cost per patient was 10% higher in pilot pharmacies ($40,596 [889] vs. $36,937 [479], P=0.001), driven by use of medications (primarily non-ART medications) and mental health services.

MTM services provided by a pharmacist and assessed outcomes. Both studies were conducted in HIV outpatient clinics. The first, a chart review study, demonstrated improved medication adherence (refilling prescriptions on average every 31 vs. 50 days, P<0.05) and a significantly greater reduction in viral load at 6 and 12 months (P<0.05) after initiating therapy for patients attending a pharmacist-led medication adherence clinic and at least 1 educational session from the clinical pharmacist (n=80) versus those not attending (n for comparison group not reported).8 The second, a prospective study of patients (n=34) who had an extensive history of treatment and attended a pharmacist-managed drug optimization clinic, reported significant improvement from baseline in CD4+ T-lymphocyte counts (mean [SD] improvement 54 [78] cells per cubic millimeter [mm³]; P<0.001) and viral loads (mean reduction 1.02 log_{10} copies per milliliter [mL]; P=0.004).9 A significant decrease in the mean drug-related toxicity score was also observed among patients experiencing drug-related toxicities (n=25, mean [SD] reduction of 1.0 [0.8] on the 4-point Radiation Therapy Oncology Group common toxicity scale, P<0.001). However, that study lacked a comparison group.

Although not including a MTM services component, several studies have shown significant correlation between improved medication adherence, as measured by pharmacy data, and reduced viral load.10-12 For example, Grossberg et al. reported that, for each 10% increase in adherence rate, viral load decreased by 0.12 log_{10} copies per mL (95% confidence interval=0.01-0.23 log_{10} copies per mL) and Fairley et al. reported that, when adherence fell below 95%, the percentage of patients with viral load consistently below 400 copies per mL fell below 60%.11,12 It is reasonable to expect that the provision of MTM services would increase adherence, as it has in other disease states, and thus reduce viral load. However, barriers to the delivery of specialized counseling services to enhance adherence in HIV/AIDS patients in community pharmacy settings have also been recognized. For example, in a statewide survey of pharmacists in North Carolina, 59% of community pharmacist respondents indicated that they did not have enough time to provide adherence counseling to their HIV/AIDS patients.13

Pilot Program Description

In January 2005, a pilot program to compensate and evaluate community pharmacy-based MTM services for patients with HIV/AIDS began in the state of California. This program, under Welfare and Institutions Code Section 14199-14199.3, allowed 10 HIV/AIDS specialty pharmacies in the state to receive compensation for the MTM services that they provided to HIV/AIDS Medi-Cal patients. The California Department of Health Care Services (DHCS) provided pilot pharmacies $9.50 per prescription dispensed to a Medi-Cal beneficiary for the 3-year term of the pilot program. The DHCS selected the 10 pilot pharmacies based on the requirements of the legislation authorizing the pilot.14 The first 10 pharmacies that applied and met the following criteria

T
The advent of combined antiretroviral therapy (ART) has increased treatment effectiveness but created new challenges for patients infected with human immunodeficiency virus (HIV) and for community pharmacists managing patients’ drug therapy. Combined ART generally consists of 3 or more HIV drugs taken together from at least 2 of the 3 main drug classes; protease inhibitors (PI), nonnucleoside reverse transcriptase inhibitors (NNRTI), and nucleoside or nucleotide reverse transcriptase inhibitors (NRTI).

Because the virus can develop resistance against any 1 drug given alone, at least 3 or more drugs, usually from 2 or more different classes, must be used at the same time. Treatment regimens containing a PI are typically among the most potent and/or durable against the virus, but often have the least tolerable side effects. Complex ART regimens contain multiple drugs with various dosing schedules, undesirable side effect profiles, and different storage requirements for many of the medications.2 Strict adherence to HIV drug therapy has been shown to be crucial to achieving optimal therapeutic outcomes such as reduced viral load, reduction of drug resistance, and improved survival.3-5

The potential of pharmacist-provided medication therapy management (MTM) services to increase medication adherence, improve health outcomes, and reduce overall medical costs has been demonstrated in community pharmacies for chronic diseases such as diabetes and hypertension.6,7 However, the effectiveness of pharmacist-provided MTM services in HIV/acquired immune deficiency syndrome (AIDS) has not been well studied. A review of the literature found only 2 studies that described the type of
were selected: (a) patient population comprising 90% or more of persons with HIV/AIDS, (b) had the ability to immediately provide specialized services rendered by a qualified pharmacist or other health care provider operating within his or her scope of practice, and (c) had pharmacists and other qualified health care providers to identify patients who should receive MTM services. Specialized services were defined as being distinct from generalized patient education and information activities already required by law and provided for in the professional dispensing fee. These services (a) were to be patient specific and individualized services provided directly by a pharmacist to the patient or, in limited circumstances, the patient’s caregiver, and (b) involved face-to-face interaction between the patient or caregiver and the pharmacist during delivery of MTM services. The possible types of MTM services outlined in the legislation were based on the definition of MTM services published by the American Pharmacists Association. Patients of pilot pharmacies chose to patronize pilot pharmacies either through their own selection process and/or based on physician referral; these decisions were made independent of this study.

Following up on previous work suggesting a potential impact of pharmacist-provided MTM services on adherence and viral load in HIV/AIDS patients who were treated in the community setting, the California HIV/AIDS pharmacy MTM services pilot program provided an opportunity to investigate a broader range of outcomes using a larger sample of patients with HIV/AIDS. The California study examined patients receiving care at pharmacies providing a wide range of MTM services and compared their outcomes with those of similar patients at other pharmacies throughout the state.

Study Objectives
The purpose of this study was to examine the first year of the HIV/AIDS pharmacy MTM services compensation pilot program. The study used pharmacy and medical claims data to describe and compare patients filling prescriptions at pilot (MTM) versus other pharmacies with respect to (a) patient characteristics; (b) intermediate outcomes, including the number and type of ART medication regimens, rates of adherence and excessive fills, use of contraindicated ART regimens, and occurrence of opportunistic infections; and (c) pharmacy and medical costs.

Methods
Description of the Intervention
The intervention in this study was participation in the DHCS compensation pilot program for MTM services. The program required that participating pharmacies be able to immediately offer MTM services; therefore, pharmacies selected for the pilot compensation program had been offering a range of MTM services before participating. Although the specific services that each pilot pharmacy must provide were not defined, all pilot pharmacies offered services to (a) manage adverse drug reactions and medication side effects; (b) evaluate patient ability to adhere to medication regimens, in consultation with physicians and case managers; and (c) tailor drug regimens to accommodate specific patient needs. Each pharmacy worked with patients and/or their physicians according to their own practice norms, and further details were not available to the researchers.

Outcome Measures
Provision of MTM services in pilot pharmacies was expected to (a) improve adherence to ART regimens, (b) result in more rational ART medication strategies (e.g., fewer contraindicated regimens, fewer medication changes per year which can decrease likelihood of developing drug resistance), (c) decrease occurrence of opportunistic infections, and (d) reduce costs through more rational medication usage and reduced need for medical services. Ten outcome measures were assessed (Table 1).

Study Design and Patient Selection
This was a cohort study examining 2005 Medi-Cal pharmacy and medical claims data for patients with HIV/AIDS served by pilot pharmacies versus other pharmacies. All study procedures were approved by the University of California San Diego and the DHCS Human Research Protection Programs. The study group, pilot pharmacy HIV/AIDS patients, consisted of Medi-Cal beneficiaries aged 18 years or older as of January 1, 2005, who were continuously enrolled from January 1, 2004, through December 31, 2005, and diagnosed with HIV/AIDS, identified by receipt of at least 1 prescription for ART and at least 1 medical claim with an HIV/AIDS-related diagnosis (primary or secondary) International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 042.0 during both the index period (from January 1 through December 31, 2004) and the study period (from January 1 through December 31, 2005). The ART medications are shown in Appendix A.

Patients were identified as pilot pharmacy patients if they had filled 50% or more of their ART prescriptions in 2005 at 1 of the 10 pilot pharmacies. Comparison group patients met the same inclusion and exclusion criteria as study patients, except that they were not identified as having filled 50% or more of their ART prescriptions in 2005 at 1 of the 10 pilot pharmacies. Individuals enrolled in managed care plans were excluded because paid claims are not generated for Medi-Cal participants enrolled in managed care.

Data Analysis
Descriptive statistics were calculated for all variables. Frequency distributions were used to describe categorical variables, and means, medians, standard deviations, and ranges were used for continuous variables. Gender, dual coverage under Medicare, race/ethnicity, ART adherence and ART medication category were expressed as percentages, and differences between groups (pilot versus other pharmacy patients) were assessed using the Pearson
chi-square test. Age and number of pharmacy visits to fill ART prescriptions were expressed as means, and differences between groups were assessed using t-tests. Differences in costs were analyzed using generalized linear models assuming a gamma distribution and log link function; predictor variables for the models included age, gender, race/ethnicity, and dual coverage under Medicare.\textsuperscript{17,18} Standardized estimates of costs were calculated for pilot and nonpilot pharmacies. Standard errors were calculated using the nonparametric bootstrap, and P values were calculated using the percentile method. DHCS payments to pilot pharmacies, $9.50 per prescription dispensed for any medication (not just ART drugs), were not included in the cost estimates and are presented separately. Statistical significance was set at $P<0.05$. All statistical analyses were performed using Stata version 9.2 (Stata Corp., College Station, TX).

### TABLE 1. Outcome Measures (2005)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of pharmacy visits</td>
<td>Number of days patient visited pharmacy to fill ART prescription or prescriptions</td>
</tr>
<tr>
<td>ART adherence level (MPR)</td>
<td>MPR = $\sum$ number days supply ART for year. 365.25 days. Nonadherent: MPR &lt; 50%. Partially adherent: MPR 50% - 79%. Adherent: MPR 80% - 120%. Excess fills: MPR &gt; 120%. Calculated using medication with highest days supply on day when multiple prescriptions were filled to avoid double counting of days.</td>
</tr>
<tr>
<td>ART medication regimen strategy</td>
<td>Categories are mutually exclusive and are assigned the therapy with the greatest number of days supplied during the year (see drug list in Appendix A). - Only 1 N(t)RTI - Multiple N(t)RTI - N(t)RTI + NNRTI - N(t)RTI + PI + NNRTI</td>
</tr>
<tr>
<td>Contraindicated ART regimen\textsuperscript{a}</td>
<td>- amprenavir + fosamprenavir - atazanavir + indinavir - zalcitabine in regimen - emtricitabine + lamivudine - stavudine + zidovudine - didanosine + stavudine - saquinavir alone - Only a single class NRTI/NtRTI regimen - Only mono or dual therapy with NRTI/NtRTI - Only triple therapy NRTI/NtRTI - except if abacavir + zidovudine + lamivudine or tenofovir + zidovudine + lamivudine</td>
</tr>
<tr>
<td>Number of ART medication regimen strategies</td>
<td>Number ART regimen strategies = $\Sigma$ regimen strategies. - Regimen strategies: each prescription fill categorized as a single ART, multiple ART, NNRTI, or protease inhibitor regimen strategy - Regimen strategies counted only once: (e.g. if patient switched from single ART to NNRTI and back to ART, number of regimen strategies = 2)</td>
</tr>
<tr>
<td>Opportunistic infection</td>
<td>See list in Appendix B</td>
</tr>
<tr>
<td>Total medication cost</td>
<td>Paid claims amount for all prescription medications</td>
</tr>
<tr>
<td>ART medication cost</td>
<td>Paid claims amount for antiretroviral therapy medications (single agent or in combination)</td>
</tr>
<tr>
<td>Non-ART medication cost</td>
<td>= Total medication cost – ART medication cost</td>
</tr>
<tr>
<td>Medical costs\textsuperscript{b}</td>
<td>Paid claims amount for: Inpatient Hospital outpatient (includes emergency department) Outpatient Mental health Laboratory/X-ray AIDS Waiver Program\textsuperscript{c}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}DHHS Panel on Antiretroviral Guidelines for Adult and Adolescents (2008).\textsuperscript{21} \textsuperscript{b}Medical costs were assigned to service categories using codes indicating type of service (i.e., Medi-Cal vendor codes). \textsuperscript{c}Under contract with the Department of Health Care Services agencies to provide home and community-based services as an alternative to nursing facility care or hospitalization.

\textsuperscript{ART} = antiretroviral therapy; \textsuperscript{MPR} = medication possession ratio; \textsuperscript{N(t)RTI} = nucleoside or nucleotide reverse transcriptase inhibitors; \textsuperscript{NNRTI} = non-nucleoside reverse transcriptase inhibitors; \textsuperscript{PI} = protease inhibitor.
Results

Medi-Cal HIV/AIDS Patients (Pilot and Other Pharmacy Patients Combined)

The study population consisted of 7,018 patients meeting the study inclusion criteria (Figure 1). Patients had a mean (SD) age of 46.5 (8.8) years, were predominantly male (80.1%), and slightly more than one-half (53.3%) had dual coverage with Medicare during 2005. The largest proportion of patients was white (46.2%), with African-American and Latino patients comprising 25.9% and 19.5% of the population, respectively.

The mean (SD) number of pharmacy visits to fill ART prescriptions during 2005 was 14.4 (8.0). More than 80% of fills were for a 30-day supply. Approximately 18% of patients were either nonadherent or only partially adherent to their ART medications. Almost equal proportions were adherent (41.6%) or had excess fills (40.0%). When classified by the type and number of ART medications received, the largest percentage (56.5%) of patients were taking a PI-based regimen (Nt(1)RTIs + PI ± NNRTI). The remainder of patients were on regimens not containing a PI; an NNRTI-based regimen (Nt(0)RTIs + NNRTI) (29.9%) or less potent multiple Nt(0)RTIs (11.4%). A small percentage (2.2%) of patients were on a single Nt(0)RTI, a treatment strategy that is not recommended.

Total annual medication cost per patient averaged (SD) $25,254 ($18,692). The largest proportion of total medication cost was for ART, which averaged $16,195 ($8,217) per patient. The difference between total and ART cost was attributable to non-ART outpatient medications.

Pilot Versus Other Pharmacy Patients

Approximately 20% of the study population received the majority of their prescription medications at a pilot pharmacy in 2005 (Table 2). Compared with nonpilot pharmacy patients, pilot pharmacy patients were slightly younger (mean 46.0 vs. 46.7 years, P<0.001). The proportion of pilot pharmacy patients who were male (76.3%) or had dual Medicare coverage (48.6%) was less than in the nonpilot pharmacy group (81.0% and 54.4%, respectively; P<0.001). The pilot pharmacy group had a larger proportion of African-American patients, compared with the nonpilot group (29.4% vs. 25.2%, respectively; P=0.001), and a smaller percentage of Latino patients (17.6% vs. 19.9%, respectively; P=0.050).

Patients of pilot pharmacies had a greater mean [SD] number of pharmacy visits to fill ART prescriptions, compared with nonpilot pharmacy patients (15.4 [10.5] vs. 14.1 [7.3], respectively; P<0.001); however, the median number of visits was 13 in both groups (Table 3). Comparing patients in the pilot pharmacy group with those served by other pharmacies, the percentage of patients classified as adherent was significantly greater (56.3% vs. 38.1%, P<0.001) and the percentage of patients with excess fills was much smaller (19.7% vs. 44.8%, P<0.001). A significantly greater number of pilot pharmacy patients were classified as nonadherent or partially adherent, compared with other pharmacy patients, although the magnitude of difference was 4 percentage points or less (P<0.001).

A significantly greater percentage of pilot pharmacy patients

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**TABLE 2** HIV/AIDS Patient Demographics [2005]

<table>
<thead>
<tr>
<th></th>
<th>Pilot Pharmacies</th>
<th>Other Pharmacies</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of pharmacies</td>
<td>10</td>
<td>2,103</td>
<td>N/A</td>
</tr>
<tr>
<td>Number (%) study patients</td>
<td>1,353 (19.3)</td>
<td>5,665 (80.7)</td>
<td>N/A</td>
</tr>
<tr>
<td>Mean [SD] age in years</td>
<td>46.0 [8.9]</td>
<td>46.7 [8.7]</td>
<td>0.016</td>
</tr>
<tr>
<td>Number (%) male</td>
<td>1,032 (76.3)</td>
<td>4,589 (81.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number (%) dual Medicare coverageb</td>
<td>657 (48.6)</td>
<td>3,059 (54.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race/ethnicity number (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Latino White</td>
<td>603 (44.6)</td>
<td>2,637 (46.5)</td>
<td>0.189</td>
</tr>
<tr>
<td>African American</td>
<td>398 (29.4)</td>
<td>1,426 (23.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Latino</td>
<td>238 (17.6)</td>
<td>1,128 (19.9)</td>
<td>0.050</td>
</tr>
<tr>
<td>Non-Latino White</td>
<td>114 (8.4)</td>
<td>474 (8.4)</td>
<td>0.944</td>
</tr>
</tbody>
</table>

*P value for Pearson chi-square test for categorical variables (sex, Medicare coverage, and race/ethnicity) and t-test for age.

bPatients also had Medicare coverage for at least 1 month during the year.

HIV/AIDS = human immunodeficiency virus/acquired immune deficiency syndrome.

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**FIGURE 1** Patient Selection From Medi-Cal Claims Database

- **Pilot Pharmacy Patients**
  - Filled $\geq$50% ART prescriptions at a pilot pharmacy (2005) (n=1,353, 19%) (n=7,018)

- **Other Patients**
  - Filled $<$50% ART prescriptions at a pilot pharmacy (2005) (n=5,665, 81%)

- **Continuously enrolled 1/1/04-12/31/05**
  - (n=1,255,843)

- **Received at least 1 ART prescription and at least 1 HIV/AIDS related diagnosis code (ICD-9-CM code 042) during index period (2004) and study period (2005)**
  - (n=7,018)
(63.8%) were on a PI-based ART regimen (N(0)RTIs + PI ± NNRTI), compared with other pharmacy patients (54.8%), P<0.001 (Table 3). The percentage of pilot pharmacy patients on less potent combination regimens was significantly smaller for each category as compared with other pharmacy patients. A significantly smaller percentage of pilot pharmacy patients (1.0%) were on the nonrecommended single N(0)RTI treatment strategy, compared with other pharmacy patients (2.4%; P<0.001).

A smaller percentage of pilot pharmacy patients were on contraindicated ART regimens as compared with other pharmacy patients (11.6% vs. 16.6%, respectively; P<0.001) (Table 3). Identified contraindications included all of those screened (Table 1), except that no patients had stavudine plus zidovudine, or saquinavir as a single agent. Pilot pharmacy patients were also significantly less likely to change their medication regimen strategy compared with patients in other pharmacies (P<0.001). For example, 56.8% of pilot pharmacy patients were able to remain on one ART regimen strategy throughout the year, compared with only 34.2% of other pharmacy patients. Almost one-quarter of other pharmacy patients used 3 or more regimen strategies during the study year, compared with only 10.8% of the pilot pharmacy patients. No significant difference in the number of patients experiencing opportunistic infections was detected between pilot and other pharmacy patients (P=0.121).

