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**REFERENCE**

Louis Comfort Tiffany (1848–1933) was the privileged son of Harriet Olivia Avery Young and Charles Lewis Tiffany, founder of Tiffany & Company. Born and raised in New York City, Tiffany was a restless and strong-willed child. In 1863, at the age of 14, he was sent to Eagleswood Military Academy in Perth Amboy, New Jersey, for a structured and disciplined education. Although the school also offered classes in art, one of his favorite subjects, life at the formal school was not to his liking. Tiffany left school in 1865 and began his artistic career as a painter. Later that year, during a trip to Europe, he visited the Victoria and Albert Museum in London, where their collection of ancient Roman and Syrian glass made a lasting impression upon him. As Tiffany admired the vivid coloration of the glass, he was convinced that the quality of contemporary glass could be improved to resemble that of the past. Upon his return to America, he enrolled at the National Academy of Design in New York City. At this time, Tiffany also studied with landscapist George Inness, whose personal interpretation of nature greatly influenced the young pupil. According to Camilla de la Bédoyère, author of Louis Comfort Tiffany Masterworks, “In 1867, at the age of just 19, Tiffany exhibited his first painting at the National Academy of Design. He would later describe his paintings as ‘One instance in time, a fragment of a happy day.’”

In 1868, Tiffany studied art in Paris under Léon Bailly, then went to Spain and North Africa the following year to study with artist Samuel Colman. They shared an interest in the ornament, forms, and patterns of Islamic and Romanesque art.

Settling back in New York City, Tiffany met Mary Woodbridge Goddard, and they married in 1872. The couple had 2 daughters and a son. Throughout the 1870s, Tiffany continued to exhibit his landscape, portrait, and still-life paintings, created in both oil and watercolor. Tiffany began experimenting with new stained-glass techniques in 1875, working first at the Thill Glasshouse in Brooklyn, New York, and then at the Heidt Glasshouse, also in Brooklyn. In 1879, he joined with Samuel Colman, Lockwood de Forest, and Candace Wheeler to form the Louis C. Tiffany and Associated Artists interior design company. The firm's most notable work was a floor-to-ceiling glass screen commissioned for the White House by President Chester A. Arthur.

During the early 1880s, Tiffany developed a type of glass that he called “Favrile” glass. The name was derived from the Latin root fabril, meaning “handmade.” Favrile was officially registered as a trademark with the U.S. Patent Office in 1894. Tiffany’s Favrile glass resembles the glass of ancient times because of its iridescence, achieved by adding metallic salts or oxides to the molten mixture. Magnolias and Irises, a stained-glass window panel, is a superb example of his work in Favrile glass. In this beautiful scene, 2 flowering magnolia trees are surrounded by a bed of purple iris flowers. In the background, a cool, mountain lake reflects the warm, multicolored sunset. This window is part of the permanent Tiffany installation at New York’s Metropolitan Museum of Art.

Despite its great success, Tiffany’s interior design firm dissolved in the spring of 1883. Tragedy struck a year later when his wife died of tuberculosis. Tiffany remarried in 1886 to Louise Wakeman Knox, and they had 4 daughters.

By the mid 1880s, the artist had formed his own glass company, called The Tiffany Glass Company, later renamed The Tiffany Glass and Decorating Company. Stained-glass church windows comprised a large segment of the company’s business during its early years. The first stained-glass Tiffany lamps were produced in 1895. Tiffany earned many awards for his magnificent work, including a grand prize at the 1901 Pan-American Exposition in Buffalo, New York. He was also a recognized leader of the Art Nouveau movement, which began as a reaction to the academic art of the 19th century. Peaking in popularity at the turn of the 20th century, Art Nouveau is characterized by organic motifs (especially floral and other plant-inspired designs) as well as flowing, curvilinear forms. With these decorations, the outside was brought inside the home, enabling people to have a closer relationship with nature.

In 1905, Tiffany completed the construction of his grand estate called Laurelton Hall on Long Island, New York. The 84-room mansion on 580 acres was a showcase for some of his finest work. Unfortunately, Laurelton Hall was destroyed by fire in 1957, but many priceless objects were rescued and are on display at The Charles Hosmer Morse Museum of American Art in Winter Park, Florida.

Although he is best known for his stained-glass creations, Tiffany also designed blown-glass items, mosaics, pottery, metal works, and jewelry. Tiffany’s stained-glass lamps are among the best-known examples of the Art Nouveau style and continue to be imitated to this day.
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ABSTRACT

BACKGROUND: Proton pump inhibitors (PPIs) are among the highest expenditure drugs covered by health care plans. During fiscal year 2001-2002, Medicaid programs nationwide spent nearly $2 billion on PPIs. Although the costs of individual PPIs vary widely, there is little variation in therapeutic effectiveness. On June 1, 2007, the North Carolina Medicaid program implemented an “instant approval” option simultaneously with a prior authorization (PA) program for PPIs with the goal of managing costs and maintaining high-quality care. Preferred PPIs included generic omeprazole and Prilosec OTC. This instant approval process (IAP) was expected to impose less administrative burden than is typically associated with PA programs by permitting physician and nonphysician prescribers to either write the PA criteria directly on a prescription form or use “MD Easy,” a preprinted form that could be faxed by the prescriber to the dispensing pharmacy. A previous study found that from the prescriber’s perspective the IAP reduced practice-related administrative burden and was associated with a reduced gap in PPI therapy when compared with traditional PA.

OBJECTIVE: To evaluate the acceptability and effectiveness of this IAP for PPIs as assessed by the outcome measures of (a) pharmacist satisfaction with the IAP; (b) physician and pharmacist satisfaction with the MD Easy form; and (c) utilization rates for preferred PPIs, comparing medical practices that used the MD Easy form with practices that did not write the PA criteria directly on a prescription form or use “MD Easy.”

METHODS: A cross-sectional design was used to assess pharmacist and physician satisfaction. A stratified random sample of 240 pharmacies was selected from 1,561 North Carolina pharmacies with claims in the Medicaid claims data file during state fiscal year 2006. Additionally, a stratified random sample of 240 medical practices was selected from 1,045 primary care practices serving Medicaid beneficiaries during 2006. Surveys were administered to pharmacists using either in-person interviews or self-administered questionnaires and to physicians using a mailed questionnaire with follow-up to nonrespondents. An interrupted time series analysis was used to evaluate the effect of the MD Easy form on switching to preferred PPIs using paid Medicaid claims of surveyed practices from calendar year 2007. Practices that reported both using the IAP and receiving the MD Easy form were defined as MD Easy users. Monthly market share data were analyzed using log negative binomial regression models to account for autocorrelation in the time series data.

RESULTS: The pharmacy survey was completed by 202 (84.2%) pharmacies selected for participation. Of 198 permanently employed pharmacists, 140 (70.7%) reported experience with the IAP for PPIs. More than two-thirds (68.6%) of the pharmacist respondents with IAP experience indicated that the IAP is better (34.3%) or much better (34.3%) than traditional PA with respect to overall administrative burden of phone calls, faxes, patient interactions, and doctor contacts. Surveys were completed by 171 (71.3%) of selected physician practices, of which 56 (32.7%) reported experience with the MD Easy forms. Of practices that recalled receiving the MD Easy forms, 52 of 56 (92.9%) reported that the forms “very much” or “somewhat” helped prevent gaps in PPI therapy; 54 of 55 (98.2%) reported that they helped identify patients affected by Medicaid PPI PA; and 100% reported that they helped physicians to follow PA requirements. Immediately after implementation of the IAP and MD Easy form, the observed market share of preferred PPIs increased by 4.1 times (95% CI = 3.57-4.62). From May to June 2007, the preferred PPI market share increased by 64.0 percentage points, from 19.3% to 83.3% (P < 0.001), for practices that reported using the IAP and receiving the MD Easy form (n = 56) and by 55.4 percentage points, from 21.8% to 77.2% (P < 0.001), for practices that either (a) reported not receiving the MD Easy form (n = 25) or (b) reported not using the IAP (n = 84) or (c) did not respond to the survey item asking about the MD Easy form (n = 4). The overall increase in preferred PPI market share after implementation of the IAP was 1.29 times higher for practices that used the MD Easy form than for those that did not based on negative binomial regression modeling; this difference approached statistical significance (95% CI = 1.00-1.68; P = 0.053).

CONCLUSION: This study suggests that an IAP for PPIs using either handwritten prescriptions or a preprinted form is an effective alternative to traditional PA. The IAP was associated with an increase in market share for preferred PPIs and was perceived by pharmacists as less administratively burdensome than traditional PA. Additional studies are needed to determine sustainability and the applicability to other prescription drugs.

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What is already known about this subject (continued)

- Traditional PA programs may be costly and burdensome to prescribers and pharmacists. Bukstein et al. (2006) found that physicians and nurses in an allergy practice averaged 1.9 and 5.6 phone calls per day, respectively, for PA, resulting in an average cost of $17.77 per PA. The specific costs of PA to pharmacies have not been identified in published literature.
- Alternatives to traditional PA, such as instant approval mechanisms, electronic PA, and web-based PA, are increasing and include the Missouri Medicaid automated electronic PA system (SmartPA) for cyclooxygenase-2 (COX-2) inhibitors, implemented in 2002, and a Medical Mutual of Ohio automated PA process (Smart Rules) for determining patient qualification for COX-2 inhibitors and antidepressants.
- Limited existing evidence suggests that alternative PA strategies may be effective and perceived as less burdensome to physicians than traditional PA. The automated electronic PA system in the Missouri Medicaid program was credited with reducing expenditures for COX-2 inhibitors by $131 per patient per year (PPP) in 2003 compared with an increase of $59 PPPY in a comparison state without PA for COX-2 inhibitors.
- A previously published study of the North Carolina Medicaid instant approval process (IAP) for PPIs reported that the market share for preferred PPIs increased from 17% to 19% in the pre-IAP period to 76% in the first month after IAP implementation. Although market share changes were similar for practices using IAP and traditional PA, the median gap in PPI therapy for patients whose prescribers used traditional PA was approximately twice the gap for the IAP (26 days vs. 12 days, respectively, p < 0.001). Of the physician practices using IAP, 81.1% believed it reduced practice-related administrative burden.

What this study adds

- This study builds on the previously published study of IAP for PPIs by focusing on the perceived administrative burden of traditional PA compared with IAP from the perspective of the pharmacist. Of responding pharmacists familiar with the IAP, 68.6% rated the IAP as being better or much better than traditional PA with respect to administrative burden to the pharmacy. Pharmacists reported that the IAP saved an estimated 21 work minutes per patient, on average, when compared with traditional PA.
- The use of a unique preprinted "MD Easy" PA form that could be faxed to prescribers to dispensing pharmacies was introduced despite concerns that the MD Easy form may make it easier to prescribe nonpreferred PPIs. However, in the first month after implementation of the IAP, the increase in preferred PPI market share was similar in practices using the MD Easy form and practices not using the MD Easy form (64.0 percentage points vs. 55.4 percentage points). In negative binomial regression modeling, the overall increase in preferred PPI market share after implementation of the IAP was 1.29 times higher for practices that used the MD Easy form than for those that did not; this difference approached statistical significance (95% CI = 1.00-1.68; P = 0.053).
- Of the pharmacies who rated the usefulness of the MD Easy form for expediting the PA form, most (95.5%) rated it good to excellent. One-third of physician practices recalled receiving the MD Easy forms, and these practices reported that the MD Easy form helped to prevent gaps in therapy (92.9%) and follow PA requirements for PPI (100%).

Medicaid expenditures for prescription drugs have increased over time at alarming rates.1 After adjusting for inflation, total U.S. Medicaid expenditures for prescription drugs more than doubled from $11.6 billion to $23.7 billion from the fiscal years 1996-1997 to 2001-2002.2 The North Carolina Medicaid program experienced an estimated 88% increase in prescription drug reimbursement between 2000 and 2005, from $795 million to $1.49 billion.3 Between fiscal years 1996-1997 and 2001-2002, similar trends in expenditure increases nationwide were observed for the broad class of drugs that treat gastrointestinal (GI) disorders. Medicaid expenditures nationwide for GI drugs increased from $1.02 billion in 1996-1997 to $1.83 billion in 2001-2002,2 driven in large part by proton pump inhibitors (PPIs). These increases were attributed to increases in the cost per user as well as growth in the number of people using GI drugs.2

PPIs are a subclass of GI drugs that are indicated for short-term therapy of acute upper GI disorders (e.g., peptic ulcers and esophagitis), pathologic gastric hypersecretory conditions (e.g., Zollinger-Ellison syndrome), and maintenance therapy for persons with healed ulcers and erosive esophagitis.5-6 PPIs are among the costliest drugs covered by health care plans.4 Although the costs of individual PPIs vary widely, there is little variation in therapeutic effectiveness among the PPIs.6

State Medicaid programs and other payers have developed and implemented a number of strategies to attempt to curb rising prescription drug expenditures while ensuring appropriate access to prescription medications.7-10 Existing evidence has shown that prior authorization (PA) is one approach that can be effective at reducing use of higher-cost medications when other equally effective and lower-cost alternatives are available.4,14,17-23 PA has been defined as a process that "restricts the use of specific medications by requiring an advance approval by the Medicaid program or its agent for the drug before dispensing to qualify for reimbursement."24 The benefit of PA to a payer is the ability to stop inappropriate utilization before it takes place. Although concerns about patient access exist, a number of published studies demonstrate safety and effectiveness of PA programs.4,14,17,20 Yet, studies of PA programs have not completely dispelled lingering criticisms. For example, high administrative costs are a major criticism of U.S. health care systems.24-27 In 1999, U.S. health care administrative costs were estimated at $294.3 billion or $1,059 per capita.26 PA-related activities and other interactions between pharmacies, prescribers, and health insurance programs contribute to these administrative costs.13,24 Using data from a national survey, Casalino et al. (2009) estimated that the cost for the time spent by U.S. health care providers to interact with health insurance plans ranges from $23 to $31 billion annually.24 They reported that the average amount of time spent weekly on authorizations was 13.1 hours by nursing staff for each physician in the practice, 1 hour per physician, and 6.3 hours for clerical staff.24 Bukstein et al.
(2006) found that the cost per PA of physician and nursing time within an allergy practice was $17.77. Administrative costs of PA are also incurred by third-party payers. For example, one Medicaid program paid an administrative fee of $20 for each PA request for PPIs.9

Less attention has been devoted to the administrative burden to pharmacies. Although pharmacists are not typically asked to submit written PA documentation to payers, they are nonetheless thrust into the middle of coverage determination activity. Traditional pharmacy PA typically involves a multi-step process in which the physician or other prescriber writes a prescription, the patient takes the prescription to the local pharmacist, the prescription is denied through the electronic claims system, the pharmacist contacts the prescriber by telephone to indicate the need for PA, the prescriber contacts the PA center to initiate the PA, the prescription is approved or denied based on clinical criteria established by the payer, and potentially the prescriber notifies the pharmacy of the PA decision. If the pharmacy is not notified of the PA decision, the pharmacy may call the PA center to inquire about the status, periodically re-run the prescription in the electronic claims system to see if it is approved, or leave the process incomplete. Often acting as a messenger from patient to prescriber to payer and back, it is ultimately the pharmacist’s responsibility to ensure that a drug is covered before dispensing it or risk denial of reimbursement for the dispensed prescription. In an era of multiple hundreds of prescriptions filled by a single pharmacist in a day, stopping the workflow to address a PA for a patient can be disruptive, even if the activity takes as little as 5 or 10 minutes to address with the patient and prescriber, mostly because of the sheer volume of PAs that a pharmacist may encounter on any given day.

Alternatives to traditional PA programs, including electronic PA and web-based PA, are beginning to emerge with the intent of improving administrative efficiency and reducing burden on providers, patients, and pharmacists while achieving cost-containment and quality of care goals. However, limited empirical evidence exists on whether the alternative mechanisms actually achieve these administrative and cost-related goals. A study of a “SmartPA” system for cyclooxygenase-2 (COX-2) inhibitors in the Missouri Medicaid program, conducted by Carroll et al. (2006), involved use of an automated electronic PA system that used clinical rules and queries of drug and medical claims data at the point of service. This study reported reduced expenditures for COX-2 inhibitors as well as significant administrative cost avoidance over traditional PA based on a decrease in PA-related calls.

The instant approval process (IAP) is another alternative to traditional PA for managing access to specific types of prescription drugs. The IAP permits physician and nonphysician prescribers to document the patient-specific approval criteria directly on a written prescription so that the pharmacist can dispense the drug without delay at the pharmacy. A previously published study assessed 2 objectives of the North Carolina Medicaid IAP for PPIs: (a) contain drug costs and (b) avoid clinical and service problems, such as gaps in therapy and clinician dissatisfaction. The previous study reported that the market share for the preferred PPIs, generic omeprazole and Prilosec OTC, increased from 17% to 19% in the pre-IAP period to 76% in the first month after IAP implementation. Although market share changes were similar for practices using the IAP and traditional PA, the median gap in PPI therapy for patients whose prescribers used traditional PA was approximately twice the gap for the IAP (26 days vs. 12 days, respectively, P < 0.001). Of the physician practices using IAP, 81.1% believed it reduced practice-related administrative burden.

The present study built on the previous study by including an assessment of the pharmacy experience and examining the use of pre-printed prescriptions. Specifically, the present study examined (a) pharmacist satisfaction with the IAP, (b) prescriber and pharmacist satisfaction with MD Easy, a pre-printed prescription form, and (c) whether the rate of switching to preferred PPIs varied between those practices that used the MD Easy form compared with those practices that did not.

### Methods

**Description of the PA Intervention**

Prior to June 2007, North Carolina Medicaid placed no coverage restrictions on PPIs. On June 1, 2007, North Carolina Division of Medical Assistance (DMA) implemented a PA program for PPIs for Medicaid beneficiaries. Out of concern for the potential burden that a PA program would place on prescribers and pharmacists, Community Care of North Carolina (CCNC), the state’s Medicaid managed care program, requested that the PA process include an IAP as an alternative option to the traditional PA system. The new PA program included 3 options for patient access to PPIs. In option 1, prescriptions for the 2 preferred medications, generic omeprazole and Prilosec OTC, were exempt from PA. Option 2 was the traditional PA process for nonpreferred PPI medications. Option 3 included a unique IAP for nonpreferred PPIs that permitted prescribers to document the patient-specific approval criteria directly on the written prescription or use a pre-printed prescription form, MD Easy. Approval criteria for nonpreferred PPIs included (a) failure with a 30-day trial of no less than 40 milligrams (mg) of omeprazole during a 12-month period; (b) use of esomeprazole magnesium (Nexium) 40 mg for diagnosis of erosive esophagitis Grade C or D; or (c) inability to swallow tablets or capsules (use of brand name solutab and liquid dosage formulations). The PA policy excluded Medicaid beneficiaries who were aged 6 years or younger, those in an eligibility category indicating pregnancy, and dual eligible beneficiaries with Medicare Part D coverage.

As part of the IAP effort, CCNC created pre-printed
Pharmacist and Physician Satisfaction and Rates of Switching to Preferred Medications Associated with an Instant Prior Authorization Program for Proton Pump Inhibitors in the North Carolina Medicaid Program

FIGURE 1 MD Easy Form: Pre-Printed Prescription Form for Proton Pump Inhibitors

<table>
<thead>
<tr>
<th>Practice Information</th>
<th>Request Date</th>
<th>/</th>
<th>/</th>
</tr>
</thead>
<tbody>
<tr>
<td>Practice Address</td>
<td>Pharmacy Information</td>
<td>Pharmacy Name</td>
<td></td>
</tr>
<tr>
<td>Practice City, State, Zip</td>
<td>Pharmacy Phone</td>
<td>Pharmacy Fax</td>
<td></td>
</tr>
<tr>
<td>Practice Phone</td>
<td>Practice Fax</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patient Information

<table>
<thead>
<tr>
<th>Patient Name</th>
<th>Patient DOB</th>
<th>Patient Address</th>
</tr>
</thead>
</table>

**Please select one of the following three options and fax to pharmacy.**

1) **Please switch patient to (select one):**

- **Omeprazole 20mg Cap**
  - Circle one: 1QD 1BID 2QD 2BID Other
  - Dispense #: __________________
  - Refill #: __________________

- **OTC Prilosec 20mg Tab**
  - Circle one: 1QD 1BID 2QD 2BID Other
  - Dispense #: (circle one): 42 84 126 168
  - Refill #: __________________

2) **Prescribers: In your own handwriting, please indicate one of the following applicable exemption criteria for override in the space provided below for the medication:**

<table>
<thead>
<tr>
<th>Originally Prescribed PPI</th>
<th>Quantity</th>
</tr>
</thead>
</table>

Directions for use & route of administration

- “Failed Omeprazole 40mg for 30 days” (within the last 12 months)
- Erosive “Esophagitis grade C” or “Esophagitis grade D” (Esomeprazole (Nexium) only)
- “Cannot swallow tablets” or “Cannot swallow capsules”

**Note:** “Dispense as written” or “Brand medically necessary” is only applicable for Prilosec 20mg or 40mg, and can only be used after the above criteria have been documented on the face of the prescription.

**Exemption Criteria (write exactly as shown)**

Refill #: __________________

(Pharmacist– For exemption criteria, use override code 1 in PA field or 2 in submission clarification field. If patient pregnant or breastfeeding, indicate 2 in the pregnancy indicator field or V22 or V23 in the diagnosis field **Override begins Jun 1, 2007.**)

3) **On or after June 1, 2007, I will initiate PA process and contact ACS at 866-246-8505 (phone) or 866-246-8507 (fax).**

**Prescriber Signature**

**Date**

**Prescriber Name (please print)**

**DEA**

**Note:** By signing this document and 1) checking the OTC Prilosec/Omeprazole substitution or 2) checking the brand name exemption criteria box above you are consenting to this being a legal prescription and the pharmacy should fill it as such. DMA policy requires documentation of exemption criteria in the patient’s chart for auditing purposes if option 2 is selected.
prescriptions, called MD Easy forms (Figure 1). Approximately 35,000 MD Easy forms were printed, 1 for each enrolled North Carolina Medicaid recipient who had a nonpreferred PPI claim during the previous year. The MD Easy forms were pre-populated with patient name, date of birth, address, prescribing practice, pharmacy, the nonpreferred drugs that the patient was currently taking, and instructions to select 1 of the 3 prescribing options. These forms were provided to each of the 14 CCNC networks to be sent to their respective primary care practices during May 2007. The new PA program with an IAP option and the deployment of MD Easy forms was intended to contain costs of PPIs, while maintaining high-quality care and reducing the administrative burden typically associated with traditional PA. The MD Easy form was also expected to facilitate patient access to a prescription through a preemptive PA process that occurs before the patient arrives at the pharmacy when picking up the next PPI refill.

Study Design and Participants
Cross-sectional and interrupted time series designs were used in this study. A cross-sectional design with a descriptive data analysis was used to assess pharmacist and prescriber satisfaction with the IAP and MD Easy form as alternatives to traditional PA for PPIs. A stratified simple random sample of 240 pharmacies was selected from 1,561 North Carolina pharmacies with claims in the North Carolina Medicaid claims data file during state fiscal year 2006 (Figure 2). Random number generation was used in each stratum to select the final sample using SAS PROC SURVEYSELECT (SAS Institute Inc., Cary, NC). Pharmacies were stratified based on the number of unique Medicaid PPI pharmacy claims as a proxy measure for pharmacy size. Three strata were defined as (a) 10 or fewer PPI prescription claims (low volume, 80 of 704 pharmacies); (b) 11 to 49 PPI claims (medium volume, 80 of 757 pharmacies); and (c) 50 or more PPI claims (high volume, 80 of 100 pharmacies; Figure 2). Both rural and urban pharmacies were represented.
employees may be less likely to have the experience to compare traditional PA and IAP.

A stratified simple random sample of 240 medical primary care practices was selected to participate in the PPI provider survey. These practices were selected from 1,045 primary care practices serving CCNC Medicaid beneficiaries with at least 1 PPI Medicaid claim during the state’s fiscal year 2006 (Figure in the sample, based on a review of the distribution of Rural-Urban Commuting Area (RUCA) scores for eligible pharmacies. For each eligible pharmacy, 1 pharmacist was selected for interview or self-administered survey based on availability at the time of an on-site visit. Although there were no sampling exclusions, survey responses of 4 temporarily employed pharmacists were excluded from the survey results because these employees may be less likely to have the experience to compare traditional PA and IAP.

A stratified simple random sample of 240 medical primary care practices was selected to participate in the PPI provider survey. These practices were selected from 1,045 primary care practices serving CCNC Medicaid beneficiaries with at least 1 PPI Medicaid claim during the state's fiscal year 2006 (Figure...
3). Random number generation was used in each stratum to select the final sample using SAS PROC SURVEYSELECT. Strata for provider practices were defined similarly to the pharmacies and were based on practice-level PPI prescribing patterns during the year: (a) low volume of PPI claims (80 of 386 practices); (b) medium volume (80 of 506 practices); and (c) high volume (80 of 153 practices; Figure 3). The sample size of 240 practices was selected with an expectation of a 60% response rate, that is, an expected sample size of 144. This sample size would allow estimation of survey outcomes with 95% confidence intervals (CI) of +/- 8 percentage points.

An interrupted time series analysis was used to evaluate the effect of the MD Easy form on channeling to preferred PPIs. Paid PPI claims for calendar year 2007 were selected for North Carolina Medicaid beneficiaries who were subject to the PA policy and linked in the CCNC Medicaid program with primary care practices that completed the physician survey. The study was approved by the University of North Carolina School of Medicine Institutional Review Board.

**Study Procedures, Data Sources, and Measurement**

**Medicaid Claims for Sample Identification and Measurement of Preferred PPI Market Share.** North Carolina Medicaid claims for PPIs were obtained from the North Carolina Division of Medical Assistance for 2 time periods for distinct purposes. First, Medicaid claims from state fiscal year 2006 were used to identify potentially eligible pharmacies and physician practices and obtain contact information for the provider surveys. Second, pharmacy claims for calendar year 2007 were obtained for time series analyses.

To construct the data file for the time series analysis, the FirstDataBank (FirstDataBank, San Francisco, CA) Specific Therapeutic Class (GC3) code “D4J” was used to select the pharmacy claims for PPI drug products. Physician survey responses were matched with calendar year 2007 pharmacy claims using CCNC practice identifier codes and Medicaid beneficiary primary care provider designations. The PPI claims were then assigned to 1 of 2 groups based on the practice survey results: (a) used the MD Easy form (i.e., reported using the IAP and receiving the MD Easy form [n = 56]) or (b) did not use the MD Easy form (n = 113, including 25 practices that answered “no” to the question “Did your practice receive any pre-populated MD Easy forms?” and 88 practices that either reported not using the IAP [n = 84] or reported using the IAP but did not reply to the question about receipt of the MD Easy forms [n = 4]). Preferred PPI market share was computed for each of the 2 groups for each month as the number of preferred PPI prescription claims divided by the total number of preferred and nonpreferred PPI prescription claims. The preferred market share percentages were plotted for 12 sequential months for calendar year 2007 separately for those practices that used the MD Easy form versus those practices that did not use the MD Easy form. This period included 5 months immediately prior to and 7 months following implementation of the PA program.

**Measurement of Pharmacist Satisfaction.** A team of investigators and pharmacists developed a brief structured interview tool to be administered to eligible pharmacists. A slightly modified version of the interview tool was developed as a self-administered questionnaire for those pharmacists not available to complete an in-person interview. The interview tool and questionnaire inquired about the pharmacist’s employment status, pharmacy experience with the PPI IAP and MD Easy form, perceived administrative burden of IAP for the pharmacist and patient compared with traditional PA, perceived usefulness of the IAP training, and overall comparison between traditional PA and IAP. The survey was pilot tested with 3 pharmacists; estimated completion time was approximately 5 minutes.

Prior to implementing data collection, 2 graduate pharmacy students completed interviewer training. In-person interviews were performed between mid-August and mid-December 2007 by these students at most pharmacy sites. For 7 pharmacies in more distant locations, regional CCNC network pharmacists performed the interviews, 6 in person and 1 by mailed questionnaire. Interviewers made initial contact in person at the eligible pharmacies and asked to conduct the brief structured interview at that time. If an interview could not be completed, a survey formatted for self-completion and a pre-addressed stamped survey return envelope were provided to the pharmacist. No attempts were made to re-contact nonresponding pharmacists. Interviewers assigned and documented unique study identification numbers on survey forms and master eligibility lists at the time of interviews. Completed interview and questionnaire responses were entered in Microsoft Excel (version 2003; Microsoft Corporation, Redmond, WA).

**Measurement of Physician Satisfaction.** The investigative team also developed a brief survey to assess the perceived usefulness and adoption of PPI IAP and MD Easy among physicians. The survey was pilot tested with 4 primary care physicians. Survey packets were sent from the North Carolina Physician Advisory Group to community case managers during August 2007. Case managers delivered cover letters, PPI practice surveys, and postage-paid pre-addressed survey return envelopes to eligible practices. Cover letters explained that only 1 primary care provider per practice should complete the form, ideally the physician with the most experience with PPI IAP. Community case managers provided a second copy of the survey to nonresponding practices approximately 6 weeks after the initial distribution. Completed survey responses were entered in Microsoft Excel (version 2003).
## Table 1: Pharmacist and Physician Satisfaction with the PPI Instant Approval Process and the MD Easy Form

<table>
<thead>
<tr>
<th>Survey Item</th>
<th>Response Options</th>
<th>PPI Prescription Volume</th>
<th>P Value&lt;sup&gt;4&lt;/sup&gt; (unweighted)</th>
<th>Total (unweighted)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacy survey results</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has this pharmacy had any experience with NC Medicaid's instant approval program for PPIs since June 1 of this year?</td>
<td>Yes&lt;sup&gt;5&lt;/sup&gt;</td>
<td>n (%)</td>
<td>n (%)</td>
<td>Total (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>33 (52.4)</td>
<td>50 (74.6)</td>
<td>57 (83.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 (47.6)</td>
<td>17 (25.4)</td>
<td>11 (16.2)</td>
</tr>
<tr>
<td>Do you believe that the instant approval process causes less burden on your pharmacy than the traditional PA process?</td>
<td>Yes</td>
<td>28 (84.8)</td>
<td>34 (68.0)</td>
<td>39 (68.4)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>5 (15.2)</td>
<td>16 (32.0)</td>
<td>18 (31.6)</td>
</tr>
<tr>
<td>[If yes] Estimate the total number of work minutes per patient, on average, that you believe are saved using the new instant approval versus the traditional PA process. Include all staff at your pharmacy in this estimate.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>25.2</td>
<td>23.3</td>
<td>16.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>21.1 minutes</td>
</tr>
<tr>
<td>Community Care of NC provided education before the roll-out of the IA program. This training included a description of the new program for PPIs, a sample MD Easy form, a list of criteria allowing instant approval, and gave an opportunity for people in your pharmacy to ask questions. Did your pharmacy receive any of the training described above?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>12 (36.4)</td>
<td>24 (48.0)</td>
<td>25 (43.9)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>21 (63.6)</td>
<td>26 (52.0)</td>
<td>32 (56.1)</td>
</tr>
<tr>
<td>Did your pharmacy receive training on the MD Easy form?</td>
<td>Yes</td>
<td>11 (34.4)</td>
<td>20 (40.0)</td>
<td>22 (38.6)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>21 (65.6)</td>
<td>30 (60.0)</td>
<td>35 (61.4)</td>
</tr>
<tr>
<td>Has this pharmacy received any of the MD Easy forms for PPI prescriptions since June 1 of this year?</td>
<td>Yes</td>
<td>15 (48.4)</td>
<td>30 (61.2)</td>
<td>39 (69.6)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>16 (51.6)</td>
<td>19 (38.8)</td>
<td>17 (30.4)</td>
</tr>
<tr>
<td>Which answer best describes the overall administrative burden of phone calls, faxes, patient interactions, and doctor contacts with instant approval compared to traditional PA process&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Traditional PA much better</td>
<td>0 (0.0)</td>
<td>2 (4.0)</td>
<td>2 (3.5)</td>
</tr>
<tr>
<td></td>
<td>Traditional PA better</td>
<td>1 (3.0)</td>
<td>3 (6.0)</td>
<td>2 (3.5)</td>
</tr>
<tr>
<td></td>
<td>No difference</td>
<td>7 (21.2)</td>
<td>11 (22.0)</td>
<td>16 (28.1)</td>
</tr>
<tr>
<td></td>
<td>Instant approval better</td>
<td>11 (33.3)</td>
<td>17 (34.0)</td>
<td>20 (35.1)</td>
</tr>
<tr>
<td></td>
<td>Instant approval much better</td>
<td>14 (42.4)</td>
<td>17 (34.0)</td>
<td>17 (29.8)</td>
</tr>
<tr>
<td>Next, use the same 5-level scale to compare your patients' satisfaction with the 2 PA processes.</td>
<td>Traditional PA much better</td>
<td>1 (3.2)</td>
<td>2 (4.0)</td>
<td>3 (5.3)</td>
</tr>
<tr>
<td></td>
<td>Traditional PA better</td>
<td>0 (0.0)</td>
<td>3 (6.0)</td>
<td>3 (5.3)</td>
</tr>
<tr>
<td></td>
<td>No difference</td>
<td>9 (29.0)</td>
<td>27 (54.0)</td>
<td>25 (43.9)</td>
</tr>
<tr>
<td></td>
<td>Instant approval better</td>
<td>11 (35.5)</td>
<td>6 (12.0)</td>
<td>17 (29.8)</td>
</tr>
<tr>
<td></td>
<td>Instant approval much better</td>
<td>10 (32.3)</td>
<td>12 (24.0)</td>
<td>9 (15.8)</td>
</tr>
<tr>
<td>Rate the usefulness of this training [using the scale provided].</td>
<td>Extremely</td>
<td>2 (16.7)</td>
<td>4 (16.7)</td>
<td>6 (24.0)</td>
</tr>
<tr>
<td></td>
<td>Very</td>
<td>4 (33.3)</td>
<td>8 (33.3)</td>
<td>7 (28.0)</td>
</tr>
<tr>
<td></td>
<td>Somewhat</td>
<td>6 (50.0)</td>
<td>12 (50.0)</td>
<td>12 (48.0)</td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Rate the usefulness of the MD Easy form for expediting the PA process [using the scale provided].</td>
<td>Excellent</td>
<td>2 (22.2)</td>
<td>5 (29.4)</td>
<td>8 (42.1)</td>
</tr>
<tr>
<td></td>
<td>Very good</td>
<td>6 (66.7)</td>
<td>7 (41.2)</td>
<td>5 (26.3)</td>
</tr>
<tr>
<td></td>
<td>Good</td>
<td>1 (11.1)</td>
<td>4 (23.5)</td>
<td>5 (26.3)</td>
</tr>
<tr>
<td></td>
<td>Fair</td>
<td>0 (0.0)</td>
<td>1 (5.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Taking all things into consideration and using the [scale], give us your overall comparison of the traditional PA and instant approval programs for Medicaid patients receiving PPIs.</td>
<td>Traditional PA much better</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td></td>
<td>Traditional PA better</td>
<td>1 (3.0)</td>
<td>4 (8.0)</td>
<td>3 (5.4)</td>
</tr>
<tr>
<td></td>
<td>No difference</td>
<td>5 (15.2)</td>
<td>9 (18.0)</td>
<td>8 (14.3)</td>
</tr>
<tr>
<td></td>
<td>Instant approval better</td>
<td>11 (33.3)</td>
<td>21 (42.0)</td>
<td>27 (48.2)</td>
</tr>
<tr>
<td></td>
<td>Instant approval much better</td>
<td>16 (48.5)</td>
<td>16 (32.0)</td>
<td>17 (30.4)</td>
</tr>
<tr>
<td><strong>Physician practice survey results</strong>&lt;sup&gt;6&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some practices received a pre-populated patient-specific MD Easy form. Did your practice receive any pre-populated MD Easy forms?</td>
<td>Yes</td>
<td>9 (64.3)</td>
<td>21 (63.6)</td>
<td>26 (76.5)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>5 (35.7)</td>
<td>12 (36.4)</td>
<td>8 (23.5)</td>
</tr>
<tr>
<td>To what degree did the pre-populated MD Easy forms help prevent gaps in therapy or days of missed therapy for your patients receiving PPIs?</td>
<td>Very much</td>
<td>5 (55.6)</td>
<td>10 (47.6)</td>
<td>15 (57.7)</td>
</tr>
<tr>
<td></td>
<td>Somewhat</td>
<td>3 (33.3)</td>
<td>10 (47.0)</td>
<td>9 (34.6)</td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
<td>1 (11.1)</td>
<td>1 (4.8)</td>
<td>2 (7.7)</td>
</tr>
</tbody>
</table>

<sup>1</sup> Calculated as the mean time saved using the new approval process compared to the traditional PA process, including all staff at the pharmacy.

<sup>2</sup> Missing value.

<sup>3</sup> Missing value.

<sup>4</sup> P values calculated for the association between satisfaction responses and PPI prescription volume.

<sup>5</sup> Pearson's chi-square test.

<sup>6</sup> Fisher’s exact test.
Pharmacist and Physician Satisfaction with the PPI Instant Approval Process and the MD Easy Form

<table>
<thead>
<tr>
<th>Survey Item</th>
<th>Response Options</th>
<th>PPI Prescription Volume</th>
<th>P Valuea</th>
<th>Total (unweighted)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low (%)</td>
<td>Medium (%)</td>
<td>High (%)</td>
</tr>
<tr>
<td>To what degree did the pre-populated MD Easy forms help identify patients affected by Medicaid PPI prior authorization?</td>
<td>Very much</td>
<td>6 (66.7)</td>
<td>15 (71.4)</td>
<td>20 (80.0)</td>
</tr>
<tr>
<td></td>
<td>Somewhat</td>
<td>3 (33.3)</td>
<td>6 (28.6)</td>
<td>4 (16.0)</td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (4.0)</td>
</tr>
<tr>
<td>To what degree did the information provided on pre-populated MD Easy forms help you follow requirements for PPI prior authorization?</td>
<td>Very much</td>
<td>7 (77.8)</td>
<td>14 (66.7)</td>
<td>17 (65.4)</td>
</tr>
<tr>
<td></td>
<td>Somewhat</td>
<td>2 (22.2)</td>
<td>7 (33.3)</td>
<td>9 (34.6)</td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>In general, how useful did you find the MD Easy form to be?</td>
<td>Extremely useful</td>
<td>4 (44.4)</td>
<td>8 (38.1)</td>
<td>13 (50.0)</td>
</tr>
<tr>
<td></td>
<td>Very useful</td>
<td>4 (44.4)</td>
<td>7 (33.3)</td>
<td>8 (30.8)</td>
</tr>
<tr>
<td></td>
<td>Somewhat useful</td>
<td>1 (11.1)</td>
<td>6 (28.6)</td>
<td>4 (15.4)</td>
</tr>
<tr>
<td></td>
<td>Not at all useful</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (3.8)</td>
</tr>
</tbody>
</table>

*aRepresents the level of statistical significance for comparisons among the 3 claims volume strata, using 1-way analysis of variance for the estimated number of work minutes saved and Pearson chi-square tests for all other comparisons.