The mean (standard error [SE]) total medication cost per patient was greater in the pilot group ($27,816 [$538]) than in the other pharmacy group ($24,651 [$234]), P<0.001, Table 4). This difference was largely attributable to a 30% greater cost for non-ART medications ($11,142 [$432] vs. $8,565 [$205], respectively; P<0.001) and less attributable to a small difference in ART medication cost ($16,657 [$212] vs. $16,087 [$112], respectively; P=0.022). Examination of expenditures for a subset of non-ART medications (medication categories with costs exceeding $500 per patient in 2005 in either the pilot or other pharmacy group) revealed that pilot pharmacy patients had appreciably higher annual costs for several therapeutic categories, compared with other pharmacy patients—for example, analgesics, gastrointestinal agents (primarily antiemetics), and blood products (Table 5). The pilot pharmacy patients also had significantly higher mental health medical services costs per patient than did the other pharmacy patients ($686 [$57] vs. $467 [$26], respectively, P=0.002; Table 4). No other medical cost differences were statistically significant. Higher medication (non-ART and ART) and mental health services resulted in a higher average total cost per patient in the pilot pharmacy group ($40,596 [$889]) than in the other pharmacy group ($36,937 [$479], P=0.001).
In addition, the California DHCS paid $2,730,053 to pilot pharmacies for MTM services provided in 2005 to all Medi-Cal beneficiaries using these pharmacies (n=14,896 patients [including 1,353 study patients] with 287,374 prescription claims; $9.50 × 287,374 prescription claims). The average annual DHCS payment per Medi-Cal beneficiary using pilot pharmacies was $183.27 ($2,730,053 per 14,896 unduplicated Medi-Cal beneficiaries in the pilot pharmacies in 2005). Considering study patients only, the average annual DHCS payment for MTM services per pilot pharmacy study patient was $1,014 ([144,352 prescription claims × $9.50] per 1,353 study patients).

### Discussion

This article describes the initial evaluation of a novel community pharmacy-based MTM compensation program for patients enrolled in Medi-Cal and diagnosed with HIV/AIDS. To our knowledge, this is the first large-scale MTM program and evaluation of its kind in patients with HIV/AIDS. The results showed that a larger percentage of pilot pharmacy patients were on PI-based ART medication regimens. Although these regimens often have more side effects, pilot pharmacy patients had a greater adherence rate and fewer ART regimen changes than did nonpilot pharmacy patients. Fewer pilot pharmacy patients were on contraindicated regimens or had excess medication fills. The rate of opportunistic infections did not differ significantly between groups. The total annual cost per patient was 10% higher in pilot pharmacies. The difference was attributable to higher medication costs (largely non-ART) and greater use of mental health services by pilot pharmacy patients. Payment from California DHCS for MTM services averaged $1,014 per pilot pharmacy study patient ($183 per patient considering all patients using pilot pharmacies).

The greater percentage of adherent patients in pilot pharmacies is consistent with findings from the Cantwell-McNelis and James (2002) study of HIV/AIDS patients attending a pharmacist-led medication adherence clinic that demonstrated improved medication adherence and decreased viral load for patients attending the clinic over a 1-year period versus those not attending. Although our study was not able to include clinical outcomes (e.g., viral load) it would be reasonable to expect that the improved adherence observed in pilot pharmacy patients will translate to improved clinical outcomes given the results of large studies using pharmacy records that have demonstrated that improved adherence is correlated with reduced viral load.10-12

In the present study, the age, gender, and race/ethnicity mix of the entire study population of HIV/AIDS Medi-Cal patients was fairly similar to that observed in 2 studies of California HIV/AIDS patients; one (Purdum et al., 2004) described the HIV/AIDS population of Kaiser California and another an HIV/AIDS nurse case-management program with pharmacy support in the inner city of San Francisco.19,20 Thus, our overall study population appears to be similar to that in California. In the present study, the pilot pharmacy group was slightly younger, had a lower percentage of males and Medicare dual-eligible patients, and a higher percentage of African-American patients than did the cohort of patients filling ART prescriptions at other pharmacies. Although these differences were statistically significant the magnitude of difference for each was small. Therefore, the demographic profile of HIV/AIDS patients receiving medications at pilot pharmacies was generally similar to that of HIV/AIDS patients receiving medications at nonpilot pharmacies across the state.

The proportion of patients experiencing opportunistic infections during this study year was low, and similar, for both groups.
The proportion of patients who were partially adherent or non-adherent in both groups is troublesome because these patients are at greater risk of developing resistance that could affect their longer-term therapy options. Future evaluation will investigate if the rates of opportunistic infections and nonadherence change during the subsequent 2 years of the pilot program.

One finding deserves special emphasis. The majority of pilot pharmacy patients remained on a single type of medication regimen strategy for the year studied, compared with patients of other pharmacies, who changed their medication regimen type more often. Even though combined ART treatment has proven effective against HIV, one of the key limitations is that the virus becomes resistant to the available drugs. The more drugs and the more drug classes that a patient is exposed to increases the likelihood of developing drug resistance. Patients who need to switch regimens often (either due to lack of efficacy or intolerance or inability to manage side effects) are essentially exhausting their future treatment options and will not remain as healthy or live as long as patients who are successful on a single regimen for as long as possible. Because the pilot pharmacy patients were able to use and stay on a potent PI-based regimen more often than the patients filling ART prescriptions at other pharmacies, the expectation is that the pilot pharmacy patients will maintain their health and live longer.

The average total cost per patient in the pilot pharmacy group was approximately 10% greater than in the other pharmacy group. Medi-Cal was the only payer in the study; therefore reimbursement rates for services and products were equal between groups (although minor variation can occur because of differences in claim amounts submitted). Thus, differences in expenditures reflected differences in utilization rates or mix of products and services. The higher cost was attributable to greater utilization of medications (largely non-ART) and mental health services.

Although statistically significant, the magnitude of difference in average ART medication cost per patient between pilot and other pharmacies was small, $570 per patient per year (3.5%). However, pilot-pharmacy patients had a greater number of pharmacy visits to fill prescriptions and higher total medication cost due mostly to non-ART medication usage. Pilot patients used more antiemetics, analgesics, and anti-convulsants. These medications are commonly used in HIV/AIDS patients to treat side effects of ART medications such as nausea and pain of peripheral neuropathy. This finding is consistent with that of March et al., who reported a positive effect of pharmacist MTM services on medication side effects, expressed in their study as a reduction in drug-related toxicities. In addition to treating side effects, the pilot pharmacy patients appear to receive more medications for psychiatric comorbidities, which is consistent with the increased expenditures on mental health services. These findings suggest that the pilot pharmacy patients may receive more appropriate HIV treatment and perhaps more comprehensive medical access and care for their other conditions, often related to their primary therapy.

There remains a need to determine the ultimate long-term benefit of patients being more adherent on appropriate combined ART regimens and using more non-ART medications and mental health services over several years. Possible savings in more costly inpatient care will be investigated when data for subsequent years of the pilot program are available. These longer-term data also will allow investigation of the cost-effectiveness of the $9.50 per prescription payments for MTM services by the California DHCS. However, with the advent of Medicare Part D, the dual-eligible Medicare patients will no longer receive medications through Medi-Cal and thus will not be available for follow-up. However, the results of this pilot may help Medicare Part D plans understand the value of community pharmacists providing MTM services to HIV/AIDS patients; especially Medicare Special Needs Plans focusing on this patient population.

Limitations

The foremost limitation of this study is that it is an evaluation of an ongoing program and may be subject to selection bias due to nonrandom assignment of HIV/AIDS patients to pharmacies. If patients who fill their prescriptions at pilot pharmacies are different from patients who fill their prescriptions at other pharmacies, then the pilot pharmacy estimated effect will include both the true pilot program effect and the baseline differential between patients. Although the 2 patient groups appeared to be similar with regard to observable variables (e.g., age, gender), nonobservable variables (e.g., willingness to follow treatment protocols, possible physician referral of more complicated patients to pilot pharmacies) may differ between groups and affect conclusions. Second, it is possible that some of the other (comparison cohort) pharmacies provided some of the same services as the pilot pharmacies, because only the first 10 pharmacies meeting program criteria were enrolled in the pilot compensation program.

Third, an inherent limitation to this analysis is its reliance on Medi-Cal retrospective claims data that do not include clinical outcomes such as viral load and CD4 counts.

Fourth, our results are relevant to California but may not reflect what would occur with a similar MTM program in patient populations with different demographic or disease characteristics. Fifth, comparison of patient outcomes and costs before and after MTM services were initiated by pilot pharmacies was not possible because the pilot pharmacies provided MTM-like specialty services for varying amounts of time before receiving the compensation from the pilot program. Finally, this was an analysis of only the first year of the pharmacy compensation pilot program. Claims data from subsequent years of the pilot program are being sought to determine whether observed differences in outcomes and treatment costs continue to be observed over the 3-year period of the pilot program.
Conclusions

Patients at pilot pharmacies appear to benefit from more specialized and patient-specific MTM services offered by pilot pharmacies. Pilot pharmacy patients were on more potent ART regimens, had higher medication adherence rates, fewer excess fills, and fewer contraindicated regimens than nonpilot pharmacy patients. Importantly, more pilot pharmacy patients remained on a single type of ART regimen throughout the study year, which decreases the likelihood of developing drug resistance and enhances the ability to maintain health over a longer period of time. Total cost per patient was 10% higher in pilot pharmacies, with the higher cost attributed to non-ART medications and mental health services. Longer-term outcomes and costs of the pilot program will be examined when data for subsequent years are available.

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DISCLOSURES

Payment to pharmacies participating in the pilot program for MTM services was funded by the state of California. There was no other external funding for this research. Teresa Miller is employed by the California Department of Health Care Services as Senior Consulting Pharmacist, Medi-Cal Pharmacy Policy Branch, California Department of Health Care Services. Her department has responsibility for implementing the pilot MTM services program subsequent to the enacted legislation.

REFERENCES


APPENDIX A

**Alphabetical List of Antiretroviral Therapy (ART) Medications by Category**

### Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (N(t)RTI)
- Abacavir sulfate
- Abacavir sulfate/lamivudine
- Abacavir/lamivudine/zidovudine
- Didanosine/magnesium/Al NaCB/sodium citrate
- Didanosine
- Didanosine/calcium carbonate/magnesium
- Didanosine/sodium citrate
- Emtricitabine
- Lamivudine
- Lamivudine/zidovudine
- Stavudine
- Zakitabine
- Zidovudine
- Tenofovir disoproxil fumarate
- Emtricitabine/tenofovir

### Nonnucleoside Reverse Transcriptase Inhibitors
- Delavirdine mesylate
- Elavirenz
- Nevirapine

### Protease Inhibitors
- Amprenavir/vitamin E
- Amprenavir/vitamin E/propylene glycol
- Atazanavir sulfate
- Fosamprenavir calcium
- Indinavir sulfate
- Nelfinavir mesylate
- Ritonavir
- Ritonavir/lopinavir
- Saquinavir
- Saquinavir mesylate
- Tipranavir

### Fusion Inhibitor
- Enfuvirtide

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**APPENDIX B**

**Opportunistic Infections and ICD-9-CM Codes**

<table>
<thead>
<tr>
<th>Opportunistic Infections</th>
<th>ICD-9-CM code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumocystis jiroveci pneumonia (PCP)</td>
<td>136.3</td>
</tr>
<tr>
<td>Toxoplasma gondii encephalitis</td>
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<tr>
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<td>Microsporidiosis</td>
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<td>Mycobacterium avium complex disease</td>
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<td>Bacterial pneumonia</td>
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<td>Bartonella infections</td>
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<td>Histoplasma capsulatum infections</td>
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<td>Varicella zoster virus (VZV) disease</td>
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<tr>
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<td>Isospora belli infections</td>
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<tr>
<td>Chagas disease (American trypanosomiasis)</td>
<td>086.0-086.2</td>
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</tbody>
</table>

*ICD = International Classification of Diseases, Ninth Revision, Clinical Modification*
Proton-Pump Inhibitor Utilization Associated With the Change to Nonpreferred Formulary Status for Esomeprazole in the TRICARE Formulary

Andrea Linton, MS; Thomas Bacon, PharmD, MS; and Michael Peterson, DVM, DrPH

ABSTRACT

BACKGROUND: The Department of Defense (DoD) placed the proton-pump inhibitor (PPI) esomeprazole in the third copayment tier on the TRICARE formulary on July 17, 2005. The change to nonpreferred formulary status for esomeprazole included a $13 copayment increase (from $9.00 to $22.00) for either a 30-day supply purchased from a community pharmacy or a 90-day supply purchased from the mail-order pharmacy and a $0 copayment if obtained from a military pharmacy but with a prior authorization (PA) requirement. The change to nonpreferred formulary status was designed to encourage the use of PPIs other than esomeprazole and to increase the use of the mail-order pharmacy for esomeprazole purchases.

OBJECTIVE: To quantify changes in (a) the TRICARE beneficiary utilization of esomeprazole relative to other PPIs and (b) the pharmacy settings used for filling esomeprazole prescriptions following implementation of a copayment increase and nonpreferred formulary status for esomeprazole.

METHODS: A census of outpatient pharmacy fill records for prescription acid-reducing medications (PPIs, histamine-2 blockers, misoprostol, and sucralfate) obtained by beneficiaries aged 18 years or older from January 1, 2005, through December 31, 2006, was examined. Interrupted time series regression analyses without a control group were used to compare the utilization of esomeprazole relative to other PPIs, as well as the pharmacy setting used to obtain esomeprazole, in the months before and after the formulary change. The rates of continued esomeprazole use, switching to other prescription PPIs (lansoprazole, omeprazole, pantoprazole, and rabeprazole), switching to non-PPI prescription acid-reducing drugs, and discontinued prescription acid-reducing medication use among existing esomeprazole users (i.e., beneficiaries who obtained esomeprazole as the last PPI fill before the formulary change) were calculated overall and for each pharmacy setting used prior to the formulary change.

RESULTS: Over the 24-month study period from January 1, 2005, through December 31, 2006, the total numbers of PPI fills and PPI users increased by 8.5% and 9.0%, respectively, and the number of esomeprazole users decreased by 4.6%. Of esomeprazole users, the percentages of individuals obtaining esomeprazole from military pharmacies and community pharmacies, respectively, decreased from 1.7% to 1.1% and from 89.7% to 81.7%, while the percentage of individuals obtaining esomeprazole from the mail-order pharmacy increased from 8.8% to 17.6%. Time series analyses yielded a positive, statistically significant growth in esomeprazole fills (β1 = 0.114; P = 0.012) during the 6-month pre-intervention period (January through June 2005) and a significant reduction in August 2005 (β2 = 0.050; P < 0.001), the month immediately following the formulary change. During the 17-month post-intervention period (August 2005 through December 2006), no statistically significant change in trend for esomeprazole fills (β3 = 0.026; P = 0.534) was observed, although a small increase in the raw number of esomeprazole fills was noted. Among the 117,801 existing esomeprazole users, 86,386 (73.3%) continued using esomeprazole, 17,676 (15.0%) switched to other prescription PPIs, 679 (0.6%) used only non-PPI prescription therapy, and 13,060 (11.1%) discontinued all prescription acid-reducing pharmacotherapy after the formulary change. Significantly higher PPI switching and acid-reducing therapy discontinuation rates were observed among men aged 18-44 years and in TRICARE enrollees relative to women, those over 45 years of age, and those who used other health insurance (P < 0.001). Individuals who used military pharmacies, where a PA requirement was implemented, were more likely to change pharmacy settings to obtain esomeprazole (43.8%) than users of community pharmacies (11.9%) or the mail-order pharmacy (22.8%). Mail-order pharmacy users were less likely to discontinue acid-reducing pharmacotherapy (4.9%) than were community (11.9%) or military (12.9%) pharmacy users (P < 0.05).

CONCLUSIONS: After adjustment for serial correlation, the formulary change was associated with a migration of approximately 5% of all PPI fills and 25% of esomeprazole fills to the preferred PPIs in the first post-intervention month. Over the 17-month post-intervention period, the trend toward increased esomeprazole use was slowed and use of the mail-order pharmacy for esomeprazole fills nearly doubled. Our observed PPI switch rate of 15.0% resembled the rate observed for another insured population that experienced a similar formulary restructuring, but was substantially lower than the rates reported for more sizeable formulary changes. Thus, the present study’s copayment differentials for third-tier medications ($19 compared with tier 1 and $13 compared with tier 2 copayments) may be less than the threshold amount required to optimize switching to preferred PPIs.

What is already known about this subject

- Current research suggests that there are no significant differences with respect to safety and efficacy among the currently available PPI formulations. While interventions to motivate the use of preferred PPIs, such as 3-tier copayment plans, therapeutic maximum allowable cost programs, and coverage for over-the-counter PPIs, have generally resulted in cost-savings for health plans, variable rates of formulary compliance and therapy discontinuation have been reported.

- A 36% PPI switch rate and a 16% acid-reducing therapy discontinuation rate were reported among publicly insured enrollees aged 66 years or older in the 12 months following a formulary change that reduced the number of covered PPIs from 4 to 1 and imposed a requirement for treatment failure with a histamine-2 blocker.

- Greater use of preferred maintenance medications in other therapeutic classes has been observed among insured populations transitioned from 2-tier to 3-tier formularies, but patients with gastroesophageal reflux disease have been reported to be less responsive to formulary changes than those with other chronic diseases.
The increasing reliance on pharmacotherapy for the management of chronic disease has significantly increased the pharmaceutical component of overall health care spending in the United States each year for more than a decade. In an effort to contain these rising costs, strategies to increase patient cost-sharing have evolved to promote the use of medications believed to be more cost-effective for the health plan. Foremost among them are multi-tiered formularies, which offer lower patient cost-shares for first-tier (generic) or second-tier (preferred brand) medications relative to nonpreferred medications placed in higher tiers. Patient response to increased cost-sharing has been the focus of numerous studies that often present inconsistent conclusions. Quasi-experimental studies of insured populations transitioned to a multi-tier formulary generally reported modest cost savings for the health plan and no adverse effect on patient compliance with critical medications, but cross-sectional studies have reported significantly greater utilization changes with increased patient cost-shares and the suggestion of an increased risk of negative patient outcomes.

Since the first proton-pump inhibitor (PPI), omeprazole, was launched in 1989, PPIs have demonstrated superior acid suppression relative to histamine-2 blockers and have been incorporated into the treatment guidelines for acid-related disorders including gastroesophageal reflux disease (GERD), *Helicobacter pylori*-negative peptic ulcer disease, and nonsteroidal anti-inflammatory drug-induced gastropathy. As new PPIs were introduced into the market, this class has grown into one of the top-selling medication classes in both total sales and market share. As a result, the PPI class has been a frequent target for patient cost-share increases as health plans have imposed incentive-based formularies, prior authorization (PA), and other utilization management techniques to encourage use of (a) preferred medications within the PPI class or (b) non-PPI acid-reducing medications to manage acid-related conditions.

While implementation of these measures has generally resulted in cost savings for health plans, variable rates of formulary compliance and therapy discontinuation have been reported. Huskamp et al. compared PPI utilization changes following the implementation of 2 different 3-tier copayment structures. In a plan that switched from a 2-tier ($6/$12 [generic/brand]) to a 3-tier ($6/$12/$24 [generic/preferred brand/nonpreferred brand]) formulary, users of nonpreferred PPIs, who experienced a copayment change from $12 to $24, were more likely to switch to a preferred product than were those whose copayment remained at $12 throughout the study (17.6% vs. 2.1%, respectively; P < 0.001), but were no more likely to discontinue therapy (18%-19% in both groups; P = 0.79). However, nonpreferred PPI users who experienced a $23 copayment change from $7 (single tier) to $30 (3-tier: $8/$15/$30) were more likely both to discontinue PPI treatment (32.0% vs. 18.9%, respectively; P < 0.001) and to switch to a preferred PPI (35.1% vs. 1.5%, respectively; P < 0.001). Huskamp et al. observed similar findings for users of angiotensin-converting enzyme (ACE) inhibitors and statins. Schneeweiss et al. reported a 36% switch rate and a 16% acid-reducing therapy discontinuation rate among publicly insured enrollees aged 66 years or older in the 12 months following a more restrictive formulary change from 4 to only 1 covered PPI and a histamine-2 receptor antagonist treatment failure requirement. Delate et al. reported a 92% decrease in the rate of PPI claims among Medicaid recipients in the month directly following the implementation of a PA requirement and an overall acid-reducing therapy discontinuation rate of approximately 22%.