*bOnly data from these respondents are included in the pharmacy responses below.

“Burden” was defined in the pharmacy survey as “phone calls, faxes, patient interactions, and doctor contacts.”

Statistical significance not calculated because of small counts in multiple cells.

Eighty-eight physicians who either reported that they did not use the IA process (n = 84) or did not respond to the question about the MD Easy forms (n = 4) were not included in these analyses.

IA = instant approval; NA = not applicable; NC = North Carolina; PA = prior authorization; PPI = proton pump inhibitor.

### Data Analysis

Pharmacist and Physician Satisfaction with IAP and the MD Easy Form. Survey responses were summarized as frequencies (number and percent) in aggregate, both unweighted and weighted to account for the stratified sampling procedure, and by sampling stratum based on annual volume of PPI prescription claims. Unweighted aggregate and stratified responses are presented. Pearson chi-square and Analysis of Variance (ANOVA) were used to test whether survey responses varied significantly by PPI claim volume strata. An a priori P value of 0.05 was used to indicate statistical significance.

Market Share of Preferred PPI Prescriptions. An interrupted time series analysis was used to assess overall pre-post changes in preferred PPI market share and compare practices that used the MD Easy form with those that did not, assessing (a) market share of preferred PPIs prior to implementing the IAP and (b) change in market share of preferred PPIs (percent of total) after implementation of the IAP. Market share data were analyzed within a log negative binomial regression model to account for the autocorrelation in the time series data. These tests were implemented using PROC GENMOD in SAS. Question (a) was tested using 5 months of market share data immediately prior to IAP implementation. Question (b) was tested using the full 12 months of market share data.

### Results

#### Pharmacist Satisfaction with IAP for PPIs

The pharmacy survey was completed by 202 of 240 (84.2%) pharmacies selected for participation (Figure 2). Study results are restricted to 198 (82.5%) permanently employed pharmacists. Approximately two-thirds (65.2% weighted, 70.7% unweighted) of these pharmacies reported experience with North Carolina’s Medicaid’s IAP for PPIs (Table 1). In stratified analyses, higher PPI volume pharmacies were more likely to report experience with IAP than lower-volume pharmacies (83.8% vs. 52.4%, respectively, P < 0.001). Of the 140 pharmacies with IAP experience, 68.6% indicated that the IAP is better (34.3%) or much better (34.3%) than traditional PA with respect to overall administrative burden of phone calls, faxes, patient interactions, and doctor contacts. Pharmacists estimated that the IAP saved 23.7 weighted work minutes per patient (unweighted, 21.1 minutes), on average, compared with the traditional PA process. Low-volume pharmacies reported greater mean time savings per patient than high-volume pharmacies (25.2 minutes vs. 16.3 minutes, P < 0.001). Of the 45 pharmacists who rated the usefulness of the MD Easy Form for expediting the PA process, 95.5% indicated a rating of good to excellent. Differences by strata in responses to the remaining survey items were not statistically significant.

#### Physician Perceptions and Satisfaction with the MD Easy Form

Surveys were completed and returned by 171 of the 240 (71.3%) selected physician practices (Figure 3). Responses are presented for the 56 of the 171 responding practices (32.7%) that reported receiving the pre-populated MD Easy forms (Table 1). Among physicians who recalled
receiving the pre-populated MD Easy forms, 92.9% reported that these forms very much or somewhat helped prevent gaps in therapy or days of missed therapy for their patients receiving PPIs. The MD Easy forms also were reported to very much or somewhat help 98.2% of responding practices identify patients affected by Medicaid PPI PA, and 100% of respondents reported that the information on the forms very much or somewhat helped them to follow requirements for PPI PA. Almost all of the practices (98.2%) rated the MD Easy forms as somewhat to extremely useful (Table 1). Survey results did not vary significantly among the strata of physician practices.

**Market Share of Preferred PPI Prescriptions**

Immediately after implementation of the PA program for PPIs, including the IAP and use of MD Easy forms, the observed market share of preferred PPIs approximately quadrupled, from 20.0% in May 2007 to 81.6% in June 2007 (95% CI = 3.57-4.62; Table 2). The increase in preferred market share between May and June was an absolute 64.0% (from 19.3% to 83.3%, P < 0.001) for practices using the MD Easy form and an absolute 55.4% (from 21.8% to 77.2%, P < 0.001) for practices not using the MD Easy form (Figure 4). The pre-IAP baseline market share of preferred PPIs in the group of practices that did not use the MD Easy form was 1.24 (95% CI = 1.10-1.40) times as high or approximately 4 percentage points higher compared with the practices that used the MD Easy form (P < 0.001). The overall increase in preferred PPI market share after implementation of the IAP was 1.29 times higher in the group that used the MD Easy form than the group of practices that did not; this difference approached statistical significance (95% CI = 1.00-1.68; P = 0.053).

**Discussion**

The trend to shift pharmacy management strategies from traditional PA programs to alternative strategies such as instant approval, electronic PA, and web-based PA is growing. Traditional PA programs have an established history of successfully moving market share to preferred drug products and limiting utilization of nonpreferred products. The downside to PA programs to date has been patient, prescriber, and pharmacy dissatisfaction, specifically the administrative costs of filling out paperwork, phoning, and faxing, as well as increased time between fills for patients seeking a medication that has a PA without immediate resolution. Third-party payers in Tennessee and New Jersey announced plans in early 2009 to launch a pilot electronic PA program. Moreover, the American Medical Association’s House of Delegates, at its June 2008 annual meeting, adopted a policy to support legislative efforts to mandate less administratively burdensome and costly pharmacy management strategies.

The current evaluation of the North Carolina Medicaid IAP for PPIs provides evidence to support the shift away from traditional PA for pharmacy benefits. The results of this study suggest that an IAP for prescription medications may be more administratively efficient for pharmacists than traditional PA processes while retaining the desired channeling effects. More than two-thirds of pharmacists in this study reported that the IAP was administratively less burdensome than traditional PA. This finding was consistent with the expectations and intent of investigators. The channeling to preferred PPI medications was similarly effective for practices that used the MD Easy form compared with those not using the MD Easy form. This finding was somewhat unexpected; the MD Easy form may make it easier for physicians to prescribe nonpreferred PPIs because the specific exemption criteria are listed directly on the form. One possible explanation for this result is the potential for a null effect of a barrier on prescribers’ decision-making processes. That is, the level of difficulty of the PA override process may not affect the switching decision because patients who meet criteria or insist on using the nonpreferred medication

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**TABLE 2**

Monthly Market Share of PPI Prescriptions in Calendar Year 2007, Stratified by Physician Practice Report of Receiving MD Easy Forms

<table>
<thead>
<tr>
<th>Month</th>
<th>PPIb Total Prescriptions</th>
<th>% Preferred PPIb</th>
<th>PPIb Total Prescriptions</th>
<th>% Preferred PPIb</th>
</tr>
</thead>
<tbody>
<tr>
<td>January</td>
<td>830</td>
<td>19.6</td>
<td>1,739</td>
<td>15.0</td>
</tr>
<tr>
<td>February</td>
<td>761</td>
<td>20.1</td>
<td>1,661</td>
<td>16.9</td>
</tr>
<tr>
<td>March</td>
<td>846</td>
<td>19.6</td>
<td>1,765</td>
<td>15.6</td>
</tr>
<tr>
<td>April</td>
<td>747</td>
<td>20.9</td>
<td>1,606</td>
<td>16.3</td>
</tr>
<tr>
<td>May</td>
<td>731</td>
<td>21.8</td>
<td>1,828</td>
<td>19.3</td>
</tr>
<tr>
<td>Pre-PAa</td>
<td>3,915</td>
<td>20.4</td>
<td>8,599</td>
<td>16.6</td>
</tr>
<tr>
<td>June</td>
<td>540</td>
<td>77.2</td>
<td>1,381</td>
<td>83.3</td>
</tr>
<tr>
<td>July</td>
<td>596</td>
<td>77.0</td>
<td>1,424</td>
<td>80.8</td>
</tr>
<tr>
<td>August</td>
<td>644</td>
<td>75.0</td>
<td>1,546</td>
<td>77.2</td>
</tr>
<tr>
<td>September</td>
<td>581</td>
<td>72.8</td>
<td>1,370</td>
<td>76.1</td>
</tr>
<tr>
<td>October</td>
<td>585</td>
<td>72.3</td>
<td>1,571</td>
<td>73.3</td>
</tr>
<tr>
<td>November</td>
<td>608</td>
<td>72.7</td>
<td>1,567</td>
<td>74.6</td>
</tr>
<tr>
<td>December</td>
<td>579</td>
<td>70.3</td>
<td>1,437</td>
<td>73.9</td>
</tr>
<tr>
<td>Post-PAa</td>
<td>4,133</td>
<td>73.9</td>
<td>10,296</td>
<td>76.9</td>
</tr>
</tbody>
</table>

a No MD Easy® category includes practices that either (a) reported not using the IAP (n = 84); (b) reported that they did not receive the MD Easy forms (n = 25); or (c) reported using the IAP but did not respond to the question about MD Easy forms (n = 4).

b Preferred PPIs are generic omeprazole and Prilosec OTC.

c For both groups combined, total PPI claims count for May 2007 was 2,559, of which 512 (20.0%) were for preferred PPIs.

d The PA program and IAP were implemented on June 1, 2007. Results marked "pre-PA" and "post-PA" represent January through May and June through December, respectively.

For both groups combined, total PPI claims count for June 2007 was 1,921, of which 1,567 (81.6%) were for preferred PPIs.
may ultimately receive the PA override, however difficult or easy to attain.

The results of this study are consistent with a limited body of published peer-reviewed literature on evaluations of automated or instant approval pharmaceutical PA programs. The evaluation of an automated PA system for COX-2 inhibitors in the Missouri Medicaid program demonstrated a shift in use of COX-2 inhibitors to less costly nonsteroidal anti-inflammatory drugs (NSAIDs). The automated PA system was credited with reducing expenditures for COX-2 inhibitors by $131 per patient per year (PPPY) compared with an increase of $59 PPPY in a comparison group without PA for COX-2 inhibitors. In addition, it was estimated that administrative costs were reduced by $150,000 to $925,000 per year based on an estimated drop in PA call center volume by 15,000 to 37,000 telephone calls per year at an estimated cost of $10 to $25 per PA request.

A previously published study of the North Carolina Medicaid IAP for PPIs reported that the average monthly PPI drug costs dropped from approximately $4 million to approximately $1.5 million immediately after implementation of the PA program. The market share for preferred PPIs increased from 17% to 19% in the pre-IAP period to 76% in the first month after IAP implementation. Although market share changes were similar for practices using traditional PA and IAP, the median gap in PPI therapy for patients whose prescribers used traditional PA was approximately twice the gap with the IAP (26 vs. 12 days, respectively, \( P < 0.001 \)). And, of the physician practices using IAP, 81.1% believed it reduced practice-related administrative burden. The present study is the first report of which we are aware to focus on PA-related pharmacy burden and use of a pre-printed prescription form.

The North Carolina Medicaid PPI PA program had the advantage of the 14 CCNC networks, its pharmacists, and regular medical management meetings to educate providers and support the effort. The ability to call on pharmacies and practices in person with existing human resources that already had established relationships was advantageous both for implementation and evaluation. One of the few drawbacks to the program was its limited scope with respect to a single drug class from a single payer. While pharmacists generally gave positive feedback about the IAP approach, it would likely be advantageous to patients, prescribers, and pharmacies if consistent phraseology for pharmacy claim PA override or procedures that cut across all drug classes and payers were developed. A more efficient IAP drug management program may be created through collaboration with other state Medicaid programs.

\*Percent of all PPI claims that were for the preferred PPIs, generic omeprazole and Prilosec OTC.

\*June 1, 2007: implementation of the IAP and MD Easy Forms for PPI medications.

\*The “Used MD Easy” trend line represents physician practices that received and rated the MD Easy form based on survey responses (n = 56). The “No MD Easy” trend line represents physician practices (n = 113) that reported (a) not using the IAP (n = 84); (b) not receiving the MD Easy forms (n = 25); or (c) using the IAP but did not respond to the question about MD Easy forms (n = 4).

IAP = instant approval process; PPI = proton pump inhibitor.
programs and private payers, using universal override procedures and criteria.

The use of IAP can be applied across many drug classes and drug product types. A program similar to the PPI IAP has been in place in North Carolina Medicaid for palivizumab since 2004. Palivizumab is a humanized monoclonal antibody that has been shown to reduce the occurrence of respiratory syncytial virus-related hospitalizations in high-risk infants. Palivizumab is both expensive and more time sensitive for administration than most other drug products, necessitating a PA program that is “user friendly” for patients, prescribers, and pharmacies. Although palivizumab requires PA in North Carolina, pharmacies can dispense the medication and be guaranteed reimbursement based on criteria and paperwork that can be submitted retroactively, allowing for the immediate delivery and administration of the drug product.

Unlike IAP for PPIs, use of MD Easy forms may not be feasible for all types of drug products. For the PPI program, there were logical and evidence-based therapeutic alternatives to nonpreferred products that provided prescribers an alternative to seeking an override. When the MD Easy form acts as a prescription for an alternative product, it allows the practice to quickly make switching and IAP decisions for all of its patients who would be affected by the PA prior to the policy taking effect. For PA policies other than therapeutic interchanges, such as limits on total daily dose, unit counts over time, or restrictions based on diagnosis with no “step therapy” or “fail first” component, the MD Easy form may act primarily as an educational tool or care alert because no new prescriptions for an alternative medication are expected.

Limitations

First, the IAP and the MD Easy form were compared with traditional PA using measurements of perceived burden. The actual administrative time and costs of each approach were not measured using direct observations and time studies. However, the perceived burden and relative acceptability of the PA approach are important considerations in efforts intended to reduce barriers to adoption of innovations.

Second, although the response rates to both the pharmacy (84.2%) and physician (71.3%) surveys were relatively high, only about one-third of responding physicians and two-thirds of responding pharmacists reported having had experience with IAP or the MD Easy form, thus limiting the sample size for this study. In addition, the survey results may be influenced by selection bias because only 1 pharmacist or physician was surveyed on behalf of each pharmacy or medical practice, and the pharmacist interviews were conducted based on pharmacist availability. It is possible that experiences of those not surveyed may differ from those of survey respondents. An attempt was made to obtain the most informed respondents by requesting participation of the physician in each practice with the most experience with the IAP for PPIs. Yet, self-selection is likely to have occurred to some extent within each physician practice.

Third, many of the survey items asked the respondents to make relative comparisons to previous PA experiences. Prior to this PA program, the North Carolina Medicaid program had nearly complete open access, without a preferred drug list or any substantially disruptive PA policies affecting large numbers of prescribers or patients. It is possible that the addition of any PA requirement, even one that involves an IAP, may tend to bias the responses in the direction of understating satisfaction because historically North Carolina Medicaid has adopted less aggressive PA policies affecting small numbers of enrollees. However, given the widespread use of PA programs across payers, this potential source of bias is unlikely.

Fourth, the use of an interrupted time-series design for studying the effect of introducing a PA policy was a natural experiment without a comparison group and is not a strong design for controlling for threats to internal or external validity. The dramatic increase in the prescribing of preferred PPIs after the PA policy implementation could potentially be attributed to other factors. For example, physicians may be more likely to adhere to the PA policy when they are aware of being observed in an investigation. The sustainability of market share results over 7 months reduces this concern because physicians were directly involved in the study for only a brief time period, the time to complete a survey. Another potential explanation for successful channeling to preferred PPIs may be the involvement of early adopters or highly performing physicians in the study. Given that the PPI prescribing patterns were summarized for responding practices rather than individual responding physicians, this concern is unlikely to represent a major threat to study validity.

Conclusion

This study provides evidence that an IAP for PPIs is an effective alternative to traditional PA approaches for prescription drugs. The method, including use of the MD Easy form, was associated with an increase in market share of preferred PPIs and was reported to be less administratively burdensome to pharmacists than traditional PA. Additional studies are needed to determine sustainability and applicability to other prescription drugs.
Disclosures

There was no external funding for this research, and the authors disclosed that there are no financial relationships or other potential conflicts of interest related to the subject of this manuscript.

Concept and design were performed primarily by Trygstad and Wegner, with the assistance of Jacobson Vann. Data collection was performed primarily by Christofferson and Humble. The data were interpreted by Feaganes, Humble, Trygstad, and Jacobson Vann. Jacobson Vann wrote the manuscript with the assistance of Trygstad and performed most of the manuscript revisions with the assistance of Humble.

References


Pharmacist and Physician Satisfaction and Rates of Switching to Preferred Medications Associated with an Instant Prior Authorization Program for Proton Pump Inhibitors in the North Carolina Medicaid Program


ABSTRACT

BACKGROUND: Diabetes mellitus requires continuous medical care and patient self-management in order to prevent short-term complications and decrease the risk of long-term complications, which can result in substantial increases in the total economic burden of the disease. Findings from randomized clinical trials have shown that improved glycemic control may reduce the risk of long-term complications as long as a target for hemoglobin A1c is not set below 7% for intensive glycemic control. However, limited data from clinical practice are available regarding the relationship between glycemic control and medical costs associated with diabetes care.

OBJECTIVE: To assess the potential relationships between glycemic levels, diabetes-related hospitalizations, and hospital costs among adult patients with either type 1 or type 2 diabetes mellitus who were assigned to a primary care provider (PCP) in a clinic that was affiliated with a managed care organization (MCO).

METHODS: A retrospective cohort analysis was conducted using data from approximately 200,000 members of the Fallon Clinic Health Plan who were assigned to a clinic PCP at any time during a 5-year study period beginning January 1, 2002, and ending December 31, 2006. Patients aged 30 years or older with at least 2 medical claims with any listed diagnosis of diabetes mellitus (ICD-9-CM code 250.xx) during the study period and 2 or more A1c values within 1 year of each other during the study period (mean 7.6 tests over 39 months; median=6.8), were identified and stratified into 1 of 5 groups defined by 1% increments of A1c, based on their mean A1c values during the entire study period. A1c data were available only for tests ordered by a clinic provider; tests ordered by other specialists in the MCO's network were absent from the database. The study follow-up period started with each patient's first A1c test (index date) and continued until plan disenrollment, death, or December 31, 2006, whichever was earlier (end date), regardless of when the diagnosis of diabetes mellitus was made. Study measures included the proportion of patients with 1 or more diabetes-related hospitalizations, number of diabetes-related inpatient stays, and the associated estimated hospitalization costs over the follow-up period. Diabetes-related hospitalizations were identified based on a diagnosis, in any of 10 diagnosis fields, for 1 of 16 selected complications of diabetes identified by the authors. Hospital costs were estimated using discharge data (diagnoses and costs calculated from cost-to-charge ratios) contained in the 2004 Healthcare Cost and Utilization Project (HCUP) database and inflated to 2007 dollars using the medical care component of the Consumer Price Index. Multivariate models controlled for age, sex, number of A1c tests, diagnosis of cancer, and follow-up time. A multivariate logistic regression analysis was conducted with the occurrence of at least 1 diabetes-related hospital admission as the dependent variable. In the logistic regression analysis, follow-up time was defined as time from the index date to the date of the first diabetes-related hospitalization, plan disenrollment, death, or the study end date, whichever occurred first. A generalized linear model with a Poisson distribution and a log link was employed to estimate the rate of hospital admissions. In the Poisson regression analysis, follow-up time was defined as duration of the entire study follow-up period and was an offset variable. Costs were estimated using a 2-part model: first, we calculated the probability of having a hospitalization, as determined by the logistic regression above; second, a generalized linear model with a negative binomial distribution and a log link was used to predict the mean total hospitalization costs for patients with an inpatient stay, with the duration of the entire study follow-up period as an offset variable. We calculated the mean per patient cost of diabetes-related hospitalizations by multiplying the probability of having a hospitalization (as determined by the first part of the model) by the mean costs for patients who had such admissions (as determined by the second part of the model).