Although the generalizability of these findings is limited by broad differences in study populations and methodologies (only one of these studies used comparison groups, while the others used time series analyses with no comparison groups), the addition of a tier or restriction to a health plan’s formulary has generally been associated with increased utilization of preferred medications in many maintenance medication classes. PPI users and patients with GERD, however, have been reported to be less responsive to formulary changes than patients diagnosed with other common chronic conditions.

Like many health plans, the Department of Defense (DoD) health plan, TRICARE, implemented formulary changes within the class of acid-reducing medications as part of an effort to

**What this study adds**

- In the first calendar month following an increase in the copayment for esomeprazole from $9 to $22 for a 30-day supply purchased from a community pharmacy or a 90-day supply purchased from the mail-order pharmacy, the percentage of PPI fills attributable to esomeprazole decreased approximately 25% and, in the 17 months following the change, use of the mail-order pharmacy doubled among esomeprazole users.

- Among the 117,801 users of esomeprazole when the formulary change was implemented, 73.3% continued using esomeprazole, 15.0% switched to a preferred PPI, 0.6% switched to non-PPI prescription medication, and 11.1% discontinued all prescription acid-reducing pharmacotherapy.

- Esomeprazole users who were enrolled in a TRICARE managed care health plan were more likely than those who used TRICARE only to obtain prescription drugs to switch to preferred PPIs (19.1% vs. 13.7%, respectively), to discontinue acid-reducing pharmacotherapy (14.7% vs. 9.9%, respectively), and to switch to a different pharmacy setting for esomeprazole fills (15.8% vs. 11.8%, respectively; all comparisons P < 0.05).

- The relatively low rates of PPI switching (15.0%) and discontinuation of prescription acid-reducing medication (11.1%) suggest that the copayment differential ($13 vs. other brand PPIs, $19 vs. generic omeprazole) was below the threshold amount needed to promote switching to preferred medications.

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contain the rising cost of its prescription drug benefit. Initially, the TRICARE formulary used a 2-tier copayment structure to encourage use of generic over brand medications. The formulary also included financial incentives, such as reduced or $0 copayments, to promote the use of military pharmacies and the TRICARE mail-order pharmacy over community pharmacies. The DoD purchases medications under a federally mandated pricing structure that allows it to stock medications at its military pharmacies and at the mail-order pharmacy at a lower cost than the reimbursements paid to community pharmacies used by TRICARE beneficiaries.

In 2005, a third copayment tier was established, and esomeprazole (Nexium) became one of the first medications to be placed in the third (nonformulary) copayment tier. The formulary change was made by consensus vote of the DoD Pharmacy and Therapeutics Committee, following review of meta-analyses that identified no significant differences with respect to safety and efficacy among the available PPI formulations. A cost-minimization analysis undertaken to rank PPIs from most to least cost-effective (based on weighted average cost per day of treatment) found esomeprazole to be the least cost-effective PPI on the formulary. The formulary change was announced on May 31, 2005, and implemented on July 17, 2005. At the time of the formulary change, the TRICARE Web site was the main method by which drug benefit changes were communicated to beneficiaries outside of the dispensing environment. The primary objective of the change was to promote the use of generic omeprazole or other brand PPIs over esomeprazole. The secondary objective was to promote the use of the mail-order pharmacy over community pharmacies for esomeprazole purchases.

The copayment structure for acid-reducing medications before and after the formulary change is presented in Table 1. Prior to July 17, 2005, generic medications required a $3 copayment and formulary brand medications required a $9 copayment for a 30-day supply from a community pharmacy or a 90-day supply from the mail-order pharmacy. Medication dispensed at military pharmacies had a $0 copayment. Effective July 17, 2005, the copayments for esomeprazole (nonformulary) were raised from $9 to $22 for a 30-day supply in community pharmacies or a 90-day supply at the mail-order pharmacy, and PA was required to obtain esomeprazole from a military pharmacy at a $0 copayment. To obtain PA, the esomeprazole prescription had to be written by a military provider or civilian provider to whom the patient was referred by a military provider, and medical necessity had to be demonstrated by (a) evidence of contraindication to the formulary agent, (b) adverse effects or therapeutic failure with the formulary agent, or (c) previous response to esomeprazole in a patient for whom changing to the preferred medication presented unacceptable risk. The PA form, containing justification for esomeprazole use over each formulary alternative, had to be signed by the prescriber and faxed or mailed to the dispensing location.

Copayment amounts for the remaining PPIs (lansoprazole, omeprazole, pantoprazole, and rabeprazole) and other acid-reducing medications (cimetidine, famotidine, nizatidine, ranitidine, misoprostol, and sucralfate) were not affected by the formulary change. No other cost-sharing or coverage changes for acid-related disorders under the TRICARE benefit were made, nor were any brand, generic, or over-the-counter (OTC) PPIs introduced or removed from the market in the 24-month period during which we assessed utilization changes among the PPI class of drugs.

### Methods

The DoD maintains an enterprise-wide information system that captures patient demographic and prescription information for all prescriptions filled by beneficiaries using their TRICARE pharmacy benefit. A fill record is created in real time when the prescription is filled regardless of whether a military, community, or mail-order pharmacy is used. The fill records are forwarded to a central data repository for processing to remove transactions that have been reversed (e.g., prescriptions that were filled but never picked up) and are coded with an auto-generated, pseudo-patient identifier that enables researchers to link pharmacy and health care service records for the same person without the inclusion of any protected health information in the study datasets. This data repository was the source of the data used in this study.

A census of outpatient pharmacy fill records for prescription acid-reducing medications (identified by First DataBank generic code number) obtained by beneficiaries aged 18 years...
The raw numbers of PPI fills and beneficiaries filling prescriptions for PPIs were calculated for each study month by PPI drug and type of pharmacy used, and the percentage of change over the 24-month study period was calculated. Interrupted time series regression analyses as described by Wagner et al. were used to compare the utilization of esomeprazole relative to other PPIs as well as the types of pharmacies used to obtain esomeprazole before and after the formulary change. The 24-month study period was subdivided into pre-intervention months (January 1, 2005, through June 30, 2005) and post-intervention months (August 1, 2005, through December 31, 2006). Because the formulary change occurred on July 17th, July could not appropriately be classified as either a pre-intervention or a post-intervention month and was thus excluded from the time series analysis. Claims from July 2005 were included in calculations of medication discontinuation and switch rates.

To assess the change in utilization of esomeprazole relative to other PPIs, the numbers of esomeprazole fills, generic omeprazole fills, and other branded PPI fills (lansoprazole, brand omeprazole, pantoprazole, and rabeprazole) were plotted as a percentage of total PPI fills by month. To assess the changes in the pharmacy setting used, the percentages of users who obtained esomeprazole from each pharmacy setting were plotted by month. Regression models were used to estimate the level and slope of each pre-intervention and post-intervention period for each fill type and pharmacy setting:

\[ Y_t = \alpha + \beta_1 \times \text{time} + \beta_2 \times \text{intervention} + \beta_3 \times \text{time after intervention} + \epsilon_t \]

where \(Y_0=\)level at month=0 (intercept); \(\beta_1=\)pre-intervention slope (change in the mean number of fills or users each month from January 2005 through June 2005); \(\beta_2=\)change in level in the month following the intervention (change in the mean monthly number of fills or users in August 2005 relative to January 2005 through June 2005); \(\beta_3=\)change in slope following the intervention (change in the trend in the mean number of fills or users each month from August 2005 through December 2006 relative to January 2005 through June 005); and \(\epsilon=\)error term.

An initial plot of the error terms, \(\epsilon_t\), over time indicated the presence of positive autocorrelation between adjacent months. Autocorrelation violates the assumptions of ordinary least-squares regression analysis and has been shown to cause underestimation of error terms and overestimation of significance of effects. Thus, we used a maximum-likelihood autoregression analysis, a technique commonly applied in time series studies. Maximum-likelihood autoregression analysis produces estimates that are more likely than those derived from ordinary
least-squares regression analysis to represent the true relationship between variables because correlated errors between adjacent months are considered in the calculation. Significance testing was 2-sided at the 95% confidence level.

For beneficiaries who obtained esomeprazole as the last PPI fill before the effective date of the formulary change, the rates of 4 outcomes were calculated: (a) continued esomeprazole use (a prescription fill for esomeprazole on or after July 17, 2005); (b) switch to another prescription PPI, including generic omeprazole; (c) switch to a non-PPI prescription acid-reducing therapy; and (d) discontinued prescription acid-reducing medication use (no prescription fills for acid-reducing medications on or after July 17, 2005). Switching and discontinuation rates were calculated by comparing esomeprazole and other prescription acid-reducing medication utilization before and after the formulary date. Outcomes were calculated by beneficiary characteristics and for each pharmacy setting used prior to the formulary change, and between-group differences were assessed for statistical significance using the Pearson chi-square test. Because long-term PPI therapy may not be appropriate for many patients, it is likely that some patients completed their esomeprazole treatment near the time of the formulary change. Therefore, we calculated rates of prescription PPI switching and therapy discontinuation following the formulary change among users of other (preferred) PPIs for comparison purposes.

All analyses focused on changes in beneficiary utilization rather than health plan expenditures both before and after the formulary change. Analysis and reporting of TRICARE drug expenditures are complicated by variability among the 3 pharmacy settings in the net acquisition cost of individual medications and by regionally or locally negotiated contracts with pharmaceutical manufacturers that prohibit disclosure of price information. All data manipulations and analyses were performed using SPSS (SPSS Inc., Chicago, IL), Base 10.0. This study was reviewed by the TRICARE Management Activity Exempt Determination Officer on February 28, 2007, and was found to be exempt under 32 CFR 219.101(b)(4).

### Results

The number and percentage of TRICARE beneficiaries who filled 1 or more prescriptions for an acid-reducing medication, PPI, or esomeprazole at any time during the study period are presented in Table 2 by gender, age group (at first fill), and enrollment status. Beneficiaries were categorized as "enrolled" if they were enrolled in a TRICARE managed care option similar to a health maintenance organization in the civilian health care sector. Enrollees are required to obtain all of their health care services within the TRICARE network of military and civilian providers. Enrollees consist primarily of active-duty service members and their families, but retired service members and their dependents may also enroll. Beneficiaries categorized as users of other health insurance programs consist of retired military service members,

### TABLE 3

<table>
<thead>
<tr>
<th>Raw Number and Distribution of PPI Fills by Type, Number of Beneficiaries, and Pharmacy Setting During Key Months</th>
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<tbody>
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<td><strong>Total number of PPI fills</strong></td>
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<td><strong>January 2005</strong></td>
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<td>318,467</td>
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<tr>
<td><strong>PPI fills by PPI type, %</strong></td>
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<td><strong>Esomeprazole</strong></td>
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<td><strong>Generic omeprazole</strong></td>
</tr>
<tr>
<td><strong>Other brand PPI</strong></td>
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<td><strong>PPI fills by pharmacy type, %</strong></td>
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<td><strong>Community pharmacy</strong></td>
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<tr>
<td><strong>Mail-order pharmacy</strong></td>
</tr>
<tr>
<td><strong>Total number of beneficiaries</strong></td>
</tr>
<tr>
<td><strong>Filled PPI prescription</strong></td>
</tr>
<tr>
<td><strong>Military pharmacy</strong></td>
</tr>
<tr>
<td><strong>Community pharmacy</strong></td>
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<tr>
<td><strong>Mail-order pharmacy</strong></td>
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<tr>
<td><strong>Filled esomeprazole prescription</strong></td>
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<tr>
<td><strong>Military pharmacy</strong></td>
</tr>
<tr>
<td><strong>Community pharmacy</strong></td>
</tr>
<tr>
<td><strong>Mail-order pharmacy</strong></td>
</tr>
</tbody>
</table>

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*(The formulary change became effective on July 17, 2005.)

*(Percent change = (change in quantity from January 2005 to December 2006)/original quantity in January 2005)*100.

*(Percentages do not add to 100 due to rounding.)*

*(Esomeprazole users who used more than 1 pharmacy setting in a given month to obtain esomeprazole are counted in multiple rows.)*

PPI = proton-pump inhibitor.
their dependents, and those who use their TRICARE pharmacy benefit to obtain prescription medications but use private insurance or Medicare as the primary payer for their health care services.

Compared with acid-reducing medication users overall, esomeprazole users were disproportionately women (64.5% vs. 57.1%), aged 65 years or older (50.7% vs. 40.2%), and more likely to use other health insurance to obtain health care (74.6% vs. 55.1%). The mean [SD] age of esomeprazole users enrolled in other health insurance programs was significantly higher (67.0 [12.8] years) than that of TRICARE-enrolled beneficiaries (49.7 [13.5] years; P<0.001).

The raw number and distribution of PPI fills by PPI type and pharmacy type, the number of beneficiaries filling prescriptions for PPIs and esomeprazole, and the distribution of beneficiaries by pharmacy type for esomeprazole fills for key months throughout the study period are presented in Table 3. Over the entire study period from January 2005 through December 2006, the raw number of PPI fills increased by 8.5%. The percentage of esomeprazole fills as a proportion of PPI fills decreased from 19.4% to 17.0%. As a proportion of all PPI fills, other brand PPI fills decreased from 71.4% to 66.2% and generic omeprazole fills increased from 9.3% to 16.8%. The proportion of PPI prescriptions filled at military pharmacies decreased from 37.4% to 31.4%, while the proportion of PPI fills at community pharmacies and the mail-order pharmacy increased from 52.5% to 56.0% and from 10.1% to 12.6%, respectively.

Similar to the trend observed for the number of PPI fills, the number of beneficiaries filling prescriptions for PPIs increased by 9.0% over the study period; however, the number of esomeprazole users decreased by 4.6%. The percentage of esomeprazole users obtaining esomeprazole from community pharmacies and military pharmacies decreased from 89.7% to 81.7% and from 1.7% to 1.1% respectively, while use of the mail-order pharmacy to obtain esomeprazole increased from 8.8% to 17.6%. Comparing the calendar months directly before (June 2005) and after (August 2005) the formulary change, the percentage of esomeprazole fills as a proportion of PPI fills decreased from 20.0% to 15.7%, and the percentage of esomeprazole users who obtained esomeprazole from the mail-order pharmacy increased from 9.4% to 10.9%.

The percentages of total PPI fills for esomeprazole, generic omeprazole, and other brand PPIs by month are plotted in
Proton-Pump Inhibitor Utilization Associated With the Change to Nonpreferred Formulary Status for Esomeprazole in the TRICARE Formulary

Figure 1. During the pre-intervention period, positive and statistically significant slopes were observed for generic omeprazole ($\beta_1=0.140$; $P=0.030$) and esomeprazole ($\beta_1=0.114$; $P=0.012$). A negative and statistically significant slope was observed for other brand PPIs ($\beta_1=-0.244$; $P<0.001$). In August 2005, directly following the formulary change, statistically significant increases in the percentages of fills for generic omeprazole ($\beta_2=1.5$%; $P<0.001$) and other branded PPIs ($\beta_2=3.3$%; $P<0.001$) were observed, corresponding to approximately 5,000 and 11,000 fills, respectively. A statistically significant decrease in the percentage of fills for esomeprazole was observed ($\beta_2=-5.0$%; $P<0.001$), corresponding to approximately 16,700 or 25% of fills relative to June 2005. During the post-intervention period, the magnitude of the positive slope for generic omeprazole ($\beta_3=0.184$; $P=0.013$) increased significantly, and the magnitude of the negative slope for other brand PPIs ($\beta_3=-0.169$; $P=0.003$) decreased significantly. A negative but nonsignificant slope for esomeprazole ($\beta_3=-0.0265$; $P=0.534$) was observed.

The percentages of esomeprazole users who used a military pharmacy, community pharmacy, or the mail-order pharmacy to fill a prescription for esomeprazole by month are shown in Figure 2. During the pre-intervention period, nonsignificant slopes for the mail-order pharmacy ($\beta_1=0.126$; $P=0.152$) and community pharmacies ($\beta_1=-0.0673$; $P=0.457$) were observed, and a small but statistically significant negative slope was observed for military pharmacies ($\beta_1=-0.0870$; $P<0.001$). In August 2005, in the month following the formulary change, statistically significant increases in the percentage of esomeprazole users who obtained esomeprazole from a military pharmacy or the mail-order pharmacy were observed ($\beta_2=0.2$% $P=0.006$; and $\beta_2=1.9$% $P<0.001$, respectively), corresponding to approximately 100 and 950 users, respectively. A statistically significant decrease in the percentage of beneficiaries who obtained esomeprazole from a community pharmacy was observed ($\beta_2=-1.8$% $P<0.001$), corresponding to approximately 900 users.

During the post-intervention period, use of the mail-order pharmacy ($\beta_2=0.252$; $P=0.009$) accelerated, use of community pharmacies ($\beta_2=-0.292$; $P=0.005$) continued to decline, and a small but significant reversal of the pre-intervention trend in the use of military pharmacies ($\beta_2=0.068$; $P<0.001$) was observed, indicating a slowdown of the rate of decline of military pharmacy use that was observed in the pre-intervention period. Across the entire class of prescription PPIs, use of military pharmacies (military pharmacy users as a proportion of all PPI users) decreased ($\beta=-0.189$; $P<0.001$) and use of community pharmacies and the mail-order pharmacy increased ($\beta=0.082$, $P<0.001$; and $\beta=0.107$, respectively).
A summary of utilization changes among existing esomeprazole users, that is, study subjects whose last PPI fill prior to the formulary change was for esomeprazole, is presented in Table 4. Among the total of 117,801 existing esomeprazole users, 86,386 (73.3%) continued to obtain esomeprazole, 17,676 (15.0%) switched to other prescription PPIs, 679 (0.6%) switched to non-PPI prescription acid-reducing medications, and 13,060 (11.1%) discontinued all prescription acid-reducing pharmacotherapy (i.e., did not fill any prescriptions for acid-reducing medications) after July 17, 2005. Among those who continued esomeprazole use, 10,942 (12.7%) changed the pharmacy setting(s) through which they obtained esomeprazole.

Men were significantly more likely than women to switch to a preferred PPI (18.0% and 13.3%, respectively; P<0.001), and individuals aged 18-44 years were more likely to discontinue all acid-reducing pharmacotherapy (25.2%) than were those aged 45-64 years (9.5%) or those aged 65 years or older (9.0%; P<0.001). Among age groups, the rates of switching to a preferred PPI revealed a bimodal pattern. Switch rates were higher for the youngest (18-44 years) and oldest (65 years and older) age groups (18.4% and 15.2%, respectively) than for the middle age group (45-64 years, 13.6%; P<0.001). TRICARE enrollees were significantly more likely than those using other health insurance plans to switch to a preferred PPI (19.1% and 13.7%, respectively; P<0.001), to switch to non-PPI prescription medications (0.8% and 0.5%, respectively; P<0.001), to discontinue all prescription acid-reducing therapy (14.7% and 9.9%, respectively; P<0.001), or to change pharmacy settings for obtaining esomeprazole (15.8% and 11.8%, respectively; P<0.001). Other smaller but statistically significant utilization changes were observed among all gender and age subgroups (P<0.05).

Because community pharmacies were used by 101,166 (85.9%) of the 117,801 existing users to obtain their esomeprazole fills, utilization patterns were determined primarily by these users,
but statistically significant differences across pharmacy settings were observed for all rates examined (P<0.05). The esomeprazole continuation rate was highest for the mail-order pharmacy users (80.9%) relative to military or community pharmacy users (70.4% and 72.4%, respectively; P<0.001). Among those beneficiaries who continued to obtain esomeprazole after the formulary change, military pharmacy users were most likely to switch pharmacy settings (43.8%), followed by the mail-order pharmacy users (22.8%) and community pharmacy users (11.9%; P<0.001). The prescription PPI switch rate and acid-reducing medication discontinuation rate were highest among military pharmacy users (15.7% and 12.9%, respectively) and lowest among the mail-order pharmacy users (13.9% and 4.9%, respectively). Among those using other prescription PPIs prior to July 17, 2005, switching and acid-reducing pharmacotherapy discontinuation rates during the 17-month follow-up period were comparable with those observed for esomeprazole: generic omeprazole (5.1% and 12.7% for switching and discontinuation, respectively), brand omeprazole (14.5% and 11.0%, respectively), lansoprazole (7.8% and 16.2%, respectively), pantoprazole (5.5% and 16.5%, respectively), and rabeprazole (4.0% and 14.2%, respectively; data not shown).

Discussion

This study examined changes in PPI utilization associated with the placement of esomeprazole in the third tier of the TRICARE formulary. The DoD’s primary objective was to promote the use of generic omeprazole or the other 4 brand PPIs over esomeprazole. Our time series analyses indicated that, in the 6 months prior to the formulary change, esomeprazole fills represented approximately 20% of the PPI fills with a trend of gradual, positive growth. Esomeprazole fills dropped to less than 16% of total PPI fills in the calendar month following its removal from the formulary. A roughly commensurate 1.5% increase in fills for generic omeprazole and 3.3% increase for other brand PPIs from June 2005 to August 2005 suggests that the DoD successfully migrated approximately 5% of the PPI fills, 25% of the esomeprazole fills, and 15% of existing esomeprazole users to the preferred PPIs and slowed the trend toward increased esomeprazole market share over the 17-month post-intervention period.

The DoD’s secondary objective was to promote greater use of the mail-order pharmacy for esomeprazole fills. A small but significant jump in mail-order pharmacy use was observed in the month immediately following the formulary change, and a significant trend toward increased mail-order pharmacy use to obtain esomeprazole was observed over the study period. The roughly 2% increase in the mail-order pharmacy usage relative to community pharmacies during the first post-intervention month was likely a combination of existing esomeprazole users switching to the mail-order pharmacy, as well as higher rates of PPI switching or therapy discontinuation among community pharmacy users relative to mail-order pharmacy users. The formulary change may have motivated some new users (i.e., those who did not fill any prescriptions for esomeprazole prior to the formulary change) to choose the mail-order pharmacy over community pharmacies for their esomeprazole fills, but the degree to which the formulary change impacted the purchase decision cannot be validated using administrative data alone. Although a positive trend toward increased mail-order pharmacy use was observed for esomeprazole and PPIs in general, use prevalence was substantially lower for the mail-order pharmacy—less than 18% for esomeprazole and less than 13% for all PPIs—than for community pharmacies during all months in the study period. Other health plans have used similar financial incentives (i.e., offering a $0 copayment of medication for the same price as a 30-day supply purchased from a community pharmacy) to promote use of mail order pharmacies.14,15 but limited research has been done to assess the extent to which the lower out-of-pocket cost motivates a patient to voluntarily use a mail-order option over a community pharmacy.16

Fewer than 2% of esomeprazole users obtained the medication from a military pharmacy during any study month, but significant utilization changes were observed among users of this setting. Following the intervention, we observed a nearly constant use of military pharmacies for esomeprazole fills, which is likely a reflection of the baseline of beneficiaries who pursued and obtained PA to fill their esomeprazole prescriptions with a $0 copayment. While the military pharmacy setting is unique to the TRICARE pharmacy benefit, utilization changes associated with the use of military pharmacies may arguably be compared with those from other low or $0 copayment plans in which a PA requirement was imposed. Delate et al. reported that approximately 50% of Medicaid enrollees who received a prescription for a PPI did not pursue PA following implementation of a PA requirement for all PPI medications.7 In the present study, approximately 44% of existing esomeprazole users who obtained the drug from a military pharmacy before the formulary change and who chose to continue esomeprazole use elected to obtain esomeprazole elsewhere at greater expense to themselves, presumably because they did not pursue or meet the esomeprazole PA requirement. Clearly, a PA requirement that applies to all PPIs is more restrictive than one that applies to esomeprazole exclusively, and the degree to which DoD enrollees can be compared with Medicaid recipients is questionable, but the magnitude and direction of the beneficiary response to the PA requirements appears comparable.

Consistent with other studies, we found that esomeprazole users were disproportionately female and older compared with users of PPIs overall17,18 and that these subgroups were generally less responsive to the formulary change. We also found that those who were TRICARE enrollees displayed a greater sensitivity to the formulary change in terms of significantly higher PPI switching and therapy discontinuation rates. These beneficiaries receive their care from TRICARE providers who are expected to assimilate formulary changes into their prescribing practice,
whereas non-TRICARE providers are unlikely to be aware of
TRICARE formulary changes. The bimodal PPI switching pattern
we observed among different age groups was reported by
Nair et al., who found formulary compliance rates to be higher in
the 18-to-25-year and 65-year-and-older age groups than in the
26-to-64-year age group. Our observation may be attributable
to the combined influence of TRICARE enrollment, which is
more common among those aged 18-44 years, and the prevalence
of multiple comorbidities, which are likely to be highest among
those aged 65 years or older. A prior study that examined the
association between PPI switching and variables hypothesized
to influence switching for well-advertised products reported lower
PPI switch rates among subjects without significant comorbidities
than among those with multiple comorbid conditions.

Underlying all formulary and drug policy changes is the poten-
tial risk of motivating a premature discontinuation of therapy. We
found no evidence that the TRICARE formulary change was asso-
ciated with an increased prescription acid-reducing medication
discontinuation rate among esomeprazole users (11.1%) relative
to users of the preferred PPIs (ranging from 11.0% to 16.5%) on
the TRICARE formulary. For esomeprazole users, our observed
therapy discontinuation rate was also lower than the stable 16%
background PPI discontinuation rate among PPI users reported
among publicly insured seniors by Schneeweiss et al.

Huskamp et al. evaluated utilization changes following the intro-
duction of a 3-tier plan restructuring strategy similar to that
imposed on TRICARE beneficiaries. Among nonpreferred PPI
users who experienced a $12 copayment increase (from $12 to
$24), the change was associated with a higher PPI switch rate
(17.6%) but was not significantly associated with the therapy
discontinuation rate, which was 18%-19% in both the inter-
vention and comparison groups. Our 15.0% switch rate from
esomeprazole to preferred PPIs was lower than the 36.4% switch
rate reported by Schneeweiss or the 23%-24% rate among com-
mercially insured populations by Hall et al. under the normal
course of treatment, but it was higher than the 2% PPI switch
rates observed among Huskamp’s comparison groups whose
2-tier plans ($6-$7 copayment differentials) underwent no for-
mulary change. Our switch rates among existing users of other
preferred PPIs on the TRICARE formulary ranged from 4.0% to
7.8% with the exception of brand omeprazole, with a switch rate
of 14.5%, similar to that observed for esomeprazole.

Although the formulary changes, target populations, and study
methodologies reported in the literature varied considerably, their
findings when combined with our results reinforce the notion that
copayment increases in the $12-$15 range can promote switching
to a preferred medication without significant increases in therapy
discontinuation. Our relatively modest switch rates to preferred
PPIs suggest that financial incentives greater than the $13 copay-
ment difference between second- and third-tier medications are
needed to achieve the formulary compliance observed among
other populations. However, a greater switch rate to preferred
medications may be achieved when applying a similar copayment
restructuring strategy to other therapeutic classes. Huskamp et al.
reported substantially higher switch rates and lower therapy
discontinuation rates among ACE inhibitor and statin users rela-
tive to PPI users, and other studies have found variable subject
responses to the same copayment restructuring for medications
in different therapeutic classes.

Like other managed care payers, the DoD faces the challenge
of communicating benefit changes to prescribers and bene-
ficiaries to effectively promote formulary compliance. During
the study period, formulary change notices published on the
TRICARE Web site were the primary means of communicating
benefit changes, and it is not clear how frequently the Web site
was used for obtaining formulary information. It is unlikely that
the formulary change affected prescribing practices beyond the
military and DoD-contracted hospitals and clinics where provid-
ers are expected to assimilate TRICARE formulary changes into
their prescribing practice. Non-TRICARE providers, who treated
nearly 75% of the esomeprazole users in our study, were probably
unfamiliar with the TRICARE drug benefit or the formulary status
of the medications they prescribed. Many beneficiaries may
not have even realized that they were using a third-tier medica-
tion unless they queried their pharmacist for other options.
Since the time of the present study, the DoD has recognized the
importance of advertising benefit changes and has initiated direct
mailings to notify beneficiaries when the formulary status of their
medications is changing.

A study that examined the impact of a letter-based notification
program in a commercially insured group found that beneficiary
mailings improved formulary compliance for many medications.
One of the highest switch rates to a formulary alternative was
associated with generic omeprazole, a finding that the authors
potentially attributed to direct-to-consumer (DTC) advertising
(for Prilosec) and consumer loyalty for the OTC product with
the same name. Our study was conducted concurrently with
an extensive marketing campaign, in which more spending was
dedicated to DTC advertising for esomeprazole than was spent
for any other prescription medication in 2005. Exposure to
DTC advertising has been associated with increased prescribing
and utilization of the advertised medication, as well as higher
rates of switching to the advertised product. The $22 copay-
ment for a 30-day supply of esomeprazole may be inadequate to
motivate beneficiaries to investigate less-familiar alternatives,
even if they can save up to $19 by doing so. These findings sug-
gest that formulary changes involving less well-advertised brands
may achieve a higher rate of conversion to preferred medication
than was observed in this study.
Limitations

Foremost among the study limitations is the absence of a comparison group. Although a comparison group would have strengthened the validity of our findings, the unique nature of the TRICARE benefit complicated the identification of a suitable comparison group. Ideally, esomeprazole utilization among military pharmacy users should be compared against that of a managed care population with low or $0 copayment transitioning to a PA requirement, while utilization among users of community pharmacies and the mail-order pharmacy is probably best compared with that of other large insured populations transitioning from a 2-tier to a 3-tier formulary. A suitable comparison group would have assisted in controlling for other potentially confounding effects of intensive DTC advertising, direct-to-physician promotions, changes in Medicare or other health plans used by numerous study subjects, and patient-specific or other factors beyond the control of the TRICARE planners. However, the strengths of this study include the uniform prescription drug benefit and the absence of other changes—such as modifications to the TRICARE benefit design or introduction of new PPI drugs—that could have affected the treatment of acid-related disorders among the study population during the study period. Despite the absence of a suitable comparison group, the direction and magnitude of our utilization changes suggest that TRICARE beneficiary response is comparable with that of other populations when exposed to similar formulary changes.

Second, although we found no evidence of increased pharmacotherapy discontinuation rates, we did not examine clinical data to assess whether patients who discontinued or switched PPI therapy had any related increase in other health care service utilization. However, previous research reported no impact on the utilization of medical services in a 12- or 30-month period following implementation of a 3-tier formulary and copayment increase. Additionally, the extent to which the formulary change was associated with changes in patients’ adherence to pre-intervention dosing levels, symptoms, or overall quality of life cannot be assessed using our methodology.

Third, costs for dataset extraction and analyses limited our study period to 24 months. The use of a 6-month pre-intervention period likely limited our statistical power to detect significant differences in pre-intervention and post-intervention trends but had little effect on our calculated rates of PPI switching and medication discontinuation. These rates could have been underestimated, however, if beneficiaries elected to switch medications or pharmacy settings in June 2005 in anticipation of the upcoming formulary change. Anticipatory stockpiling during June 2005 may also have resulted in a biased estimation of the immediate effects of the formulary change if beneficiaries obtained esomeprazole fills early to avoid the higher copayment later. Post-intervention trends and the nature of acid-related conditions do not suggest the presence of seasonal effects.

Finally, the absence of data about nonprescription medication usage may have inflated our acid-reducing therapy discontinuation rates if some users elected to switch to nonprescription medications only. This behavior would more likely be seen among users of military pharmacies where many OTC medications, including omeprazole OTC, are available to DoD beneficiaries at no cost. The TRICARE benefit, however, provides no coverage for OTC medications at community pharmacies, where the beneficiaries’ cost to purchase OTC medications would exceed a PPI prescription copayment if the OTC medication was used daily. Prior studies reported significant switch rates from prescription PPIs to omeprazole OTC when the OTC medication was available at a lower member cost-share. No such financial incentive is available under TRICARE; thus, it is difficult to assess the extent to which omeprazole OTC utilization may have impacted our findings.

Conclusions

Moving esomeprazole to the third tier of the TRICARE formulary and changing the copayment from $9 to $22 for a 30-day supply obtained at a community pharmacy were associated with a 25% reduction in the number of esomeprazole fills in the calendar month following the change, slowdown of the trend toward increased esomeprazole use, and acceleration in the use of the mail-order pharmacy for esomeprazole fills in the post-intervention period. The significantly lower sensitivity to the formulary change that was seen among individuals who used TRICARE only for their prescription fills but obtained their health care through other plans highlights the challenge of improving formulary compliance without prescriber involvement, particularly when the nonpreferred medication is highly advertised. In the case of the PPI class or other medication classes in which multiple therapeutic equivalents are available at different costs, health plans attempting to transition users to preferred medications should consider larger third-tier copayments; more robust interventions, such as a PA requirement for third-tier medications; step therapy (if applicable); mandatory use of a mail-order pharmacy for third-tier medications; or complete removal of the nonpreferred medication from coverage.
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DISCLAIMER

The thoughts and opinions expressed in this paper are those of the authors and do not necessarily represent the official policy or position of the United States Department of Defense.

REFERENCES


Case Study of the Effects of Office-Based Generic Drug Sampling on Antibiotic Drug Costs and First-Line Antibiotic Prescribing Ratios

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ABSTRACT

BACKGROUND: Health plans and members benefit from the substitution of lower-cost drugs that achieve the same clinical outcomes as higher-cost drugs. Previous research suggests that generic sampling programs produce drug cost savings overall, but the effects attributable to acute therapies are unknown. Encouraging physicians to prescribe less expensive, first-line antibiotics may help reduce direct drug costs associated with prescribing potentially unnecessary, and more expensive, second-line agents.

OBJECTIVES: To determine the effects of an automated, office-based generic drug sampling kiosk on (a) prescribing of first-line oral antibiotic agents as a ratio of total antibiotic prescribing and (b) average antibiotic drug cost per claim.

METHODS: This managed care organization of 2.3 million members with pharmacy benefits collaborated with a vendor that developed an automated generic drug kiosk that allows for the dispensing of samples of generic medications within the prescriber’s office. Among the samples contained in the kiosk were 6 generic, first-line oral antibiotics, representing 6 unique drug-strength options. Drug costs were defined as the ingredient cost of the drug claim, which includes plan cost, member cost share, and any dispensing fees or administrative program costs associated with the sampling program. In a difference-in-difference analysis, changes in outcome measures (antibiotic drug cost per claim and dispensing rates of first-line antibiotics) from 2003 (baseline year) to 2005 (post-implementation year) were compared among kiosk prescribers (n=179) and nonkiosk prescribers who were part of the same provider network (n=7,236). A cross-sectional analysis of the same outcome measures compared kiosk (n=396) and nonkiosk prescribers (n=10,267) in 2006. All statistical analyses were performed using t-tests of log-transformed data.

RESULTS: The mean cost per claim dropped by $4.14 (12.3%) from $33.56 in 2003 to $29.42 in 2005 for the kiosk prescribers and by $3.35 (8.8%) from $38.26 in 2003 to $34.91 in 2005 for nonkiosk prescribers, but the mean change from 2003 to 2005 in the difference-in-difference analysis was not statistically significant (P=0.123). The first-line antibiotic prescribing ratio declined by 2.1 absolute points from 49.1% in 2003 to 47.0% in 2005 for the kiosk prescribers and by 3.4 points from 46.0% in 2003 to 42.6% in 2005 for the nonkiosk prescribers, but the difference-in-difference analysis showed that the change was not statistically significant (P=0.901). A cross-sectional analysis of 2006 data revealed significant differences between the kiosk prescribers versus their nonkiosk network counterparts in both first-line antibiotic prescribing rates (42.0% vs. 41.4%, respectively; P=0.028) and antibiotic cost per claim ($28.44 vs. $32.40, respectively; P<0.001). While the results of the cross-sectional analysis are statistically significant, the practical significance of the results is less evident.

CONCLUSIONS: The inclusion of antibiotic samples in a generic drug sampling kiosk did not lead to significant changes in antibiotic prescribing or in lower average cost per antibiotic claim after 1 year of program participation (2005) for kiosk prescribers compared with nonkiosk prescribers. However, anecdotal evidence suggested that the program was popular among prescribers.

A cross-sectional analysis of the second year of participation (2006) found that prescribers with access to a generic sampling kiosk prescribed first-line antibiotics more often (53.4% more often than nonkiosk prescribers) and had a lower cost per antibiotic claim than their nonkiosk counterparts ($28.44 vs. $32.40, P<0.001).

Generic samples for antibiotics are unlikely to produce significant direct drug cost savings but may have intangible benefits that, when combined with dispensing generic medication samples to treat chronic conditions, contribute to a successful generic sampling program.

What is already known about this subject

• The dispensing of product samples contributes to increased utilization of the sampled product, with physician samples accounting for 75% of physician promotional expenditures by brand-name pharmaceutical manufacturers in the United States. A generic drug sampling program should influence generic drug utilization in much the same way that brand drug sampling influences brand drug utilization.
• One previously published study found a 1.2-point higher generic dispensing ratio (GDR) (55.3% vs. 54.1%) in the first year for prescribers participating in a generic drug sampling kiosk program compared with nonkiosk prescribers. In the second year, the GDR difference narrowed to 0.8 points, 59.9% vs. 59.1%. Direct drug cost savings for the program were $1,321 per kiosk prescriber in year 1 (2005) and $719 in year 2 (2006).

What this study adds

• The inclusion of antibiotic samples in a generic drug sampling kiosk did not lead to significant changes in antibiotic prescribing or in lower average cost per antibiotic claim after 1 year of program participation (2005) for kiosk prescribers compared with nonkiosk prescribers. However, anecdotal evidence suggested that the program was popular among prescribers.

Rising health care costs continue to prompt health plans, among other stakeholders, to identify and promote cost-effective health care services. There is an inherent value in the promotion of lower-cost drug therapies (e.g., generic drugs) that achieve the same outcome as a higher-cost drug.
Antibiotics represent a therapeutic category in which there is an opportunity to affect such utilization because many products are commercially available at varied costs with relatively predictable treatment outcomes.