RESULTS: 9,887 patients met study selection criteria. Mean A1c level was <7% for 5,649 (57.1%) patients, 7% to <8% for 2,747 (27.8%), 8% to <9% for 1,002 (10.1%), 9% to <10% for 312 (3.2%), and 10% or more for 177 (1.8%). Over a mean (median) 40 (40) months of follow-up (interquartile range 30-50 months), 28.7% (n=2,838) of patients had 1 or more diabetes-related hospital admissions. In the logistic regression analysis, odds of having at least 1 diabetes-related hospital stay did not significantly differ for patients with mean A1c of <7% compared with patients in most higher mean A1c categories (7% to <8%, 8% to <9%, or 9% to <10%); however, odds of having a diabetes-related hospitalization were significantly higher for patients with mean A1c of 10% or more compared with patients with mean A1c of <7% (odds ratio = 2.63, 95% confidence interval = 1.36-3.33).

In the negative binomial regression analysis of those with at least 1 hospital admission, estimated costs per hospitalized patient increased by mean A1c level. In the Poisson regression analysis, the rate of diabetes-related hospitalizations significantly increased by A1c level (13 per 100 patient-years for patients with mean A1c of <7% vs. 30 per 100 patient-years for mean A1c of 10% or more when covariates were held at mean levels, P<0.001). In the 2-part model results, adjusted mean estimated costs of diabetes-related hospitalizations per study patient were $2,792 among those with mean A1c of <7% and $6,759 among those with mean A1c of 10% or more.

CONCLUSIONS: In this managed-care plan, the odds of having at least 1 diabetes-related hospitalization were not significantly associated with higher mean A1c except for patients with mean A1c of at least 10%. However, higher mean A1c levels were associated with significantly higher estimated hospitalization costs among those with at least 1 hospitalization and with higher rates of diabetes-related hospital utilization per 100 patient-years.

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Diabetes mellitus is a growing public health problem that adversely affects the lives of millions of individuals around the world.\textsuperscript{1,2} This disease requires continuous medical care and patient self-management in order to prevent short-term complications and decrease the risk of long-term complications.\textsuperscript{3} These complications can result in substantial increases in the total economic burden of the disease. The American Diabetes Association (ADA) has estimated that the annual cost of diabetes in the United States was approximately $174 billion in 2007.\textsuperscript{4}

Previous studies have found some evidence that better glycemic control among patients with type 2 diabetes may be associated with lower health care resource use and costs.\textsuperscript{5-9} Oglesby et al. (2006), using data from October 1, 1998, through April 30, 2003, found that diabetes-related costs were 16% and 20% lower for patients with good control (hemoglobin A1c 7% or less) compared with fair (A1c more than 7% to 9% or less) and poor control (A1c more than 9%), respectively.\textsuperscript{8} Aside from that study, previous research examined the association between glycemic control and health care resource use and costs using older data (1992-2003) and variable definitions of glycemic control. For example, Menzin et al. (2001) used data from 1994 through mid-1998 to assess short-term inpatient (hospital or skilled nursing facility) admissions and costs associated with poor control (A1c more than 9%), respectively. This study sought to test the hypothesis that poorer glycemic control is associated with higher rates of diabetes-related hospitalizations and costs among patients with diabetes mellitus treated in clinical practice.

### Methods

#### Data Sources

Data from the Fallon Clinic (Worcester, Massachusetts) covering the 5-year period from January 1, 2002, through December 31, 2006 (study period), were used to explore the relationship between glycemic control and diabetes-related hospitalizations. The Fallon Clinic is a multispecialty group clinic with a predominantly managed care population of approximately 200,000 patients at the time of study initiation. The study data set consisted of 4 files: an enrollment file, an inpatient hospital claims file that included claims with a place of service indicating an inpatient setting and date of service span exceeding 1 day, a pharmacy file, and a clinical laboratory file. The clinical laboratory file included all tests that were ordered by a Fallon Clinic provider. Patients’ data were de-identified, with a unique, encrypted identifier available to link the 4 files. The study was approved by the Fallon Clinic Institutional Review Board.

Because only billed charge data, not cost data, were available in the study database, we used 2004 data from the Healthcare Cost and Utilization Project (HCUP)\textsuperscript{10} to estimate costs for hospitalizations related to diabetes, which were assigned to the hospitalizations observed in the claims database. HCUP is a nationally representative, multisource database that contains International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes and charges, as well as a separate file to convert charges to costs using institution-specific cost-to-charge ratios (i.e., a single cost-to-charge ratio for each hospital, applied to all admissions for that hospital).

#### Patients and Follow-Up

Because laboratory data were available only for tests ordered by a Fallon Clinic physician, the initial sample selection was limited to patients with Fallon Clinic Health Plan membership assigned to a Fallon Clinic primary care provider (PCP) for at least 1 month during the 5-year study period. From that group, patients were selected for study if they were aged 30 years or older as of January 1, 2002, had at least 2 medical claims with a diagnosis of type 1 or type 2 diabetes (ICD-9-CM codes 250.xx) during the 5-year study period, had at least 2 A1c values measured within any 1-year period during the study period (in order to exclude patients who received an A1c test for screening only), had at least 12 months of follow-up after their first A1c test, and had no hospitalizations with overlapping dates of service. Specifically, for patients with more than 1 hospitalization record, each record could not have an admission date falling in between the admission and discharge date of another record.

Each eligible study patient’s A1c level was defined as the
mean of all of his or her A1c values available during the follow-up period. The study follow-up period began with the date of a patient’s first A1c test during his or her enrollment (index date), regardless of the date on which the patient was diagnosed with diabetes, and continued until the disenrollment date from the health plan, death, or the study end date (December 31, 2006), whichever occurred first. Thus, patients had variable lengths of follow-up. Patients were stratified into 5 study groups based on their mean A1c levels: <7%, 7% to <8%, 8% to <9%, 9% to <10%, and 10% or more, to assess the association of 1% differences in mean A1c with diabetes-related hospitalizations and associated costs.

Study Measures

We evaluated diabetes-related hospitalizations based on any diagnosis listed on inpatient claims, on which a total of 10 diagnosis fields were available. Hospitalizations could occur at any point after the first A1c test and, if the first A1c test preceded the diabetes diagnosis, could have occurred prior to the first diabetes diagnosis date. Using ICD-9-CM codes, we identified 16 diabetes-related complications, both short and long term (Appendix A). The short-term complications were used in a previous study, conducted by the present study’s authors, of the association between costs and glycemic control. The long-term complications are common conditions related to diabetes, such as ischemic heart disease, nephropathy, neuropathy, and retinopathy. If one of these conditions was listed as the primary diagnosis or one of the 9 other listed diagnoses, the hospitalization was considered to be diabetes-related.

The study measures for hospitalization included the proportion of patients with 1 or more stays and the number of such hospitalizations per 100 patient-years. Additionally, we assessed the average cost per patient for these hospitalizations. Because cost data were not available in the study database, we applied nationally weighted mean cost data from the 2004 HCUP data based on an assigned reason for hospitalization (1 of 16 diabetes-related complications, Appendix B). We used mean HCUP costs instead of the median value, since the mean better reflects financial impact to the hospital for the average discharge. These data are weighted to represent all national inpatient admissions. If a primary diagnosis was used to identify the hospitalization as diabetes-related, we calculated a mean cost for that admission using all HCUP hospitalizations with the same primary diagnosis. If a nonprimary diagnosis was used to identify the hospitalization as diabetes-related, we included only the estimated attributable cost associated with that admission, as follows. First, we identified all of the diagnosis-related group (DRG) codes for each type of diabetes-related hospitalization in HCUP separately and combined all diabetes-related hospitalizations with the same DRG code into 1 group. Then, within each DRG, we estimated the average cost for patients with and without the specific diagnosis and calculated the difference between these 2 mean costs as the estimated attributable cost. Lastly, we assigned the attributable cost found in HCUP to each diabetes-related hospitalization in the claims database. For patients with more than 1 nonprimary diabetes-related diagnosis, the first-named diagnosis was used. For example, if both the second and third diagnoses were diabetes-related, the second diagnosis was used in the HCUP estimating procedure. Costs from HCUP were adjusted to 2007 dollars using the medical care component of the Consumer Price Index. Cost estimates for diabetes-related hospitalizations were used to calculate the per patient hospitalization costs.

Statistical Analyses

Descriptive statistics for age, sex, and duration of follow-up were calculated for each mean A1c level. The proportion of patients with 1 or more diabetes-related hospitalizations and the number of such admissions per 100 patient-years (admission rate) were assessed on both an unadjusted and adjusted basis. Adjusted proportions were estimated using a multivariate logistic regression model controlling for age, sex, number of A1c tests, diagnosis of cancer (based on ICD-9-CM codes 140.xx-208.xx), and time from the index date (i.e., date of the first A1c test) to the date of the first diabetes-related hospitalization, disenrollment, death, or the study end date, whichever occurred first. Adjusted average rates of admission were estimated using a generalized linear model with a Poisson distribution and a log link with the duration of the entire study follow-up period (i.e., time from index date until disenrollment, death, or the study end date, whichever occurred first) as an offset variable. We also controlled for age, sex, number of A1c tests, and diagnosis of cancer.

The adjusted average hospitalization cost was estimated using a 2-part model. First, we calculated the probability of having a hospitalization, as determined by the logistic regression above; second, a generalized linear model with a negative binomial distribution and a log link was used to predict the mean cost of diabetes-related hospitalizations only for patients with an inpatient stay, with the duration of the entire study follow-up period as an offset variable, controlling for the same variables listed above. We calculated the mean cost of diabetes-related hospitalizations per study patient by multiplying the probability of having a hospitalization (as determined by the first part of the model) by the estimated mean cost for patients who had a hospitalization (as determined by the second part of the model). For each analysis, after estimating the model, all covariates except for A1c level were held at their mean values and the expected odds, rates, or costs were calculated for each of the 5 mean A1c levels. All data analyses were conducted using the Statistical Analysis System (SAS) software package, version 9.1 (SAS, Inc., Cary, NC), and a 2-sided $P<0.05$ was considered significant.
### Results

**Patient Characteristics**

Initial selection of all health plan members aged 18 years or older with at least 1 medical claim for type 1 or type 2 diabetes (ICD-9-CM of 250.xx) and assignment to a Fallon clinic PCP at any time during the study period yielded 16,184 patients. Of these, 9,887 met all selection criteria (Figure 1). The mean (SD) age was 66.6 (12.4) years, and approximately 52% of patients were male (Table 1). The mean (SD) number of A1c tests per patient during the follow-up period was 7.6 (4.3), with an interquartile range (IQR) of 4 to 10 tests and a median of 7 tests. The mean (SD) A1c was 7.0% (1.1%) with IQR of 6.2%-7.5% and median of 6.8%; 4,238 patients (42.9%) had a mean A1c of 7% or more, and 177 patients (1.8%) had a mean A1c of 10% or more. The mean (SD) follow-up duration was approximately 40 (14) months (IQR= 30-50 months).

There were important differences in terms of age ($P<0.001$), sex ($P=0.001$), and length of the follow-up period ($P=0.002$) across study groups defined by mean A1c levels (Table 1). Mean age decreased as mean A1c values increased, from 68.1 years for patients with mean A1c < 7% to 54.0 years for mean A1c of 10% or more. The proportion of patients who were younger than 50 years of age was 8.3% for patients with mean A1c < 7% compared with 42.4% for patients with mean A1c of 10% or more, perhaps reflecting a greater preponderance of patients with type 1 diabetes in the higher A1c group. In addition, the percentage of male patients generally increased with A1c levels (50.2% among patients with mean A1c < 7%, compared with 58.8% among those with mean A1c of 10% or more). Length of follow-up was shorter for patients at higher mean A1c levels; the mean length of the follow-up period ranged from 33.9 months (mean A1c of 10% or more) to 41.7 months (mean A1c of 7% to < 8%).

### Association Between Mean A1c Levels and Diabetes-Related Hospitalizations

Table 2 shows the most common diagnoses associated with hospitalizations defined as diabetes-related. For patients with mean A1c of < 7% (n = 3,046 hospitalizations), the top 5 diagnoses included ischemic heart disease (44.0%), electrolyte imbalance (13.5%), pneumonia (10.8%), urinary tract infection (9.4%), and stroke (5.8%). For patients with mean A1c of 10% or more (n = 121 hospitalizations), the top 5 diagnoses included ischemic heart disease (28.1%), hyperglycemia (15.7%), electrolyte imbalance (10.7%), urinary tract infection (9.1%), and hypoglycemia (8.3%).

Table 3 presents the results of the logistic regression for the proportion of patients with 1 or more hospitalizations and the Poisson regression for the hospitalization rate. A total of 2,841 (28.7%) patients were hospitalized with a diabetes-related diagnosis during follow-up, accounting for 5,874 total hospital stays and 18.0 admissions per 100 patient-years for the sample overall. After controlling for differences among study cohorts in age, sex, number of A1c tests, diagnosis of cancer, and follow-up time, the adjusted proportion of patients with 1 or more diabetes-related hospitalizations was significantly lower for those with a mean A1c < 7% versus those with a mean A1c of 10% or more. When covariates were held at their mean values in the logistic regression equation, the adjusted proportions of patients hospitalized were 19.5% for patients with mean A1c < 7% and 33.9% for patients with mean A1c of 10% or more. Compared with the reference group of patients with mean A1c of < 7%, the adjusted odds ratio for being hospitalized for diabetes-related complications for patients with mean A1c of 10% or more was 2.13 (95% confidence interval [CI] = 1.36-3.33). However, relative to the < 7% group, logistic regression
## TABLE 1  Baseline Characteristics and Unadjusted Inpatient Stays

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Full Sample</th>
<th>&lt; 7%</th>
<th>7% to &lt; 8%</th>
<th>8% to &lt; 9%</th>
<th>9% to &lt; 10%</th>
<th>≥ 10%</th>
<th>P Value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>9,887</td>
<td>5,649</td>
<td>2,747</td>
<td>1,002</td>
<td>312</td>
<td>177</td>
<td></td>
</tr>
<tr>
<td>Age in years n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-49</td>
<td>1,107 (11.2%)</td>
<td>470 (8.3%)</td>
<td>275 (10.0%)</td>
<td>181 (18.1%)</td>
<td>106 (34.0%)</td>
<td>75 (42.4%)</td>
<td></td>
</tr>
<tr>
<td>50-64</td>
<td>2,577 (26.1%)</td>
<td>1,353 (23.7%)</td>
<td>734 (26.7%)</td>
<td>330 (32.9%)</td>
<td>112 (35.9%)</td>
<td>63 (35.6%)</td>
<td></td>
</tr>
<tr>
<td>65 or older</td>
<td>6,203 (62.7%)</td>
<td>3,841 (68.0%)</td>
<td>1,758 (63.3%)</td>
<td>491 (49.0%)</td>
<td>94 (30.1%)</td>
<td>39 (22.0%)</td>
<td></td>
</tr>
<tr>
<td>Age in years mean (SD)</td>
<td>66.6 (12.4)</td>
<td>68.1 (11.8)</td>
<td>66.7 (12.0)</td>
<td>62.9 (13.0)</td>
<td>57.2 (14.1)</td>
<td>54.0 (12.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sex n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5,133 (51.9%)</td>
<td>2,837 (50.2%)</td>
<td>1,417 (54.1%)</td>
<td>529 (52.8%)</td>
<td>176 (56.4%)</td>
<td>104 (58.8%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Female</td>
<td>4,754 (48.1%)</td>
<td>2,812 (49.8%)</td>
<td>1,260 (45.9%)</td>
<td>473 (47.2%)</td>
<td>136 (43.6%)</td>
<td>73 (41.2%)</td>
<td></td>
</tr>
<tr>
<td>Duration of follow-up (months)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>39.6 (13.5)</td>
<td>39.1 (13.4)</td>
<td>41.7 (13.3)</td>
<td>39.2 (13.3)</td>
<td>34.6 (13.2)</td>
<td>33.9 (12.8)</td>
</tr>
<tr>
<td>Mean (IQR)</td>
<td></td>
<td>40 (30-50)</td>
<td>40 (29-50)</td>
<td>43 (33-55)</td>
<td>40 (30-48)</td>
<td>35 (24-44)</td>
<td>35 (23-41)</td>
</tr>
<tr>
<td>Number of A1c tests</td>
<td>Mean (SD)</td>
<td>7.6 (4.3)</td>
<td>6.6 (3.7)</td>
<td>9.3 (4.5)</td>
<td>9.0 (4.9)</td>
<td>7.7 (4.7)</td>
<td>6.2 (5.2)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td></td>
<td>7 (4-10)</td>
<td>6 (4-9)</td>
<td>9 (6-12)</td>
<td>8 (5-12)</td>
<td>7 (4-10)</td>
<td>5 (3-7)</td>
</tr>
<tr>
<td>Patient mean A1c value&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>7.0 (1.1)</td>
<td>6.2 (0.4)</td>
<td>7.4 (0.3)</td>
<td>8.4 (0.3)</td>
<td>9.4 (0.3)</td>
<td>10.8 (0.8)</td>
</tr>
<tr>
<td>Mean (IQR)</td>
<td></td>
<td>6.8 (6.2-7.5)</td>
<td>6.3 (5.9-6.6)</td>
<td>7.4 (7.2-7.7)</td>
<td>8.4 (8.2-8.6)</td>
<td>9.4 (9.2-9.7)</td>
<td>10.7 (10.2-11.2)</td>
</tr>
<tr>
<td>Patients with 1 or more diabetes-related admissions&lt;sup&gt;d&lt;/sup&gt; n (%)</td>
<td>2,841 (28.7%)</td>
<td>1,522 (26.9%)</td>
<td>855 (31.1%)</td>
<td>327 (32.6%)</td>
<td>88 (28.2%)</td>
<td>49 (27.7%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean number of diabetes-related admissions per 100 patient-years&lt;sup&gt;d&lt;/sup&gt;</td>
<td>18.0</td>
<td>16.5</td>
<td>18.0</td>
<td>22.6</td>
<td>20.0</td>
<td>24.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean costs per patient per year for diabetes-related admissions&lt;sup&gt;d&lt;/sup&gt;</td>
<td>$1,280</td>
<td>$1,115</td>
<td>$1,438</td>
<td>$1,637</td>
<td>$1,608</td>
<td>$1,533</td>
<td>$1,533</td>
</tr>
</tbody>
</table>

<sup>a</sup>Each patient’s A1c level was defined as the mean of all A1c values obtained for that patient over a follow-up period that ranged from a minimum of 12 months to a maximum of 5 years (2002-2006). The columns represent categorizations of each patient based on the patient’s mean per test A1c. The means shown in the table rows are the per patient means of each patient’s per test mean, and medians in the table rows are the per patient medians of each patient’s per test mean.

<sup>b</sup>Analysis of variance (F test) for variables measured on an interval scale and Pearson chi-square for categorical variables.

<sup>c</sup>Study follow-up was defined as time from index date until plan disenrollment, death, or the study end date, whichever occurred first.

<sup>d</sup>Diabetes-related admissions were defined by the presence of 1 of 16 diabetes-related complications defined by the authors (Appendix A). A1c = hemoglobin A1c; IQR = interquartile range; SD = standard deviation.

## TABLE 2  Top 5 Reasons for Diabetes-Related Hospitalizations, by Mean A1c Value<sup>a</sup>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>&lt; 7%</th>
<th>7% to &lt; 8%</th>
<th>8% to &lt; 9%</th>
<th>9% to &lt; 10%</th>
<th>10% or More</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>3,046</td>
<td>1,787</td>
<td>740</td>
<td>180</td>
<td>121</td>
</tr>
<tr>
<td>Reason for hospitalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>1,341</td>
<td>440</td>
<td>824</td>
<td>321</td>
<td>67</td>
</tr>
<tr>
<td>Electrolyte imbalance</td>
<td>410</td>
<td>13.5</td>
<td>189</td>
<td>89</td>
<td>19</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>329</td>
<td>10.8</td>
<td>162</td>
<td>55</td>
<td>16</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>286</td>
<td>9.4</td>
<td>127</td>
<td>51</td>
<td>13</td>
</tr>
<tr>
<td>Stroke</td>
<td>178</td>
<td>5.8</td>
<td>110</td>
<td>46</td>
<td>NA</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>15</td>
<td>8.3%</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>10</td>
</tr>
</tbody>
</table>

<sup>a</sup>Each patient’s A1c level was defined as the mean of all A1c values obtained for that patient over a follow-up period that ranged from a minimum of 12 months to a maximum of 5 years (2002-2006). The means shown in the table represent categorizations of each patient based on the patient’s mean per test A1c. An NA designation for a particular diagnosis code indicates that the code was not one of the top 5 diagnoses for patients with the specified mean A1c level.

A1c = hemoglobin A1c; NA = not applicable.
revealed no significant difference in the proportions of patients hospitalized in the groups with mean A1c 7% to < 8%, 8% to < 9%, or 9% to < 10%.

In the Poisson regression analysis, there was a significant positive association between hospitalization rate per 100 patient-years and mean A1c level (P < 0.001). On an adjusted basis, patients with mean A1c of 10% or more had 2.25 times (95% CI = 1.87-2.70) as many hospitalizations as patients with mean A1c of < 7% (29.7 hospitalizations per 100 patient-years vs. 13.2 per 100 patient-years, respectively, when covariates were held at mean values). Patients with mean A1c of 7%-< 8%, 8%-< 9%, and 9%-< 10% had 1.18, 1.64, and 1.72 times as many hospitalizations for diabetes-related complications, respectively, as patients with mean A1c of < 7% (all P < 0.001).

### Association Between A1c Levels and Inpatient Costs

Table 4 displays the results of the second part of the 2-part model, a negative binomial regression predicting costs for all patients who had a hospitalization, and shows that among those patients with at least 1 hospital stay, increasing mean A1c level was associated with higher costs per hospitalized patient. In the results derived from multiplying the 2 parts of the model, the adjusted average cost of hospitalization per study
patient with A1c < 7% was $2,792, compared with $6,759 for patients with A1c of 10% or more (Figure 2).

Discussion

Our study demonstrated that in patients with type 1 or type 2 diabetes, the adjusted rates of diabetes-related hospital admissions per 100 patient-years increased significantly with higher levels of A1c. The adjusted rate of diabetes-related hospitalizations for patients with a mean A1c of 10% or more, who represented 1.8% of our sample, was more than twice that of patients with a mean A1c of < 7%. Among patients with at least 1 hospitalization, corresponding average adjusted costs increased with A1c levels. Study patients with a mean A1c of 10% or more had higher diabetes-related hospital costs than study patients with mean A1c of < 7%.

In a previous study, we analyzed Fallon Clinic data from 1994 to 1998 and found that diabetes patients with poor glycemic control, defined as mean A1c of more than 10%, had substantially higher hospitalization rates for selected short-term complications compared with those with fair control (mean A1c 8%-10%) or good control (mean A1c < 8%). In the current study, we extended the analysis to a broad list of 16 diabetes-related diagnoses and found a similar trend: hospitalization rates increase with higher A1c levels. This new analysis evaluated individual point levels for A1c and used the current ADA recommendation of less than 7% as well controlled.

However, more recent data suggest that diabetes-related complications may be increased in patients with therapy targeted to very tight glycemic control. Intensive treatment of patients with type 2 diabetes to a target A1c of less than 7% can lead to adverse cardiovascular outcomes. Alternatively, a recent large meta-analysis suggests that such intensive therapy may lower the risk of coronary heart disease but not stroke or overall mortality. This controversy suggests that more research is need to further clarify the risk-benefit ratio for use of intensive treatment to bring A1c levels below 7% in type 2 diabetes. In contrast, for patients with type 1 diabetes, results of the Epidemiology of Diabetes Interventions and Complications study (EDIC), a 9-year follow-up of patients previously enrolled in the Diabetes Control and Complications Trial (DCCT), suggested that patients assigned to intensive glycemic control in the DCCT (mean A1c 7.4% at the end of DCCT observation) had lower rates of cardiovascular disease events after 9 years of post-DCCT follow-up compared with patients assigned to conventional glycemic control in DCCT (mean A1c 9.1% at end of DCCT observation). The findings in this study are consistent with those of other published studies. Wagner et al. (2001) studied patients from a large Washington health maintenance organization from 1992-1997 and found that patients whose A1c improved had lower costs and fewer primary care visits but no significant difference in inpatient admissions. Gilmer et al. (2005) reported that in a large Minnesota health plan, higher A1c in patients with either type 1 or type 2 diabetes predicted higher total health care costs for patients with A1c > 7.5%. However, Gilmer et al. also noted that while A1c is an important clinical predictor of costs, other clinical predictors, such as coronary heart disease, hypertension, and depressive symptoms, are also highly predictive.
follow-up period and found that diabetes-related costs were 32% higher for patients above the target A1c level (7%) than for patients at or below the target level. Grouping patients with type 2 diabetes by glycemic control (good [A1c ≤ 7%], fair [> 7% to ≤ 9%], and poor [>9%]), Oglesby et al. (2006) found diabetes-related costs to be 16% and 20% lower for patients with good control compared with fair and poor control, respectively.

Our study provided new information that has not been reported in previous medical literature. To our knowledge, this is the first study to show a significant, positive, and graded relationship between 1-point A1c intervals and rates of diabetes-related hospitalizations. Additionally, it was conducted using an extended follow-up period (over 3 years, on average).

Limitations
This study had several limitations. First, the definition of “diabetes-related” was based on up to 10 different diagnoses on inpatient claims and a broad list of diagnoses developed by the authors. Although this method has not been validated, the authors have previously published work using this method.
Second, because the laboratory data file contains only tests ordered by Fallon Clinic providers, tests ordered by nonclinic specialists in the MCO’s provider network were missing from the database. The effect of the omission of these tests on study results is unknown. Third, the Fallon Clinic database does not contain information on the duration of patients’ disease or the severity of comorbidities that might be potential confounders of study measures used in this analysis. In addition, other factors that may be viewed as confounders, such as type and number of antidiabetic medications, were not controlled for in the analysis because these variables would be expected to be highly correlated with A1c levels and not truly independent.

Fourth, we included both type 1 and type 2 diabetes patients in the study sample because we do not have confidence in distinguishing between types using claims data. A fifth digit ending in zero or 2 includes “Type 2 or unspecified,” and if the type is unknown then type 2 is to be coded.17 The younger age of patients with higher mean A1c levels suggests the possibility of a higher prevalence of patients with type 1 diabetes in that group. The effect of this pattern on study results is unknown. Fifth, calculating a mean of all observed A1c values to classify patients is not sensitive to changes over time in A1c levels, suggesting that future work using alternative approaches (e.g., based on time spent at various levels of glycemic control) may be of interest. Sixth, the study’s reliance on claims data rather than medical records data may raise concerns about clinical accuracy.18-19 However, our previous study, which used 1994-1998 data from the same database, found that roughly 75% of the ICD-9-CM diagnosis codes for hospitalizations matched the actual diagnoses in the medical record.6

Seventh, we applied standard cost data derived from the national HCUP database to patients from the Fallon Clinic because only billed charge data were available in the database, which may introduce potential bias to the cost analysis. Eighth, this study involved a relatively small sample size for an observational study (e.g., there were only 177 patients in the group with mean A1c of 10% or more). Ninth, this study evaluated the relationships between hospital costs for diabetes-related complications and glycemic control. To the extent that better control may lead to savings in other types of costs (e.g., direct medical costs associated with outpatient services or indirect costs associated with productivity), our analysis may be viewed as conservative.

Conclusions

In a sample of 9,887 managed care patients with either type 1 or type 2 diabetes, we showed a significant, positive, and graded relationship between 1-point A1c intervals and rates of diabetes-related hospitalizations per 100 patient-years. Future research to examine the effects of the severity of diabetes and comorbidities may be important in targeting interventions to improve outcomes and reduce costs.


### ICD-9-CM Codes for Diabetes and Diabetes-Related Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Identifiers</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>250 xx</td>
<td></td>
</tr>
<tr>
<td>Selected acute complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>250.1x</td>
<td>Diabetes with ketoacidosis</td>
</tr>
<tr>
<td></td>
<td>250.2x</td>
<td>Diabetes with hyperosmolarity</td>
</tr>
<tr>
<td></td>
<td>250.3x</td>
<td>Diabetes with other coma</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>250.8x</td>
<td>Diabetes with other specified manifestations</td>
</tr>
<tr>
<td>Septicemia</td>
<td>038 xx</td>
<td>Septicemia</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>480 xx</td>
<td>Viral pneumonia</td>
</tr>
<tr>
<td></td>
<td>481 xx</td>
<td>Pneumococcal pneumonia</td>
</tr>
<tr>
<td></td>
<td>482 xx</td>
<td>Other bacterial pneumonia</td>
</tr>
<tr>
<td></td>
<td>483 xx</td>
<td>Pneumonia due to other specified organism</td>
</tr>
<tr>
<td></td>
<td>484 xx</td>
<td>Pneumonia in infectious diseases classified elsewhere</td>
</tr>
<tr>
<td></td>
<td>485 xx</td>
<td>Bronchopneumonia, organism unspecified</td>
</tr>
<tr>
<td></td>
<td>486 xx</td>
<td>Pneumonia, organism unspecified</td>
</tr>
<tr>
<td>Kidney infections</td>
<td>590 xx</td>
<td>Infections of kidney</td>
</tr>
<tr>
<td>Cystitis</td>
<td>595 xx</td>
<td>Cystitis</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>599.0x</td>
<td>Urinary tract infection, site not specified</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>680 xx</td>
<td>Carbuncle and furuncle</td>
</tr>
<tr>
<td></td>
<td>681 xx</td>
<td>Cellulitis and abscess of finger and toe</td>
</tr>
<tr>
<td></td>
<td>682 xx</td>
<td>Other cellulitis and abscess</td>
</tr>
<tr>
<td></td>
<td>686 xx</td>
<td>Other local infections of skin and subcutaneous tissue</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>790.7</td>
<td>Bacteremia</td>
</tr>
<tr>
<td>Electrolyte imbalance</td>
<td>270 xx</td>
<td>Disorders of fluid, electrolyte, and acid-base balance</td>
</tr>
<tr>
<td>Selected microvascular complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic retinopathy</td>
<td>250.5x</td>
<td>Diabetes with ophthalmic complications</td>
</tr>
<tr>
<td></td>
<td>361.9</td>
<td>Unspecified retinal detachment</td>
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<tr>
<td></td>
<td>362.0x</td>
<td>Diabetic retinopathy: background retinopathy, proliferative diabetic retinopathy</td>
</tr>
<tr>
<td></td>
<td>362.8x</td>
<td>Other retinal disorders</td>
</tr>
<tr>
<td></td>
<td>379.23</td>
<td>Vitreous hemorrhage</td>
</tr>
<tr>
<td></td>
<td>14.7xb</td>
<td>Operations on vitreous</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>250.4x</td>
<td>Diabetes with renal manifestations</td>
</tr>
<tr>
<td></td>
<td>585 xx</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td></td>
<td>55.6xb</td>
<td>Transplant of kidney</td>
</tr>
<tr>
<td>Diabetic neuropathy</td>
<td>250.6x</td>
<td>Diabetes with neurological manifestations</td>
</tr>
<tr>
<td>Selected macrovascular complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>410.xx</td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>411.xx</td>
<td>Other acute and subacute forms of ischemic heart disease</td>
</tr>
<tr>
<td></td>
<td>412.xx</td>
<td>Old myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>413.xx</td>
<td>Angina pectoris</td>
</tr>
<tr>
<td></td>
<td>414.xx</td>
<td>Other forms of chronic ischemic heart disease</td>
</tr>
<tr>
<td>Stroke</td>
<td>433.xx</td>
<td>Occlusion and stenosis of precerebral arteries</td>
</tr>
<tr>
<td></td>
<td>434.xx</td>
<td>Occlusion of cerebral arteries</td>
</tr>
<tr>
<td></td>
<td>436</td>
<td>Acute but ill-defined cerebrovascular disease</td>
</tr>
<tr>
<td>Diabetic peripheral circulatory disorders</td>
<td>250.7x</td>
<td>Diabetes with peripheral circulatory disorders</td>
</tr>
<tr>
<td></td>
<td>440.2x</td>
<td>Atherosclerosis of native arteries of the extremities</td>
</tr>
<tr>
<td></td>
<td>707.1x</td>
<td>Ulcer of lower limbs, except pressure ulcer</td>
</tr>
</tbody>
</table>

*aComplications defined by the authors as diabetes-related.

bIndicates an ICD-9-CM procedure code.

### HCUP Mean Cost per Diabetes-Related Hospitalization

<table>
<thead>
<tr>
<th>Complication</th>
<th>Primary Diagnosis HCUP Cost ($)</th>
<th>Nonprimary Diagnosis HCUP Attributable Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td>8,790</td>
<td>2,384</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>10,570</td>
<td>5,494</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>17,807</td>
<td>314</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>7,184</td>
<td>3,755</td>
</tr>
<tr>
<td>Septicemia</td>
<td>17,319</td>
<td>13,288</td>
</tr>
<tr>
<td>Kidney infections</td>
<td>7,407</td>
<td>1,924</td>
</tr>
<tr>
<td>Cystitis</td>
<td>8,628</td>
<td>1,763</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>7,174</td>
<td>2,935</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>7,808</td>
<td>2,993</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>12,860</td>
<td>9,185</td>
</tr>
<tr>
<td>Electrolyte imbalance</td>
<td>6,366</td>
<td>2,065</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>6,675</td>
<td>1,500</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>16,225</td>
<td>2,845</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>9,097</td>
<td>1,141</td>
</tr>
<tr>
<td>Stroke</td>
<td>10,443</td>
<td>3,632</td>
</tr>
<tr>
<td>Peripheral circulatory disease</td>
<td>18,613</td>
<td>3,182</td>
</tr>
</tbody>
</table>

*Complications defined by the authors as diabetes-related (Appendix A).*

*Costs were derived from the 2004 HCUP data and inflated to 2007 dollars using the Medical Care component of the CPI.*

*CPI = Consumer Price Index; HCUP = Healthcare Cost and Utilization Project.*
Review of Regulatory Programs and New Opioid Technologies in Chronic Pain Management: Balancing the Risk of Medication Abuse with Medical Need

David Fishbain, MD, FAPA; Sandra Johnson, JD, LLM; Lynn Webster, MD, FACP, FASAM; Laurence Greene, PhD; and Joanne Faysal, BS

The complaint of pain is among the most common reasons that patients seek health care, and it is a leading cause of disability in our society. Approximately 130 million people in the United States report suffering from chronic pain, often in multiple anatomic locations simultaneously. Patient-reported pain is associated with estimated economic costs that range between $100-$150 billion annually in the United States. As generally recognized by pain medicine specialists, an essential component to managing legitimate chronic pain is opioid therapy. However, over the last 2 decades, greater numbers of opioid medication prescriptions have been accompanied by disturbing increases in accounts of opioid misuse, abuse, and diversion. As recently described by Strassels (2009) in this journal, the societal and economic costs of opioid abuse are considerable. Compared with nonabusers, opioid abusers use significantly more medical services, experience far greater numbers of opioid- and nonopioid-related adverse events, and are at high risk for abuse-related diseases.

Regarding opioid therapy, a cornerstone of effective pain management involves the challenges of providing appropriate analgesia for patients with legitimate pain while, at the same time, reducing risks of aberrant drug-related behaviors and preventing their negative outcomes. Current efforts to meet these challenges include applying effective strategies for diagnosing the underlying causes of pain; using valid screening tools to identify patients who are at risk for abuse; regularly monitoring patients for potential misuse and abuse; following government-based regulatory policies and guidelines of established pharmacy and medical organizations for prescribing and dispensing opioids; and participating in prescription drug monitoring programs (PDMPs). In addition, manufacturers have recently begun marketing novel opioid formulations with technologies intended to deter abusers who tamper with products to extract active substances for administration through alternative methods, including intravenous injection and nasal snorting. The primary purpose of this article is to provide the managed care pharmacy community with an overview of these various strategies for achieving balance involving opioid need versus the risk of abuse. For essential background information, we begin with brief summaries of key definitions of pain, current views on pathophysiology, and pain pharmacotherapies.

Defining Pain

The International Association for the Study of Pain (IASP) defines pain as an “unpleasant sensory and emotional experience associated with actual or potential tissue damage.” In addition, the IASP acknowledges that reported pain without tissue damage or any known pathophysiological cause is common in chronic pain patients. This problem is not necessarily associated with psychological dysfunction, psychiatric illness, factitious illness, or malingering and may be related to a physician’s inability to diagnose pathophysiological dysfunction because of the current level of scientific development. An example of this phenomenon is fibromyalgia, a disease characterized by an apparent lack of pathophysiological cause. Because of this lack fibromyalgia was originally labeled “psychogenic rheumatism.” However, up-to-date evidence utilizing recently developed technology (e.g., magnetic resonance imaging [MRI] and positron emission tomography [PET] scanning) indicates that fibromyalgia is probably a central sensitization syndrome characterized by abnormal pain processing. Nonetheless, in spite of the findings from newer technologies, it should be noted that there is usually a significant psychiatric comorbidity (e.g., depression, anxiety) found in patients with chronic pain. At the present time, the preponderance of the evidence indicates that the psychiatric comorbidity may be a result of the pain rather than its cause, since in most cases, psychiatric comorbidity follows pain development. However, generally the presence of psychiatric comorbidity, whatever its cause, complicates pain treatment. Proper prescribing comes from balancing these perspectives.

Specific definitions of pain are based on its persistence over time and underlying physical and psychological causes. Acute pain is a protective mechanism that typically develops from a specific physical cause and resolves in a short time following causal resolution. Chronic pain is commonly defined as persistent pain that lasts beyond the ordinary duration of time that an injury needs to heal. As defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), pain disorder refers to the complaint of chronic pain in which psychological factors play a major role in the onset, severity, exacerbation, or maintenance of pain. However, pain disorder is not synonymous with chronic pain.
The complaint of pain may also be a means to fill other agendas, such as obtaining opioids for illegitimate purposes.

Regarding causal factors, pain is commonly designated by the terms nociceptive, neuropathic, inflammatory, functional, somatoform, or existential. While acute pain mainly results from nociceptive stimuli, chronic pain can be produced via nociceptive, neuropathic, existential, or mixed stimuli. Inflammatory pain is the result of increased nociceptor excitability in response to inflammatory mediators. Existential pain, which is essentially anguish, often results in the overstatement of physical pain and commonly promotes addiction. Existential pain may be responsive to opiates; however, chronic use of opiates in patients with primarily existential pain promotes dysfunction and/or addiction.