Despite the existence of clinical guidelines that outline appropriate circumstances under which an antibiotic should be prescribed and which agent may be the agent of choice, data suggest that antibiotics are still prescribed inappropriately for a variety of diagnoses. The unnecessary prescribing of antibiotics contributes to antibiotic resistance and increased health care costs. Inappropriate antibiotic prescribing increases costs for patients as well as for payers and society. If burdened with high-cost drug regimens, some groups of patients, including those who are elderly or low-income, may forego treatment for their chronic disease states or for their infection if they are unable to afford their medication. Most first-line antibiotics are available generically and offer a significant cost savings over their branded, broader-spectrum counterparts. Hanson and colleagues have developed guidelines for prescribing low-cost antibiotics in outpatient settings that call for the use of first-line antibiotics for many common infections. Many of these proposed treatments provide therapeutic value for less than $15 per prescription to cash-paying (uninsured) patients.

Interventions that have sought to change antibiotic prescribing patterns have their roots in inpatient or institutional settings and largely focused on decreasing antimicrobial resistance. The Infectious Diseases Society of America outlines recommendations for the implementation of such interventions. These recommendations include interactive, web-based, or other prescriber education interventions; the development of practice guidelines or protocols that may assign responsibility to the prescriber; and the reduction of pharmaceutical promotion directly to prescribers. Additionally, the use of an interdisciplinary “antimicrobial team” has been suggested to be effective in monitoring antimicrobial prescribing and intervening in cases of suboptimal prescribing.

More recently, interventions that aim to manage antibiotic prescribing have been implemented and evaluated in outpatient or community settings. Examples of community-based programs that have sought to influence antibiotic prescribing habits include confidential prescriber feedback and education and clinical decision support systems based in either the prescriber office or in community pharmacies. From a payer perspective, health plans can implement multi-tier copayment designs, based around sound formulary decision making, to further promote the utilization of more cost effective therapies. In general, such an intervention can be applied to a formulary, to a targeted therapeutic category (e.g., antibiotics), or to certain types of drug products (e.g., generics).

The managed care organization (MCO) in this study is a regional Blue Cross/Blue Shield plan located in Pennsylvania that provided prescription drug coverage for 2.2 million members in 2005 and 2.3 million members in 2006. In August 2003, the MCO partnered with MedVantx, a privately held corporation that provides generic drug samples, including first-line antibiotics, directly to physician offices via an automated dispensing kiosk. Information about this managed care intervention and its effect on the overall (all drug) generic dispensing ratio (GDR) in this MCO was published previously. The previous study found a 1.2-point higher GDR (55.3% vs. 54.1%) in the first year for prescribers participating in a generic drug sampling program (kiosk prescribers) compared with nonkiosk prescribers within the plan’s physician network. In the second year, the GDR difference narrowed to 0.8 points, 59.9% versus 59.1%. Direct drug cost savings for the program were $1,321 per kiosk prescriber in year 1 (2005) and $719 in year 2 (2006).

Recognizing the need to promote and provide a simple tool that would allow prescribers to change their prescribing habits, the MCO sought to examine an existing program that could provide prescribers with generic first-line oral antibiotic samples in their offices. Antibiotic samples were initially included in the kiosk program as part of a larger effort to change the prescriber’s mindset around generic drug prescribing in general, encompassing both long-term and short-term therapies. Anecdotal evidence had suggested that physicians preferred having access to samples of antibiotics as part of the sampling program, whether because of a perception of increased patient compliance or a broader approach to generic prescribing; thus, the antibiotic samples were believed to provide an intangible benefit to the program. The antibiotic samples were specifically selected for this analysis because of uncertainty about both the financial impact of their inclusion in the program and their specific impact on antibiotic prescribing practices. The present study sought to identify the effect of the generic dispensing kiosks on the prescribing of first-line versus second-line antibiotics and whether or not changes in such practices translate into drug cost savings on a per claim basis.

Methods

Generic Sampling Program

In August 2003 the MCO partnered with the vendor to implement a program by which network prescribers would be provided with a generic drug sampling kiosk in their office. The program began as a pilot study in 10 select physician practices that were targeted due to high-volume prescribing (>5,000 prescriptions per year) and/or a below-average GDR compared with their network peers. As of November 2008, the program has more than 800 providers participating in the kiosk generic drug sampling program.

The kiosk is a free-standing unit approximately the size of a bank automated teller machine and has the ability to dispense generic samples in a 30-day supply or sufficient quantity of antibiotics for a complete treatment cycle. There are 21 unique medications from 10 different therapeutic categories, representing 36 options based on dosage strength. Specifically, the kiosk contains...
samples of 6 unique oral antibiotic medications, representing 8 unique options by dose and strength (Table 1). The cost of the drug samples is automatically billed to the MCO, and no cost is incurred by the physician practice. Further, the program provides the generic samples at no cost ($0 copayment) to the member. Samples can be dispensed to any of a kiosk prescriber’s patients. Multiple health plans participate in the MedVantx program, but each MCO pays only for those samples provided to its members.

The office-based generic dispensing kiosk was complemented by an academic detailing service that is provided by a clinical pharmacist who is a full-time employee of the MCO. Academic detailing provides the prescribers involved in the program a variety of services, including education on benefit structures, feedback on prescribing patterns, and discussions on the impact of prescribing habits on member out-of-pocket cost, compliance, and adherence. Specific to the promotion of prescribing first-line antibiotics, the academic detailing focuses on the unique concerns surrounding opportunities for therapeutic substitution and the impact of antibiotic resistance on cost and quality outcomes. The academic detailing service was provided to all physician practices participating in the generic sampling program, but also was provided for large physician practices that were not participating in the program. Approximately 40% of the MCO’s network receives academic detailing services.

Study Groups
Kiosk prescribers (intervention group) are physicians or other health care professionals with prescribing rights who operate out of network primary care (family practice or internal medicine) physician practices that have been targeted by the MCO, based upon their prescribing practices, to engage in the program. Program participation is voluntary and is coordinated at the physician practice level (i.e., all prescribers within a participating practice are considered to be kiosk prescribers). Nonkiosk prescribers (comparison group) are any other primary care (family practice or internal medicine) physicians or other health care professionals with prescribing rights who are in the MCO’s physician network. The same criteria applied for both the first (2005) and second (2006) study years.

First-Line Antibiotics
For purposes of this study, the oral antibiotic agents in the generic drug sampling kiosk were determined to represent first-line therapeutic options. This determination was made based on their inclusion in clinical practice guidelines, evidence provided in peer-reviewed publications, and recommendations in professional reference literature as first-line drugs of choice for common diagnoses seen in the community setting such as upper respiratory tract infections or uncomplicated urinary tract infections. Understanding that the antibiotic samples provided by the sampling program do not constitute all of the available first-line oral antibiotics, we developed a comprehensive list of first-line antibiotics including other agents such as first-generation cephalosporins, penicillins, first-generation macrolides, and tetracyclines at the national drug code (NDC) level, which allows for the inclusion of all strengths and dosage forms. Inclusion of antibiotic agents on this list was based upon support from peer-reviewed and reference literature. The list of second-line agents was comprised of all other oral antibiotics, including fluoroquinolones, second- and third-generation cephalosporins, amoxicillin/clavulanate, and second-generation macrolides.

Statistical Analysis
Prescribing rates and drug costs were calculated for first- and second-line antibiotics using MCO drug claims data on file. Drug cost was defined as the ingredient cost for each drug claim, which includes plan cost, member cost share, and any dispensing fees or administrative program costs associated with the sampling program. For each prescriber, drug costs per claim (total cost of drugs prescribed divided by total number of claims) and first-line antibiotic prescribing rates (number of first-line antibiotic claims divided by number of all antibiotic claims) were calculated for 2005 (post-implementation) and 2003 (baseline). Only those kiosk or nonkiosk prescribers who had claims data in both 2003

### TABLE 1 First-Line Antibiotics

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Strength</th>
<th>Dose Form</th>
<th>Package Qty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>250mg</td>
<td>Capsule</td>
<td>30</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>500mg</td>
<td>Capsule</td>
<td>30</td>
</tr>
<tr>
<td>Cephalaxin</td>
<td>250mg</td>
<td>Capsule</td>
<td>28</td>
</tr>
<tr>
<td>Cephalaxin</td>
<td>500mg</td>
<td>Capsule</td>
<td>28</td>
</tr>
<tr>
<td>Doxycycline Hyclate</td>
<td>100mg</td>
<td>Capsule</td>
<td>14</td>
</tr>
<tr>
<td>Penicillin VK</td>
<td>500mg</td>
<td>Tablet</td>
<td>40</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>250mg</td>
<td>Capsule</td>
<td>40</td>
</tr>
<tr>
<td>Sulfamethoxazole/trimethoprim</td>
<td>800mg/160mg</td>
<td>Tablet</td>
<td>20</td>
</tr>
</tbody>
</table>

Other first-line oral antibiotic medications\(^a\)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td></td>
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<tr>
<td>Ampicillin</td>
<td></td>
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<tr>
<td>Cefadroxil</td>
<td></td>
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<tr>
<td>Cefazolin</td>
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<tr>
<td>Cephalaxin</td>
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<tr>
<td>Declomycin</td>
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<tr>
<td>Demeclocycline</td>
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<tr>
<td>Dicloxacin</td>
<td></td>
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<tr>
<td>Doxycycline</td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td></td>
</tr>
<tr>
<td>Geocillin</td>
<td></td>
</tr>
<tr>
<td>Minocycline</td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td></td>
</tr>
<tr>
<td>Sulfamethoxazole/trimethoprim</td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)National Drug Code numbers for branded versions of generic first-line antibiotics were also included as first-line antibiotics.
and 2005 were included in the analysis. Each prescriber was assigned a weight based upon his or her 2005 prescribing volume (number of claims multiplied by a constant so that sample size remained unchanged by weighting); thus, each prescriber’s mathematical contribution to the study results was proportionate to his or her volume of claims. This calculation produced results equivalent to standard industry measures (e.g., aggregated total costs divided by aggregated total claims) but allowed for statistical testing. To perform a difference-in-difference analysis, 2003 outcomes were subtracted from 2005 outcomes, and the study groups (kiosk vs. nonkiosk) were compared using two-sided t-tests. Because of a substantial increase in program participation from 2005 to 2006, direct comparisons could not be made between the samples of kiosk prescribers from year 1 of the program (2005) and year 2 (2006). Therefore, an additional by-group cross-sectional comparison was conducted to assess the drug cost per claim and first-line antibiotic prescribing rates for kiosk versus nonkiosk prescribers for 2006 alone. A distinct weight was invoked for these analyses based upon 2006 claims volume per prescriber, again multiplied by a constant to keep sample size unchanged. Again, two-sided t-tests were employed.

To account for skewness, all values (first-line prescribing rates and costs per claim for all 3 study years) were log-transformed (after adding 1 to each value to account for values of zero [0] because there is no natural logarithm of 0) for statistical testing. However, because of the descriptive and exploratory nature of the study, we did not retransform the values; instead, untransformed values are shown in the tables and text for ease of reading.

Analyses were performed using SPSS version 17.0 (SPSS, Chicago, IL) using an a priori significance level of 0.05.

### Results

For kiosk prescribers (n=179), the mean first-line antibiotic prescribing rate decreased from 49.1% in 2003 to 47.0% in 2005, an absolute 2.1% decrease (median=–2.32%, SD=13.02%; Table 2). For nonkiosk prescribers (n=7,236), the first-line antibiotic prescribing rate decreased from 46.0% in 2003 to 42.6% in 2005, an absolute 3.4% decrease (median=–3.5%, SD=14.59%). The difference between kiosk and nonkiosk prescribers (testing the change in log-transformed values from 2003 to 2005) was not statistically significant (P=0.901). Mean antibiotic cost per claim decreased from $33.56 in 2003 to $29.42 in 2005 for kiosk prescribers, a $4.14 decrease (median=–$3.56, SD=$8.19). Nonkiosk network prescribers saw their mean antibiotic cost per claim decrease by $3.35 (median=–$2.84, SD=$16.77), from $38.26 in 2003 to $34.91 in 2005. The difference between kiosk and nonkiosk prescribers (again testing the change in log-transformed values from 2003 to 2005) was also not statistically significant (P=0.123).

In 2006, kiosk providers (n=396) exhibited significant differences in both mean first-line antibiotic prescribing and mean antibiotic cost per claim compared with nonkiosk providers (n=10,267; Table 2). Kiosk prescribers prescribed first-line antibiotics 42.0% of the time (median=41.7%, SD=14.1%). By comparison, their nonkiosk counterparts prescribed first-line antibiotics 41.4% of the time (median=40.1%, SD=17.5%; P=0.028). The mean cost per claim for antibiotics written by kiosk prescribers was $28.44 (median=$27.42, SD=$8.43) compared with $32.40 (median=$29.59, SD=$28.84) for their nonkiosk counterparts (P<0.001).

### Discussion

A difference-in-difference analysis of changes in first-line antibiotic prescribing rates and mean antibiotic cost per claim from baseline through the first full year of participation in a generic drug sampling program did not reveal a significant difference among kiosk providers as compared with their nonkiosk network counterparts. However, a cross-sectional analysis of the same outcome measures, conducted 2 years after program implementation, identified significantly greater first-line prescribing rates and lower average costs per claim for prescribers who participated in the program than for those who did not. Kiosk physicians prescribed first-line antibiotics 0.6% more often and had a mean antibiotic cost per claim of $3.96 less than their nonkiosk counterparts.

While the 2006 results were statistically significant, their practical significance, especially that of the first-line antibiotic prescribing rate difference (0.6%), is less evident. A previous study of the same generic sampling program identified a larger overall GDR among kiosk prescribers (59.9% vs. 59.1% for nonkiosk prescribers) and estimated a return on investment of 3:1.
for the duration of the original study period, suggesting that the program, overall, is successful and sustainable. The results of this analysis suggest that the availability of full-course antibiotic samples likely contributes little to the overall cost outcomes of the program. However, the results also suggest that the antibiotic samples are unlikely to be financially detrimental, as kiosk prescribers exhibited positive cost outcome differences compared with nonkiosk prescribers in 2006. A longer-term analysis of the program would clarify the ongoing financial risks or benefits of providing short-term antibiotic samples as part of a generic drug sampling program.

In addition to a positive overall financial return for the program, the continued increase in prescriber participation serves as a measure of prescriber acceptance of the program. As of November 2008, generic sampling kiosks are located in 217 practice sites across Pennsylvania that allow over 800 prescribers access to generic samples for their patients. To date, 37,735 samples have been dispensed to members of the MCO in 2008, representing a significant cost savings to members who obtained the samples at no cost, without a trip to the pharmacy. To accommodate the increased participation in the program, the MCO has since hired additional clinical staff to support this program as part of the academic detailing initiative.

Anecdotal evidence provided by kiosk prescribers suggests that they were satisfied with being able to provide their patients with antibiotic samples, stating that the samples may improve patient compliance by improving patient convenience, allowing the member to leave the office with the drug therapy in hand. Other prescribers have commented that the presence of antibiotics in the kiosk was the primary reason that compelled them to participate in the program. Additional health plan data suggest that antibiotics, in many cases, were utilized more frequently than were other samples upon a prescriber's initial participation in the program. Such anecdotal evidence suggests that an intangible benefit exists for the inclusion of antibiotic samples as part of a generic drug sampling program. The absolute value of the apparent benefit of including antibiotics in a generic drug sampling intervention must be determined by each health plan after examining the needs of its membership and network providers.

An additional potential benefit of including antibiotics in the sampling kiosks that is not readily quantifiable in the analysis conducted for this study is that the generic drug sampling program acts as a complementary program to the academic detailing services provided by the health plan. The kiosk helps facilitate the practical application of the detailing message (appropriate prescribing) that is delivered by the clinical consultants and clinical pharmacists who interact with the network prescribers. Future research examining the effects of improved antibiotic prescribing practices on outcomes such as treatment success rates and antibiotic resistance rates would be valuable to health plans and communities alike.

After careful consideration of the data and perceived intangible benefits, the MCO concluded that antibiotics should be included only in a generic drug sampling program whose primary objective is the promotion of generic drug samples for the treatment of chronic conditions. The dispensing of samples for the treatment of short-term (i.e., less than 1 month) conditions with no anticipated additional treatment is not supported by substantial positive cost outcomes data and appears to have a limited impact on prescribing practices but may provide intangible benefits as a value-added service when part of a larger program. At the time of this writing, the antibiotic samples continue to be part of the kiosk-based generic drug sampling program to help maintain a broad approach to generic sampling and to complement the academic detailing interventions performed by the MCO.

The addition of full-course antibiotic therapies to a generic drug sampling program represents one type of intervention that a health plan can undertake to affect a change in antibiotic prescribing practices, and it is likely that a multimodal approach would be the most effective means of promoting appropriate antibiotic prescribing. Physician education, member communications, incentive-laden tiered formulary benefit structures, pay-for-performance initiatives, and other interventions, such as a kiosk-based generic drug sampling program have the potential to provide incremental benefits when combined.

Limitations
The foremost limitation of this research was that it was a practical business application and not subjected to scientifically rigorous methods such as the use of randomization or a matched comparison group. The prescribers that comprised the intervention group in the present study were targeted specifically by the investigators or volunteered to participate in the program and were not meant to be a representative sample of the MCO's network physicians. As such, the kiosk prescribers are likely to be more engaged in understanding their prescribing practices or motivated to disperse generics (or first-line antibiotics) than their nonkiosk counterparts. Additionally, the generalizability of the study results to populations outside of the specific MCO is limited. Regional prescribing practices may further limit generalizability of the study.

Second, this intervention involved more than the generic drug sampling program, and the contribution of an academic detailing service confounds the results in a manner that we cannot determine. However, approximately 40% of the prescribers not participating in the generic sampling program received the same academic detailing service. Still, there may be a confounding effect in comparing the intervention group and the comparison group, since academic detailing was not uniformly performed among all nonparticipants.

Third, other confounding variables must be taken into account when interpreting the results of the study. Market changes that are largely outside the control of the investigators or the MCO may affect the impact of a health care business initiative. Such changes include the publication of new scientific evidence or professional
guidelines that advocate for specific clinical practices, increased community awareness through the media, or other local public health initiatives. However, the authors did not identify a specific factor that affected kiosk prescribers more or less than their non-kiosk network counterparts.

The impact of the kiosk intervention on medical utilization patterns such as revisit rates or emergency department visits was not addressed. However, since clinically significant differences in study outcomes were not found between the study groups, it would be unlikely that the groups would exhibit significant medical utilization pattern differences that could be attributed directly to the kiosk intervention. Finally, per-member and per-patient antibiotic utilization rates were not evaluated. Future research should examine the complex relationship of antibiotic use and disease-specific medical resource utilization, including the possibility that increased access to low-cost antibiotics increases utilization of antibiotics.

Conclusions

Study findings suggest that a generic drug sampling program should not be limited exclusively to short-term medications such as antibiotics due to a lack of substantial positive cost outcomes data. The return on investment from a generic drug sampling program lies in savings accrued by promoting the use of generic medications to treat chronic disease states. The long-term benefits of dispensing generic medications, such as first-line antibiotics, for short-term use are difficult to quantify. However, a generic sampling program for short-term use medications may be an effective part of a program whose primary purpose is to promote generic prescribing for all drugs.

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Disclosure

No outside funding supported this study. The authors disclose no potential bias or conflict of interest relating to this article.

Study concept and design were primarily the work of Culley, with input from Conklin and O’Donnell. Data collection was performed by O’Donnell with assistance from Conklin. Conklin interpreted the data with the assistance of Culley and O’Donnell, and wrote the manuscript with the assistance of Culley. Revision of the manuscript was shared equally by Conklin and Culley.