Pain disorder, a somatoform disorder, refers to the complaint of pain in which psychological factors play a large role in the development and severity of the pain. Pain disorder can be further differentiated into pain disorder with or without the presence of an underlying medical condition. Patients with pain disorder typically present with persistent complaints of pain in one or more areas with a lack of physical cause and concomitant social impairment or distress due to their pain. Additionally, the complaint of pain in somatoform disorder is not associated with any dishonesty or malingering and cannot be correlated to any other mood, anxiety, or psychotic disorder.

Differences in the causes of pain and length of its occurrence aid in determining the most appropriate management. Pharmacologic therapy may be utilized to help reduce, manage, and/or eliminate the pain, particularly when it is due to physical mechanisms, while antidepressants can help to alleviate any psychological causes or manifestations of pain. Furthermore, patients can experience more than one type of pain simultaneously, making treatment more complex. A multidisciplinary approach to the management of pain—including physical, occupational, and psychosocial therapy—may thus be effective for reducing pain and treating common comorbidities such as depression. It is important to note that the experience of pain is subjective. There is no test or assay to positively diagnose pain; therefore, physicians must rely on the information provided to them by their patients. Opioid abusers can use this knowledge to their advantage to deceive physicians and obtain prescription opioids for personal use and/or diversion.

Pathophysiology of Pain—A Brief Review

A comprehensive review of the pathophysiology of pain goes well beyond the scope of this article. As follows, we present an overview of current views on the underlying mechanisms of pain as they relate to opioid therapy. Numerous publications address pain pathophysiology in considerable depth.

As previously stated, pain can involve dysfunction or injury to diverse neural pathways, as well as various psychiatric causes, wherein no specific pathway pathology may exist. Nociceptive pain, initiated by thermal, chemical, or mechanical stimuli, is attributable to signals transmitted along ascending pathways from peripheral pain receptors to the spinal cord and the thalamus. The thalamus functions as a relay station, sending signals to various areas of the cerebral cortex. Descending pathways can inhibit pain signaling through the release of neurotransmitters including norepinephrine and serotonin. Accordingly, antidepressant medications that modulate serotonin and norepinephrine levels are commonly prescribed to treat pain and related psychiatric disorders.

Neuropathic pain, which is due to neural lesions or nervous system dysfunction, can be (a) induced by ectopic firing of nerves in axons or cell bodies; (b) a result of injured nerves releasing peptides, contributing to an inflammatory response; or (c) caused by inhibition of pathways in the brain and spinal cord involved in transmitting peripheral signals. Neuropathic pain is typified by numbness and tingling or burning sensations in the region innervated by the nerve and can be triggered by light touch. Prolonged neuropathic dysfunction can also result in spontaneous activity, emotive conduction caused by aberrant signaling of adjacent neurons, sensitization, and neuroplasticity.

While the viscera are generally impervious to chemical and noxious stimuli, there is a defined visceral sensitivity to mechanical stimuli, which is primarily mediated by inflammation. Inflammatory pain refers to spontaneous pain and hypersensitivity due to tissue damage or inflammation. Sensory afferent nerves are sensitive to inflammation and its chemical mediators, including bradykinins, prostaglandins, and leukotrienes. These mediators can directly activate nociceptors or recruit inflammatory cells to maintain or intensify inflammation. Stimulation of afferent neurons by inflammatory substances can cause peripheral sensitization, a change in neuronal function, or central sensitization, eventually leading to a chronic pain syndrome. Inflammation and its corresponding pain may also assist in the healing process by limiting mobility and increasing sensitivity to prevent further damage of the injured area.

Functional pain (non-nociceptive or non-neuropathic) may be due to abnormal pain processing or functioning of the nervous system, resulting in allodynia and hyperalgesia. Fibromyalgia is a prototypical example of functional pain. Currently, the underlying cause of fibromyalgia is unknown, but diagnosis is based on the complaint of widespread pain lasting at least 3 months in 11 out of 18 tender point sites upon digital palpation. Sensitization occurs following repeated, constant, or intense stimuli of damaged tissue (peripheral sensitization) or neurons within the central nervous system (central sensitization). Both plasticity of the nociceptor and release of inflammatory mediators are involved in sensitization. When sensitization occurs, fewer stimuli are required to activate
neurons, but a similar or exaggerated intensity of pain is produced.30 An important physiological event that contributes to the development of sensitization is wind-up. Wind-up is a continuous and/or an increased firing rate of neurons following repeated stimulation independent of whether a stimulus is present or not.31

Neuroplasticity refers to remodeling or adaptation of neurons following prolonged or repeated activation of neurotransmitters and the various neuronal pathways.32 Remodeling involves phenotypic and structural changes, increased excitability, and decreased firing threshold of neurons. The results of neuroplasticity are sensitization, restructuring, and overexpression of ion channels and receptors such as N-methyl-D-aspartate receptors, activation of the hypothalamic-pituitary-adrenal axis, vasoconstriction, and neural reorganization.21,31,33 Neuroplasticity can result in a decreased threshold for pain and opioid tolerance, thereby increasing the sensation of pain and reducing the effects of analgesia.34

Pharmacotherapy of Pain

It is important to differentiate the various types of pain during diagnosis, as each type is ideally managed with targeted therapies. Inflammatory pain is reduced upon healing of the injury, while the swelling and pain can be reduced using anti-inflammatory medicines such as nonsteroidal anti-inflammatory drugs (NSAIDS) or corticosteroids. The treatment of nociceptive and neuropathic pain includes both opioids and a variety of psychoactive drugs.35 Treatments vary depending on the location of pain and the system involved; however, opioids can be used to treat pain emanating from anywhere within the nervous system (Figure 1).36 However, with the onset or progression of sensitization as described earlier, larger doses of opioids may be required to attain adequate analgesia, which can also contribute to the development of opioid dependence. While the prevalence rates for drug dependence are no greater in pain populations than in the general population, there are subgroups of chronic pain patients at an increased risk of dependence; typically, these are patients with an existing addiction predisposition.36 Thus, comprehensive monitoring is essential.

Antidepressants and anticonvulsants have been shown to assist in pain reduction by affecting neurotransmitters involved in modulating pain signals and by providing relief from psychological comorbidities.37 In addition, as there is a strong correlation between pain and psychiatric comorbidities, any reduction in pain through physical therapy, analgesics, or even narcotics can also help to reduce psychiatric symptoms. Three agents are approved by the U.S. Food and Drug Administration (FDA) for treating fibromyalgia: the second-generation anticonvulsant pregabalin and the dual-reuptake inhibitors duloxetine and milnacipran. For the management of fibromyalgia, guidelines from the American Pain Society (APS, 2004) cite strong evidence for efficacy for only 2 drugs, amitriptyline and cyclobenzaprine, and modest evidence of efficacy for tramadol, the selective serotonin reuptake inhibitor fluoxetine, pregabalin, venlafaxine (a dual-reuptake inhibitor), milnacipran, and duloxetine.38 In addition, the APS guidelines found no evidence of efficacy for corticosteroids, NSAIDS, or opioids and therefore do not recommend their use in patients with fibromyalgia syndrome.38

According to the Merck manual, treatment for somatoform pain disorders revolves around treatment of both the psychiatric symptoms (e.g., antidepressants or psychotherapy) as well as the pain symptoms (e.g., analgesics).39 In addition, opioids can be a safe and effective treatment option for reducing pain in patients with somatoform disorder.39 However, there is a risk of the patient developing abuse or drug dependence, especially in patients with a history of drug abuse, and comprehensive monitoring should be utilized to prevent or reduce the risk of the development of dependence.36

Opioid Use and Abuse

Although Americans represent only 4.6% of the world population, they consume 80% of all opioids and 99% of all hydrocodone worldwide.40 Hydrocodone is the most frequently prescribed drug in the United States, with 120 million prescriptions written between 2005 and 2006.40 According to the Drug Enforcement Administration (DEA) Automation of Reports and Consolidated Order Systems (ARCOS), cumulative distribution

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**Figure 1** Use of Pathophysiologic Pain Mechanisms in Psychopharmacology

- **Descending Modulation**
  - Anticonvulsants
  - Opioids
  - Tricyclic/SNRI Antidepressants

- **Central Sensitization**
  - Anticonvulsants
  - Opioids
  - NMDA-Receptor Antagonists
  - Tricyclic/SNRI Antidepressants

**Peripheral Sensitization**

- Local Anesthetics
- Topical Analgesics
- Anticonvulsants
- Tricyclic Antidepressants
- Opioids

---

*Source: Fishbain*35

*Act at all 3 targets.*

CNS = central nervous system; NMDA = N-methyl-D-aspartic acid; PNS = peripheral nervous system; SNRI = serotonin-norepinephrine reuptake inhibitor.
of opioids has steadily increased from 2003 through 2007, with hydrocodone and oxycodone showing the largest distributions (Figure 2).41

When used appropriately, opioids provide effective analgesia for pain. However, there is a significant degree of illicit use of opioids that may include abuse, diversion, and addiction. These aberrant behaviors can result in death and societal harms. Specific definitions related to the use and abuse of opioids have been established by the Federation of State Medical Boards (Table 1).42

The fear of addiction may affect decisions made by both physicians and patients in determining the optimum treatment for chronic pain. While it is true that patients on long-term opioid treatment could possibly become addicted, Fishbain et al. (2008) determined in a review of 67 studies that the rates of abuse and addiction in chronic pain patients with or without previous or current history of drug abuse were 3.27% and 0.19%, respectively.36 These findings suggest that patients with a history of drug abuse may require more stringent monitoring or referral to a pain specialist and/or psychiatric services.

Opioids are among the most frequently abused class of drugs. The 2008 National Survey on Drug Use and Health (NSDUH) revealed that approximately 4.7 million Americans took pain medications for nonmedical use within the last month.43 The NSDUH also found that pain relievers were among the most common drug classes for initial drug abuse, the second-ranked drug class associated with abuse or dependence, and the fourth-ranked drug class for which abuse-related treatment was sought among persons aged 12 years or older.43 The Drug Abuse Warning Network (DAWN) report for 2006 from the Substance Abuse and Mental Health Services Administration (SAMHSA) attributed 741,425 emergency room (ER) visits to the nonmedical use of prescription or over-the-counter pharmaceuticals or dietary supplements, accounting for 42.5% of the ER visits associated with drug misuse or abuse that year.44 Nonmedical use of hydrocodone or hydrocodone combinations was associated with 57,550 ER visits, similar to the 64,888 ER visits associated with nonmedical use of oxycodone or oxycodone combinations.44 Data from 8 poison control centers over 12 months in 2003 indicated that hydrocodone and oxycodone were involved in numerous reports involving opioid abuse and misuse.45 In addition, data from the Centers for Disease Control and Prevention (CDC) indicate that in 2006, 37% of poison-related deaths involved opioids.46
Factors Contributing to a Rise in Opioid Abuse

A variety of factors have contributed to the increased abuse of opioids. Increasing volume of opioid prescriptions is a primary factor that influences availability and diversion for nonmedical use. A 2007 survey conducted by the National Institute on Drug Abuse (NIDA) revealed that of respondents in the 12th grade who reported inappropriate use of prescription opioids, approximately 70% were obtained from a friend in the illicit marketplace, serves as the primary source of obtaining opioids listed include hydrocodone, oxycodone, methadone, morphine, buprenorphine, codeine, and hydromorphone. Internet pharmacies, which began in 1999, have provided a readily available avenue for abusers to obtain drugs.

Table 1: Selected Definitions of Terms Related to the Use and Abuse of Opioids for Pain Treatment

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addiction</td>
<td>“Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include the following: impaired control over drug use, craving, compulsive use, and continued use despite harm.”</td>
</tr>
<tr>
<td>Physical dependence</td>
<td>“Physical dependence is a state of adaptation that is manifested by drug class specific signs and symptoms that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist. Physical dependence, by itself, does not equate with addiction.”</td>
</tr>
<tr>
<td>Tolerance</td>
<td>“Tolerance is a physiologic state resulting from regular use of a drug in which an increased dosage is needed to produce a specific effect, or a reduced effect is observed with a constant dose over time. Tolerance may or may not be evident during opioid treatment and does not equate with addiction.”</td>
</tr>
<tr>
<td>Pseudoaddiction</td>
<td>“The iatrogenic syndrome resulting from the misinterpretation of relief-seeking behaviors as though they are drug-seeking behaviors that are commonly seen with addiction. The relief-seeking behaviors resolve upon institution of effective analgesic therapy.”</td>
</tr>
</tbody>
</table>

Opioid Use for Chronic Pain Management—Regulatory and Legal Issues

State and federal agencies provide legal and regulatory standards for prescribing and dispensing opioids. State medical boards have the primary authority for regulating physician behavior. Multiple federal agencies contribute to the monitoring and risk management of controlled substances. The FDA monitors medications via review of clinical data to ensure accurate marketing of drugs, thereby ensuring that drugs are safe and effective for human consumption. The DEA’s mission is to enforce the controlled substance laws and regulations, as well as to arrest any persons involved in the manufacturing or distribution of illegal substances. The SAMHSA works through various programs to provide effective mental health and substance abuse treatment resources, reduce and prevent the abuse of illegal drugs, and collect and analyze behavioral health data. The NIDA is responsible for conducting and disseminating research across a variety of fields in an effort.
to improve drug abuse/addiction-related prevention, treatment, and policy. The Office of National Drug Control Policy (ONDCP) is responsible for creating policies, strategies, and priorities for the U.S. drug control policy.

In the early 1990s, studies of the state medical boards indicated that they did not conform to current standards of practice in pain treatment and that the board's actions may have penalized doctors who were prescribing controlled substances appropriately. In 1997, the Federation of State Medical Boards (FSMB) assembled pain, substance abuse, and regulatory experts to develop Model Guidelines for the Use of Controlled Substances for the Treatment of Pain. The DEA endorses the FSMB guidelines in anticipation that they will help physicians adhere to pain management standards and help law enforcement officials determine whether pain medication is being appropriately prescribed. The FSMB guidelines, updated in 2004, recognized controlled substances as appropriate for the treatment of pain, encouraged physicians to adequately treat pain with opioids, addressed physicians' fears of regulatory scrutiny, and supported the concept of physicians maintaining appropriate and updated education about pain management. The FSMB also made recommendations regarding practice management including, but not limited to, documentation, informed consent, monitoring, and adherence to state and federal laws. The FSMB guidelines include a provision that physicians will not be judged solely on the basis of the amount of medication or length of treatment of pain with controlled substances. As of April 2010, the FSMB website reported 24 state medical boards that had adopted all or part of model guidelines.

The Controlled Substance Act (CSA) is a federal statute under which the DEA enforces the regulation of the manufacture, importation, possession, use, and distribution of certain substances. Drugs with addictive properties are listed on a schedule depending on their level of risk and medical usefulness. Schedule I drugs, including heroin and marijuana, are considered to be without medical benefit and may not be prescribed in clinical practice. Schedules II through V list substances. Schedule II includes oxycodone, hydrocodone, and propoxyphene. Schedule III includes methylphenidate and buprenorphine. Schedule IV includes clonidine and clonazepam. Schedule V includes lisdexamfetamine and tizanidine.

The revised Screener and Opioid Assessment for Patients in Pain (SOAPP-R) and Opioid Risk Tool (ORT) are predictive tools to assess the risk of developing aberrant behaviors for chronic pain patients being considered for long-term opioid therapy. The Screening Instrument for Substance Abuse Potential (SISAP) assesses the potential substance abuse history of a patient prior to treatment, and the Diagnosis, Intractability, Risk, Efficacy (DIRE) questionnaire can be utilized to assess the potential benefit and harm of opioid treatment for a given patient.

Risk stratification tools may help physicians determine which patients are at a higher risk of developing an addiction to opioids or are possibly misusing their medications.

Strategies to Reduce the Burden of Opioid Abuse

Opioid abuse is a complex problem that requires a multifaceted management strategy that engages many organizations and professionals, including state and federal governments, pharmaceutical companies, physicians, and pharmacists. Education of providers is an important mechanism to reduce opioid abuse; a 2005 survey indicated that only about one-half of pharmacists and one-fifth of physicians reported having received training on identifying prescription drug diversion.

In order to reduce the incidence of opioid abuse among patients seeking pain relief, and to thwart abusers with hidden agendas from obtaining opioids from physicians, several methods can be utilized. The first is proper patient assessment for the initiation of opioid therapy. Recommendations from the American Pain Society and American Academy of Pain Medicine include conducting a thorough history and physical exam inclusive of psychosocial factors, family history, and risk assessment.

A comprehensive benefit-to-harm assessment should also be conducted, and the appropriate diagnostic analysis should be performed to determine an underlying cause of the pain, including possible physical and psychological etiologies. Patients with somatoform pain disorder tend to provide vague complaints of pain regarding location and sensation.

Risk stratification tools may help physicians determine which patients are at a higher risk of developing an addiction to opioids or are possibly misusing their medications. The revised Screener and Opioid Assessment for Patients in Pain (SOAPP-R) and Opioid Risk Tool (ORT) are predictive tools to assess the risk of developing aberrant behaviors for chronic pain patients being considered for long-term opioid therapy. The Screening Instrument for Substance Abuse Potential (SISAP) assesses the possible substance abuse history of a patient prior to treatment, and the Diagnosis, Intractability, Risk, Efficacy (DIRE) questionnaire can be utilized to assess the potential benefit and harm of opioid treatment for a given patient.

Once initiated on opioids, patients should be regularly monitored for treatment efficacy, movement towards treatment goals, improvements in functionality and quality of life measures, adverse events, aberrant behaviors, and medication adherence. Aberrant behaviors include doctor shopping, unauthorized self-increased dosing, drug hoarding, requesting specific drugs, and aggressively demanding higher dosages. Behaviors that are more predictive of drug abuse/misuse/diversion include forging prescriptions, stealing drugs, using alternative methods of ingestion such as snorting or injecting.
oral drugs, recurrent prescription losses, and simultaneous use of illicit drugs.71
For high-risk patients or those displaying aberrant behaviors, random urinalysis and pill counts can help to monitor adherence and possible diversion.71 One example of this monitoring involves patients on opioid therapy who show no opioids in their systems through urinalysis; these patients might be diverting their opioids rather than taking them. Urinalysis and pill count methods can also be used in low-risk patients to monitor adherence. The Current Opioid Misuse Measure (COMM) and the Pain Assessment and Documentation Tool (PADT) can be used to assess patients currently on opioid therapy who may be exhibiting aberrant behaviors associated with misuse of opioid medications.72,73

Prescription Drug Monitoring Programs to Thwart Doctor Shopping.
In recent years, state-specific PDMPs have been established in an attempt to reduce prescription drug diversion.74 As of January 2009, 38 states had laws to establish PDMPs, 32 of which were operational.75 These monitoring programs collect and analyze statewide data regarding the prescribing, dispensing, and use of prescription drugs in real time. The data can assist state law enforcement and regulatory groups in identifying possible illegal prescribing, dispensing, and acquisition of controlled substances.

PDMPs consist of 3 main components: (a) collection of prescription data from physicians and pharmacists, (b) storage and processing of the data, and (c) establishment of regulations to determine who can access the data.76 States vary regarding the specifics of their PDMPs, including details of who must provide data and what data are required, which schedule(s) of drugs are to be monitored, how often the data are collected, and who can access the prescription information. Typically, law enforcement agencies with appropriate documentation (e.g., a warrant) and licensure boards can access the data in association with ongoing investigations, and physicians and pharmacists can access data on their own patients.76 The purpose of allowing physicians and pharmacists access to data within PDMPs is to prevent abuse or diversion by identifying patients who may be doctor shopping.