References


Resistance to In-Office Dispensing of Generic Antibiotic Samples

Stephen J. Kogut, PhD, MBA, RPh, and Linda M. Spooner, PharmD, BCPS

In this issue of JMCP, Conklin, Culley, and O’Donnell describe the results of an initiative to foster greater use of generic antimicrobial medications through the use of an in-office automated generic medication samples kiosk. A similar report describing the result of this initiative on overall rates of generic product use and cost was previously published in the June 2007 issue of JMCP. In the current study examining the impact of the kiosk program on prescribing of antimicrobial drugs specifically, the authors found that rates of “first-line” (generic) antimicrobial use, measured as a proportion of all antimicrobial prescriptions, were similar among network prescribers with versus without access to the medication kiosks (42.0% vs. 41.4%, respectively; \( P = 0.028 \)) in 2006, the most recent year measured. For the same year, the authors report a lower average cost per antimicrobial claim among prescribers with kiosk access ($28.44) than among those without access ($32.40; \( P < 0.001 \)).

The authors also compared mean cost per antibiotic claim and rates of use of “first-line” (generic) antibiotics between the 2 groups using a difference-in-difference analysis that measured change from the pre-intervention year (2003) to the post-intervention year (2005). They found that rates of use of “first-line” (generic) antibiotics declined among both groups during this 2-year period, from 49.1% to 47.0% (-2.1%) among prescribers having access to the samples kiosks and from 46.0% to 42.6% among the other network providers (-3.4%). The between-group difference in the magnitude of this reduction was not found to be statistically significant. Average cost per claim was also less in 2005 as compared with 2003 for both groups (changes from $33.56 to $29.42 for the kiosk users versus $38.26 to $34.91 for the other network providers), yet the between-group difference in magnitude of the reduction in antibiotic drug cost was also found to be statistically insignificant.

The premise of this intervention is a logical one. In many instances, lower-cost generic medications are a cost-effective substitute for higher-priced brand name products, particularly in generic substitution, and also when it is within the boundaries of evidence-based care to utilize a generic drug from a different therapeutic class in place of a branded product that does not have a generic substitute (i.e., therapeutic selection). Increasing access to generic antimicrobials via the use of in-office medication kiosks represents a novel approach in attempting to reduce the over-prescribing of broad spectrum higher-cost antibiotics. Yet this method of facilitating access to generic antibiotics raises a range of important issues, including what constitutes appropriate antimicrobial drug use from the perspective of the health plan, the implications of drug dispensing in the absence of pharmacist involvement, and overall, the role of drug sampling programs within our health care system. Moreover, this study provides another example of the drug product being parsed from the service, with technology having a fundamental role in reshaping the order fulfillment process. Specifically, pharmacists are increasingly providing patient education and counseling without having a direct role in the order-fulfillment function because newer dispensing technologies are enabling order fulfillment with diminishing pharmacist involvement. Yet, order fulfillment in the absence of pharmacist counseling raises substantial concerns with respect to patient safety and promoting appropriate medication use. Thus, we believe that it is imperative that the health professions, regulators and health plans consider the broader implications of newer technologies, such as the medication sampling kiosk initiative described in this study.

Does Facilitating Access to Generic Antibiotics Affect Providers’ Selection of Therapy?

The purported aim of the study was to increase the prescribing of agents described by the authors as first line. However, the apparent aim of this initiative was to increase the rate of utilization of lower-cost generic medications, of which many but not all are first-line anti-infective therapies in every circumstance. For example, for the treatment of community-acquired pneumonia in adult outpatients who have received a beta-lactam or macrolide within the previous 3 months, a respiratory fluoroquinolone is recommended, and no product from this category is currently available in a generic form. Thus, we believe the authors would have been more accurate in stating that the study’s aim was to increase the use of lower-cost antibiotics. Alternatively, the analysis could have been restricted only to infection types and clinical circumstances where first-line antibiotics are available in generic form, for example in the treatment of uncomplicated urinary tract infections. We also note that while Conklin et al.’s study included analyses to determine the statistical significance of between-group differences in prescribing rates and per-claim cost, the study employed a non-randomized design that did not control for potentially important covariates. While randomization was likely impractical, the researchers could have assessed potential differences in group composition such as prescriber specialty, size of practice, or a provider’s past prescribing patterns (other than volume). The authors note that the program targeted high-volume prescribers and those having below average generic use rates. Yet no data are provided to present these characteristics in comparison with those of network prescribers without access to the samples kiosks. Stratification according these and other characteristics would have likely yielded interesting findings. Furthermore, we wonder if the kiosks were more likely to be installed within group practices that used payment incentives to prescribe...
generic products. Or perhaps the kiosks were more likely to be used by physicians receptive to newer technologies or who hold more contemporary viewpoints regarding the efficacy of generic medications. Differences in location, population demographics, and office policies towards pharmaceutical representatives and sampling are also potentially important covariates.

The sole substantial between-group difference noted in the paper is a lower cost per claim among kiosk prescribers ($28.44) as compared with non-kiosk prescribers ($32.40) in 2006. Yet because rates of prescribing of first-line antibiotics were nearly identical during this period, this difference in cost likely reflects a different mix of first-line antibiotics; the dispensing kiosks contained only a subset of the first-line antibiotics that were included in the claims analysis. This issue could have been explored more thoroughly by presenting dispensing rates for each first-line antibiotic product for the 2 study groups. Additionally, while the authors state that cost calculations included administrative costs associated with the sampling program, detail is lacking regarding the nature and breakdown of such costs. Relevant costs may include, for example, the costs of licensing and maintaining the kiosks, provider training and service, patient education materials, and restocking the machines. It is not clear if these or other costs were included in the cost calculations. Nevertheless, the authors do not overemphasize the statistically significant difference in per-claim costs for 2006, but instead highlight the results of the difference-in-difference analysis, which revealed that the sampling initiative did not appear to improve rates of use of first-line antibiotics beyond that measured for network providers overall. The authors should be given credit for reporting this nonsignificant finding.

The Role of Academic Detailing

Another aspect of the study that warrants discussion is the academic detailing service, which was apparently an additional and cross-cutting intervention. The authors indicate that an employee of the managed care organization, specifically a clinical pharmacist, provided academic detailing and education on a number of topics, including appropriate antibiotic prescribing. Conklin et al. acknowledge that many infections, including acute upper respiratory tract infections, do not require initiation of any antibiotic therapy, and that the convenient presence of the kiosks could potentially have promoted the overuse of antibiotics for clinically inappropriate indications. It is well known that antibiotic therapy for numerous infections in adults, including acute sinusitis, bronchitis, and pharyngitis, as well as acute otitis media in children, is generally not beneficial. Yet, a recent analysis of data from the United Kingdom General Practice Research Database demonstrated that the number of cases of upper respiratory infection, sore throat, or otitis media needed to treat with antibiotics in order to prevent 1 serious complication (e.g., mastoiditis, pneumonia) is more than 4,000.

Additionally, one must question whether the prescribers received education regarding current evidence-based recommendations for treating lower respiratory tract infections, including community-acquired pneumonia, which may require utilization of “more expensive, second-line” antibiotics in patients with underlying comorbidities or recent antibiotic use. It is critical that prescribers be made aware of the differentiating factors (e.g., adverse effects, dosing frequency, drug interactions) when selecting narrower spectrum, less expensive agents as opposed to broader spectrum, branded antibiotics in order to optimize outcomes and prevent treatment failures. One may wonder if further facilitating access to antibiotics via these kiosks will contribute to the ever-rising incidence of antibiotic resistance among community-acquired pathogens.

It would have been interesting for the authors to reveal more detail regarding the scope of messages and role of the academic detailing pharmacist. Nevertheless, because the academic detailing service was provided to all prescribers having access to the generic samples kiosk, and also to many other prescribers not having access to the generic samples, it is not possible to determine the effect of the academic detailing service on generic antimicrobial prescribing rates.

Drug Sampling and the Role of the Pharmacist

At a broader level, we have concerns about the practice of in-office dispensing and specifically the exclusion of pharmacist involvement from the dispensing process. The use of the in-office dispensing kiosks provides an avenue for order fulfillment that does not include a drug utilization review (DUR) as performed by a pharmacist prior to dispensing. In the process of conducting the DUR, drug-drug interactions are often discovered and appropriateness of antibiotic choice and dosing regimen are reviewed. Through this process, errors are often identified and avoided through consultation and recommendations made to the prescriber. This process is especially critical for antibiotics, which have the potential to result in clinically significant interactions with a multitude of chronic maintenance medications. For example, numerous generic antibiotics, including several of those included in the kiosk in this study (amoxicillin, cephalaxin, doxycycline, sulfamethoxazole/trimethoprim) interact with warfarin, and may cause significantly elevated prothrombin times and increased risk of bleeding. If interactions such as these are not recognized, patient harm may result, and the risk is more than theoretical. Results of a large nationally representative survey revealed that warfarin is second only to insulin use as a leading cause of drug-related adverse events treated in emergency departments. The lack of a pharmacist DUR component could also have medicolegal ramifications, as antibiotics are one of the most frequently associated medication categories associated with malpractice claims.

Another implication of the lack of pharmacist involvement in the dispensing process is the absence of the medication counseling typically provided by the pharmacist to the patient at the time of dispensing. Important counseling points for proper antibiotic use include the management and prevention of common antibiotic-related adverse effects. A recent study published by Shehab and colleagues in Clinical Infectious Diseases noted that antibiotics
caused 19.3% of all adverse drug reaction-related visits to the emergency department from 2004 through 2006. The authors estimated that more than 142,000 emergency department visits every year were a direct result of antibiotic-related adverse events, with an overall rate of 10.5 emergency department visits per 10,000 outpatient office visits at which an antibiotic was prescribed. This research highlights the value of independent DUR performed by the pharmacist in dispensing the medication to the patient, confirming that prescribed therapies are appropriate given a particular patient’s clinical circumstances and concomitantly prescribed therapies, and ensuring that patients have an accessible resource for receiving drug information and counseling throughout the course of therapy. Such patient education includes instruction regarding the importance of completing the entire course of antibiotic therapy, rather than discontinuing the medication once symptoms resolve, and reinforcing the importance of proper storage of the antibiotics. The pharmacist can also explain why antibiotics should never be shared with others, including family members and friends. There are a number of key points that should be impressed upon the patient when an antibiotic is dispensed, and we wonder if the patient education provided in the office setting measures up against the level of educational services provided by community pharmacists. Lastly, we note that the pharmacist serves as a double check for identifying drug allergies.

Do Standards for Drug Utilization Review Apply to Sampling?
It is beyond the scope of this commentary to detail the myriad benefits of pharmacy care services and the pharmacist’s role in medication management. We note that Congress recognized the importance of medication therapy management (MTM) in the Medicare Prescription Drug Improvement and Modernization Act of 2003, and MTM is recognized as an eventual “cornerstone” of the Part D benefit. MTM notwithstanding, the DUR function as provided by pharmacists has been established as a standard of practice, as described in the Model State Pharmacy Act and Model Rules of the National Association of Boards of Pharmacy, and including the state of Pennsylvania where this study was conducted. Specifically, the rules and regulations of the Pennsylvania Board of Pharmacy require pharmacists to perform a prospective drug review (PDR) in attempting to “identify potential drug therapy problems that might result from therapeutic duplication, drug-drug interactions, incorrect dosage, incorrect duration of drug treatment, drug-allergy interactions, and clinical abuse or misuse.” We wonder if this standard of care is met by dispensing physicians distributing antibiotic samples using the medication kiosks. We recognize that the requirement for a pharmacist PDR apparently does not extend to physicians dispensing in the office setting. Yet we posit that the PDR requirements for pharmacy exist for good reason, and thus should be considered a standard of care to be applied across all settings. In the institutional setting, Joint Commission standards for safe medication use apply to sample medication distribution. For example, actual or potential adverse drug events and errors must be addressed, education is provided where appropriate, and patient-specific medication information must be made available. It is our understanding that these standards apply to outpatient functions existing within medical centers accredited by the Joint Commission. We argue that these standards of care are no less valid as applied to the prescribers studied here.

One may argue that a pharmacist-conducted DUR is not typically a facet of the office-based dispensing of brand-name drug samples either, and this practice has been commonplace for years. Yet just because the practice has been in existence for years does not mean that it should continue. Increasingly, institutions are eliminating brand-name drug sampling for reasons relating to patient safety and equity, and because of the influence on prescribing decisions (e.g., starting patients on relatively expensive drug therapy). Examples of such institutions are provided in a report by the Prescription Project, created with support from the Pew Charitable Trusts; the effort “promotes evidence-based prescribing and works to eliminate conflicts of interest in medicine due to pharmaceutical marketing to physicians.” The group’s April 2008 report Pharmaceautical Samples highlights several example policies excerpted from high-profile institutions. These include the use of vouchers supplied by the institution which can be used by the patient to acquire prescription drugs at reduced or no cost, and the establishment of funds for directing charitable donations to purchase medications for those in need. Many of these programs are directed through and overseen by the medical center’s pharmacy services. Additionally, the American Society of Health-System Pharmacists has expressed strong opposition to the practice of drug sampling, urging that “the use of drug samples within the institution be eliminated to the extent possible.” The American Medical Association has also called for academic medical centers to eliminate the use of drug samples. These positions appear to be founded primarily upon concerns regarding manufacturer influence, whereas issues pertaining to safe medication use have seemed to receive lesser emphasis.

The impact of drug sampling programs on quality of care is difficult to evaluate. Whereas brand drug sampling has been utilized as a marketing tactic for many years, there exists a paucity of research describing the impact of drug sampling on patient safety, despite potential concerns about the lack of involvement of the pharmacist in the dispensing process. However, the published literature contains at least 1 review of studies examining the consequences of drug sampling. Of the 23 articles identified in a review conducted by Groves et al., most studies addressed the impact of drug sampling on prescribing and program costs, while little was found regarding the impact of drug sampling on patient safety specifically, and with no reports addressing safety published in recent years.

In conclusion, Conklin et al.’s study brings to the forefront numerous issues with respect to medication sampling programs and antibiotic utilization. The greatest concern we have is the potential for compromised patient care and safety. While new technologies hold great promise for improving the effectiveness, safety, and efficiency of medication use, they must be assessed by
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considering their impacts on each of these outcomes. We wonder if the health plan considered adequately the potential threats to desirable clinical outcomes in its implementation of physician dispensing of generic antibiotics from medical office-based kiosks. This research by Conklin et al. informs about some drug cost outcomes and highlights how much we don’t know about the subject, including clinical and service outcomes.

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REFERENCES

By almost any measure, the Medicare prescription drug benefit (Part D) is a resounding success. Twenty-five million Medicare beneficiaries enjoyed guaranteed access and choice of a drug benefit in 2008. Based on the bids submitted by Part D plans for 2009, the Centers for Medicare and Medicaid services (CMS) estimates that the average monthly premium for standard Part D coverage will be $28, an amount 37% lower than originally projected when the benefit was established in 2003. More than 85% of Medicare Part D beneficiaries report being satisfied with their drug benefit. Finally, the program has been far less costly to taxpayers than expected—now estimated to be $243.7 billion less than the originally projected budget for the period 2004-2013.

A key reason for the economic success of Part D is that it uses competition among Medicare prescription drug plans (PDPs) and pharmacies to control costs. The PDPs are free to use formularies and cost-sharing incentives (e.g., multi-tier copayment structures) to encourage use of generic medicines, preferred brands, and choice of pharmacies for long-term therapies. Plans negotiate rebates with manufacturers and reimbursement with pharmacies in order to offer competitive premiums to beneficiaries. To optimize the use of appropriate medicines, Part D also established a mechanism for enrollees with multiple chronic conditions and high drug costs (estimated to be 8%-14% of beneficiaries) to receive medication therapy management (MTM) services from health professionals, including pharmacists.

Impact of Part D on Pharmacies
The pharmacy profession plays an important role in the delivery of the Medicare drug benefit. Part D simultaneously increased overall medication use by 158 million prescriptions in 2006, increased generic drug utilization (from 60.3% in 2006 to 67.8% in the first quarter of 2008), and provided a payment mechanism for MTM services, all of which are potentially in the economic interest of pharmacies. However, the competitive model inherent in Part D also creates downward pressure on reimbursement rates for prescriptions dispensed in community pharmacies. The net economic effect of Part D on community pharmacies—and independent stores in particular—has not been empirically measured in a systematic way.

In the October 2008 issue of JMCP, Carroll reported the results of a financial model of the effect of Part D on the profitability of independent community pharmacies. Carroll concluded that for a “typical” pharmacy with $3.49 million in total sales in 2005, the gross margin on prescriptions decreased from 22.7% to 22.0% under part D in 2006, and net income declined by about $28,000 (-22%). The most influential factor was the assumed decrease in gross margin on prescription sales due to Part D reimbursement rates that would otherwise have been higher if enrollees had remained cash or Medicaid customers. In sensitivity analyses, Part D always reduced net income to the pharmacy but never created a net loss.

Carroll’s analysis must be interpreted carefully due to important limitations. First, the most influential assumptions about payer mix and gross margin by payer were based on the average of 431 pharmacy owners’ self reports (it is unknown how many drew their estimates from actual financial statements). Second, the results may not apply to all pharmacies because the 22% decline in net income is predicated on the “typical” store having only 8% of total sales from nondispensing activities. In a pharmacy with a larger base of nondispensing revenue, the percentage decline in net income would be smaller. Third, the model focused exclusively on income from prescription dispensing; potential gains in revenue from medication therapy management services, vaccine administrations, and nonprescription sales were not considered. Fourth, the model compared only 2006 (the first year of Part D) with 2005. The impacts of changes that could be helpful to community pharmacies—such as expanded coverage of vaccinations, educational outreach to reduce confusion during open enrollment periods, and potentially favorable long-term effects such as increased medication adherence attributable to expanded coverage and lower out-of-pocket costs to beneficiaries — were not considered.

These limitations mean that the impact of Part D on pharmacy profits may now be less than Carroll estimated for 2006; this assessment is corroborated by recently released data from 2007 that reveal stable sales and a slightly higher gross margins compared with 2006. Still, Carroll’s main conclusion is intuitive: the competitive model for Part D probably reduces the profitability of dispensing prescriptions. As Carroll points out, the declining margin on prescription sales is a 2-decade trend driven by the conversion of cash-paid prescriptions to insurance-paid prescriptions. The future of community pharmacy lies less in dispensing and more in patient-care services such as MTM.

In a commentary appearing in the November/December 2008 issue of JMCP, Spooner described a “bleak future for independent community pharmacy under Medicare Part D.” In addition to the factors modeled by Carroll, Spooner cited 2 issues with...
Part D that created economic difficulties for independent community pharmacies: slow payments to pharmacies from Part D plans and administrative burden on pharmacy staff during open enrollment. Moreover, he noted that independent community pharmacies have historically operated smaller stores than chains and thus have less front-end revenue to offset lower margins on prescriptions. Spooner argues that the closing of 1,152 independent community pharmacies in 2006 was in part attributable to Part D. In fact, it is unclear how many of these pharmacies were actually closed as distinguished from being sold to other companies and thus no longer classified as “independent.” We are also aware of no systematic evidence that Part D was the direct cause of these closures. It may be more accurate to describe these issues as transitional challenges that could have been expected with the largest modification to Medicare (and to the pharmaceutical marketplace) since the program’s inception. Recent policy changes have addressed the first year transitional challenges. Confusion at open enrollment was publicly acknowledged by CMS as an issue in June 2006, and the excess burden on pharmacies was quickly reduced by an array of CMS outreach and educational efforts. The Medicare Improvements for Patients and Providers Act of 2008 will require plans to pay pharmacies within 14 days starting January 2010. This aggressive payment timeline should make the payment terms of Part D more financially attractive than those of most third-party plans. The number of pharmacies classified as independent community pharmacies was stable from 2006 to 2007 and profitability was up slightly in 2007 compared with 2006. These numbers suggest that after grappling with significant transition-year challenges in 2006, independent community pharmacies have fulfilled Carroll’s prediction that despite some shrinkage of margins, stores remain profitable even under the most conservative assumptions.