PDMPs can be used as a reactive or proactive system, with most states using a reactive system. States such as Maine have PDMPs that are capable of delivering both reactive and proactive reports. As a reactive system, information about a potential abuser is produced only following an inquiry made by a prescriber or managed care organization.77 In proactive systems, state program personnel regularly review records to identify any suspicious activities and generate unsolicited reports that are then forwarded to physicians, pharmacists, and regulatory agencies in an effort to reduce diversion before it occurs (e.g., before a prescription is filled at a pharmacy).77 A 2006 survey of 262 prescribers in Maine who had received an unsolicited report found that 42.1% confirmed that the patient was misusing prescriptions, suggesting that prescribers were using the unsolicited reports in the way that the designers of proactive PDMPs intended.78 In the same survey, only 3 of 354 prescribers (0.8%) did not find the PDMP useful in helping “clinicians and pharmacies to monitor patients’ controlled substance prescriptions,” and only 6 (1.7%) did not find the PDMP useful in controlling “doctor shopping” to obtain controlled substances.78 For the 34 pharmacy providers (“dispensers”) who responded to the survey, only 1 (2.9%) did not find the PDMP useful in helping clinicians and pharmacies to monitor controlled substance prescriptions and control “doctor shopping” to obtain controlled substances.78

The U.S. General Accountability (formerly, Accounting) Office (2002) found that while a PDMP may reduce diversion within the state in which it is used, an increase in diversion among surrounding states without PDMPs may occur.74 Accordingly, the U.S. Department of Justice, the Integrated Justice Information Systems (IJJIS Institute), and other groups have collaborated on the PDMP Information Exchange (PMIX) project, which assists in the exchange of prescription information between states.79 This interstate communication may reduce the number of patients who doctor shop across state lines. The presence of PDMPs in all 50 states would increase the effectiveness of PMIX programs and further reduce doctor shopping across state lines.

The U.S. Government Accountability (formerly, Accounting) Office (GAO) also reported that in Kentucky, the incorporation of a PDMP reduced the average time necessary for regulatory agencies to conduct investigations of possible diversion from 156 days to 16 days.78 Furthermore, only 2 of the 10 states with the greatest number of OxyContin prescriptions had operational PDMPs, compared with 6 of the 10 states with the fewest prescriptions for this drug.79

New Drug Formulations Intended to Deter Abuse
To address the serious public health concerns of opioid abuse and diversion, new formulations are being developed with the goal of reducing the attractiveness and drug-liking qualities of conventional opioid formulations. The new technologies are designed to hinder the extraction of active ingredients and to thereby control their bioavailability and prevent administration through alternative routes (Table 2). There are 3 main categories of new abuse-deterring technologies: (a) physical barrier mechanisms, which are designed to inhibit manual and chemical extraction of active substances; (b) agonist-antagonist formulations, which release opioid antagonist agents when abusers tamper with products; and (c) aversive substances, which release agents that cause unpleasant side effects when abusers consume opioid products in excess.80
The FDA has made clear that new products intended to deter misuse and abuse will not be able to make a claim of “abuse resistance” in product labeling or marketing in the absence of data from long-term epidemiologic studies that show actual reduction in “abuse and addiction and the consequences of those behaviors.” However, the FDA also recognizes that long-term surveillance data will not be available for some time and in the interim has stated that it would allow inclusion in the label of the physiochemical features of the product if there are “sufficient data indicating that the formulation would be resistant to manipulation.” Among the specific concerns are the creation of a false sense of security contributing to less conservative prescribing.

In April 2010, the FDA approved a new formulation of OxyContin that cannot be crushed or otherwise reduced to a particle size that would permit snorting, and the new formulation of OxyContin will replace the current formulation. However, despite the expectation that the new formulation would deter abuse of OxyContin, the FDA did not permit label or marketing claims of safety or abuse deterrence and required the manufacturer to use the REMS that was developed for hydromorphone ER (Exalgo) that was approved on March 1, 2010, by the FDA.

### Combinations with the Opioid Antagonist Naltrexone

Naltrexone, an opioid antagonist, is being studied in combination with opioids such as morphine or oxycodone as an abuse-deterrent formulation. Taken whole, the naltrexone remains intact, passes through the gastrointestinal tract without being absorbed, and does not affect the analgesic potential of the opioid. However, if crushed, chewed, or chemically manipulated, the naltrexone is released, which causes competitive binding at the mu-opioid receptors and inhibition of the euphoric effects of the opioid.

The FDA approved extended-release morphine sulfate (ERMS) in combination with naltrexone (Embeda) on August 13, 2009, the first of the new opioid formulations to gain approval (Table 2). Preliminary clinical trials yielded the following outcomes for comparisons of ERMS with naltrexone and conventional opioid formulations ingested intact: (a) bioequivalent opioid availability for ERMS alone and ERMS with naltrexone; (b) negligible plasma concentrations of naltrexone in a small percentage of subjects who ingested ERMS with naltrexone capsules, indicating that the antagonist largely remains sequestered in normal use; and (c) a 30% or greater reduction in morphine-induced euphoria for more than 50% of subjects who received naltrexone with immediate-release morphine sulfate (MSIR) compared with subjects who received MSIR alone. In comparisons of whole and crushed formulations of ERMS with naltrexone, scores for subject-reported euphoria and drug-liking did not differ significantly. The latter result suggests that the new formulation has the potential to deter abuse because its manipulation through crushing was not associated with an increase in euphoria and drug-liking. However, the FDA advisory committee in its meeting to review the new drug application for ERMS with naltrexone expressed concern that the new formulation would not prevent extraction of morphine sulfate (for intravenous administration) that would exclude naltrexone. For this reason, the FDA prohibited the marketing of this product with a claim that there is a reduction in the risk of abuse.

### Combinations with Aversive Agents

The addition of aversive substances to opioid formulations may limit abuse potential by creating an unpleasant effect if the product is taken at a higher-than-recommended dose, or...
if the product is tampered with. An immediate-release oxycodone formulation has been developed (Acurox, Table 2) that contains subtherapeutic levels of niacin.88 This formulation also incorporates a technology, called Aversion, that employs gelling ingredients to deter intravenous injection of dissolved tablets and nasal snorting of crushed tablets.89 When taken in small doses, niacin produces no negative effects.90 However, when niacin is taken in large amounts (more than 300 milligrams [mg]), it may cause flushing, itching, sweats, chills, and a feeling of discomfort that lasts for 1 to 3 hours.80 Results from a manufacturer-conducted clinical trial on the niacin-containing oxycodone product indicated that it (a) provided significantly greater analgesia than a placebo, (b) did not affect the safety profile of oxycodone, (c) reduced drug-liking effects of oxycodone in direct proportion to the amount of niacin consumed, and (d) increased disliking scores/aversion compared with oxycodone HCl.90 An important factor in the abuse potential of a drug is the ability to extract the pure oxycodone from the formulation. Extraction tests revealed that only trace amounts of oxycodone could be extracted from the niacin-containing product in approximately 6 hours, making it unattractive to users seeking a “quick high.” Similar analysis of currently available oxycodone formulations resulted in extraction of approximately 80% oxycodone in less than 10 minutes.88

The FDA advisory committees (Anesthetic and Life Support Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee) met jointly on April 22, 2010, to consider NDA 22-451 for this new formulation of oxycodone (Acurox), “the first immediate-release opioid since Talwin Nx.”91 The committees voted against recommending approval, concluding that insufficient evidence is available to support claims that the niacin formulation has abuse-deterrent effects.91 In addition to opioid formulations that incorporate niacin, other aversive agents include unpleasant odor- and taste-altering agents and capsaicin, which induces a burning sensation when the product is crushed or dissolved and then taken through alternative methods.82

Gel-Based Matrix
PTI-821 (trade name Remoxy) is controlled-release oxycodone suspended in a water-insoluble, highly viscous matrix with a hard gelatin outer capsule. The manufacturer is seeking approval for dosage strengths ranging from 5 mg to 40 mg.92 When swallowed whole, PTI-821 and controlled-release oxycodone yielded similar plasma oxycodone levels, but when crushed and taken with either water or alcohol, PTI-821 yielded lower plasma oxycodone concentrations compared with controlled-release oxycodone treated in the same manner.93 Patients with moderate-to-severe osteoarthritis of the knee or hip who were given PTI-821 reported a 30% reduction in pain intensity after 5 weeks of treatment compared with a 20% reduction in pain intensity for patients given placebo ($P = 0.043$).94

Another barrier formulation, designated COL-003 for research purposes, has a patented design that encapsulates sustained-release oxycodone in fatty/waxy particles. The “micro-particles” resist chewing and crushing, thereby deterring extraction of opioid substances and dose dumping through alternative routes of administration. Assessing the safety and pharmacokinetics of COL-003, Fleming et al. (2008) found that the formulation maintained its sustained-release properties in various tampering conditions.95 Moreover, plasma concentrations of oxycodone were bioequivalent for chewed versus intact COL-003 formulations, indicating that abusers would not achieve their objective of a rapid high through tampering with the capsule.

Conclusions
Opioid therapy is an important element in pain management programs for patients with legitimate chronic pain that does not respond to preliminary treatments. However, a balance is essential to prevent opioid abuse and diversion. In addition, clinicians must apply diagnostic procedures to identify patients who would benefit from or require referral to appropriate specialists. The various strategies for treating chronic pain effectively and, at the same time, deterring opioid abuse and diversion involve proper patient assessment and diagnosis, risk stratification, and regular monitoring. Unfortunately, opioid abusers have discovered ways to bypass the regulatory systems and obtain drugs through doctor shopping, feigning pain, and utilizing Internet pharmacies. A multidisciplinary approach that includes state and federal prescription monitoring programs in conjunction with new abuse-deterrent drug formulations may contribute to curtailting opioid abuse and diversion in the future.

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Review of Regulatory Programs and New Opioid Technologies in Chronic Pain Management: Balancing the Risk of Medication Abuse with Medical Need


It Depends on What “Mean” Means: Averaging Versus Event Patterning in Analyses of Administrative Claims Data

Kathleen A. Fairman, MA, and Frederic R. Curtiss, PhD, RPh, CEBS

In 1963, the late Bobby Bragan, then manager of the Milwaukee Braves, poked fun at the statistics commonly used by baseball analysts, observing that “according to the percentage people” a person who was standing “with one foot in the oven and one foot in an ice bucket” was, on average, “perfectly comfortable.” Nearly 5 decades later, the problem highlighted by Bragan’s colorful assessment of the limitations of summary statistics has grown exponentially, especially in health care. Bombarded daily with an estimated 34 gigabytes of information in nonwork activities alone, American health care consumers are exposed to an overwhelming amount of statistical information about any health care condition that they choose to investigate. For example, a Google search on the term “H1N1 vaccine” returns more than 3 million hits in 0.28 seconds. The resulting potential for data overload should prompt us to pay close attention to how we package and summarize these data.

It is perhaps not surprising that a great deal of research in numerous medical specialties focuses on consumers’ perceptions of data about their health risks, often finding that consumers either underestimate their risk or fail to take action based on known risks. For example, in a case-control study of genetic counseling for BRCA1/2 testing in a sample of women with a family history of breast or ovarian cancer, Armstrong et al. (2005) found that 43 of 200 (21.5%) cases (i.e., patients who had undergone genetic counseling) and 21 of 181 (11.6%) controls perceived their lifetime risk of developing breast cancer as high. Risk was perceived as low for 121 of 200 (60.5%) cases versus 145 of 181 (80.1%) controls. Similarly, Moore et al. (2010) studied a sample of African-American women seeking care in urban health centers, finding that overweight and normal-weight women reported the same perceived risk of weight-related illnesses; and Holmes et al. (2007) studied auditory symptoms and hearing protection use in adults aged 18 to 27 years, finding that few used hearing protection consistently, although 6% reported hearing loss and 20% reported symptoms including ear pain and tinnitus after exposure to loud noises. Slightly rephrased, perhaps the issue at the heart of all of these studies is to what extent health care consumers believe that summary statistics, such as averages, actually apply to them.

The challenge for managed care, as both a user and purveyor of data and information, is to ensure that data-weary consumers are provided with accurate but comprehensible summaries of which behaviors and treatments are most likely to benefit instead of harm. This task, already challenging because of the complexity of health care information, has been made even more difficult by the increasing use and promulgation of retrospective observational research designs. That is, when health care outcomes are analyzed retrospectively, the only limits to the methodological options available are the imaginations and budgets of the investigators. The resulting myriad of measures and outcomes in the published research literature can cause both conflicting findings and bewilderment about what study results really mean. Retrospective analyses of administrative claims data pose several particular challenges in summarizing risks and benefits. A few key examples are discussed in this editorial.

Are Average Laboratory Values Clinically Meaningful?

In this issue of JMCP, Menzin et al. describe the results of a retrospective observational analysis of the association between glycemic control and diabetes-related hospitalizations in a sample of 9,887 patients aged 30 years or older with type 1 or type 2 diabetes who were treated in the primary care clinic of a managed care organization. All study subjects had at least 2 claims with a diagnosis of diabetes mellitus (International Classification of Diseases, Ninth Revision, Clinical Modification codes 250.xx) and at least 2 hemoglobin A1c tests administered within any 12-month period from January 1, 2002, through December 31, 2006. A diabetes-related hospitalization was defined as a hospital stay in which any of 10 available diagnosis fields on the hospital claim contained any of 16 diagnoses, including not only known microvascular and macrovascular complications (e.g., retinopathy, nephropathy, and ischemic heart disease) but also possibly related conditions as defined by the study authors (e.g., septicemia, urinary tract infection, and electrolyte imbalance).

Notably, the measure of glycemic control used in the study by Menzin et al. was average A1c value—that is, the sum of all A1c values obtained for the patient over a follow-up period from a minimum of 1 to a maximum of 5 years, divided by the number of tests. Because the clinic’s laboratory data file includes only tests ordered by clinic providers, most tests ordered by specialists were not included in the A1c average.

In this use of the average per test A1c as the predictor of interest, Menzin et al. departed from some previous work in this topic area, which related glycemic control to medical
utilization by patterning events in sequence. For example, a widely cited historical cohort study by Wagner et al. (2001) classified a sample of patients with diabetes (predominantly type 2, mean age 60 years) into cohorts based on whether they had achieved improvements in glycemic control from 1992 through 1993 and sustained those improvements in 1994; subsequent health care utilization was examined from 1994 through 1997.\textsuperscript{11} Wagner et al. observed a significant association between better glycemic control and lower total health care costs in 1995 through 1997 (but not in 1994); when analyzed by subgroup, these savings were statistically significant only for those with baseline A1c levels of at least 10%. Rates of primary care use were lower for the patients with improved glycemic control in all follow-up years, but hospital utilization did not significantly differ by cohort in any follow-up year.\textsuperscript{11} Similarly, Gilmer et al. (2005) found in a study of patients with type 1 or type 2 diabetes that higher baseline A1c, measured at the start of a follow-up period of up to 3 years, predicted higher subsequent total health care costs, although comorbid heart disease, depression, and hypertension were more important predictors.\textsuperscript{12}

Despite the inconsistency of the method used by Menzin et al. with some previous work, the method of contemporaneous measurement of average A1c as a predictor and health care utilization as an outcome measure has been used in previously published work, including a previous study by Menzin et al.\textsuperscript{13,14} Moreover, methodological limitations aside, studies of this question have generally concluded that, primarily among patients with very high A1c levels (e.g., at least 10%), improvement in A1c is associated with health care cost reduction.\textsuperscript{10-14}

In discussing the limitations of their work, Menzin et al. appropriately note that "calculating a mean of all observed A1c values to classify patients is not sensitive to changes over time in A1c levels" and suggest the use of alternative approaches in future research. Although accurate, this statement perhaps does not go far enough to describe the impact of using an average laboratory test value. In the study by Menzin et al., hospitalizations were measured from the date of the first A1c test until the earlier of plan disenrollment, death, or the study end date. It is possible that for an unknown number of study patients, the hospital stay(s) identified as outcomes preceded all but 1 of the A1c measures that were used to predict them, and the mean (SD) number of A1c tests for the full sample was 7.6 (4.3). Thus, this analytic approach violates a key factor in the so-called "Bradford Hill's considerations" in determining the likelihood that an association is attributable to a causal relationship: "the factor must precede the outcome it is assumed to affect."\textsuperscript{15}

Averaging in Measures of Medication Possession Ratio and Cost Sharing

Studies of average laboratory values are not the only examples of problems in summary measures that are frequently used in analyses of administrative claims data. One of the most common measures, medication possession ratio (MPR), is broadly defined as a ratio of medication availability (supply) to time spent in treatment or intended treatment. However, in practice MPR has been operationalized in numerous ways, sometimes to the detriment of the applicability of study findings to typical clinical practice.

For example, in some previous work, the numerator of the MPR has been defined as a simple sum of all days supply for all medications dispensed during the time period of interest. For patients taking more than 1 drug within a therapeutic class—including those switching from one drug or strength to another or receiving augmentation of therapy with additional drug(s)—the days supply values for all drugs were summed.\textsuperscript{10-18} Reports of studies in which this method was used often indicate that MPR was truncated at 1.0 (100%) because the resulting summed days of therapy exceeded the number of calendar days studied.\textsuperscript{10,17} When assessing patients making product or strength switches, this calculation is particularly problematic because the drug supply remaining after a switch date is unlikely to be consumed. For example, if a patient is initially dispensed a 30-day supply of Drug A and switches to Drug B after 7 days of treatment, a 23-day supply of Drug A is unconsumed and therefore should not be counted towards MPR. To account for this problem, better designs use a more complicated calculation, the assessment of days covered (sometimes called an assessment of medication gaps), in which (a) calendar days with and without medication are identified by summing the fill date plus days supply for each initial fill and refill of the medication(s) of interest, and (b) days with and without medication are summed across the study period.\textsuperscript{10,20}

Choice of denominator also affects the validity of the MPR calculation. Although it is common to measure the denominator as time from the therapy start date to therapy end date, often defined as the fill date plus days supply for the patient's final claim,\textsuperscript{16,18} doing so can produce findings that are misleading or confusing.\textsuperscript{10} For example, a patient who fills only the initial prescription and has no subsequent refills has a calculated MPR of 100%. MPRs calculated using this approach should be interpreted cautiously if they are used at all. Better—that is, more clinically relevant—designs measure the ratio of days supply to a fixed calendar time frame that represents an intention to treat,\textsuperscript{17} such as the first 12 months following the start date of therapy.\textsuperscript{10}

Another measure that is sometimes misinterpreted, average out-of-pocket cost per prescription or per month of therapy, appears commonly in the literature on patient cost sharing.\textsuperscript{20,21} Often used when specific benefit design information is unavailable to researchers, average out-of-pocket cost is a problematic measure because it is not truly exogenous (independent) but is itself a function of drug selection. Thus, the researcher who uses mean copayment as a predictive measure could be
measuring either the effect of the patient’s out-of-pocket cost or the effect of the medication choice. Systematic bias can occur if, for example, a health plan’s pharmacy and therapeutics committee has selected preferred brand drugs based on tolerability or efficacy, with more tolerable or efficacious drugs assigned preferred status (and therefore lower copayment). Similarly, patient out-of-pocket cost is generally lower for generic than brand medications. In a class such as antidiabetic medications, in which generic metformin is both more tolerable and safer than newer brand oral antidiabetic drugs,22-24 a systematic relationship between lower cost-sharing amount and a more favorable drug safety profile is introduced. In both of these situations, an analysis that uses mean copayment as an independent variable is biased to find an association between lower cost-sharing amount and greater persistence with therapy. In better designs, researchers have access to and control for specific benefit design features, including copayment amounts for each medication and other relevant factors, such as formularies, step therapy policies, and prior authorization requirements.

The Tradeoff Between Expediency and Accuracy: How to Choose?

There is no such thing as a perfect research study. All studies have limitations, usually made necessary by an inability to account for every possible source of bias or confounding—although, of course, some studies have more limitations than others. We have argued previously that the most important aspects of any research report are clarity and transparency, which allow readers and decision makers to determine the degree of potential bias and the usefulness of study conclusions for their organizations.25 Still, a primary endpoint outcome measure that is clinically invalid informs no one. How should a researcher choose a measure, and how should a managed care decision maker interpret it?

Perhaps a good rule of thumb is that if one cannot imagine a clinician using an outcomes measure in the way that it is being used in a research study, it is probably not an appropriate measure. For example, try to picture a clinician saying something like this to a patient with type 2 diabetes: “Well, Mrs. Smith, thanks to treatment with metformin, your A1c has declined from 8.0% at your first test, to 7.5% in your second test, and your latest A1c reading was 7.0%. Still, the average of these 3 test values is 7.5%, which puts you at elevated risk of complications. It’s time to add a new medication.” Similarly, one cannot picture a clinician saying to a patient: “During the past 3 months, I have started you on 4 different medications and you have stopped taking all 4 after only 1 week. But, when I sum up the days supply of all of your dispensed drug tablets, including those that you consumed and those that are still sitting in your medicine cabinet, and I divide that sum by 90 treatment days, I get a ratio of 133%. So, good job. I’ll see you at your checkup next year.”

As in many things in life, the more difficult path is often the better path in analyses of administrative claims data. “Quick and easy” approaches—like measuring independent and dependent variables contemporaneously, calculating average laboratory test values over an entire study period, and assessing MPRs without accounting for realistic clinical patterns such as drug switching and augmentation—may be a means to rapid calculation and dissemination of study findings, but they are also potentially misleading. In another editorial in this issue, we argue that an excess volume of poorly targeted communications to prescribers about drug safety may threaten the degree to which prescribers respond to information about true drug-related risks to their patients.26 Perhaps the same is true of information that is provided to health care consumers and decision makers without sufficient consideration of whether a study design is clinically meaningful. Researchers who use observational study designs should take time to think through the logical connections between realistic clinical scenarios and study methodology to ensure that research results will have real-world applicability. To do otherwise does not serve the needs of clinicians or their patients.

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Quality Improvement Opportunities in Prescriber Alert Programs

Frederic R. Curtiss, PhD, RPh, CEBS, and Kathleen A. Fairman, MA

Battles may be won, but the war against threats to patient safety continues, and time will tell if escalation of the war will reduce casualties. Brent James, MD, the well-known advocate of process improvement, several years ago described himself as a “terrorist” for health care safety.1 Despite Dr. James’ commitment to escalate the war in an attempt to reduce medical errors, particularly errors that harm, it will be difficult to eliminate adverse drug events (ADEs) entirely because of the myriad of factors that pose risks to patient safety including drug-drug, drug-disease, and drug-patient nuances.2,3 But, the certainty of ADEs does not diminish the importance of the mission to reduce patient harm from avoidable ADEs. This mission includes strategic actions, such as proactive avoidance of unnecessary and potentially harmful drug therapy, downward dose adjustment, and even discontinuation of drug therapy as part of high-quality medication therapy management.4,5

However, the size of the target is vague because the actual rate of patient harm associated with potentially avoidable ADEs is both controversial and difficult to estimate accurately. Some have argued that even the most frequently cited figures, such as the Institute of Medicine’s estimate that between 44,000 and 98,000 inpatients in the United States die annually as a result of preventable medical errors including ADEs,6 are either exaggerated by failure to account for patients’ baseline health status or “not well substantiated” because of their reliance on the “highly subjective” opinions of study investigators about which events are avoidable.7,8 Additionally, these estimates are widely publicized, represent a large portion of the research on the effects of ADEs,8,11 and are commonly cited as evidence of the need for automated prescribing techniques to reduce ADEs throughout the health care system;2 yet, they do little to inform managed care decision makers about risks to patients in ambulatory care, who represent the vast majority of beneficiaries with public or private insurance.

Gurwitz et al. (2003) used a rigorous and labor-intensive methodology, including thorough reviews of patient charts and incident reports, systematic evaluation of all potential ADEs by multiple raters, and assessments of inter-rater reliability, to estimate the incidence, severity, and preventability of ADEs in a cohort of approximately 30,000 predominantly Medicare + Choice (managed care) enrollees who received care in a large multispecialty group practice.5 During 30,397 person-years of observation over the 12-month period from July 1999 through June 2000, the investigators identified 1,523 events (rate of 50.1 per 1,000 person-years), more than 70% of which resulted in symptoms that persisted for more than 1 day. Of the 1,523 ADEs, 431 (28.3%) were deemed to be “serious” (e.g., fall with fracture, hemorrhage requiring transfusion or hospitalization, delirium, urticaria); 136 (8.9%) were “life-threatening” (e.g., hemorrhage with hypotension, hypoglycemic encephalopathy, acute renal failure); and 11 (0.7%) were fatal, including bleeding, drug toxicity events, anaphylaxis, peptic ulcer, neutropenia, hypoglycemia, and antibiotic-associated diarrhea. Less serious but “significant” events (e.g., nonurticarial skin rash, hemorrhage not requiring transfusion or hospitalization, fall without fracture, and oversedation) constituted 945 (62.0%) of all ADEs. Of 421 ADEs judged as preventable (27.6% of ADEs), 167 (39.7%) were serious, 72 (17.1%) were life-threatening, and 5 (1.2%) were fatal. Thus, of approximately 30,000 elderly enrollees, a total of 244 (0.8%) experienced ADEs that were both preventable and severe during the 12-month follow-up.

Still, the overall rate of preventable ADEs identified by Gurwitz et al., 13.8 per 1,000 person-years (approximately 1.4% of enrollees), suggests a problem that should be addressed by managed care. Studies in nonelderly populations support this assessment, albeit not always with a methodology as rigorous of that of Gurwitz et al., usually concluding that there is a small but troublesome rate of potentially preventable ADEs in ambulatory care.12 Using a pre-implementation versus post-implementation design and multivariate analyses, Devine et al. (2010) studied prescriptions written in a large multispecialty clinic, finding that prior to the implementation of computerized provider order entry (CPOE), 911 of 5,016 (18.2%) prescriptions contained errors, although only 8 of these errors (0.9%, or 0.16% over all prescriptions) caused harm to the patient.13 After implementation of CPOE, the error rate declined to 423 of 5,153 (8.2%), with 5 of these (1.2%, or 0.10% over all prescriptions) causing harm.

Managed Care Efforts to Avoid ADEs

In the April 2010 issue of JMCP, Feifer and James described an analysis of the geographic variation in drug safety incidents and prescriber responsiveness to a retrospective drug utilization review (DUR) intervention in which an integrated medical and pharmacy claims database was mined using “thousands of algorithms” to generate alerts, which were then transmitted to prescribers by fax or mail.14 Ollendorf in an accompanying commentary addressed some pertinent questions regarding the takeaway messages from this research.15 Programs such as that described by Feifer and James are common in managed care, using a variety of methods and data sources, and proponents argue that use of technology to provide patient- and
drug-specific information to prescribers has the potential to reap both clinical and economic benefits by reducing ADEs and enhancing compliance with health plan formularies. However, key information not presented in the report by Feifer and James is of interest to the reader wanting to know how a program of this type contributes to quality improvement.

Foremost is the effect of the large volume of the alerts, reported by Feifer and James as an average of 128 alert messages per 1,000 health plan beneficiaries in 2008. The authors defined an alert “event” as a “potential drug safety issue that generated an alert to 1 or more prescribers.” By any measure, this is a lot of messages about drug safety, more than 1.6 million letters or fax communications to prescribers of the approximately 12.6 million health plan members in 1 year alone. Although Feifer and James do not report the distinct number of health plan members affected, the proportion could be as high as 13% in 1 year. Feifer and James indicate in their Limitations section that “prescribers could have received the same alert for the same patient on multiple occasions,” making it likely that the actual proportion of patients affected is much less than 13%. More importantly, if the 1.61 million alerts reported by Feifer and James were generated for typical utilization of 0.7 pharmacy claims per member per month or about 8 pharmacy claims per member per year for the 12.6 million members, approximately 1.6% of pharmacy claims generated an alert.

It seems reasonable to ask whether clinicians view alerts provided in this quantity, presumably received from only one of the many pharmacy benefit management companies and health plans with which a typical provider interacts daily, as valuable information or as “noise.” To err on the side of minimizing the number of “false negatives” (i.e., failing to provide a drug safety alert for a potentially important ADE) runs the risk of creating so much “false positive” noise that prescribers may not “hear” the true-positive risks to patient safety. The consequent Chicken Little phenomenon (i.e., we can’t believe everything that we are told) is no small consideration.

Drug Safety Alerts as Signal or Noise: The Role of Severity

We know from research with electronic prescribing systems that prescribers ignore or override the majority of drug safety alerts. In a study of 233,537 medication safety alerts generated by an electronic prescribing system and provided to 2,872 clinicians over 9 months in 2006, Isaac et al. (2009) found that clinicians overrode 90.8% of the drug interaction alerts and 77.0% of the allergy alerts, accepting only 9.4% of drug alerts overall (allergy alerts represented 1.7% of all drug alerts whereas drug interaction alerts represented 98.3%). The high probability of false-positive alerts for some of the messages is evident in the low rate of acceptance (7.1%) of drug interaction alerts judged to be low severity, although these low-severity drug interaction alerts represented only 7.6% of all safety alerts. Clinicians accepted 7.3% of moderate-severity drug interaction alerts, which represented 29.1% of all alerts, and 10.4% of high-severity drug interaction alerts, which represented 61.6% of all alerts. Although there may be some comfort in the positive relationship between the acceptance rate and the severity of the drug interaction alert, the number of alerts in the electronic prescribing system reported by Isaac et al. was large; 6.6% of all attempted prescriptions resulted in at least 1 alert.

The problems with CPOE that were identified by Isaac et al. are not unique. In a systematic review of the literature on the causes and consequences of physician overrides in CPOE alerting systems, Van Der Sijs et al. (2006) found that drug safety alerts were overridden 49%-96% of the time, except for high-severity alerts for overdose, which were overridden 27% of the time. In summarizing the results of 3 studies that examined the reasons for overrides, the primary reason was “alert fatigue caused by poor signal-to-noise ratio because the alert was not serious, was irrelevant, or was shown repeatedly.” Additional reasons included the importance of the treatment relative to the risk, physicians’ confidence in their own sources of information, or patient resistance. An additional factor was longer alert length, which made the alerts difficult to interpret. Notably, the “alert fatigue” problem appeared to produce potentially serious consequences for patients. In studies with override rates of 57%, 90%, and 80%, respectively, ADEs associated with the overridden alerts were identified in 2.3%, 2.5%, and 5.9%.

Knowledge of alert severity is important not only because it affects physician behavior, but also because it may be associated with the degree to which an ADE can be prevented—that is, higher-severity events are somewhat more likely to be preventable. In the study by Gurwitz et al., only 421 of 1,523 ADEs (27.6%) overall were judged as preventable. However, ADEs were more likely to be judged preventable if they were serious (38.7%), life-threatening (52.9%), or fatal (45.5%).

Similarly, using a patient survey (response rate 55%) with subsequent chart review in adult outpatients of 4 adult primary care practices in Boston (2 hospital-based and 2 community-based), Gandhi et al. found an overall ADE rate of 27.4%, of which 39.2% was either preventable ("due to errors that could have been entirely avoided," 11.0%) or ameliorable ("severity or duration could have been substantially reduced," 28.2%). Of 181 ADEs, 157 (86.7%) were judged as “significant” (less serious), of which 60 (38.2%) were judged as preventable or ameliorable. Of 24 events judged as serious, 11 (45.8%) were preventable or ameliorable.

Drug Safety Alerts as Signal or Noise: The Role of Therapeutic Class

The study by Gurwitz et al. identified a notable relationship between therapeutic class and the avoidability of ADEs. For example, Gurwitz et al. judged as preventable 93 of 203 (45.8%) ADEs associated with diuretics. ADEs associated with
anticoagulants and cardiovascular medications were deemed preventable in 43 of 121 (35.5%) and 103 of 396 (26.0%) cases, respectively. In contrast, ADEs associated with antibiotics and steroids were less often avoidable, in only 13 of 224 (5.8%) and 11 of 80 (13.8%) cases, respectively.9

Thus, it is perhaps not surprising that physician responsiveness to alert warnings also varies substantially by therapeutic class. In their analysis of prescriber overrides of alert warnings in electronic prescribing, Isaac et al. found that high-severity interactions with low acceptance rates included a methylxanthine such as theophylline prescribed with a cardioselective beta-blocker such as atenolol (acceptance rate 3.4%) or a tetracyclic antidepressant such as mirtazapine prescribed with a serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressant such as venlafaxine (acceptance rate 4.8%).18 These examples can be compared with high-severity interactions with high alert acceptance rates, such as amiodarone prescribed with either a macrolide such as azithromycin or a quinolone such as levofloxacin, both interactions with prescriber acceptance rates of about 40%.

In addition to its strong association with ADE preventability and provider response, therapeutic class is also important because a few therapeutic classes appear to account for a majority of ADEs, suggesting the possibility of more efficient systems that would generate a lower volume of alerts. Gurwitz et al. found that 5 therapeutic classes—cardiovascular medications, antibiotics, diuretics, nonopioid analgesics, and anticoagulants—were involved in 73.8% of ADEs. Similarly, in a study of preventable drug-related morbidity (PDRM) indicators in 49,658 patients treated in 9 general practices in England, Morris et al. (2004, measuring care provided from 1999-2002) found that just 4 problems accounted for 59.6% of 507 avoidable PDRMs.20 These were: (a) use of an oral or topical nonsteroidal anti-inflammatory drug (NSAID) for at least 3 months in a patient with hypertension or congestive heart failure; (b) use of an angiotensin-converting enzyme (ACE) inhibitor without monitoring creatinine level; (c) use of an ACE inhibitor without monitoring potassium level; and (d) use of a hypnogenic/anxiolytic with a long half-life.

A systematic review performed by Howard et al. (2006) identified the specific drugs most commonly associated with preventable drug-related hospital admissions caused by either inappropriate prescribing, lack of appropriate monitoring, or patient nonadherence.21 Only 17 studies were found to be reasonably valid from among 30 relevant studies, and 11 study reports contained sufficient detail to examine the causative drugs. Four drug classes accounted for more than one-half of all drug-related admissions attributed to ADEs or overtreatment: antiplatelets including aspirin when used as an antiplatelet (17.3%), diuretics (16.0%), NSAIDs (12.0%), and anticoagulants (8.9%). Of 1,406 preventable drug-related admissions, 1,263 (approximately 90%) were related to adverse drug reactions or overtreatment, versus 7% for undertreatment and 3% for patient adherence problems. This research by Howard et al. showed that despite a large number of studies of drug-related hospital admissions, including potentially preventable hospital admissions, more information is needed on the underlying causes of these admissions in order to develop interventions to improve patient safety.

**Increasing the Signal While Reducing the Noise: Efforts to Improve Alerting Systems**

Considered together, the evidence available to date suggests an opportunity to reduce the noise and improve the ratio of true-positive drug alerts of importance to patient safety, continuously improving the quality of alerting systems by using information about severity level or therapeutic class to eliminate altogether or reduce the volume of alerts that are associated with a low rate of drug therapy change. Unfortunately, the report by Feifer and James contains no information about whether the volume or response to safety alerts categorized by severity or therapeutic class. Moreover, although Feifer and James acknowledge that they did not adjust their estimates for age, calculating adjustments of this type would appear to yield large benefits in additional information. At the state level, we calculate that 30% of the variance in the alerting rates reported by Feifer and James is explained by mean age.19,22 For automated systems like that reported by Feifer and James and used by other managed care organizations, more detailed “mining” of the data on drug alert characteristics and outcomes represents a critically important, and to date largely neglected, area for quality improvement and future peer-reviewed research.

Weingart et al. (2009a) examined 279,476 drug interaction alerts in an electronic prescribing system from the first half of 2006. An expert panel judged that 402 ADEs may have been prevented, of which 49 were serious, 14 might have resulted in permanent disability, and 3 might have resulted in death.23 When assessed by severity of harm, the nearly 300,000 alerts may have prevented 39 hospitalizations, or a rate of 1.2 potentially avoidable hospitalizations per 100,000 alerts. Considering all potentially avoidable health care utilization, estimated cost savings totaled $402,619, approximately $1.44 per alert message. However, 331 alerts were needed to prevent 1 ADE. Because 10% of alerts accounted for 60% of ADEs, Weingart et al. concluded that alerts deemed to be of low value should be suppressed.

**Can Better Assessment Methods Yield Better Targeting?**

In addition to more detailed ongoing monitoring of drug therapy change rates by therapeutic class and severity level, automated alert warning systems could greatly benefit from the findings of studies with better research designs. Particularly important in the Feifer and James analysis is the inability to attribute a change in drug therapy to communication of the alert; instead, changes made within a specified time frame
following the issuance of the alert were assumed to be alert-driven. Although a randomized study design could be used to make this assertion with better certainty, withholding alerts in cases of true risk to patient safety raises ethical concerns. Alternatively, it would be a relatively simple matter to construct a comparison group from employer health plans without the drug alerting program and measure the rate of relevant drug therapy changes that occur in the absence of communication of alert messages for the trigger events defined as potential risks to drug safety. The degree of physician responsiveness to drug-related messages is often overstated by studies that fail to account for changes that would have been made even without the intervention. For example, Altavela et al. (2008) found that 23.5% of drug therapy recommendations that would have been made by clinical pharmacists to physicians, but that were concealed from the physicians using a controlled research design, were adopted by the physicians anyway.24

Also embedded in the significant questions left unanswered by research on the real effects of automated alerting systems on patient safety is rate of receipt of these messages by prescribers. Unlike an electronic prescribing system that requires an action by the prescriber at the point of care, we do not know what proportion of the mail or fax alerts were actually received and interpreted by the prescribers. A more sensitive safety alert system may request return-response affirmation of receipt of the alert and indication of the action taken (e.g., unimportant, no change necessary; discontinued drug X).

Also needed is more information about the quality of these interventions in terms of prescriber perception and satisfaction. Weingart et al. (2009b) found that only 47% of 184 clinicians using an electronic prescribing system were satisfied with the drug interaction and safety alerts. Common problems cited by survey respondents included false-positive alerts triggered by discontinued medications (58%), alerts that failed to account for appropriate drug combinations (46%), and excessive volume of alerts (37%).25

The challenge to reduce drug-related threats to patient safety is large. The quest for meaningful interventions must be mindful of sensitivity and specificity such that clinicians are required to interpret and take action on high-quality alerts that pose a real threat to patient safety. A great deal of feedback is necessary for such continuous quality improvement to occur. The risk of not doing so is significant, manifest in the proportion of clinicians that may not hear the warnings amid the noise. On the other hand, electronic interventions will soon engulf the practice of medicine, perhaps relegating retrospective DUR safety alerts delivered by snail mail and fax to George Orwell’s Room 101.26 In any case, all that we do in managed care should be guided by a focus on continuous quality improvement, as simple as ABC or PDCA (plan, do, check, act).

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22. Squared Pearson correlation between mean age and alerting rate, Table 2 in the report by Feifer and James.