Mixed Messages

The pharmacy profession seems divided in its response to Part D. Not surprisingly, the Academy of Managed Care Pharmacy is supportive of this competitive model based on managed care principles. The American Pharmacists Association (APhA) and National Association of Chain Drug Stores (NACDS) have moved to expand and demonstrate the value of pharmacists’ therapy management services. APhA and NACDS have developed a formal service model for MTM services that includes the core elements of medication therapy review, personal medication records, a medication-related action plan, intervention and/or referral, and documentation and follow-up.

In contrast, some independent community pharmacists believe they should be exempted from competition with chain pharmacies to maintain higher margins on prescription dispensing. The so-called “Community Pharmacy Fairness Act of 2007,” introduced in the last Congress, would create an exemption to antitrust laws to permit independent pharmacies to negotiate collectively with health plans and pharmacy benefit management companies (PBMs) over payment rates and other contract terms of Medicare Part D. Proponents hope that this shelter from competition with chain pharmacies will result in the ability to bargain for greater reimbursement under Part D. The Congressional Budget Office estimated that enacting the bill would cost $640 million over the 2008-2018 period. More dangerous than the cost to taxpayers, however, is the precedent. In testifying against the proposal, David Wales, Deputy Bureau of Competition Director of the Federal Trade Commission, stated: “Giving health care providers...a license to engage in price fixing and boycotts in order to extract higher payments from third-party payers would be a costly step backward, not forward, on the path to a better health care system.” In light of the fiscal and budgetary pressures now facing our nation and our health care system, costly protections from competition for these businesses are unlikely. More importantly, the act of seeking an antitrust exemption sends the wrong message to policymakers and the public by emphasizing pharmacy’s role in drug distribution rather than appropriate medication use.

The Opportunity for Forward-Thinking Pharmacists

We are heading to a reformed health care system that will emphasize and reward higher value and better quality in the delivery of health care. Community pharmacists could be at the forefront of this change by following 3 specific steps:

First, define and embrace a new model of pharmacist care that asserts a more active role in Medicare enrollees’ health, unequivocally and with a unified voice. Part D created an historic opportunity for pharmacists to fulfill the role of medication therapy managers and adapt their practices to patient-focused services that add value to the health care system by improving outcomes and lowering the costs of inappropriate medication use. Hepler and Strand’s 1990 call to action, “Opportunities and responsibilities in pharmaceutical care” was lauded by the profession and adopted as a mission for the future of pharmacy practice and education. It seems extraordinarily prescient today: “Pharmacy has shed the apothecary role but has not yet been restored to its erst-while importance in medical care...Pharmacists and their institutions must stop looking inward and start redirecting their energies to the greater social good...Pharmacists must abandon factionalism and adopt patient-centered pharmaceutical care as their philosophy of practice. Changing the focus of practice from products and biological systems to ensuring the best drug therapy and patient safety will raise pharmacy’s level of responsibility and require philosophical, organizational, and functional changes...Pharmacy’s reprofessionalization will be completed only when all pharmacists accept their social mandate to ensure the safe and effective drug therapy of the individual patient.”

Nearly 20 years later, these changes have begun to occur in the professional education of pharmacy students, but more outward focus in practice is needed to earn this social mandate.
describing its own evolution, APhA connects the dots between Part D and the reprofessionalization of pharmacy: “Medication therapy management, a component of the Medicare Part D prescription drug benefit launched in 2006, provides the means for pharmacists to complete the transformation of their profession from one focused on the drug product to a clinical service focused on the patient.”

Second, the profession must walk the talk. In order to compete in the future, community pharmacies have to change the business model from one that has them beholden to the commodity they put in a bottle. This requires the development and demonstration of new business models focused on the value that pharmacists can create from the profession’s unique position in the health care system. Focusing on the unmet needs of patients in the community will reveal new opportunities to deliver screening services, preventive care (including immunizations), drug information and education, drug utilization reviews, and support for adherence to chronic therapies. Organizations such as Mirixa and Outcomes Pharmaceutical Health Care have developed innovative models, networks of independent and chain pharmacies, infrastructure, and payment opportunities for delivering and documenting non-dispensing services. The experience of one of these organizations is described by Barnett et al. in a coincident article in this issue of JMCP. An important next step is to define the pharmacist’s role in the “patient-centered medical home” and other emerging models of team-based health care delivery. Some pharmacy chains have already captured a new foothold in the marketplace by answering consumer demand for more convenient access to clinicians with retail clinics. Independent community pharmacies could compete favorably by building upon and even improving this model in collaboration with local practitioners.

Third, develop credible evidence of the value of these services. In addition to the report by Barnett et al, pilot efforts published to date suggest that MTM services provided to Medicare beneficiaries may indeed improve medication use and outcomes. However, more robust data measuring the clinical and economic impact of MTM are needed. At a recent Medicare Payment Advisory Commission (MedPAC) meeting in November, 2008, analysts reported that information about the effectiveness of MTM programs is lacking. Evidence of these programs’ effect on medication adherence, appropriate prescribing, drug spending, and utilization of other services are of particular interest to Medicare. The evidence must be “high quality,” meaning that studies should be representative and should employ optimal experimental and quasi-experimental designs. The formation of the Pharmacy Quality Alliance (PQA) shortly after the implementation of Part D was a major laudable move by pharmacy leaders to develop performance measures against which the value of pharmacy services may be measured and new compensation models developed. Expanding upon PQAs starter set of medication utilization-based measures to include consensus metrics for clinical and economic outcomes is an important next step.

Fourth, use the quantitative evidence from step 3 to develop and advocate for performance-based payment models. If the data support it, the profession could also advocate for expanded coverage of drug therapy management within the broader context of health care reform—and not only from Medicare. With Medicaid and private payers, independent community pharmacists could negotiate coverage for MTM services on the condition that data are systematically collected in the process of care, to better understand the value of the services. This approach could be thematically modeled on the Medicare coverage policy option known as “coverage with evidence development.” As the body of performance metrics and evidence of value for MTM services grow, pharmacies may also share economic risk with payers for the return on investment in MTM services.

Finally, there are ways for independent community pharmacies to enhance their competitiveness within Part D while enhancing access to pharmacy services for seniors. Part D’s retail pharmacy access standards dictate that at the state level, each PDP must have in its network at least 1 retail pharmacy within 2 miles of 90% of beneficiaries in urban areas, within 5 miles of 90% of beneficiaries in suburban areas, and within 15 miles of 70% of beneficiaries in rural areas. Recognizing that a high proportion of independent community pharmacies serve rural and suburban areas, if existing Part D access standards were applied differently, more rural independent pharmacies could realize much greater market power in Part D; this objective could be accomplished without sweeping legislative changes or unseemly quests for antitrust exemptions.

Reimbursement for MTM services under Medicare Part D has created an historic opportunity for the pharmacy profession to step further into the role of managing medication therapy outcomes as well as delivering medications to patients. While there is still a lot of work to do, the course has been charted and organized pharmacy is making progress in delivering and quantifying value. Over the years, many politicians and policymakers have come to recognize and respect the fiercely competitive and innovative spirit of independent community pharmacists. While Medicare Part D isn’t perfect, it has been improved since 2006 and we believe that in seeking legislative relief from competitive prescription reimbursement contracts, independent community pharmacists could be taking policymakers’ eyes off the ball—creating a distraction that will consume valuable time, energy, and political capital. Securing payment for proven quality and value delivered to patients in a competitive environment is the sustainable business model for pharmacists, just as it is for all providers in this rapidly changing health care system. Rather than a curse, Medicare Part D is the kind of opportunity that pharmacy’s leaders have sought for decades.
Medicare Part D: Good for Patients and an Opportunity for Pharmacists

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DISCLOSURES

Benner reports no conflicts of interest related to the subjects discussed in this article. Kocot was Senior Advisor to the Administrator of the Centers for Medicare and Medicaid (CMS) from 2004-2007. At CMS, Kocot was a member of the agency’s senior management team during the implementation of Part D; he was also a key contributor in the launch of the Pharmacy Quality Alliance (PQA). Prior to that, he was Senior Vice President and General Counsel at the National Association of Chain Drug Stores.

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19. Hepler and Strand received the Remington Honor Medal, the profession’s highest honor, for this paper in 1997.


Prior Authorization and Clopidogrel Use—The Truth Lies in the Details

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In the midst of the high-stakes game to reduce heart attacks, Jackevicius et al. reported in October 2008 that “removal of a [prior authorization (PA)] program led to improvement in timely access to clopidogrel for coronary stenting and improved cardiovascular outcomes."1 In fact, the PA requirement was replaced with a “limited use” policy for clopidogrel (Plavix) in the Canadian province of Ontario in September 2003, and this policy change was associated with a 4-point decline in major cardiovascular events measured 1 year after hospitalization for acute myocardial infarction and percutaneous coronary intervention (PCI) with stenting among patients aged 65 years or older. Rates of the primary cardiovascular outcome—a composite measure of death, recurrent acute myocardial infarction, repeat PCI, and coronary-artery bypass grafting—were 15% in the 41-month PA period from April 2000 through August 2003 versus 11% in the 19-month limited-use period from September 2003 through March 2005 (P=0.02). Rates of death during the PA period and the limited-use period did not differ significantly (5% vs. 4%, respectively; P=0.42).

Jackevicius et al. attributed the improvement in cardiovascular outcomes to increased use of clopidogrel following relaxation of the PA requirement. The percentage of patients who used the Ontario Drug Benefit (ODB) program to fill prescriptions for clopidogrel in the first 30 days following hospital discharge for myocardial infarction and PCI with stenting increased from 35% under PA to 88% under the limited-use policy, and the median time from discharge to the first clopidogrel claim declined from 9 days to 0 days.1

Not surprisingly given the morbidity, mortality, and economic cost of heart disease, estimated to have resulted in the deaths of approximately 43,000 Canadians and 514,000 Americans in 2002,2 the report by Jackevicius et al. garnered media attention. The popular press reported that clopidogrel “flowed more freely to stent patients and outcomes improved."3 One headline stated that “Policy Change Improves Cardiovascular Outcomes,"4 and a press release disseminated by the lead author’s academic institution declared that “Faster Medication=Fewer Heart Attacks."5 Although the study’s lead author acknowledged that PA policies vary by payer, she contended in an interview conducted shortly after publication of the study that its findings had broad applicability in the United States.6 However, as Fairman and Curtiss pointed out in their March 2008 review of a report on value-based insurance design, press accounts rarely contain the details necessary for a decision-maker to evaluate a study report’s validity, much less its applicability to populations with clinical or demographic characteristics unlike those of the study sample.7 Careful examination of the study’s context, sample and methods is warranted.

The “PA” Process Was Atypically Burdensome

Close examination of Ontario’s complex process of drug coverage and reimbursement suggests that the “PA” requirement studied by Jackevicius et al. differed substantially from PA as typically administered in the United States. The ODB formulary provides access to over 3,400 medications. Drugs not listed in the formulary may be requested by a prescriber in writing through a process known as the Individual Clinical Review (ICR) or simply “Section 8,”8,9 in reference to the section of the Ontario Drug Benefit Act that originally defined the ICR process. Requests for ICR coverage are reviewed on a case-by-case basis.8,9

Prior to September 4, 2003, clopidogrel was not listed in the ODB formulary.8 The only mechanism for reimbursement of the drug under ODB was through the ICR process. In 2003, this process required the physician to provide a written request (usually in the form of a letter) containing a “concise clinical description and therapeutic plan” including a specific diagnosis, objective evidence of drug efficacy (if the patient had already been taking the drug), details of the dosage, duration and response for formulary alternatives, concomitant drug therapy, laboratory results, etc.8 The administrative burden of Ontario’s ICR program is compounded by the fact that each ICR request and approval is both drug and strength specific. In the event of dose changes requiring a different strength or dosage form of a given drug, a new ICR request is generally required.8,9

By September 2005, ODB had developed a standard template form and several drug-specific forms to streamline the ICR process to some degree,9 but at the time of the clopidogrel coverage change, the process was primarily manual. ODB administrative data for fiscal year 2004 (April 1, 2003 through March 31, 2004) show that 41,936 requests for clopidogrel coverage were received, and ODB approved 36,339 of those requests (86.7%), at an expense of CAD$24.4 million (CAD$671 clopidogrel cost per PA approval).10

However, the typical response time for these requests was lengthy. In ODB’s fiscal year 2002, the average turnaround for ICR requests was 15.3 days, with 33% of requests taking in excess of 3 weeks to resolve.11 Since 2002, ODB no longer reports an average turnaround. By fiscal year 2004, 44% of all ICR requests took in excess of 3 weeks to resolve.10 These data suggest that the problem of excessive waits associated with the ICR process...
may have been getting worse. Consistent with these reports of the overall poor performance of the ICR system, the upper end of the interquartile range for time from hospital discharge until first clopidogrel use in the Jackevicius study was 39 days, indicating that under ICR 25% of study patients experienced a delay of more than 5.5 weeks before receiving clopidogrel.1

In contrast to the “PA” (ICR) process studied by Jackevicius et al., a typical PA process in the United States involves completion of a telephone call or 1-page form, sometimes including pre-printed diagnoses specific to drug and indication.12-17 Although virtually no systematic investigations of PA response times are available in the peer-reviewed literature, payers report standard response times ranging from 2-4 days, faster for more urgent requests.14,15,17 An operational and performance analysis of an Iowa Medicaid PA program in which 93% of PA requests were made by telephone reported a mean response time of 73 minutes for new requests.18

“PA” Was Not “Removed:” The Limited-Use Process Was Actually a Form of PA

The “limited-use” status that replaced ICR for certain users of clopidogrel on September 4, 2003, in Ontario resembles a typical PA intervention in the United States in its use of defined criteria for coverage and in terms of the time involved. Under the limited-use provision, drugs are on formulary, but the patient must meet specific predefined clinical criteria for coverage (Table 1).

The ODB’s change to limited-use status for clopidogrel was apparently an attempt to improve efficiency in the administrative process and facilitate access to the drug for acute indications. Whatever the motivation, the limited-use process that has been in effect in Ontario, Canada, since the “removal” of PA requires the prescriber to record a number corresponding to an applicable criterion on the prescription order form. The dispensing pharmacist enters this number in the prescription claim record for adjudication. In addition to the 3-digit limited-use code provided in the criteria, pharmacies are also required to submit a special authorization number corresponding to the hospital in which the patient was hospitalized.8,10 Even this allegedly more liberal process has been criticized both for its inconvenience to prescribers (pharmacists must frequently contact prescribers to verify invalid or omitted codes prior to submitting a claim to ODB), and for the intentional provision of incorrect codes in order to achieve coverage for patients.20 Coverage of clopidogrel for indications outside of the criteria listed in Table 1, such as “secondary prevention of ischemic events for patients intolerant or allergic to ASA [aspirin] or ticlodipine,” continues to be available only through the ODB’s ICR program.21,22

The Clopidogrel Utilization Measure Was Inaccurate

A fact that is too often forgotten in interpreting analyses of administrative claims is that researchers do not have access to all utilization of a drug or service, only to the utilization billed to the particular payer that served as the data source for the study. To the credit of Jackevicus et al., they acknowledge in their study report that they “were not able to ascertain whether certain patients elected to pay for the medication directly, were given samples, or had a private drug plan that covered the medication.”1 They do not acknowledge, however, is how serious this study limitation is in light of Ontario’s drug coverage structure and the incentive provided to patients to obtain clopidogrel by a means other than the slow ICR process.

The drug reimbursement system in Ontario is complex and not readily transferable to the United States. An especially significant difference between the 2 countries is the overlap of public and private systems in Ontario. The ODB program primarily provides drug coverage for those aged 65 and older and for those receiving social assistance (i.e., low income). Additionally, a means-based program is available for those whose out-of-pocket drug expenses are high relative to their income.8,9,12,23 Others are often covered by employer-sponsored drug plans, individual drug plans, or through federal programs targeted to specific groups (e.g., First Nations and Veterans Affairs). Dual coverage is possible, but its incidence is poorly understood. In some cases, Ontarians may be able to retain employer-sponsored benefits after retirement and beyond age 65. Federal programs such as those for Veterans’ Affairs Canada and for First Nations also continue coverage regardless of age. Paterson et al’s recent study of dual coverage among seniors in Ontario estimated that, from 2000 to 2005, 15%-20% of Ontario senior citizens filled at least 1 prescription that was paid by a private insurer, with new drugs “represented disproportionately in private drug claims” rather than in the ODB database.24

The combination of the administrative burden of the ICR process and unacceptably long wait times for potentially urgent medications meant that the ICR process was not accessed unless absolutely necessary. As a practical matter, many patients prescribed clopidogrel could easily access the drug through a private

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>ODB Coverage Criteria for Clopidogrel Beginning September 2003*</th>
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<tr>
<td>Limited Use Code</td>
<td>Criteria</td>
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<tr>
<td>375</td>
<td>For patients immediately post-hospitalizationb for non-ST segment elevation ACS*</td>
</tr>
<tr>
<td>376</td>
<td>For patients immediately pre- or post-PCI14</td>
</tr>
</tbody>
</table>

*aDerived from the Ontario Ministry of Health and Long Term Care, Ontario Drug Benefit Formulary/Comparative Drug Index, Edition No. 38, Update B.8,29
bThe first prescription must be written by a physician based at the hospital where the patient was hospitalized.
ACS, as defined by the CURE study, includes hospitalized patients with unstable angina or non-ST segment elevation myocardial infarction.
14Therapy may be initiated up to 10 days prior to PCI.
ACS = Acute Coronary Syndrome, CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Events; ODB = Ontario Drug Benefit, PCI = percutaneous coronary intervention.
reimbursement source rather than wait for ICR approval. Thus, the effect of dual coverage on the problem of “data capture”—the degree to which claims paid by ODB failed to provide a complete picture of clopidogrel utilization—was particularly problematic.

Paterson et al.’s analysis of clopidogrel use by Ontario enrollees aged 65 years or older who were dually covered—meaning that they received prescription drug coverage both through ODB and a private insurance plan—provides a sense of the scope of the problem. In the second quarter of 2003, just prior to the change from ICR to limited use, clopidogrel claims per 1,000 prescription drug utilizers (those who filled at least 1 prescription for any medication) by payer were 6.3 for ODB and 53.2 for private insurance. One year later, in the second quarter of 2004, clopidogrel use rates per 1,000 utilizers were 16.3 for ODB and 65.0 for private insurance. Therefore, for those with dual ODB—private coverage, ODB paid for and recorded in its database only about 11% of clopidogrel use under ICR (“PA”) and only about 20% under limited use.

Paterson et al.’s findings indicate that a substantial portion of clopidogrel use in Ontario was not captured in the dataset used by Jackevicius et al. More important, Paterson et al.’s findings also suggest a proportional shift in payment source. Following the change to limited use, a portion of the clopidogrel claims that would have been paid by private insurance were instead paid by ODB. Thus, an unknown amount of the change in clopidogrel utilization measured by Jackevicius et al. represents nothing more than a shift in payer source from private insurance (claims data not captured) to ODB (claims data captured), and the actual degree of increase in utilization of clopidogrel in the Jackevicius et al. sample is unknown.

The Observed Outcomes Could be the Effects of a Policy Change, Improvements in Quality of Care or Something Else—Use of Drug-Eluting Stents Skyrockets

Interrupted time series, the statistical technique employed by Jackevicius et al., quantifies trends in a phenomenon of interest over time, comparing events in the time period before and after an intervention. In an interrupted time series that lacks a comparison group, a key question is whether the pre-intervention trend adequately represents the equivalent of a true comparison group, a key question is whether the pre-intervention analysis lacking comparison groups are especially vulnerable to the problem of coincident events—other changes taking place simultaneously with the intervention but not controlled in the analysis. Changes taking place from the “PA” period to the limited-use period, but not controlled in the Jackevicius et al. analysis, included reductions in the baseline prevalence of several chronic comorbidities among study subjects (all P<0.001); these include diabetes mellitus (declined from 17% to 13%), cardiac dysrhythmia (declined from 13% to 9%), and hypertension (declined from 33% to 28%).

A much larger threat to the validity of the results attributed to clopidogrel access by Jackevicius et al. was the coincident explosion in the use of drug-eluting stents in PCI procedures, beginning at approximately the start of the limited-use period. Given the association between drug-eluting stents and reduction in risk of target-vessel revascularization after stenting, this major change in practice patterns was likely, to an unknown extent, to be responsible for the changes in cardiovascular outcomes observed in the Jackevicius et al. study. Jackevicius et al. stated that drug-eluting stents were not introduced in Canada until 2002. Actually, a sirolimus-eluting stent was not approved for use in Canada until late in 2002 (November), and a paclitaxel-eluting stent was not approved until September 2003. Drug-eluting stents were therefore uncommon in what Jackevicius et al. describe as the clopidogrel PA period.

Use of drug-eluting stents began to skyrocket at the end of calendar year 2003. Jackevicius et al. report that “drug-eluting stents comprised approximately 40% of stent use in the cohort beginning in the prior-authorization period.” Actually, the indication that the 40% rate of stent use began in the “prior-authorization” period is potentially misleading; the data reported in the Appendix for the reference for this statement are shown only for the months of December 2003 through March 2005, all after “removal” of the “PA” for clopidogrel, with a mean 38% use of drug-eluting stents at the time of PCI in Ontario, Canada. In the United States, the use of drug-eluting stents as a proportion of all stent procedures increased dramatically in just 8 months from 2.5% in April 2003 to 54.9% in December 2003. In Ontario, funding restrictions may have resulted in a slower uptake of drug-eluting stents, with Tu et al. reporting that 45% of PCI-stent patients received drug-eluting stents in December 2003.

While Jackevicius et al. acknowledge that this factor “potentially confounds our results,” they do not report the proportion of patients in the 2 periods that received drug-eluting stents and dismiss the apparent difference in the 2 study periods by stating that “the use of drug-eluting stents has a modest effect on reducing target-vessel revascularization and has not been shown in clinical trials to reduce reinfarction.” This assessment discounts the results reported by Tu et al. (2007), who found a significantly lower 2-year rate of target-vessel revascularization for patients receiving drug-eluting stents as compared with a propensity score-matched cohort of patients receiving bare-metal stents in Ontario, Canada, between December 1, 2003, and March 31, 2005 (7.4% vs. 10.7%, P<0.001).

This characterization of the facts by Jackevicius et al. regarding the use of drug-eluting stents in Ontario, Canada, also fails to mention that while Tu et al. did find a nonsignificant difference in myocardial infarctions between their drug-eluting stent and bare-metal stent cohorts, 3 of the 4 outcome measures favored drug-eluting stents. In addition to a lower rate of target-vessel revascularization, Tu et al. found a lower 2-year rate of death with drug-eluting stents (4.3% vs. 6.1%, P<0.001) and a lower
combined rate of death or reinfarction (9.3% vs. 10.5%, P<0.02).27

Absent a comparison group, it is also difficult to determine whether other medical innovations or improvements in quality of care for cardiac diseases affected the changes in cardiovascular outcomes measured by Jackevicius et al. For example, serotonin receptor reuptake inhibitors (SSRIs) have antiplatelet properties.32 The effect is sufficient to cause Glassman and Bigger (2007) to propose that studies of outcomes in patients with drug-eluting stents should include “surveillance for SSRI-clopidogrel interactions.”33 The use of SSRIs also has been shown to reduce the rate of death and recurrent myocardial infarction in depressed patients following myocardial infarction.34

Clinical and Cost Outcomes — Value for Money in Antiplatelet Therapy

Although recognizing the limits of their observational research design, Jackevicius et al. argue that “the likelihood of a true causal association [between increased clopidogrel use and improved cardiovascular outcomes] is strengthened by the striking temporal inverse correlation between the increased use of clopidogrel and the decreased [cardiovascular] event rate, the biologic plausibility around this observation, and its consistency with current evidence about the type of benefits in clinical outcomes that are expected with clopidogrel.”1 The question of biologic plausibility is indeed particularly important when evaluating trend data.

The evidence that we have in hand today calls for lifelong use of aspirin (acetylsalicylic acid, or ASA, in Canada) in acute coronary syndrome (ACS) patients (i.e., secondary prevention) at a dose of 162-325 mg per day, as both a loading dose and a maintenance dose, with the addition of clopidogrel for 9-12 months at 300 mg initially (loading dose) and 75 mg per day thereafter.35 For secondary prevention in PCI patients, aspirin should also be used lifelong at 162-325 mg per day initially and thereafter. Clopidogrel should be used at 300-600 mg as a loading dose and 75 mg daily for 9-12 months after PCI. For other cases of secondary prevention in patients with cardiovascular disease, there are not sufficient data to support the addition of clopidogrel to aspirin.

Clopidogrel alone is an expensive alternative to aspirin; aspirin costs less than 5 cents per day of therapy,28 about 1% of the cost of the highly-advertised clopidogrel, which had an actual average discounted cost per day of US$4.40 at year-end 2008.37 The “cost comparison of antiplatelet drugs” in the present ODB “Request for Plavix (clopidogrel)” ICR form shows an annual cost of CAD$5.37 for aspirin (325 mg enteric coated) versus CAD$876.00 for Plavix.21 For primary prevention of cardiovascular events, there is no evidence that adding clopidogrel to aspirin offers any advantage over aspirin alone, and its use increases the risk of bleeding.38 There are no data on the safety of the combined use of aspirin and clopidogrel for longer than 30 days after acute myocardial infarction or beyond 12 months after ACS.38

Effects of PA or Step-Therapy Interventions — The Truth Lies in the Details

Gleason30 and Curtiss31 observed previously that managed care pharmacy interventions are not homogenous, and the effects of a PA or step-therapy intervention depend upon the details of the structure and operation of the intervention. Curtiss pointed specifically to population-based observational research performed in Canada that compared step-therapy programs in 2 different provinces for the period from January 1996 to November 2002.41 The more restrictive step-therapy program in British Columbia placed cyclooxygenase 2 (COX-2) inhibitors as fourth-line therapy after at least 3 nonsteroidal anti-inflammatory drugs (NSAIDs), compared with the program in Ontario that recommended step-therapy for COX-2 inhibitors. The “special authority approval” required in the British Columbia program was associated with a 25% increase in prevalence of use of NSAIDs, including COX-2 inhibitors (from 8.7% to 10.9%) in persons aged 66 years or older versus a 51% increase in the prevalence of use of NSAIDs (from 10.9% to 16.5%) in Ontario.41 In addition to the likely higher unfavorable clinical and cost outcomes from adverse cardiovascular events associated with the use of rofecoxib,32 the rate of hospital admissions due to gastrointestinal (GI) hemorrhage increased significantly in Ontario by about 16%, or a rate of 2 admissions per 10,000 older adults above the expected value (P<0.01).41 There was no increase in hospital admissions per 10,000 older adults in British Columbia with its more restrictive step-therapy intervention for COX-2 inhibitors, a lower overall absolute rate of use of all NSAIDs, and lower rate of increase in the use of all NSAIDs following the market introduction of the COX-2 drugs.41 This study provides the “flip side” of the issue studied by Jackevicius et al.—that a well-run program to restrict medication use to patients most likely to benefit from it has the potential to provide not only cost savings but, more importantly, a measure of safety in the use of newly approved medications.

Balancing Access and Safety and the Potential Price of Inaction

In evaluating studies of the purported negative consequences of PA, it is important to remember that the clinical and economic consequences of failing to require prior authorization of some drugs may be high. A case in point is provided by Choudhry et al.’s (2008) analysis of clopidogrel use by lower-to-middle income Medicare beneficiaries aged 65 or older enrolled in the Pennsylvania Pharmaceutical Assistance Contract for the Elderly (PACE) program from 2003-2004.41 PACE participants paid copayments of $5-$10 with no deductibles, formularies, preferred drug lists, or prior authorization requirements. For a sample of 4,977 new clopidogrel users who had “complete health records” for the 3 years prior to clopidogrel initiation, Choudhry et al. searched all diagnoses recorded in Medicare claims data (Parts A and B) for evidence of indications for clopidogrel use. Only 47% of new clopidogrel users met “literature-based”
criteria (hospitalization for ACS or PCI within previous 35 days or for stroke within previous 6 months; diagnosis of peripheral artery disease [PAD] in previous 3 years; hospitalization for upper gastrointestinal bleed within previous 3 years), and only 56% met “purposely broad” criteria that included 2 additional categories: (a) any of the following at any point in the previous 3 years: hospitalization for ACS, stroke, or GI bleed, or coronary revascularization (PCI or coronary artery bypass graft [CABG] surgery), or diagnosis of PAD; and (b) any of the following in 30 days after the first clopidogrel claim: hospitalization for ACS or stroke, PCI or CABG, or diagnosis of PAD. A remarkably low 39% of new clopidogrel users met U.S. Food and Drug Administration (FDA)-approved indications for its use.

Putting into perspective the implications of their work for health care policy, Choudhry et al. suggested that clopidogrel “represents an increasingly common problem in pharmacotherapy: a newer, costly, branded product that is equivalent to an older, far less expensive agent for many patients but more effective for a well-defined subset of patients.” Suggesting that the patients without indications for clopidogrel were “very likely prescribed this therapy for primary prevention,” Choudhry et al. pointed to the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial as evidence that patients without a clear indication for clopidogrel might be exposed to unnecessary risk of harm.\(^\text{43-45}\) CHARISMA patients with “clinically evident atherothrombosis” (n=12,153) randomized to clopidogrel plus aspirin experienced a “marginally significant reduction” in a composite rate of myocardial infarction, stroke or death from cardiovascular causes (6.9% for clopidogrel+aspirin vs. 7.9% with for placebo+aspirin; relative risk [RR]=0.88; 95% CI=0.77-0.998; P=0.046). However, among patients with “multiple atherothrombotic risk factors without documented cardiovascular disease” (n=3,284) clopidogrel use was associated with increased rates of death from all causes (3.4% for clopidogrel+aspirin vs. 3.8% for placebo+aspirin; \(P=0.04\)) and from cardiovascular causes (3.9% vs. 2.2%, respectively; \(P=0.01\)).\(^\text{44-45}\) Raising a number of possible biological explanations for the increased death rate associated with clopidogrel use in asymptomatic patients, study authors concluded that “whatever the explanation, it appears that until proven otherwise, clinicians should avoid dual antiplatelet therapy in patients without established vascular disease.”\(^\text{44}^\text{a}\)

In the Choudhry et al. sample, financial costs of potentially unnecessary use of clopidogrel were high; patients who failed to meet the “extended” criteria were dispensed a mean of 239 clopidogrel tablets at a cost of $937 per patient per year (2005 dollars). Applying the rates of estimated “non-evidence-based” use in their sample to nationwide expenditures for clopidogrel, $3.5 billion in 2005, Choudhry et al. suggested that “health care [payers] and individuals in the United States” potentially “spent almost $1.5 billion in 2005 for clopidogrel in instances in which it … has not been demonstrated to be superior to aspirin.”\(^\text{43}^\text{a}\)

Prior Authorization and Clopidogrel Use—The Truth Lies in the Details

Clopidogrel had a discounted cost of $4.40 per day at year-end 2008, or $1,600 per patient per year, enough by itself to push a Medicare Part D beneficiary about two-thirds of the way to the coverage gap (“donut hole”) each year.\(^\text{46}\) Propelled by physician promotion and direct-to-consumer advertising,\(^\text{47}\) clopidogrel (Plavix) rang up $3.08 billion in community pharmacy sales in the United States in 2007, making it the fifth-highest expenditure drug, up 38.1% in sales from 2006 when it ranked seventh,\(^\text{48}\) and up 146% in 5 years from sales of $1.26 billion in 2002.\(^\text{49}\) And, clopidogrel is expected to be joined soon in the United States by prasugrel (Effient), which will push spending higher on newer drugs to prevent “clots.”

In the face of the heavy promotion of Plavix and the growing promotion of Effient even before it is approved by the FDA, the assessment of the relationship of clopidogrel “PA” and cardiovascular outcomes in 1 Canadian province deserves a bright spotlight. But, even in dim light, one can see that the observational study by Jackevicius et al. should be viewed with a clear understanding of the pitfalls inherent in methodologies that measure events with coincident timing, which may or may not be causally related. The PA “removal” was really a change in the administrative process; the database did not capture all of the use of clopidogrel; and a multitude of factors including the coincident explosion in use of drug-eluting stents could explain the cardiovascular outcomes observed in the administrative claims data. The primary purpose of PA—targeting drug therapies in an efficient manner to those patients most likely to benefit and least likely to be harmed, while providing value for money for patients, third-party payers, and (in some cases) taxpayers—seems especially appropriate and evidence-based when applied to clopidogrel. While a great deal of money is riding on the outcome of the debate about the real value of PA interventions, more money is at stake.

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There is Value in Anecdotal Reports of Relief from Migraine with Botulinum Toxin

To the Editor:

I am writing in response to the commentary in the June 2008 JMCP issue “Botox, Migraine, and the American Academy of Neurology: An Antidote to Anecdote.”¹ The authors argue for halting the use of botulinum toxin type A for the treatment of migraine, yet several of their arguments are non sequiturs, and they ignore statements they make that argue for its continued use.

They state that, because “administrative claims data documented increases in the use of acute migraine-related medications and in overall pharmacy and medical costs”, the treatment couldn’t be effective. But the statistic (however it was calculated) in no way proves this. Possibly the average cost for patients went up, but isn’t it possible that, for a subset of those patients, costs went down and the treatment was effective?

They state that “some have noted that some patient subpopulations may benefit from such treatment for some headache types”, but then they simply sidestep this because “identifying these patients will be difficult.” Our current inability to identify the patients who would benefit from a treatment is no argument for halting its use. In fact, if there are open questions about its effectiveness, then the correct response would be to continue studying it, not give up on it.

Lastly – anecdotes are not meaningless. We may find that, statistically, a treatment seems to have no value; but if there are many anecdotes to the contrary (and, using Google as the authors did, you will find many such anecdotes with respect to this treatment), there is a good chance that our studies are defective.

On a personal note, my spouse suffers from migraines. After trying many different treatments with no success, she found that Botox provides her with relief. She had no desire for cosmetic change, and her headaches are not stress-induced, as the authors argue might be an underlying reason for its desired use. Also, given that she had tried other treatments, and she had no particular reason to be partial to Botox, I highly doubt that this is a placebo effect (otherwise, why would she not have experienced the placebo effect with the other treatments?). Bottom line, this treatment – for her – works. Relegating it to the trash heap relieves her to years of unnecessary suffering.

We must all try to remember that these sufferers are people, not just statistics. If anecdotal evidence keeps inconveniently popping up, it’s our responsibility to ensure that we don’t ignore it.

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The Authors Respond:

There has been a long-standing, uneasy tension between “anecdotal medicine” and “evidence-based medicine.” The tension certainly reveals that there is no ultimate solution to the dilemma that every patient is unique but also that health care cannot be allowed to proceed in the chaos of “do whatever you want.” As a doctor I certainly respect individual patient variation. And, I also respect that science may reveal what personal perspective does not.

Specifically, one of the other long-standing dilemmas of health care has been the placebo effect. This is much more complex than most people realize. Placebo effect is not “no effect.” It is true effect, but it is derived from internal cerebral mechanisms which are not the consequence of the direct action of an external therapeutic agent. Rather, the effect is derived from the internally-generated emotive consequence of utilizing the external therapeutic agent.

In headaches particularly, placebos routinely show a 30%+ response rate. To see this, simply look up several double-blind, placebo-controlled clinical trials of your choice studying medications or other treatments for headache. Then look at the placebo “arm” of the study. Routinely there are 30% or more of the patients who responded to the placebo. If it is not a controlled study and the placebo effect is specifically exploited (using a placebo with intentional “selling” of the treatment), then a 50% or more response rate is sometimes observed.

I guarantee you that when these patients respond to the placebo they do not believe they are responding to a placebo. They believe it is the effect of the agent. In fact, where they don’t believe the agent will be effective the placebo effect is quelled.

So, can we see an effect in some patients for a treatment that is actually a placebo? Yes, this is clearly established. And, the patient will not believe this is the mechanism. We are not suggesting that this is what happened to Winett’s wife; we are observing what is known about the situation broadly.

One of the very specific problems in regard to Botox was the dilemma that no one offered a reasonable pathophysiologic explanation of why it should work. Of course, we all recognize that medicine doesn’t “know it all” and there is always the possibility of a new pathophysiologic mechanism being found. This is, in part, why Botox was allowed to be used for so very long before

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The author discloses no commercial or other financial conflict of interest relating to this letter.
the American Academy of Neurology (AAN) stepped in and said there was no solid support for its use. Everyone waited to see if a new pathophysiologic explanation explaining its effectiveness would be found. But, this never materialized.

Also, as you have referenced, many of us wondered if the mechanism of Botox relief was really via stress-induced tension mechanisms. Personally, I still think this is the actual route for its effectiveness. (I realize that some patients may disagree.) I won’t debate this with them, nor try to convince them of my position. It must suffice that this is my personal explanation unless a better explanation comes along.

Certainly, we in neurology did realize that there were some patients who wanted Botox for “migraine” while the real agenda was a cosmetic service covered by insurance. I’m by no means implying that this explanation was present in the case with Winett’s wife. But it did happen in practice.

One of my university colleagues was using Botox for migraine and he specifically avoided the cosmetic issue by only injecting deep neck muscles so that no cosmetic effect could be argued. He had some patients who responded for a while. Those patients who did respond reportedly did so for only a few months before it “wore off.” And, my colleague stopped prescribing it for migraine (eventually “voting with his feet” on this subject).

Botox is a very expensive treatment. While placebos work, it is desirable to use the least expensive one. And, if this is really effective via stopping the excessive muscle contraction we reference in “tension” then it is questionable whether paralyzing a muscle is the most appropriate way to produce that outcome.

I did not personally prescribe Botox for headaches because I was never sure of its mechanism and I wondered if permanent denervation would become a problem. The latter did not occur (thankfully). The patients I sent to the university tended to drift off of Botox after a while.

As you recognize, our commentary came on the heels of the release of the AAN position statement.1 I long held my personal beliefs about the subject, but we did not author the commentary until this became supported by authoritative and full review of the data by the AAN.

We note that Winett is not precluded from obtaining Botox for his wife. But, the current position paper of the AAN may require the Winetts to vote with their feet (i.e., pay for the drug out of pocket) rather than having that cost borne by others via insurance. If patients truly believe in the use of Botox for this purpose, the path is still open.

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